

STUDY PROTOCOL

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Preoperative sequential short-course radiation therapy and FOLFOX chemotherapy versus long-course chemoradiotherapy for locally advanced rectal cancer: a multicenter, randomized controlled trial (SOLAR trial)

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Abstract

Background Preoperative (chemo)radiotherapy has been widely used as an effective treatment for locally advanced rectal cancer (LARC), leading to a significant reduction in pelvic recurrence rates. Because early administration of intensive chemotherapy for LARC has more advantages than adjuvant chemotherapy, total neoadjuvant therapy (TNT) has been introduced and evaluated to determine whether it can improve tumor response or treatment outcomes. This study aims to investigate whether short-course radiotherapy (SCRT) followed by intensive chemotherapy improves oncologic outcomes compared with traditional preoperative long-course chemoradiotherapy (CRT).

Methods A multicenter randomized phase II trial involving 364 patients with LARC (cT3–4, cN+, or presence of extramural vascular invasion) will be conducted. Patients will be randomly assigned to the experimental or control arm at a ratio of 1:1. Participants in the experimental arm will receive SCRT (25 Gy in 5 fractions, daily) followed by four cycles of FOLFOX (oxaliplatin, 5-fluorouracil, and folinic acid) as a neoadjuvant treatment, and those in the control arm will receive conventional radiotherapy (45–50.4 Gy in 25–28 fractions, 5 times a week) concurrently with capecitabine or 5-fluorouracil. As a mandatory surgical procedure, total mesorectal excision will be performed 2–5 weeks from the last cycle of chemotherapy in the experimental arm and 6–8 weeks after the last day of radiotherapy in the control

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arm. The primary endpoint is 3-year disease-free survival, and the secondary endpoints are tumor response, overall survival, toxicities, quality of life, and cost-effectiveness.

Discussion This is the first Korean randomized controlled study comparing SCRT-based TNT with traditional preoperative LC-CRT for LARC. The involvement of experienced colorectal surgeons ensures high-quality surgical resection. SCRT followed by FOLFOX chemotherapy is expected to improve disease-free survival compared with CRT, with potential advantages in tumor response, quality of life, and cost-effectiveness.

Trial registration This trial is registered at Clinical Research Information under the identifier Service KCT0004874 on April 02, 2020, and at Clinicaltrial.gov under the identifier NCT05673772 on January 06, 2023.

Keywords Rectal neoplasm, Neoadjuvant radiotherapy, Short-course radiation, Consolidation chemotherapy, Disease-free survival, Randomized controlled phase II trial, Protocol

Background

Preoperative chemoradiotherapy (CRT) has long been the established treatment for locally advanced rectal cancer (LARC), effectively reducing the risk of local recurrence [1, 2]. However, despite the benefits, approximately one-third of patients with LARC experience relapse following preoperative CRT and surgery, with distant metastasis being the most common pattern of failure [2–6]. Recently, promising results of total neoadjuvant therapy (TNT) have been achieved in two trials: reduced disease-related treatment failure in the RAPIDO trial [4, 6] and increased disease-free survival (DFS) in the PRODIGE 23 trial [6]. As a result, TNT has emerged as the recommended treatment for LARC, emphasizing the need for timely and effective systemic therapy to eradicate micrometastases [7].

The main distinction between TNT and traditional preoperative CRT lies in the use of intensive chemotherapy before surgery. The RAPIDO and PRODIGE 23 trials differ in terms of tumor location, cT stage, cN stage, and circumferential resection margin status. Moreover, the TNT protocols vary in the sequence of treatments, types and cycles of neoadjuvant chemotherapy, and types of radiotherapy employed [4–6]. Currently, ongoing trials are evaluating different neoadjuvant treatment options for LARC.

While preoperative CRT has served as the standard treatment for LARC over the years and continues to be utilized in many countries, including South Korea [8, 9], short-course radiotherapy (SCRT) followed by delayed surgery has demonstrated comparable down-staging and surgical outcomes to CRT [10, 11]. Although systemic chemotherapy can be combined with both types of radiotherapy, a greater number of cycles of systemic chemotherapy can be scheduled with SCRT than CRT during the same treatment period.

Herein, we propose a neoadjuvant treatment protocol consisting of SCRT and four cycles of FOLFOX chemotherapy. Our randomized controlled trial aims to compare the 3-year DFS of patients with LARC treated with either preoperative CRT or SCRT followed by FOLFOX

chemotherapy before total mesorectal excision (TME). We hypothesized that our protocol would yield superior systemic treatment effects compared to traditional CRT, reducing the total treatment period from the initiation of neoadjuvant treatment to the completion of adjuvant chemotherapy, and enhancing patient convenience.

Methods

Study setting

The present study is a parallel-group, multicenter, superiority, randomized, phase II trial. The participants will be enrolled in nine tertiary academic hospitals in South Korea. The trial flow scheme is presented in Fig. 1.

Endpoints

The primary endpoint is the 3-year DFS, which is measured from the time of randomization until locoregional failure, metastasis, secondary cancer, or all-cause mortality. The data of patients who have not experienced any events by the time of the analysis will be censored at the last follow-up date. The Kaplan-Meier method will be used to calculate the survival rates. The secondary endpoints are the pathological complete response (pCR) rate; proportions of pathologic tumor regression grade (TRG) (Dworak [12], Mandard [13], AJCC TRG system [14]); R0 resection (microscopically clear resection) rate; 60-day postoperative surgical morbidity and mortality; treatment-related toxicity using the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0); compliance with the study protocol defined as the completion of preoperative treatment, surgery, and adjuvant treatment; TRG based on magnetic resonance imaging (MRI) [15]); quality of TME [16]; 5-year DFS; 3/5-year overall survival (OS); loco-regional recurrence; distant metastasis; 3-year peripheral neuropathy grade (CTCAE v5.0); questionnaires of quality of life (QoL) using the Korean version of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) version 3.0 [17]; QLQ-CR29 [18]; Low Anterior Resection Syndrome (LARS) score [19]; 5-item version of the International

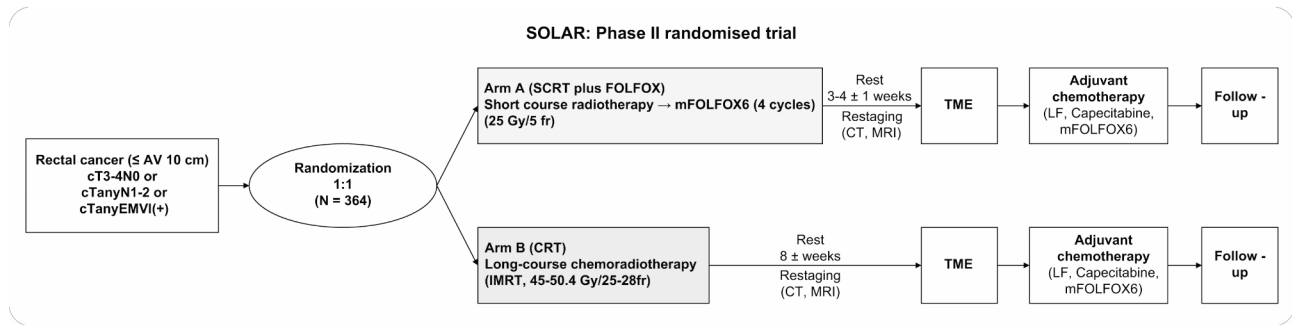


Fig. 1 Flowchart of the SOLAR trial. SCRT, short-course radiotherapy; FOLFOX, 5-fluorouracil with oxaliplatin; CRT, chemoradiotherapy; CT, computed tomography; MRI, magnetic resonance imaging; TME, total mesorectal excision

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1) A male/female adult aged between 20 and 75 years	1) Colon cancer or rectal cancer located more than 10 cm from the anal verge
2) Race: Asian	2) Stage I rectal cancer (clinical stage cT1-2N0)
3) Eastern Cooperative Oncology Group performance status 0–2	3) Clinically or pathologically diagnosed distant metastasis (cTanyNanyM1)
4) Pathologically confirmed rectal cancer (rectal cancer located 10 cm or low from the anal verge in pelvis MRI)	4) Familial adenomatous polyposis
5) Histologic type: adenocarcinoma, mucinous carcinoma, and signet ring cell carcinoma	5) Hereditary nonpolyposis colorectal cancer
6) Locally advanced rectal cancer with one or more of the following factors based on pelvis MRI: cTanyN1-2, cT3-4N0, or presence of extramural vascular invasion	6) History of chemotherapy or radiotherapy within 6 months
7) MRI findings such as pelvic lymph node metastasis, anal sphincter invasion, and T4b are not included in the exclusion criteria, which cases will be enrolled by the researcher’s discretion	7) History of colorectal cancer or other malignant tumors within 5 years
8) Patients with appropriate organ (bone marrow, kidney, liver) function	8) Currently under treatment of malignant tumors (except for cured nonmelanoma skin or in situ cervical cancer)
9) A person who understands the study and willing to provide informed consent	9) Comorbidities that make it difficult to undergo chemotherapy or radiotherapy
	10) Bone marrow suppression with neutrophil count < 2 × 10 ⁹ /L or platelet count < 100 × 10 ⁹ /L prior to the first chemotherapy
	11) Peripheral sensory neuropathy with functional impairment (grade 2 or higher)
	12) Severe renal function impairment (creatinine cleaning rate 30 ml/min or less)
	13) Severe hepatic dysfunction
	14) Genetic problems such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
	15) Taking tegafur, gimeracil, oteracil complex and those within 7 days of discontinuation
	16) Taking sorivudine, brivudin
	17) Significant heart disease or myocardial infarction within the last 6 months
	18) Hereditary diseases or history of coagulopathy
	19) Central nervous system disorders with disability or mental disorders
	20) Pregnant or lactating women
	21) Currently participating in other clinical trials or receiving research medication
	22) Unhealed wounds, fractures, peptic ulcers, abscesses in the abdominal cavity
	23) Active gastrointestinal bleeding
	24) Active infection requiring injection with antibiotics
	25) Emergency surgery
	26) History of hypersensitivity to drug in the study protocol
	27) Dihydropyrimidine dehydrogenase deficiency
	28) Not willing to participate

MRI, magnetic resonance imaging

Index of Erectile Function (IIEF-5) [20]; retrograde ejaculation from inclusion to 2 years after surgery; and cost-effectiveness (direct cost, indirect cost, and quality-adjusted life-year).

Study population, screening, and randomization

Patients with LARC are eligible for enrollment in this trial. They will be identified by the investigators and referred to the institutional multidisciplinary team for eligibility verification. The primary investigator will take charge of the final enrollment based on the inclusion/

exclusion criteria (Table 1). Eligible patients who are willing to participate receive details of the study. After providing written informed consent at each hospital, the participants will be randomly assigned to either Arm A (experimental arm: SCRT plus mFOLFOX6) or Arm B (control arm: CRT). Block randomization at a ratio of 1:1 will be performed and managed by the central clinical research coordinator.

Preoperative treatment

The participants in Arm A will receive SCRT (25 Gy in 5 fractions on consecutive days) followed by four cycles of mFOLFOX6 at 2-week intervals. The mFOLFOX6 regimen is composed of leucosodium 400 mg/m² (or levoleucovorin 200 mg/m² or leucovorin 400 mg/m²) and oxaliplatin (85 mg/m²) administered IV for 2-h and 5-fluorouracil (5-FU) 400 mg/m² bolus followed by continuous infusion of 5-FU 2400 mg/m² for over 46 h. The participants assigned to Arm B will receive CRT: a total dose of 45–50.4 Gy in 25–28 fractions given 5 times a week concurrently with capecitabine at a dose of 825 mg/m² (twice daily) or bolus 5-FU 400 mg/m² with leucovorin 20 mg/m² (or levoleucovorin 10 mg/m²) on 1–4 days of the first and fifth week of CRT. Radiotherapy will be administered using 3-dimensional conformal or intensity-modulated radiotherapy. Clinical target volume will be delineated according to the guideline of the Radiation Therapy Oncology Group [21]. Details of radiation treatment planning will be determined at the discretion of participating radiation oncologists. Treatment-related toxicity will be monitored throughout the preoperative phase and chemotherapy dose modification can be made according to the protocol and investigator's decision.

Surgery

The surgery timing from the start of radiotherapy is comparable between the two arms. After the completion of preoperative treatments, the tumor will be reevaluated with computed tomography (CT) scan and MRI within 4 weeks before the scheduled surgery. TME will be performed at 2–5 weeks from the last cycle of preoperative chemotherapy in Arm A and at 6–8 weeks (maximum resting period of 10 weeks) after the last day of radiotherapy in Arm B. Surgical resection aims at achieving complete resection of primary tumor using TME with regional lymph node dissection. The type of surgical approach (open, laparoscopic, or robotic), starting point and direction of mesocolic and mesorectal detachment, location of major vascular ligation, splenic flexure mobilization, intestinal anastomosis, stoma creation, and surgical instruments will follow each investigator's discretion. Postoperative complications will be recorded on the case report form for up to 60 days following surgery.

Surgical resection will be performed by a colorectal surgeon with sufficient knowledge and experience in rectal cancer surgery and treatment. All participating surgeons should have completed a fellowship in colorectal surgery and experience in more than 50 cases of rectal cancer surgery. The designated questionnaire presented in Supplementary Table 1 will be used for the recruitment of hospitals and surgeons. Each hospital has designated radiation oncologist(s), oncologist(s), pathologist(s), and radiologist(s) specializing in rectal cancer. The historical

data on TME performed by the participating hospitals and surgeons is presented in Supplementary Fig. 1. The surgeons must submit unedited rectal cancer surgery videos to obtain approval from the research steering committee before the study participation. To ensure the quality of surgery and standardized surgical procedures, discussion on rectal cancer surgery and video presentation will be performed at the investigator meetings twice a year during the enrollment period.

Postoperative chemotherapy

Adjuvant chemotherapy is recommended for all patients and initiated within 4 weeks following TME. The decision to use adjuvant chemotherapy and the timing of its initiation will be determined by the investigators in charge of chemotherapy based on each patient's postoperative condition. The duration of adjuvant chemotherapy is about 4 months, resulting in a total chemotherapy period of 6 months. Both arms will receive adjuvant chemotherapy according to the pathological stage as follows: capecitabine or 5-FU with leucovorin (or leucosodium or levoleucovorin) for ypStages 0 to I and mFOLFOX 6 for ypStages II to III. In case of Stage IV confirmed before or at the time of surgery, additional treatment is determined by the institutional multidisciplinary team.

Pathological evaluation

Pathological evaluation will be performed by the dedicated pathologists specializing in rectal cancer at each institution according to the AJCC Cancer Staging manual, 8th edition [14], and recorded using the pathological report form of the study, which includes the number of harvested/metastatic lymph nodes, length of proximal/distal/circumferential resection margin, and TRG using at least one of the three TRG systems (AJCC [14], Dworak [12], and Mandard [13] TRG system). The quality of the resected specimen will be classified for mesorectum and sphincter complex in case of abdominoperineal resection [22].

Follow-up

Each participant will undergo regular follow-up until 5 years following surgery for history and morbidity/toxicity assessment, physical examination, measurement of carcinoembryonic antigen (CEA), and assessment of questionnaires of QoL. Toxicity will be evaluated and recorded according to CTCAE v5.0. Furthermore, CEA will be measured at 3 months following surgery and every 6 months thereafter. Abdominopelvic and chest CT scans will be performed every 6 months during the first 2 years and then annually during the following 3 years. QoL assessment using EORTC questionnaires QLQ-C30 and QLQ-CR29, LARS score for all patients, and IIEF-5

for male patients will be performed at 3, 6, 12, and 24 months.

Translational research

Translational research using tumor tissue and blood will be conducted to interpret the clinical outcomes, treatment response, and prognosis in association with the molecular biological characteristics of rectal cancer. A specified protocol for the collection and preparation of fresh tissue and blood at different treatment stages will be given to all participating hospitals. Participation in the translational components of this trial is optional and subject to regional capacities. Samples will be collected and used after obtaining participant consent.

Sample size calculation

The 3-year DFS following preoperative CRT is expected to be 70% based on literature [23–27]. We hypothesized that the experimental arm would have a 10% improvement in 3-year DFS compared with the control group. This corresponds to a hazard ratio of 0.626 between the two arms (experimental /control). Assuming an 80% statistical power, a one-sided alpha level of 0.05, a minimal accrual duration of 36 months, and a minimal follow-up of 36 months, a total of 113 events will be needed to observe the expected difference using the one-sided log-rank test. Assuming a 5% rate of patients who are not informative or lost to follow-up, a total of 364 patients will be enrolled in this study, with 182 patients in each group.

Statistical analysis

The primary endpoint will be analyzed according to the intention-to-treat principle in patients who are randomized and receive preoperative treatments. Secondary analyses will be conducted using the per-protocol principle, considering only patients with sufficient compliance with the protocol. The Kaplan–Meier curve will be used to analyze the survival outcomes and the log-rank test for the prognostic factors. The chi-squared test will be employed to compare categorical data between the two groups and Student's *t*-test for continuous variables. The effect of covariates on the endpoints will be evaluated using the Cox proportional-hazards model. QoL, assessed using questionnaires, will be expressed as mean, standard deviation, median, minimum, and maximum values. A mixed model for repeated-measure analysis with the assumption of an unconstructed covariance structure will be applied for QoL comparison. Least-square mean estimates will be calculated for *post hoc* analyses to compare the two treatment groups at each time point and evaluate any changes from the baseline scores. All tests will be two-sided, and P -value < 0.05 will be considered to indicate statistically significant

differences. This trial has no plan for interim analysis. Missing data for the primary endpoint will be censored at either the last assessment date or the trial deadline, whichever is earlier. Because the primary endpoint is presented as recurrence or not, there are no outlier data. If there are missing values for the secondary endpoints, the last observation carried forward method will be employed to impute for the missing data with the most recently available data, and the Grubb and Cochran tests will be adopted to determine outliers if suspected.

Data collection and management

Data will be collected using an electronic clinical research form (eCRF) system approved by the steering committee. Each study site is responsible for data entry, and the principal investigator is responsible for confirming the final data. During the study period, a monitoring team from the contract research organization (CRO) will regularly contact and visit all sites, with occasional visits as necessary. To ensure that the study is conducted according to the protocol, the completeness, consistency, and accuracy of the data entered in the eCRF will be evaluated at each visit of the CRO. All adverse events are graded according to CTCAE v5.0 and recorded in the eCRF. The investigators are responsible for evaluating the causal relationship between protocol treatments and each event. Furthermore, they will report severe adverse events to both their institutional review board and the principal investigator. The independent Data and Safety Monitoring Board (DSMB) will monitor the recruitment, reported adverse events, and data quality when 10% (36), 30% (109), 50% (182), 70% (255), and 100% (364) of the participants are enrolled. The goal is to ensure that the study conforms to the current standards of Good Clinical Practice, with focus on the safety interests of the patients. The DSMB will provide the principal investigator with recommendations regarding potential trial modification, continuation, or premature termination.

Current status

The study protocol was approved by the ethics committee of Kyungpook National University Chilgok Hospital on October 17, 2019 (No. KNUCH 2019-09-004-001) as well as the approval of ethics committees of all other participating institutions. Patients have been enrolled in the study since September 2021, and as of July 16, 2023, a total of 182 patients have been recruited.

Discussion

Recent clinical studies have achieved promising results in reducing distant metastasis in LARC using TNT compared with surgery first or traditional preoperative CRT followed by surgery. Although the long-term outcomes of TNT in terms of OS and DFS are still awaited, TNT

has emerged as an alternative to conventional treatment, potentially redefining the standard of care. At the time of launching the present trial, only one randomized clinical trial (POLISH II [27]) has been published. Thereafter, several randomized clinical trials using TNT have been published (RAPIDO [4], PRODIGE23 [6], STELLAR [5], FOWARC [28], CAO/ARO/AIO-12 [29], and OPRA [30]). These clinical trials differ in terms of the inclusion criteria, treatment schedules, type of radiotherapy and chemotherapy, and primary endpoints, the details of which can be found in Kang's review article [31]. Because there are various combinations of them, a head-to-head comparison among all currently developed regimens is impossible.

This SOLAR trial compares the neoadjuvant treatment protocols (SCRT followed by four cycles of mFOLFOX6 vs. CRT) in rectal cancer with cT3–4, cN+, or extramural venous invasion. This trial is designed for mid- or low rectal cancer (tumor height ≤ 10 cm from the anal verge) as upper rectal cancer can sometimes be treated like colon cancer and surgery can be modified as tumor-specific mesorectal excision [32]. As regards the chemotherapy duration, we adopted four cycles of mFOLFOX6 because the ypCR rate was as low as 11% with SCRT followed by three cycles of mFOLFOX6 in our initial experience [33]. Meta-analysis of 17 studies comparing SCRT followed by consolidation chemotherapy with CRT supports using at least four cycles of consolidation chemotherapy following SCRT to achieve improved ypCR and DFS over preoperative CRT alone [34]. Because SCRT followed by four cycles of CAPOX achieved significantly higher ypCR rate and 3-year OS than CRT alone in the STELLAR trial [5] involving patients with cT3–4 or cN+, the results of this SOLAR trial are awaited.

Although the RAPIDO trial used SCRT in a TNT arm, it compared a TNT regimen with longer chemotherapy duration with conventional CRT in LARC with high-risk features such as cT4, mesorectal fascia involvement, cN2, lateral lymph node metastasis, and extramural venous invasion [4]. The PRODIGE 23 trial included patients with LARC (cT3–4 or cN+) and administered induction chemotherapy with FOLFIRINOX in a TNT group [6]. The CAO/ARO/AIO-12 [29] and OPRA [30] trials compared induction and consolidation chemotherapies, and the results favored consolidation chemotherapy in the aspects of ypCR and organ preservation.

In this SOLAR trial, all patients are planned to undergo TME, without the option for nonoperative management, which is a trending approach for LARC. We plan to develop criteria for accurately diagnosing clinical complete response by leveraging the clinical and pathologic outcomes of this study, thereby informing future treatment protocols involving watchful waiting.

Our current treatment protocol presents a practical alternative, addressing concerns about potential over-treatment associated with TNT and the missed treatment opportunity of a watchful waiting strategy.

Studies comparing the cost-effectiveness of various preoperative treatment options in patients with LARC are scarce. The direct medical cost was lower in SCRT than in CRT [35]. Practically, patients should visit the hospital for 25–30 consecutive days for CRT, which influences indirect cost and QoL. This can pose a particular challenge in situations where cancer treatment is centered at designated hospitals or in countries with low health-care budgets. Two recent trials, the POLISH II [36] and ESCORT trial [9], compared the cost-effectiveness of two preoperative strategies, namely, SCRT plus chemotherapy and CRT in patients with LARC. These trials demonstrated that SCRT plus consolidation chemotherapy was more cost-effective than CRT for direct and/or indirect costs. To achieve patient-centered care, new treatments should improve not only the oncological outcomes but also the QoL for patients undergoing treatment. In this regard, the SOLAR trial will also include cost-effectiveness analysis as a secondary endpoint.

The quality of surgical resection is well known to be a crucial factor in local control and sphincter preservation following preoperative treatment and surgical resection [37]. In particular, surgical quality assessment is important in evaluating the effects of new preoperative treatments when TME is performed. Recent clinical trials have reported a wide range of complete TME, R0 resection, and sphincter preservation rates for LARC. The rates of complete TME were 81% in POLISH II and 86% in PRODIGE 23 trials; however, the rates were not reported in the RAPIDO and STELLAR. Furthermore, in POLISH II, PRODIGE 23, RAPIDO, and STELLAR trials, the R0 resection rates ranged from less than 80 to 90% and the rates of a permanent stoma during the initial TME ranged from 14 to 48%. These outcome variations may be partly attributed to differences in the inclusion criteria among the studies. Although TME with sufficient quality is currently accepted as a logical approach, the quality control of surgery may not be as standardized as that for preoperative treatment protocols. Thus, we paid particular attention to surgical quality control in our study to minimize surgical outcome variations. We are only inviting surgeons who had completed a fellowship in colorectal surgery and met the minimum criteria for experience in TME. The TME procedures of each surgeon are evaluated by the research steering committee through a review of unedited video. The details of surgical procedures such as TME and sphincter preservation will be regularly discussed in the investigator meetings to maintain consensus on surgical procedures until enrollment of the last case.

Conclusions

The present trial is a multicenter prospective randomized controlled trial comparing SCRT followed by mFOLFOX6 and CRT as two preoperative treatments for LARC. Based on the similar effect on local control between SCRT and CRT as well as the potential systemic effect of neoadjuvant systemic chemotherapy, we hypothesized that preoperative treatment with SCRT and mFOLFOX6 would lead to longer DFS. Quality control measures are implemented to reduce surgery-related complications and achieve competent sphincter preservation, while ensuring adequate local tumor control.

Abbreviations

5-FU	5-Fluorouracil
CRT	Chemoradiotherapy
CEA	Carcinoembryonic antigen
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DSMB	Data and Safety Monitoring Board
eCRF	Electronic clinical research form
EOTRC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
IIEF	International Index of Erectile Function
ITT	Intention-to-treat
LARC	Locally advanced rectal cancer
LARS	Low Anterior Resection Syndrome
MRI	Magnetic resonance imaging
OS	Overall survival
pCR	Pathological complete response
QoL	Quality of life
SCRT	Short-course radiotherapy
TME	Total mesorectal excision
TNT	Total neoadjuvant therapy
TRG	Tumor regression grade

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12885-023-11363-7>.

Supplementary Material 1

Supplementary Material 2

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Authors' contributions

GSC is the Chief Investigator. GSC, and JSP conceived study idea, designed, orchestrated multi-center trial, and organized funding. MKK, SYP, JGK, BWK, and SJB contributed to the trial design, and protocol development. JSP and HK planned and performed statistical analyses. MKK and SYP drafted this protocol manuscript and contributed equally to this study. JSP, SYP, JHB, SHC, ANS, HJK, DWK, JYK, EJP, GWH, JK, JHK, CHK, IJP participated in coordination and execution of the study. All authors provided input into the manuscript. All authors have read and approved the final version of the manuscript for publication.

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Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study protocol, patient information, and consent were approved by the ethics committee of the Kyungpook National University Chilgok Hospital on October 17, 2019 and the IRBs of all participating institutions. Furthermore, the trial is approved by the Ministry of Food and Drug Safety (2020004284) on June 04, 2020. Patients will receive information (purpose, potential advantages, risks) about the study and be asked to sign a consent prior to enrolment. Each participant will complete written informed consent before enrollment. This study complies the principles of both Declaration of Helsinki rules and the Good Clinical Practices guidelines.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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References

- Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Ollier JC, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med*. 2006;355(11):1114–23.

2. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, Becker H, Raab HR, Villanueva MT, Witzigmann H, 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):1926–33.
3. Nilsson PJ, van Etten B, Hospers GA, Pahlman L, van de Velde CJ, Beets-Tan RG, Blomqvist L, Beukema JC, Kapiteijn E, Marijnen CA, et al. Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer—the RAPIDO trial. *BMC Cancer*. 2013;13:279.
4. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM-K, Roodvoets AGH, Nagtegaal ID, Beets-Tan RGH, Blomqvist LK, 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.
5. Jin J, Tang Y, Hu C, Jiang LM, Jiang J, Li N, Liu WY, Chen SL, Li S, Lu NN, et al. Multicenter, Randomized, Phase III Trial of short-term Radiotherapy Plus Chemotherapy Versus Long-Term Chemoradiotherapy in locally advanced rectal Cancer (STELLAR). *J Clin Oncol*. 2022;40(15):1681–92.
6. Conroy T, Bosset JF, Etienne PL, Rio E, Francois E, Mesgouez-Nebout N, Vendrely V, Artignan X, Bouche O, Gargot D, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(5):702–15.
7. Benson AB, Venook AP, Al-Hawary MM, Azad N, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Garrido-Laguna I, et al. Rectal Cancer, Version 2.2022. NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2022;20(10):1139–67.
8. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rodel C, Cervantes A, Arnold D, Committee EG. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl4):iv22–iv40.
9. Cho MS, Bae HW, Chang JS, Yang SY, Kim TH, Koom WS, Shin SJ, Choi G-S, Kim NK. Short-term outcomes and cost-effectiveness between long-course chemoradiation and short-course Radiotherapy for locally advanced rectal Cancer. *Yonsei Med J*. 2023;64(6):395–403.
10. Erlandsson J, Holm T, Pettersson D, Berglund A, Cedermark B, Radu C, Johansson H, Machado M, Hjern F, Hallbook O, 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):336–46.
11. Liu SX, Zhou ZR, Chen LX, Yang YJ, Hu ZD, Zhang TS. Short-course Versus Long-course preoperative radiotherapy plus delayed surgery in the treatment of rectal Cancer: a Meta-analysis. *Asian Pac J Cancer Prev*. 2015;16(14):5755–62.
12. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *Int J Colorectal Dis*. 1997;12(1):19–23.
13. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, Roussel A, Jacob JH, Segol P, Samama G. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer*. 1994;73(11):2680–6.
14. Amin MB, American Joint Committee on Cancer, American Cancer Society. AJCC cancer staging manual, eighth edition / editor-in-chief. In: Amin MB, editors Edge M, FACS and 16 others ; Donna M. Gress, RHIT, CTR - Technical editor ; Laura R. Meyer, CAPM - Managing editor. edn. Chicago IL: American Joint Committee on Cancer, Springer; 2017.
15. Patel UB, Brown G, Rutten H, West N, Sebag-Montefiore D, Glynne-Jones R, Rullier E, Peeters M, Van Cutsem E, Ricci S, et al. Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer. *Ann Surg Oncol*. 2012;19(9):2842–52.
16. Nagtegaal ID, van de Velde CJ, van der Worp E, Kapiteijn E, Quirke P, van Krieken JH. Cooperative Clinical investigators of the dutch Colorectal Cancer G: macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol*. 2002;20(7):1729–34.
17. Sprangers M, Cull A, Bjordal K, Groenvold M, Aaronson N. Life ESGoQo: the European Organization for Research and Treatment of Cancer approach to quality of life assessment: guidelines for developing questionnaire modules. *Qual Life Res*. 1993;2(4):287–95.
18. Whistance R, Conroy T, Chie W, Costantini A, Sezer O, Koller M, Johnson C, Pilkington S, Arraras J, Ben-Josef E. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. *Eur J Cancer*. 2009;45(17):3017–26.
19. Kim CW, Jeong WK, Son GM, Kim IY, Park JW, Jeong S-Y, Park KJ, Lee S-H. Validation of Korean version of low anterior resection syndrome score questionnaire. *Annals of Coloproctology*. 2020;36(2):83.
20. AHN T-Y, Lee D-S, KANG W-c HONG, J-H, KIM Y-S. Validation of an abridged Korean version of the International Index of Erectile function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Korean J Urol* 2001;535–40.
21. Myerson RJ, Garofalo MC, El Naqa I, Abrams RA, Apte A, Bosch WR, Das P, Gunderson LL, Hong TS, Kim JJ, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. *Int J Radiat Oncol Biol Phys*. 2009;74(3):824–30.
22. Campa-Thompson M, Weir R, Calcetera N, Quirke P, Carmack S. Pathologic processing of the total mesorectal excision. *Clin Colon Rectal Surg*. 2015;28(01):043–52.
23. Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, Kahlenberg MS, Baez-Diaz L, Ursiny CS, Petrelli NJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol*. 2009;27(31):5124–30.
24. Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, Park JO, Kim SY, Kim TY, Kim JH, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial. *Lancet Oncol*. 2014;15(11):1245–53.
25. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. 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):1215–23.
26. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, Ackland SP, Schache D, McClure B, McLachlan SA, 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):3827–33.
27. Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Krynski J, Michalski W, Oledzki J, Kusnierz J, Zajac L, 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):834–42.
28. Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, Chen D, Cao J, Wei H, Peng X, et al. Neoadjuvant Modified FOLFOX6 with or without Radiation Versus Fluorouracil Plus Radiation for locally advanced Rectal Cancer: final results of the chinese FOWARC trial. *J Clin Oncol*. 2019;37(34):3223–33.
29. Fokas E, Schlenska-Lange A, Polat B, Klautke G, Grabenbauer GG, Fietkau R, Kuhnt T, Staib L, Brunner T, Grosu AL, et al. Chemoradiotherapy Plus induction or consolidation chemotherapy as total neoadjuvant therapy for patients with locally advanced rectal Cancer: long-term results of the CAO/ARO/AIO-12 Randomized Clinical Trial. *JAMA Oncol*. 2022;8(1):e215445.
30. Garcia-Aguilar J, Patil S, Gollub MJ, Kim JK, Yuval JB, Thompson HM, Verheij FS, Omer DM, Lee M, Dunne RF, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. *J Clin Oncol*. 2022;40(23):2546–56.
31. Kang MK. Implications of recent neoadjuvant clinical trials on the future practice of radiotherapy in locally advanced rectal cancer. *World J Gastroenterol*. 2023;29(6):1011–25.
32. Lopez-Kostner F, Lavery IC, Hool GR, Rybicki LA, Fazio VW. Total mesorectal excision is not necessary for cancers of the upper rectum. *Surgery*. 1998;124(4):612–8.
33. Song SH, Park JS, Kang MK, Choi GS, Park SY, Kim HJ, Kim JG, Kang BW, Baek JH, Baek DW, et al. Initial experience of preoperative short-course radiotherapy followed by oxaliplatin-based consolidation chemotherapy for locally advanced rectal cancer. *Int J Colorectal Dis*. 2021;36(6):1279–86.
34. Liao CK, Kuo YT, Lin YC, Chern YJ, Hsu YJ, Yu YL, Chiang JM, Hsieh PS, Yeh CY, You JF. Neoadjuvant Short-Course Radiotherapy followed by consolidation chemotherapy before surgery for treating locally advanced rectal Cancer: a systematic review and Meta-analysis. *Curr Oncol*. 2022;29(5):3708–27.
35. Hanly P, C elleachair A, Skally M, O'Neill C, Sharp L. Direct costs of radiotherapy for rectal cancer: a microcosting study. *BMC Health Serv Res*. 2015;15:1–7.
36. Wang S, Wen F, Zhang P, Wang X, Li Q. 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):1–8.
37. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, Van Krieken JHJ. Preoperative radiotherapy

combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med.* 2001;345(9):638–46.

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