Radiation Oncology

STUDY PROTOCOL

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Efficacy and safety of MR-guided adaptive simultaneous integrated boost radiotherapy to primary lesions and positive lymph nodes in the neoadjuvant treatment of locally advanced rectal cancer: a randomized controlled phase III trial

Haohua Wang[1,2], Xiang Zhang[1], Boyu Leng[1], Kunli Zhu[1], Shumei Jiang[1], Rui Feng[1], Xue Dou[1], Fang Shi[1], Lei Xu[1*] and Jinbo Yue[1*]

Abstract

Background In locally advanced rectal cancer (LARC), optimizing neoadjuvant strategies, including the addition of concurrent chemotherapy and dose escalation of radiotherapy, is essential to improve tumor regression and subsequent implementation of anal preservation strategies. Currently, dose escalation studies in rectal cancer have focused on the primary lesions. However, a common source of recurrence in LARC is the metastasis of cancer cells to the proximal lymph nodes. In our trial, we implement simultaneous integrated boost (SIB) to both primary lesions and positive lymph nodes in the experimental group based on magnetic resonance-guided adaptive radiotherapy (MRgART), which allows for more precise (and consequently intense) targeting while sparing neighboring healthy tissue. The objective of this study is to evaluate the efficacy and safety of MRgART dose escalation to both primary lesions and positive lymph nodes, in comparison with the conventional radiotherapy of long-course concurrent chemoradiotherapy (LCCRT) group, in the neoadjuvant treatment of LARC.

Methods This is a multi-center, randomized, controlled phase III trial (NCT06246344). 128 patients with LARC (cT3-4/N+) will be enrolled. During LCCRT, patients will be randomized to receive either MRgART with SIB (60–65 Gy in 25–28 fractions to primary lesions and positive lymph nodes; 50–50.4 Gy in 25–28 fractions to the pelvis) or intensity-modulated radiotherapy (50–50.4 Gy in 25–28 fractions). Both groups will receive concurrent chemotherapy with capecitabine and consolidation chemotherapy of either two cycles of CAPEOX or three cycles of FOLFOX between radiotherapy and surgery. The primary endpoints are pathological complete response (pCR) rate and surgical

*Correspondence:
Lei Xu
len.xu@hotmail.com
Jinbo Yue
jbyue@sdfmu.edu.cn

Full list of author information is available at the end of the article

difficulty, while the secondary endpoints are clinical complete response (cCR) rate, 3-year and 5-year disease-free survival (DFS) and overall survival (OS) rates, acute and late toxicity and quality of life.

Discussion Since dose escalation of both primary lesions and positive nodes in LARC is rare, we propose conducting a phase III trial to evaluate the efficacy and safety of SIB for both primary lesions and positive nodes in LARC based on MRgART.

Trial registration The study was registered at ClinicalTrials.gov with the Identifier: NCT06246344 (Registered 7th Feb 2024).

Keywords Locally advanced rectal cancer (LARC), MR-guided adaptive radiotherapy (MRgART), Simultaneous integrated boost (SIB), Primary lesion, Positive lymph node, pCR, Surgical difficulty, Randomized controlled trial

Background

Locally advanced rectal cancer (LARC), typically stage II (cT3-4/N0) or stage III (cT1-4/N1-3), requires multimodal treatment. Surgical resection alone is associated with a high rate of local recurrence [1, 2]. Neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME), on the other hand, can better control local recurrence in LARC patients. However, the overall pathological complete response (pCR) rate and clinical complete response (cCR) rate are still low, and there is an inconsistency between them [3, 4], Therefore, the preservation of the anus is still a challenge. Optimizing neoadjuvant treatment strategies, including strategies such as increasing concurrent chemotherapy and increasing the dose of radiotherapy, is essential to improve tumor regression and anal preservation.

Radiotherapy is an important treatment for controlling local recurrence and downstaging LARC [5–9]. A common cause of cancer recurrence in rectal cancer is that tumor cells metastasise nearby positive lymph nodes, such as the lateral pelvic lymph nodes [10, 11]. These sites can serve as refuges where the cancer can regroup and either recur at the original site or spread to other areas [2]. Various studies [5, 12, 13] have also investigated the role of radiotherapy dose escalation in promoting tumor regression. Seldom have these studies examined dose escalation to both the primary lesions and positive lymph nodes. One of the major limiting factors is the tradeoff between destruction of the cancer itself and collateral damage to the neighboring healthy tissues. However, recent advances in the field have made great strides in overcoming this obstacle. MR-guided adaptive radiotherapy (MRgART) allows direct imaging of the target and organs at risk (OAR), combined with optimization of the treatment plan for anatomical changes, to deliver high-quality dose escalation regimens to improve treatment response while protecting OAR such as the bladder, femoral heads, and the small bowel [14].

We hypothesize that by implementing simultaneous integrated boost (SIB) to both the primary lesions and positive lymph nodes based on MRgART, we can improve the cCR and pCR rates without increasing surgical difficulty, while maintaining tolerable safety.

Methods/design

Aim and study design

Our study is a multi-center, randomized, controlled phase III trial to evaluate the efficacy and safety of SIB to both the primary lesions and positive lymph nodes based on MRgART for LARC. Eligible patients will be randomized 1:1 into experimental and control groups, both of which will undergo long course concurrent chemoradiotherapy (LCCRT), consolidation chemotherapy and TME surgery. During LCCRT, the experimental group will receive SIB dose escalation based on MRgART, while the control group will receive conventional dose without MRgART. The follow-up period is 60 months. Figure 1 depicts the study flow.

Primary endpoints

- pCR rate.
- Surgical difficulty.

Secondary endpoints

- Clinical complete response (cCR) rate.
- 3-year and 5-year disease-free survival rates.
- 3-year and 5-year overall survival rates.
- Acute toxicity (CTCAE v5.0).
- Late toxicity (LENT/SOMA score).
- Overall quality of life (QLQ-C30).
- Quality of life (QLQ-CR29).

Exploratory endpoints

Biomarkers that may predict efficacy - including, but not limited to gene mutations, PD-L1 expression, tumor mutation burden, gut intratumoral microbiota, lymphocyte subsets and imaging markers - will be investigated in tumor tissue, blood, and stool samples.

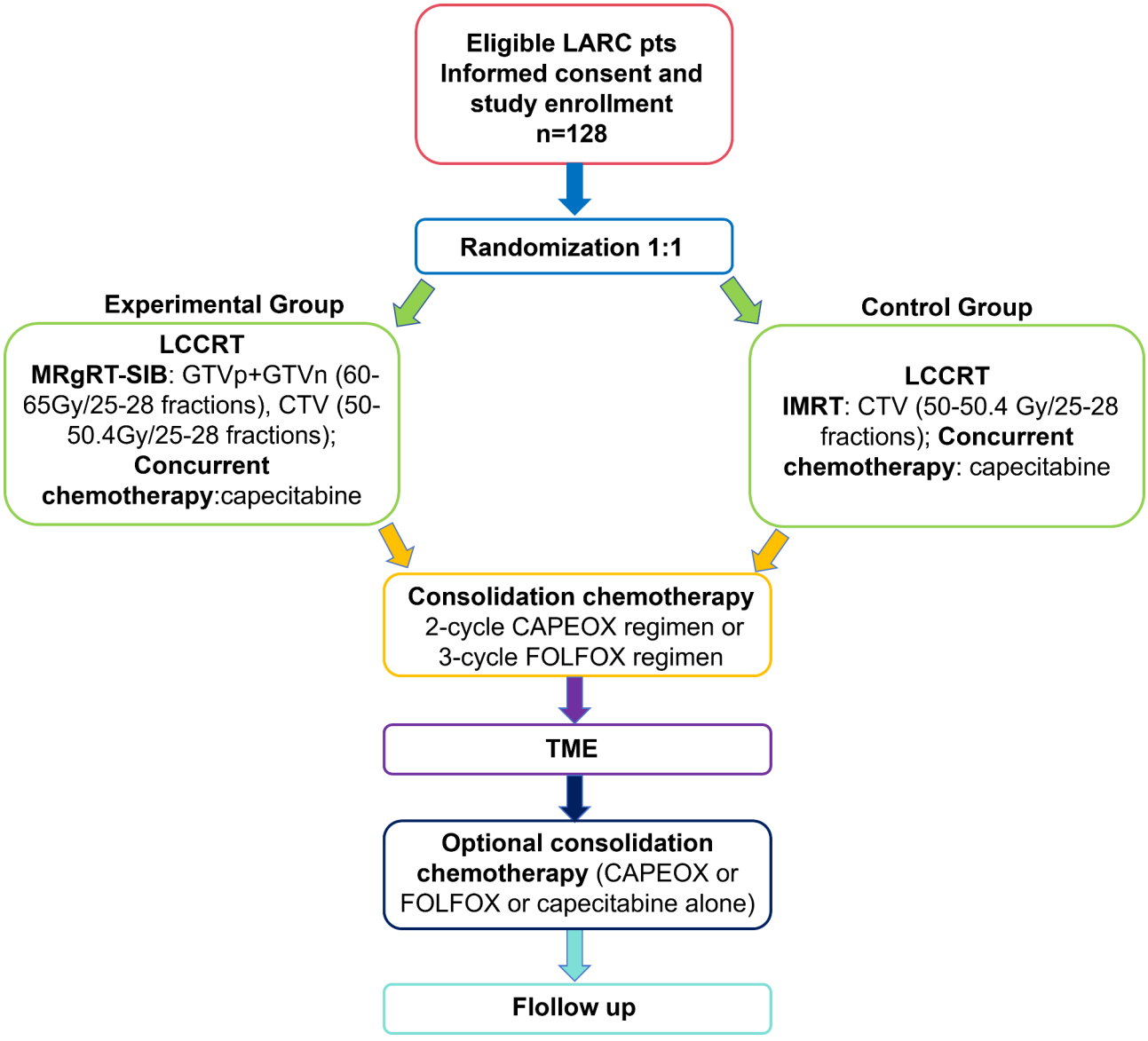

Fig. 1 Workflow. LARC: locally advanced rectal cancer; LCCRT: long course concurrent radiotherapy and chemotherapy; MRgART-SIB: MRI-guided simultaneous integrated boost radiotherapy; CAPOX: capecitabine and oxaliplatin; FOLFOX: 5-fluorouracil, leucovorin and oxaliplatin; TME: total mesorectal excision

Investigators

The investigators, all experienced radiation oncologists, will recruit a total of 128 patients from multi-tumor centers in China. Treatment will be administered according to the study protocol at these centers. The study will have a 24-month enrollment and a 60-month follow-up period.

Inclusion criteria

- Histopathology confirmed rectal adenocarcinoma.
- The tumor location ≤ 10 cm from the anal verge.
- Age ≥ 18 years.
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–1 .

Primary treatment-naive tumors confirmed by endorectal ultrasound or MRI- revealed cT3-4/N+tumors as classified by the 8th edition of the AJCC staging system.

- Patient survival ≥ 6 months.
- Normal major organ function (within 14 days prior to enrollment) and suitability for receiving chemoradiotherapy.
- Ability to provide tissue and blood samples for translational research.

Exclusion criteria

- History of prior chemotherapy, radiotherapy, or surgical treatment for rectal cancer, including transanal tumor resection.
- Locally recurrent rectal cancer.
- History of familial adenomatous polyposis.
- Active Crohn's disease or ulcerative colitis.
- Allergy or hypersensitivity history to 5-fluorouracil and/or oxaliplatin.
- History of difficulty or inability to take or absorb oral medications.
- Diagnosis of malignancy other than rectal cancer within the past 5 years (excluding completely cured basal cell carcinoma, squamous cell carcinoma of the skin, and/or in situ carcinoma treated with radical resection).
- Distant metastasis, i.e., cM1, confirmed through imaging or biopsy.
- History of pelvic radiotherapy.
- Pregnant or lactating women.
- The presence of any severe or uncontrollable systemic illness.

Study intervention/treatment and procedures

During LCCRT, patients will be randomized to receive either MRgART with SIB (60–65 Gy in 25–28 fractions to primary lesions and positive lymph nodes; 50–50.4 Gy in 25–28 fractions to the pelvis) using a 1.5T Unity MR-linac (Elekta AB, Stockholm, Sweden) or conventional dose (50–50.4 Gy in 25–28 fractions). Figure 2 illustrates the advantages of MRgART over non-adaptive radiotherapy. By daily recontouring the target and OAR online on a daily basis and optimizing the treatment plans accordingly, we can minimize the impact of interfractional motion, thereby achieving dose escalation to primary lesions and positive lymph nodes, while protecting the small bowel, femoral heads and bladder. Both groups will receive concurrent chemotherapy with capecitabine (825

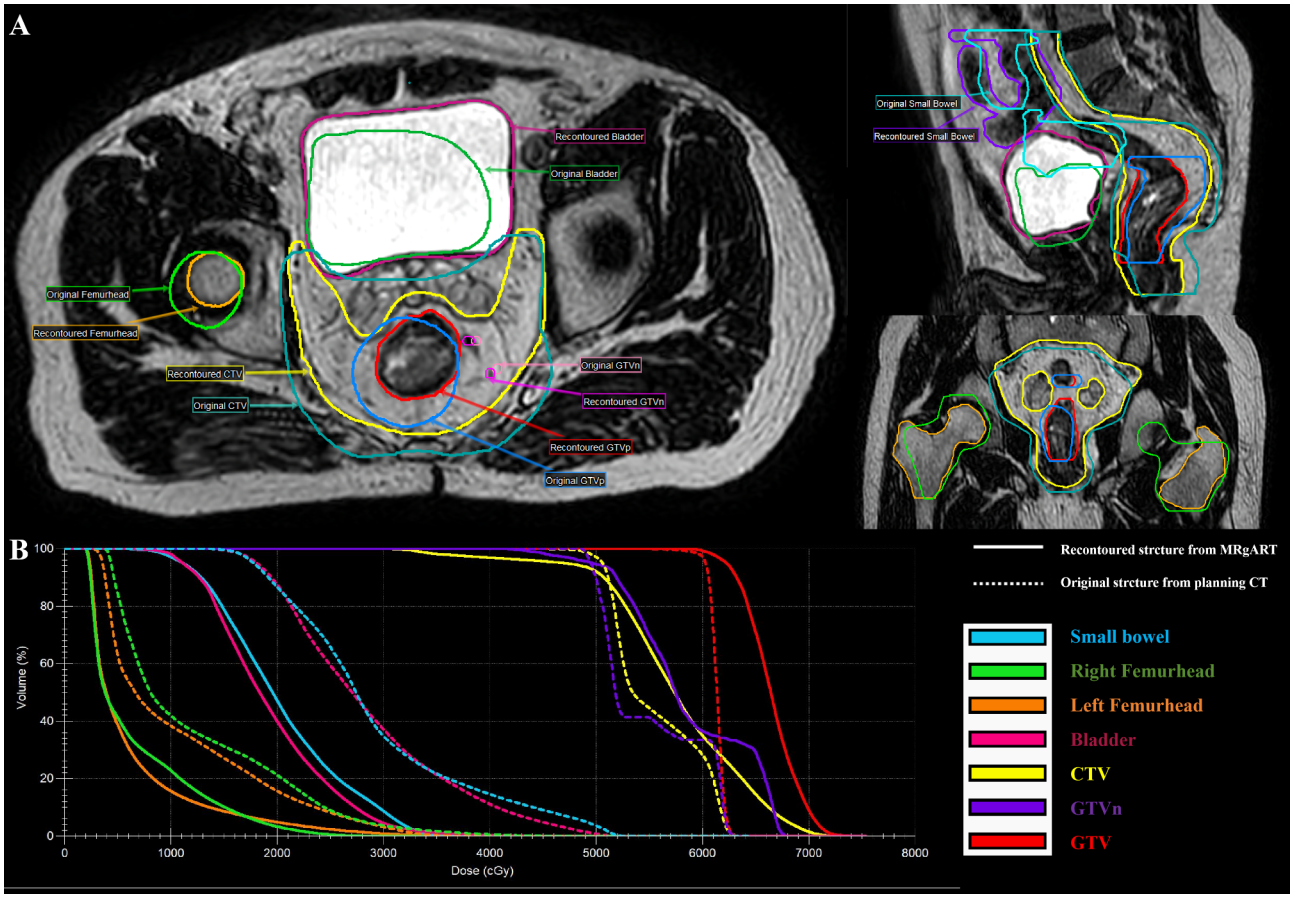

Fig. 2 The difference between online adaptive contouring on MR images and using the original contour from planning CT images. (**A**) The upper image demonstrates the transfer of the planning CT by rigid alignment to the MR scanned prior to daily radiotherapy, highlighting the ability of adaptive radiotherapy to adjust to anatomical changes on the same day. (**B**) The dose–volume histogram (DVH) displays the relevant organs at risk (OAR) and tumor targets in corresponding colors using dashed lines for the original plan based on CT and solid lines for the optimized plan based on MR. The optimized plan improves target coverage while reducing the dose to the OAR

mg/m^2, po, twice daily) and consolidation chemotherapy of either two-cycle of CAPEOX (capecitabine 1000 mg/m^2, po, twice daily, d1-d14+oxaliplatin 130 mg/m^2, every 3 weeks per cycle) or three-cycle of FOLFOX (oxaliplatin 85 mg/m^2, levo-leucovorin calcium 200 mg/m^2, and 5-FU 2400 mg/m^2, every 2 weeks per cycle) between radiotherapy and surgery. With regard to the interval between radiotherapy and surgery, our approach, based on findings from the GRECCAR-6 trial [15, 16], is to allow a minimum period of 7 weeks. This preference is with the understood caveat that some patients may not tolerate surgery well in the short term after completion of consolidation chemotherapy, and that this interval may need to be extended on a case-by-case basis at the clinician's discretion. We recommend that the maximum interval should not exceed 11 weeks. The TME surgery will be followed by optional consolidation chemotherapy at the discretion of the physician.

Safety visit: A safety follow-up visit will occur 30 days (±7 days) after the last study drug administration or before starting any new antitumor therapy, whichever occurs first.

Survival visit: After the safety visit, the subjects will be followed for survival, with contact every 90 days (±7 days) (telephone visits acceptable) to gather information on survival and any subsequent systemic anti-neoplastic therapy. For patients who discontinue the study for reasons other than disease progression, information on disease progression will also be collected. Long-term follow-up will continue until the patient's death or the end of the trial. If the patient does not have a safety visit, the survival visit should be calculated from the end of treatment. Additional file 1 (**Appendix I**) lists the study procedures, including screening activities, for all trials.

Assessment of efficacy parameters

Degree of pelvic fibrosis and surgical difficulty

With reference to the Phase 2 TIMING clinical trial [17] at Memorial Sloan Kettering Cancer Center (MSKCC), "Surgical difficulty" is defined as the impact of pelvic tissue fibrosis following neoadjuvant therapy on the difficulty of subsequent TME. Fibrosis slows down healing of surgically incised, thus increasing bleeding, the time of retention of the abdominal drain, and may be secondary to anastomotic fistula or perineal infection, among other confounding factors. The details of "Surgical difficulty" will be evaluated according to the following procedures:

- Surgical time: from opening to closing the abdomen (min).
- Conversion to open surgery: yes or no.
- Retention time of the abdominal drain (min).
- Amount of hemorrhage.
- Pelvic fibrosis: none, light, medium, or heavy.
- Intestinal obstruction: yes or no.
- Edema: none, light, medium, heavy.
- Surgical site or perineal infection: yes or no.
- Anastomotic fistula: yes or no.
- Anastomotic bleeding: yes or no.
- Prophylactic stoma: yes or no.
- Permanent stoma: yes or no.
- Perineal incision healing status: A, B, C.
- Transient urinary tract dysfunction: urinary catheter removal time (min).

Evaluation of therapeutic efficacy

pCR status is defined as the absence of viable tumor cells in the resected specimen. The specimen will be assessed by at least two independent pathologists. Patients will undergo regular check-ups at the following time points: before chemoradiotherapy, during chemoradiotherapy, during consolidation chemotherapy, and at each visit during follow-up. cCR [18] is defined as substantial downsizing without residual tumor or only residual fibrosis (with low signal on high b-value diffusion-weighted imaging (DWI), if available), absence of suspicious lymph nodes on MRI, absence of residual tumor on endoscopy or presence of only a small residual erythematous ulcer or scar, negative biopsies from the scar, ulcer, or former tumor location, and absence of palpable tumor on digital rectal examination. The tests will comprise a complete blood count, blood biochemistry (including aspartate aminotransferase, alanine aminotransferase, creatinine, and blood urea nitrogen), urine routine, thyroid hormone levels, cardiac zymography, serum tumor markers (CEA, CA199, CA724, CA242, CA125, CA50, etc.), imaging (pelvic MRI, abdominal CT, and chest CT), as well as endoscopy and digital rectal examination. The efficacy of imaging will be evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST v.1.1). Treatment decisions will be based on the results of tumor assessments until the first objective imaging evidence of disease progression. If patients complete or discontinue treatment for reasons other than disease progression, a tumor imaging assessment should be performed at the time of completion or discontinuation of treatment. Imaging assessments should continue at the protocol-specified time points until one of the following occurs: initiation of new anti-neoplastic therapy, objective disease progression, death, or study discontinuation, whichever occurs first.

Toxicity and safety

Throughout the trial, the investigator will monitor potential adverse events (AEs) and document their severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

version 5.0. The investigator will also characterize the AEs based on their cause, toxicity grade, and treatment response. Safety follow-up will be performed during and up to 1 month after treatment to monitor acute adverse events. Late adverse events occurring after the first month of treatment will be assessed regularly at 3 months, 6 months, 1 year and 3 years using the LENT-SOMA scoring system.

Quality of life

After enrollment, patients will be assessed for quality of life (QoL) using the EORTC QLQ-C30 and EORTC QLQ-CR29 at 3 months, 6 months, 1 year, and 3 years. The change in QoL will be compared to each patient's pretreatment QoL.

Discontinuation/withdrawal/loss to follow-up

If a patient discontinues treatment or withdraws, such patient will be followed up on to monitor for adverse events. For those who discontinue but continue to attend study visits, all procedures listed in the study flow in Appendix I will be completed. Withdrawals not due to disease progression require end-of-treatment imaging. Upon completion of the protocol, patients may discontinue treatment, enter the safety follow-up phase, and then enter the survival follow-up phase. If a patient misses a visit, the investigator may attempt to contact the patient, reschedule the visit, and document the results as soon as possible.

Statistical analysis

The primary endpoint of the trial is the pCR rate, which has historically been 15% at our research center. Based on clinical experience, we hypothesize a projected pCR rate of 35%.

Statistical assumptions include unilateral $\alpha=0.05$, power=0.80, P0=15% and P1=35%. Assuming a dropout rate of 10%, the planned sample size is 128 (64 in each group). R language version 4.0.2 (or higher) will be used for analyses, using a one-tailed 0.05 superiority test and reporting group comparisons with 95% confidence intervals and p values. Measurement data will be reported as the mean ± standard deviation or median (minimum, maximum), and count data will be reported as frequencies (percentages).

Quality assurance and quality control

Following Good Clinical Practice (GCP) guidelines, the investigator will establish and maintain a quality assurance and quality control system in accordance with appropriate standard operating procedures. This will ensure that the trial is conducted and that the data are collected, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

Data collection and management

Clinical trial documentation will be in accordance with GCP requirements. The Department of Radiation Oncology Research Centre will archive and manage relevant data for 5 years to ensure accessibility. Safety and environmental risks should be considered in the storage of documents.

Discussion

In recent years, the treatment of rectal cancer has advanced in terms of both efficacy and function. After nCRT, anal preservation options for patients with low or very low rectal cancer include general anal preservation surgery for patients with sufficient tumour regression, as well as Watch and Wait (W&W) strategy [19] for patients with cCR. Those strategies are particularly important in the treatment of low or very low rectal cancer, as they not only improve treatment efficacy but also increase the rate of anal preservation, thereby maintaining patients' QoL. In fact, we would like to incorporate our SIB radiotherapy regimen to maximize tumor regression in patients with low-lying tumors who are on the borderline of anal preservation, thus allowing for general surgical sparing. On the other hand, for patients with tumors located extremely low and where surgical sparing is not feasible, we aim to further increase the cCR rate in this subgroup, which would subsequently enhance the rate of anal preservation through the W&W strategy.

Several trials have evaluated intensified neoadjuvant strategies, such as the total neoadjuvant therapy modality, new concurrent chemotherapy regimens and SIB dose escalation radiotherapy, combined with immunotherapy, with the explicit aim of achieving optimal tumor regression. The specific objective is to attain higher rates of pCR or cCR. Supplementary file 2 (Appendix II) provides details of clinical trials that have studied intensified neoadjuvant chemoradiotherapy for LARC.

The Morpheus trial [12] assessed the effectiveness of image-guided adaptive endorectal brachytherapy in achieving a complete clinical response in operable cT2-3ab N0M0 rectal cancer patients. Participants who received external beam radiotherapy (EBRT) of 45 Gy in 25 fractions with 5-FU/capecitabine were then randomly assigned to the EBRT escalation group or adaptive brachytherapy booster group (30 Gy in 3 fractions), and the brachytherapy group had a higher cCR rate (90% vs. 50%). In the OPERA trial [20], patients were randomly assigned to two groups. Group A received external beam chemoradiotherapy (EBCRT) (45 Gy in 25 fractions+capecitabine), and group B received intensified Contact X-ray brachytherapy (CXB) treatment (90 Gy in 3 fractions) after EBCRT. At 24 weeks, the cCR rates were 64% (group A) and 92% (group B, $p<0.001$). Both studies showed that dose escalation of intrarectal brachytherapy

improved cCR rates and organ preservation. However, the OPERA trial enrolled patients with positive lymph nodes but did not increase the dose to those nodes, while the Morpheus trial excluded patients with positive lymph nodes. Indeed, a number of clinical studies have investigated the efficacy of dose escalation using MRgART in rectal cancer, including THUNDER 2 [21], SUNRISE [22] and preRADAR [23]. Nevertheless, the dose escalation site of these trials has invariably been limited to the primary lesion, with positive lymph nodes excluded. In our trial, we will include LARC patients with positive lymph nodes, both the primary lesions and positive nodes will receive SIB (60–65 Gy in 25–28 fractions to primary lesions and positive lymph nodes; 50–50.4 Gy in 25–28 fractions to the pelvis).

Dose escalation, which is associated with increased toxicity (bowel dysfunction, urinary incontinence, and sexual dysfunction) [24, 25], did not improve the pCR rate in the RECTAL-BOOST study [5]. There are two explanations for this result. First, the dose escalation cohort did not reach the target of 65 Gy, with a minimum PTV-enhanced dose of 58.9 Gy due to OAR dose constraints. Second, the inter-fractional motion effect persisted due to the lack of adaptive radiotherapy. Consequently, the dose escalation programme was imprecisely administered, resulting in greater gastrointestinal toxicity. MRgART, in contrast, allows direct imaging of the target and OAR. Combined with optimization of the treatment plan for anatomical changes, this approach permits high-quality dose escalation regimens to improve treatment response while simultaneously protecting OAR such as the bladder, femoral heads and the small bowel, especially when using a SIB strategy.

Compared to non-adaptive approaches, daily adaptive radiotherapy using MR-Linac demonstrates superior target zone coverage and OAR preservation [26, 27], potentially improving treatment tolerability and with limited severe toxicity [28]. Indeed, the safety and feasibility of SIB-based dose-escalation MRgART protocols for LARC have already been published [21, 23, 29], with subsequent confirmation by several interim analyses have confirmed this safety and feasibility [22, 30]. However, none of these studies have administered SIB to the primary lesions and positive lymph nodes. In our study, SIB of positive lymph nodes may result in more surrounding normal tissue being exposed to a higher dose, which may increase overall toxicity. On the other hand, daily MRgART could reduce toxicities to OAR such as the bladder. Therefore, the overall toxicities are not clear and warrant further evaluation of the safety and feasibility of our protocol.

Furthermore, despite numerous studies using different radiation doses and SIB modalities, data on long-term outcomes and late toxicity are limited [31]. Therefore, we include the effect of dose escalation on surgical difficulty as a primary endpoint and late toxicity and quality of life as secondary endpoints.

In conclusion, we propose to implement SIB to both the primary lesions and positive lymph nodes based on MRgART. Our hypothesis is that this approach will lead to potential advances in the treatment of LARC, including improvements in the cCR rate, pCR rate, and anal preservation rate, without compromising surgical difficulty or increasing tolerable toxicity.

Abbreviations

LARC	Locally advanced rectal cancer
nCRT	Neoadjuvant chemoradiotherapy
TME	Total mesorectal excision
pCR	Pathological complete response
OAR	Organs at risk
MRgART	MR-guided adaptive radiotherapy
SIB	Simultaneous integrated boost
Gy	Gray
LCCRT	Long course concurrent chemoradiotherapy
cCR	Clinical complete response
GCP	Good clinical practice
W&W	Watch and wait
CR	Complete response
EBRT	Endorectal brachytherapy
EBCRT	External beam chemoradiotherapy
CXB	Contact X-ray brachytherapy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-024-02506-6.

Supplementary Material 1

Supplementary Material 2

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Author contributions

YJB was the principal investigator (PI) of this study. YJB and XL were involved in planning the study. XL was responsible for patient recruitment. Medical treatment and follow-up were provided by XL. WHH was the study coordinator and drafted the manuscript. YJB and XL participated in manuscript revision. All the authors have read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The Ethics Committee of the Affiliated Cancer Hospital of Shandong First Medical University approved the final protocol (Grant No. SDZLEC2023-390-02) in accordance with the Declaration of Helsinki and GCP principles. Formal approval is required for any change to the protocol that affects the conduct, patient benefit or safety of the trial. Patients will

provide written informed consent after receiving a thorough explanation of the rationale, benefits and potential side effects. The trial will adhere to local regulations (clinicaltrail.gov identifier: NCT06246344).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Sciences, Jinan, China
[2]Cheeloo College of Medicine, Shandong University Cancer Center, Shandong University, Jinan, Shandong, China

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