


BMJ Open Contact radiotherapy for rectal cancer (CORRECT): study protocol for a multicentre randomised phase II trial

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ABSTRACT

Introduction Non-operative management of early-stage rectal cancer is increasingly recognised as a subject of significant clinical and research interest. Contact X-ray brachytherapy (CXB) offers an alternative to surgery in appropriately selected cases. Current clinical evidence suggests the use of CXB in combination with chemoradiotherapy (CRT). Although proven effective, no randomised evidence exists for the combination of CXB and short-course radiotherapy (SCRT). In this Swedish national randomised phase II trial, we aim to compare the combination of CXB with either CRT or SCRT in patients with early-to-intermediate rectal cancer.

Methods and analysis A total of 110 eligible, operable patients with early-to-intermediate rectal cancer (cT1–cT3ab), with tumours measuring <5 cm in largest diameter, involving <50% of the rectal circumference, N0–N1 (≤3 nodes <8 mm in diameter), located ≤10 cm from the anal verge and MX/MO, are randomised into two arms: standard arm (A) CXB with CRT and experimental arm (B) CXB with SCRT. The contact radiotherapy for rectal cancer (CORRECT) trial aims to evaluate whether the experimental treatment is non-inferior to standard treatment with respect to the primary endpoint 2-year organ preservation rate. On demonstrating non-inferiority in oncological outcomes compared with CXB+CRT, the combination of CXB+SCRT could pave the way for establishing a new standard of care for organ preservation in early-to-intermediate rectal cancer for patients who wish to avoid surgery.

Ethics and dissemination CORRECT is conducted in accordance with research ethical approval (2024-02762-01) granted by the Swedish Research Ethics Committee on 4 June 2024. Informed consent will be obtained from all trial participants. The trial results will be published in international peer-reviewed journals.

Trial registration number NCT06501053.

INTRODUCTION

The standard of care for patients with early-stage rectal cancer is radical total mesorectal excision (TME) surgery. However, this approach is associated with significant morbidity,^{1,2} risk for recurrence³ and, in many cases, necessitates a permanent stoma, which adversely affects the patient's quality of life.⁴ Intentional non-surgical, organ-preserving

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This Swedish national multicentre randomised phase II study is the first trial to directly compare current evidence-based combination treatment—consisting of contact X-ray brachytherapy and chemoradiotherapy—with contact X-ray brachytherapy in combination with short-course radiotherapy.
- ⇒ The contact radiotherapy for rectal cancer trial will be conducted within the national Swedish watch-and-wait programme, ensuring consistent, high-quality clinical, endoscopic and radiological surveillance.
- ⇒ If oncological outcomes will demonstrate the non-inferiority of the experimental treatment, this approach could establish a new standard of care in organ preservation for patients with early-to-intermediate rectal cancer who seek to avoid surgery.
- ⇒ The experimental treatment, which shortens the treatment duration from 5 weeks to just 1 week and omits chemotherapy, provides a more convenient option for both patients and the healthcare system.
- ⇒ Since concurrent chemotherapy is omitted in the experimental arm, this may potentially lead to less effective treatment for larger tumours.

management has emerged as a strategy based on treatment intensification, with the objective of achieving higher rates of complete clinical response (cCR) and eliminating the need for surgery.⁵ Studies assessing organ preservation in early-stage rectal cancer have reported favourable outcomes, with organ preservation rates reaching approximately 50%.^{6–9}

Following the publication of the OPERA trial,¹⁰ the combination of contact X-ray brachytherapy (CXB) and chemoradiotherapy (CRT) has been established as a highly effective, evidence-based organ-preserving treatment option for patients with early-to-intermediate rectal cancer. In the OPERA trial, CXB was administered in combination with long-course CRT. Conversely, the combination of short-course radiotherapy

(SCRT) and CXB has primarily been used in elderly or comorbid patients who are unsuitable for long-course CRT.¹¹ Recently, an international multi-institutional report demonstrated favourable outcomes for planned organ preservation using SCRT together with a contact brachytherapy boost.¹² However, no randomised data currently exist for this combination therapy, nor are there trials directly comparing CRT+CXB with SCRT+CXB.

The hypothesis of the contact radiotherapy for rectal cancer (CORRECT) trial is that the combination of CXB+SCRT is non-inferior to CXB+CRT with respect to the primary endpoint, the 2-year organ preservation rate. Additionally, we hypothesise that the chemotherapy-free, radiation-only experimental treatment (CXB+SCRT) is associated with reduced toxicity compared with CXB+CRT.

METHODS AND ANALYSIS

Study design

This Swedish national randomised phase II trial (online supplemental file 4) uses a patient-preference design (figure 1). As surgery remains the current standard of care, all patients are offered surgical management. Those patients who wish to avoid surgery are offered non-operative management.

Randomisation and stratification

After screening, participants eligible for CORRECT are randomised 1:1 to one of two arms:

Arm A (standard arm): CXB (90 Gy in three fractions) combined with CRT (45–50 Gy delivered in 1.8–2 Gy fractions over 5 weeks) with concurrent capecitabine chemotherapy (900 mg/m² two times per day).

Arm B (experimental arm): CXB (90 Gy in three fractions) combined with SCRT (25 Gy in five daily fractions).

The investigators are not blinded to group allocations due to the routine nature of the clinical procedures. The stratification criteria are treatment centre, cT1–T2 versus cT3a–b, tumour diameter <3 cm versus ≥3 cm, distance from anal verge <6 cm versus ≥6–10 cm.

Depending on the tumour diameter, the sequence of treatments in both arms will be as follows: if the tumour is <3 cm, a CXB dose of 90 Gy is applied in an outpatient setting in three fractions of 30 Gy with 2 weeks between each fraction. Within the following 2 weeks, patients will receive either CRT or SCRT. If the tumour is ≥3 cm, patients will receive CRT or SCRT first. After a rest, the CXB dose of 90 Gy is applied in an outpatient setting in three fractions of 30 Gy with 2 weeks between each fraction (figure 2).

Study population

Table 1 summarises inclusion and exclusion criteria. A total of 110 eligible, operable patients with early-to-intermediate rectal cancer (cT1–cT3ab), with tumours measuring <5 cm in largest diameter, involving <50% of the rectal circumference, N0–N1 (≤3 nodes <8 mm in

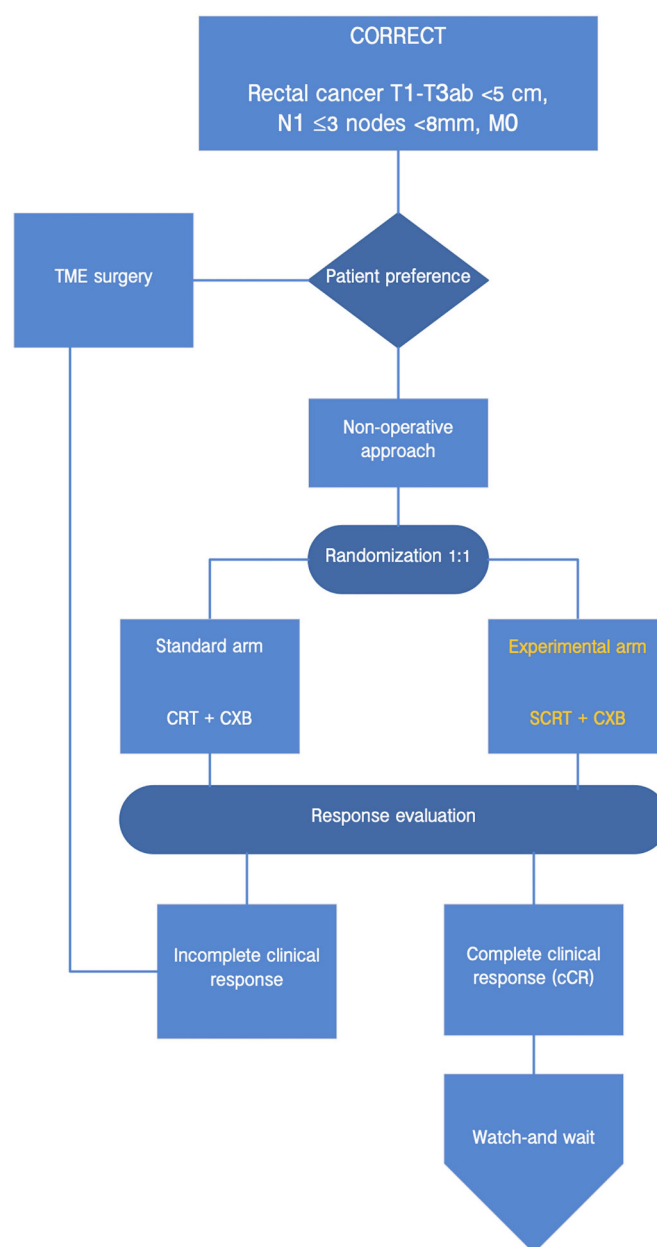


Figure 1 CORRECT study design. CORRECT, contact radiotherapy for rectal cancer; CRT, chemoradiotherapy; CXB, contact X-ray brachytherapy; SCRT, short-course radiotherapy; TME, total mesorectal excision.

diameter), located ≤10 cm from the anal verge and MX/M0, will be enrolled in the trial.

Endpoints and outcome measures

The primary endpoint of the study is the proportion of patients achieving successful organ preservation 24 months after the initiation of treatment. Organ preservation is deemed unsuccessful under the following conditions: (a) if the rectum is surgically removed or (b) if the patient experiences non-salvageable locoregional failure.

Secondary endpoints are acute and late treatment-related toxicity, proportion of patients with a clinical complete response at 14 and 24 weeks, postoperative complications within the first 30 days after TME surgery,

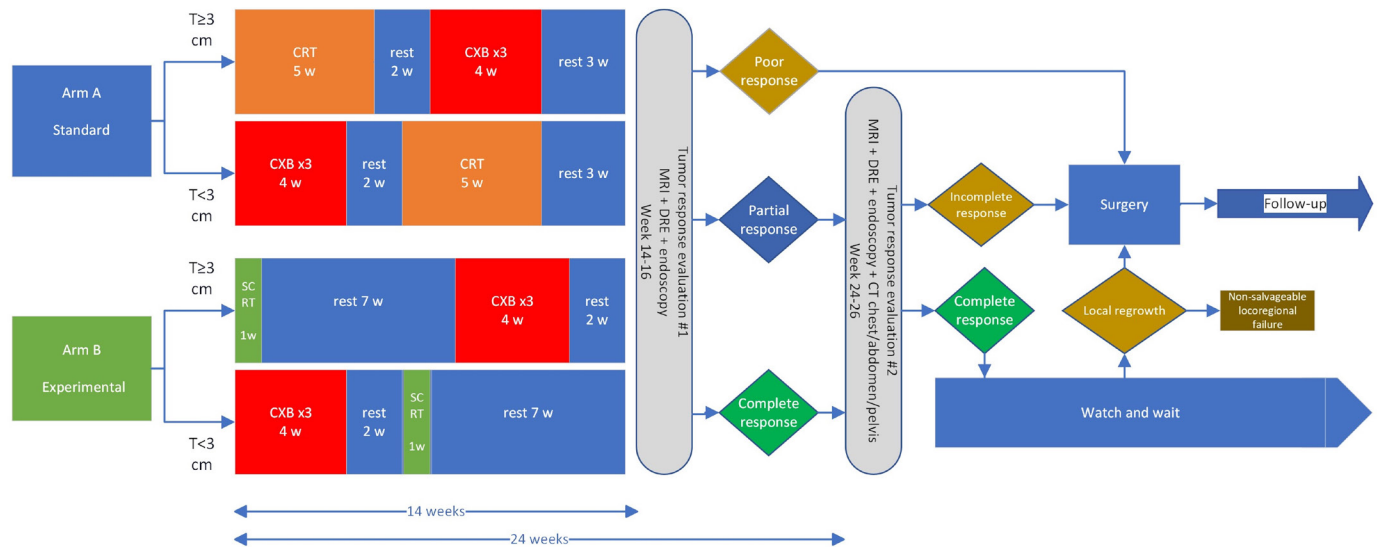


Figure 2 CORRECT study flow chart. CORRECT, contact radiotherapy for rectal cancer; CRT, chemoradiotherapy; CXB, contact X-ray brachytherapy; DRE, digital rectal examination; SCRT, short-course radiotherapy.

proportion of patients with a stoma at 12 and 24 months, metastasis-free survival at 24 months, locoregional failure at 24 months, overall survival at 24 months, TME-free survival at 24 months, rate of R0 salvage TME resections, tumour regression grade in the surgical specimen (R0, ypT0, ypTNM), rate of sphincter preservation at 24 months, Health-Related Quality of Life (HRQoL) measured by EORTC general and colorectal cancer-specific quality of life questionnaire (QLQ-C29 and QLQ-CR30, online supplemental material; baseline and at 3, 6, 12, 24, 36, 48 and 60 months) and bowel function by LARS score (online supplemental material; baseline, 3, 6, 12, 24, 36, 48 and 60 months).

Follow-up

Response evaluation, including digital rectal examination, MRI and endoscopy, is conducted at two time points: 3 months and 6 months after the initiation of treatment. Clinical responses are categorised as follows:

1. Clinical complete response (cCR),
2. Clinical near-complete response, or
3. Incomplete response.

At the second response evaluation (6 months), patients who have not achieved cCR are advised to undergo TME surgery. Patients achieving cCR are enrolled in a watch-and-wait programme (figure 2).

Table 1 CORRECT trial inclusion and exclusion criteria

Registration inclusion criteria	Registration exclusion criteria
<ol style="list-style-type: none"> 1. Operable patient 2. Written informed consent 3. 18 years or above 4. ECOG performance status 0–1 5. Adenocarcinoma of the rectum 6. cT1–cT3ab 7. <5 cm largest diameter 8. <50% of circumference (assessed by MRI and endoscopy) 9. N0–N1 (≤ 3 nodes <8 mm largest diameter) 10. MX/M0 11. Tumour accessible to CXB, lower tumour border ≤10 cm from the anal verge 12. No comorbidity preventing treatment 13. Follow-up possible 	<ol style="list-style-type: none"> 1. Inoperable patient 2. T3cd, T4, T ≥5 cm, >50% of circumference 3. Tumour >10 cm from anal verge 4. N2 status or N1 ≥8 mm diameter 5. Metastatic disease (M1) 6. Previous pelvic irradiation 7. Tumour with extramural vascular invasion 8. Poorly differentiated tumour 9. Simultaneous progressive cancer 10. Tumour invading the external anal sphincter or growth within 1 mm of the levator 11. Tumour within 1 mm from MRF 12. Patient unable to receive CXB or CRT 13. Any concurrent medical illness that would preclude protocol therapy 14. Poor compliance 15. Concurrent enrolment in another clinical trial using an investigational anticancer treatment within 28 days prior to study treatment 16. Total DPD deficiency

CRT, chemoradiotherapy; CXB, contact X-ray brachytherapy.

Sample size

External beam radiotherapy can be delivered at any participating Swedish radiotherapy centre, whereas only two Swedish centres are performing CXB (Uppsala and Stockholm) in this study. About 80%–90% of eligible patients are expected to prefer organ preservation. With a significance level of 5% and 80% power, a success rate of 80% and 20% non-inferiority limit and a 10% drop-out rate, a total of 110 patients (55 in each arm) must be enrolled to demonstrate that the experimental treatment is non-inferior. For the selection of the non-inferiority margin, the International Conference on Harmonisation E10 Guideline suggests¹³ that the non-inferiority margin M should be chosen to satisfy at least the following two criteria: (1) The ability to claim that the test treatment is not inferior to the active control and, at the same time, is superior to the placebo (even though the placebo is not included in the non-inferiority trial) and (2) the non-inferiority margin should be suitably conservative.

That is, the margin should account for the variability associated with the response. In clinical trials, equivalent limits for therapeutic equivalence generally depend on the nature of the intervention, targeted patient population and clinical endpoints (efficacy and safety parameters) for the assessment of therapeutic effect. If the response rate is 80%, then a non-inferiority margin of 15–20% should be chosen for non-inferiority trials.¹⁴

Safety

An early safety analysis will be performed to identify early failures in the two arms in the CORRECT study. A failure is defined as an unsuccessful organ preservation (removal of rectum or locoregional failure). Early failures during the first or second response assessments will be distinguished from failures due to regrowth or recurrent disease at a later stage. The interim analysis in this study will specifically focus on early failures, whereas the final analysis will encompass all types of failures.

Stopping rule: non-salvageable locoregional failure rate >10% checked after 30 treated patients.

Trial status

Start: March 2025; recruitment status: recruiting; projected primary completion: November 2029; projected study completion: November 2032.

ETHICS AND DISSEMINATION

CORRECT is conducted in accordance with the principles of the Declaration of Helsinki (www.wma.net). The research ethical approval by the Swedish Research Ethics Committee has been granted (2024-02762-01) on 4 June 2024. All protocol modifications will be reported to the Swedish Research Ethics Committee. The trial received a ClinicalTrials.gov trial identifier NCT06501053. Karolinska University Hospital (reg. no. 232100–0016), a public teaching hospital organised under the laws of Sweden, through the Department of Radiotherapy,

Theme Cancer, with its offices at Eugeniavägen 3, 171 64 Solna, Sweden, is the trial sponsor. The trial sponsor will have access to the final trial dataset. The trial results will be published in international peer-reviewed journals.

Data management

Data management, national coordination and independent data monitoring will be performed by the Clinical Trials Office at Karolinska University Hospital, Stockholm, Sweden, via the REDCap database (14.5.41, Vanderbilt University) using electronic case report forms. Randomisation will be conducted using the ALEA randomisation tool. The sponsor will have access to the final trial dataset.

Patient and public involvement

Patients and/or the public were not involved in this study.

DISCUSSION

The Lyon R96-02 randomised trial was the first prospective study to demonstrate that the addition of CXB to external beam radiotherapy increased clinical complete response from 2% to 24% and resulted in higher rates of long-term sphincter preservation and organ preservation in patients with T2-3 rectal cancer.^{15 16} The international multicentre randomised phase III trial OPERA (NCT02505750) was specifically designed to evaluate the role of dose escalation using CXB in improving the chance of organ preservation with a randomisation between standard CRT of 45 Gy combined with either an external boost of 9 Gy or internal CXB of 90 Gy.¹⁷ OPERA demonstrated that the addition of CXB boost significantly improved the 5-year organ preservation rate in cT1-3bN0-1 rectal cancer patients when compared with chemoradiation with an external boost, with organ preservation rates of 79% versus 56%, respectively. Particularly impressive organ preservation rates of 93% were reported in patients with tumours smaller than 3 cm.¹⁰

CORRECT is a natural successor of the OPERA trial aiming to determine whether a combination of CXB+SCRT is non-inferior to CXB+CRT regarding the primary endpoint 2-year organ preservation rate. The combination of short-course radiotherapy and CXB has predominantly been used in elderly and comorbid patients deemed unsuitable for long-course chemoradiotherapy.¹¹ A recent international multi-institution report demonstrated favourable outcomes in planned organ preservation using SCRT in combination with CXB.¹² However, no randomised data are currently available on this combination therapy. Furthermore, no trials have directly compared CRT+CXB and SCRT+CXB.

The 20% non-inferiority margin in this trial is expected to correspond to a 10% relative difference in efficacy between treatment arms, assuming an 80% organ preservation rate in the standard arm. The actual relative difference will be evaluated concerning non-efficacy benefits, including safety, toxicity, convenience and cost.

The primary advantages of the CXB+SCRT treatment regimen include a shorter treatment duration—1 week of SCRT compared with 5 weeks of CRT—and the elimination of chemotherapy, thereby reducing associated toxicities. If non-inferiority is demonstrated, the combination of CXB+SCRT has the potential to become a new international standard of care for patients with early-to-intermediate rectal cancer who seek to avoid surgery.

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Contributors Conceptualisation and study design: AV, PJN, JF and AM. Data collection and investigation: PJN, JF, RM, CR, IS, LB, AM and AV. Data analysis and interpretation: PJN, RM, LB, AM and AV. Writing: PJN, JF, RM, CR, IS, LB, AM and AV. Supervision and project administration: AV, PJN and JF. Funding acquisition: AV, PJN and AM. Ethical approval: AV and PJN. AV is the guarantor.

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