Neoadjuvant chemoradiation therapy combined with immunotherapy for microsatellite stable ultra-low rectal cancer (CHOICE II): study protocol of a multicentre prospective randomised clinical trial


ABSTRACT

Introduction Neoadjuvant chemoradiotherapy (nCRT) could bring tumour shrinking and downstaging and increase the probability of organ preservation for patients with low rectal cancer. But for ultra-low rectal cancer, there is little possibility for organ preservation. Immunotherapy has been shown to have significant survival benefits in microsatellite instability-high patients but poor response in microsatellite stable (MSS) patients. Studies have demonstrated that radiotherapy and immunotherapy have synergistic effects in cancer treatment. There is no existing evidence about the clinical efficacy of immunotherapy combined with nCRT for patients with MSS ultra-low rectal cancer.

Method and analysis This trial is an open-labelled multicentre prospective randomised controlled trial (NCT05215379) with two parallel groups and allocation ratio 1:1 (nCRT+immunotherapy vs nCRT group). Eligible participants will be aged 18–75 years, with a desire for anus preservation, confirmed cT1–3aN0–1M0 for microsatellite stable ultra-low rectal cancer.

Trial registration number NCT05215379.

INTRODUCTION

The incidence of rectal cancer in China is significantly higher than other countries, accounting for over 50% of all colorectal cancer (CRC) cases. For patients with low rectal cancer, anterior resection and abdominoperineal resection (APR) are the standard surgical approaches, both of which require the resection of rectum and even anus and result in the perioperative mortality, anastomotic leak, sexual problems and extensive effects on quality of life (QoL). Although anus-preserving surgical approaches have been proposed such as intersphincter resection (ISR) and conformal sphincter preservation operation, there is little probability for patients with ultra-low rectal cancer to preserve the rectum and anus.

Neoadjuvant chemoradiotherapy (nCRT) has been recommended as the standard treatment for locally advanced rectal cancer, but the adoption of nCRT in early stage rectal cancer is ambiguous. nCRT could bring tumour shrinking and downstaging, and thus increase the possibility of organ preserving for patients with rectal cancer. But
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for patients with ultra-low rectal cancer, the possibility of organ preservation is still rather low even after receiving nCRT. Approximately, 15%–20% patients would occur a pathological complete response (pCR) after nCRT, which is defined as the absence of tumour cells in surgical specimens. Apart from pCR, a phenomenon of complete clinical response (cCR) also exists. cCR is defined as the absence of clinical, endoscopic or radiographic evidence of a tumour. Habr-Gama et al initially reported that patients with cCR could be managed with non-operative ways termed as watch-and-wait (W&W), and the oncological outcomes were identical to those of patients who achieved a pCR. Subsequent studies have supported the finding that W&W is a safe approach for organ preservation and QoL, especially for patients with ultra-low rectal cancer. However, the rate of cCR after nCRT remains unsatisfactory, ranging from 5% to 30%, and improving the cCR rate in patients with ultra-low rectal cancer after nCRT is of great importance to patients’ QoL, particularly those with early stage cancer.

Immunotherapy has been shown to have significant survival benefits in deficient mismatch repair (dMMR)/microsatellite instability-high (MSI-H) metastatic CRC, but poor response in proficient mismatch repair (pMMR)/microsatellite stable (MSS) CRC. However, pMMR/MSS CRC accounts for >90% of all CRC cases, which indicates that most patients with CRC cannot benefit from immunotherapy. Studies have demonstrated that radiotherapy and immunotherapy have synergistic effects in cancer treatment. The expression levels of programmed death ligand-1 (PD-L1) and density of CD8+ tumour-infiltrated lymphocytes were reported to increase after radiation, suggesting the potential benefit of combining radiotherapy and immunotherapy. In the VOLTAGE trial, researchers reported the clinical efficacy and safety of nCRT and subsequent immunotherapies. pCR was confirmed in 30% of the patients with MSS. Given these findings, we hypothesised that nCRT combined with immunotherapy could improve the cCR rate in patients with MSS and benefit organ preservation as well as improve QoL in patients with ultra-low rectal cancer.

Taken these above together, a randomised controlled study will be carried out to verify the efficacy of combining nCRT and immunotherapy in patients with MSS ultra-low rectal cancer who will initially undergo APR.

METHODS

Study design

This study is an open-labelled multicentre prospective randomised controlled trial (NCT05215379) with two parallel groups and allocation ratio 1:1. Figure 1 summarises the study design. Eligible patients will be randomised into an experimental group (nCRT+immunotherapy) or control group (only nCRT).

Potential participants will be recruited in 18 medical centres across China. This study was approved by the Ethics committee of Changhai Hospital and other medical centres (grant number: CHEC2022-118). All the recruited patients will sign the informed consent.

Objectives

The objective of the trial is to determine the clinical efficacy of immunotherapy in combination with nCRT in patients with MSS ultra-low rectal cancer.

The primary endpoint of the study was the cCR rate, and the secondary endpoints included the organ preservation (W&W and local excision) rate, anus preservation rate, pCR rate, disease-free survival (DFS), overall survival (OS) and QoL.

Eligibility criteria

Eligible participants for this study will be aged 18–75 years, with a desire for anus preservation, confirmed cT1–3aN0–1M0 rectal adenocarcinoma, confirmed MSS type, inferior margin of ≤5 cm from the anal verge. The exclusion criteria will include a history of CRC; intestinal obstruction, intestinal perforation, intestinal bleeding that required emergency surgery; allergy to capecitabine, oxaliplatin, programmed death-1 (PD-1) monoclonal...
Inclusion criteria:

Patients with ultra-low rectal cancer who are initially to receive APR

⇒ With a desire to preserve the anus.
⇒ Aged 18–75 years.
⇒ cT1–3aN0–1M0 rectal adenocarcinoma.
⇒ MSS type.
⇒ Inferior margin of ≤5 cm from the anal verge.
⇒ An Eastern Cooperative Oncology Group performance status of 0–1.
⇒ No antitumour or immunotherapy was received before enrolment.
⇒ Normal laboratory tests.

Exclusion criteria:

⇒ Presence of metastasis.
⇒ History of CRC.
⇒ Intestinal obstruction, intestinal perforation, intestinal bleeding that required emergency surgery.
⇒ Allergy to capecitabine, oxaliplatin, programmed death-1 (PD-1) monoclonal antibody.
⇒ History of pelvic radiation.
⇒ Treated with corticosteroids or other immunosuppressive agents within 14 days before the study.
⇒ Presence of autoimmune disease or any other unstable systemic diseases.
⇒ Pregnant or lactating women.

APR, abdominoperineal resection; CRC, colorectal cancer; MSS, microsatellite stable.

Antibody; a history of pelvic radiation, treatment with corticosteroids or other immunosuppressive agents within 14 days before the study; and presence of autoimmune disease or any other unstable systemic diseases. Detailed inclusion and exclusion criteria are listed in Box 1. All the qualified patients will sign the informed consent form (online supplemental material 1).

Study procedures

All potential patients will first receive a baseline assessment, including information on demographics, medical history, disease characteristics before enrolment, and systematic physical examination, and relevant laboratory and imaging tests (chest CT, liver MRI), abdominal and pelvic MRI). After completion of the baseline assessment, all eligible patients will be randomised into the experimental group or the control group.

Experimental group

Patients will receive 50 Gy (2 Gy/day×25 days) radiotherapy with concurrent capecitabine twice daily. After the radiotherapy, patients will be administered two cycles of CAPOX. And the reassessments will be the same as experimental group.

cCR was determined by a multidisciplinary team based on digital rectal examination (DRE) and endoscopy. Endoscopic findings consistent with cCR included a flat white scar with or without telangiectasias and a lack of ulceration or nodularity. MRI of the pelvis could be used as a supplement for the judgement of cCR but is not the main standard of cCR. An intermediate status of near cCR (ncCR) was found between cCR and residual tumour. Endoscopic findings of ncCR included mucosal blanching and/or telangiectasia, but with mild mucosal unevenness, and DRE showed normal or palpable irregularities or nodules ≤2 cm in diameter (online supplemental materials 2 and 3).

If the patients achieved a cCR, the W&W approach was performed. If ncCR is achieved, the patients were re-evaluated by the multidisciplinary team to determine whether W&W, local excision or tumour microenvironment (TME) should be performed. The rest of the patients received TME. pCR was defined as the absence of any remaining viable cancer cells in specimens, and all sampled regional lymph nodes (ypT0N0) and tumour regression grade were assessed according to previously reported criteria (table 1).

Follow-up

Once the cCR was confirmed, the patient was managed using the W&W approach. Endoscopy and a series of examinations, including DRE, pelvic MRI and carcinoembryonic antigen, were performed every 3 months for the first 2 years and then every 6 months. Chest CT and abdominal CT or MRI were performed every 6 months. Local regrowth was defined as any sign of tumour recurrence, such as new rectal wall thickening and an enlarged mesorectal mass, in the rectal wall on DRE, endoscopy or imaging findings. Local regrowth was an indication for salvage surgery via TME. Patients were examined using chest CT, liver MRI and abdominal and pelvic CT or MRI to fully detect metastases.

Data collection and management

A group of researchers will be responsible for contacting patients to assess outcomes at baseline and at follow-up visits. Data will be stored in Electronic Data Capture (EDC) system developed by Healife Group with access to all the researchers. For security reasons, an external hard drive will be used to back up the database regularly. Another group of researchers will be responsible for assessing outcomes and data analysis. Personal information will be maintained only by the researchers at the institution where data will be collected.

Management of adverse event

Adverse event (AE) will be rated following the Common Terminology Criteria for Adverse Events (V.5.0). Any AEs
including dermatologic, gastroenterological, endocrine, pulmonary, rheumatological, musculoskeletal, infusion reactions, cardiovascular, haematologic, renal, neurological and ophthalmological events that occurred during the study will be monitored and followed up until the end of the study. The detailed management of AE and immune-related AEs will be documented.

Quality control

In order to ensure the quality of this trial, all the clinical data unloading to the EDC system will be re-evaluated and verified. All the researchers will be trained in the principal centre, especially researcher of the imaging department and pathology department. All the recruited patients will be examined, treated and evaluated strictly according to this study protocol. The clinical data will be documented correctly by the researchers in each medical centre through the EDC system. The clinical research associate will check the documented data every month to confirm the accuracy of all the data.

The parameters of MRI staging and cCR will be standardised (online supplemental materials 2 and 3). Every diagnosis of cCR and the adoption of W&W will be discussed and reassessed by the MDT in the principal centre.

Surgery will be performed by experienced surgeons in each centre. Radical surgery will follow the principles of TME. The video of the whole surgical procedure will be submitted and reviewed by the professional surgeons in the principal centre. Local excision will be a surgical transanal traditional or endoscopic full thickness rectal wall excision, with a bowel margin of 1 cm. All the specimens will be processed and examined by professional pathologists.

Sample size

This is a multicentre, prospective, randomised controlled trial. The significance level of the sample size estimation hypothesis test is unilateral $\alpha=0.05$, and the test power is 0.8. According to literature and clinical practice, the proportion of cCR after neoadjuvant therapy is 20%. In the single-arm study of nCRT combined with immunotherapy carried out by our centre, the cCR rate reached 40%. Using the PASS 2021 software, assuming a cCR of 40% in the experimental group and 20% in the control group, considering that 10% of cases will be lost, the sample size required for each group is 90 cases.

Table 1 Pathological assessment of tumour regression grading (TRG) after neoadjuvant therapy

<table>
<thead>
<tr>
<th>Tier</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>TRG 0</td>
<td>No residual tumour cells</td>
</tr>
<tr>
<td>TRG 1</td>
<td>Single cell or small group of cells</td>
</tr>
<tr>
<td>TRG 2</td>
<td>Residual cancer with desmoplastic response</td>
</tr>
<tr>
<td>TRG 3</td>
<td>Minimal evidence of tumour response</td>
</tr>
</tbody>
</table>

Statistical analysis

Clinical data will be analysed using SPSS software (V.26.0). Continuous variables are summarised using medians and ranges, and categorical variables are described using frequencies and percentages. Comparisons between groups were performed using Fisher’s exact test or the $\chi^2$ test. Statistical significance was set at $p<0.05$. DFS was defined as the duration from the date of randomisation to the date of the first recurrence (local, distant or mixed) or death. Recurrence was defined as the identification of suspicious imaging findings or a biopsy-proven tumour. OS was calculated from the date of randomisation. The QoL was assessed by EORTC QOL Core Questionnaire (EORTC QOL-C30). The populations analysed for efficacy will be patients who complete the whole neoadjuvant therapy, and the population analysed for safety will be the patients who have ever received immunotherapy. Subgroup analysis towards the gene status will be carried out.

Allocation sequence

Permuted block randomisation using computer-generated random numbers will be used to produce the randomisation sequence, and the treatment arm will be decided by opening the randomisation envelope at the time of successful screening. The randomisation is stratified by T stage and N stage. The randomisation process will be performed by someone who is not part of the research team. Due to the nature of the intervention, participants and clinicians could not be blinded. The results will be analysed by statisticians independent of the research team.

Patient and public involvement

No patient involved.

DISCUSSION

The probability of organ preservation for low rectal cancer has improved with the advances in surgical techniques and the adoption of nCRT. But little is the possibility of patients with ultra-low rectal cancer for organ preservation. The new concept of W&W by identifying cCR at restaging and avoiding surgery has been proved to be oncologically safe and could improve functional outcomes. However, the cCR rate after nCRT was still low. Here, in this, we aim to elevate the cCR rate for patients with ultra-low rectal cancer by combining immunotherapy and nCRT.

nCRT is much better tolerated than postoperative chemoradiotherapy and has proven to be very effective in downstaging rectal cancer. nCRT followed by TME has improved surgical quality and decreased the local relapse rate. As a result, local control is no longer the Achilles heel in rectal cancer treatment, it is time to focus to improve functional outcomes. Especially for the elderly and for those with several comorbidities, radical resections are major procedures with substantial morbidity...
and mortality. More than half of patients undergoing TME surgery and nCRT will have long-term anorectal and urogenital dysfunction. Habr-Gama et al first reported the implementation of W&W in patients who achieved a cCR after nCRT. This specific strategy has been shown to significantly improve the QoL of patients without affecting long-term survival. However, the current cCR rate following nCRT remains low. Martens et al reported that of 141 patients with rectal cancer who underwent nCRT, only 24 (17%) achieved a cCR. Perez et al showed that for patients with \( T < N \), only 16 (16.2%) achieved a cCR following nCRT. In a meta-analysis by Dattani et al, 692 patients were included in 17 studies, of which the proportion of patients with cCR was 22.4%.

Immunotheorpes that target the interaction of PD-1 with its ligand, PD-L1, have ushered in the modern oncology era. Anti-PD-(L)1 rejuvenates tumour-specific cytotoxic T cells that already reside in the TME, causing their activation, proliferation and trafficking to micrometastatic deposits. Immunotherapies have shown promising results in patients with dMMR/MSI-H metastatic CRC. However, little is known regarding neoadjuvant immunotherapy in patients with pMMR/MSS. Although neoadjuvant chemotherapy can downstage tumours preoperatively, neoadjuvant immunotherapy aims to enhance systemic immunity against tumour antigens, eliminating micrometastatic tumour deposits that would otherwise be the source of postsurgical relapse. Moreover, neoadjuvant immunotherapy, while the primary tumour is in place, as opposed to adjuvant therapy directed only against micrometastatic disease after resection, leverages higher levels of endogenous tumour antigens present in the primary tumour to enhance T cell cytotoxicity. Recent studies have shown that radiotherapy and immunotherapy have synergistic effects in cancer treatment. The expression levels of PD-L1 and density of CD8\(^+\) tumour-infiltrating lymphocytes were reported to increase after radiation, suggesting the potential benefit of combining radiotherapy and immunotherapy. The Japanese VOLTAGE trial initially reported the results of nCRT followed by nivolumab and surgery in patients with locally advanced rectal cancer, and a 30% pCR rate was observed in patients with MSS, indicating the potential advantage of immunotherapy in nCRT but further randomised controlled trials are still required.

To conclusion, this trial intends to verify the efficacy of combining nCRT and immunotherapy in patients with MSS ultra-low rectal cancer. To our knowledge, this will be the first randomised controlled trial by adding immunotherapy into nCRT, and hope this trial will provide high level evidence to the organ preservation strategy of patients with ultra-low rectal cancer.

Contributors LZ, GY and RW drafted the manuscript. HJ, TZ, ZP, HF and AP contributed to the methodology. YY, XZ, HG, XG and ZL contributed to revise the manuscript. WZ contributed to the design and funding of the study.

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Provenance and peer review Not commissioned; externally peer reviewed.

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