BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065010
Article Type:	Protocol
Date Submitted by the Author:	23-May-2022
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Keywords:	RADIOTHERAPY, Colorectal surgery < SURGERY, Gastrointestinal tumours < ONCOLOGY, Magnetic resonance imaging < RADIOTHERAPY, Clinical trials < THERAPEUTICS

Towards Response ADAptive Radiotherapy for organ preservation for intermediate risk rectal cancer (preRADAR): protocol of a phase I dose-escalation trial

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Key words: rectal cancer, radiotherapy, dose-escalation, clinical trial, organ preservation.

Word count: 3953/4000

ABSTRACT (297 words)

Introduction Organ preservation is associated with superior functional outcome and quality of life (QoL) compared to total mesorectal excision (TME) for rectal cancer. Only 10% of patients are eligible for organ preservation following short course radiotherapy (SCRT, 25Gy in 5 fractions) and a prolonged interval (4-8 weeks) to respones evaluation. The organ preservation rate could potentially be increased by dose-escalated radiotherapy. Online adaptive magnetic resonance-guided radiotherapy (MRgRT) is anticipated to reduce radiation-induced toxicity and enable radiotherapy dose-escalation. This trial aims to establish the maximum tolerated dose (MTD) of dose-escalated SCRT using online adaptive MRgRT.

Methods and analysis The preRADAR is a multicentre phase I trial with a 6+3 dose-escalation design. Intermediate risk rectal cancer patients (cT3c-d(MRF-)N1M0 or cT1-3(MRF-)N1M0) interested in organ preservation are eligible. Patients are treated with a radiotherapy boost of 2x5Gy (level 0), 3x5Gy (level 1), 4x5Gy (level 2) or 5x5Gy (level 3) on the gross tumour volume in the week following standard SCRT using online adaptive MRgRT. The trial starts on dose level 1. The primary endpoint is the MTD based on the incidence of dose limiting toxicity (DLT) per dose level. DLT is a composite of maximum one in nine severe radiation-induced toxicity and maximum one in three severe postoperative complications, in patients treated with TME or local excision (LE) within 26 weeks following start of treatment. Secondary endpoints include the organ preservation rate, non-dose limiting toxicity, oncological outcomes, patient-reported QoL and functional outcomes up to two years following start of treatment. Imaging and laboratory biomarkers are explored for early response prediction.

Ethics and dissemination The trial protocol has been approved by the medical ethics committee of the UMC Utrecht. The primary and secondary trial results will be published in international peer-reviewed journals.

Registration details NL8997 at the Netherlands Trial Registry (NTR) https://www.trialregister.nl/

ARTICLE SUMMARY

Strengths and limitations of the study (5/5)

- Dose-escalated short course radiotherapy (SCRT) is expected to increase the probability of organ preservation compared to standard-dose SCRT.
- The new technique of online adaptive magnetic resonance guided radiotherapy (MRgRT) is anticipated to reduce radiation-induced toxicity and enable dose-escalated SCRT.
- Dose-escalated SCRT is administered as neoadjuvant monotherapy since it has a favourable toxicity profile compared to chemoradiation (CRT) and SCRT followed by systemic therapy.
- The definition of dose-limiting toxicity (DLT) is based on what patients would 'trade off' for a higher probability of organ preservation.
- Since late toxicity can occur for several years after radiotherapy, it cannot be included as DLT in this dose-finding trial.

INTRODUCTION

Introduction of multimodal treatment consisting of neoadjuvant (chemo)radiotherapy and total mesorectal excision (TME) has improved oncological outcomes for patients with rectal cancer in the previous decades [1,2]. Multimodal treatment unfortunately is associated with long-term impaired quality of life (QoL) and bowel, urinary and sexual dysfunction [3,4]. In recent years, organ preservation has become possible for rectal cancer patients who reach a (near) clinical complete response (cCR) after neoadjuvant (chemo)radiotherapy: patients with minimal or no residual tumour on physical examination, endoscopy and magnetic resonance imaging (MRI) after neoadjuvant treatment can be managed by local excision (LE) and/or active surveillance instead of TME [5]. When performed in appropriately selected patients, organ preservation has similar oncological outcomes as TME [6]. Since the morbidity of TME is averted, including the formation of an ostomy, organ preservation is associated with superior QoL and functional outcome [7,8].

The majority of patients with rectal cancer would rather opt for organ preservation than TME [9,10]. The chance of reaching a cCR and therewith eligibility for organ preservation depends on the neoadjuvant treatment schedule and the timing of response evaluation, among other clinical factors [11–13]. The standard neoadjuvant treatment for intermediate risk rectal cancer according to the Dutch guideline (cT3c-d(MRF-)N0M0 and cT1-3(MRF-)N1M0) is short course radiotherapy (SCRT, 25 Gy in 5 fractions) [14]. After SCRT and a 4-8 weeks interval, the complete response rate is approximately 10% [15]. This rate is low compared to complete response rates of approximately 16% following chemoradiation (CRT, 50 Gy in 25 fractions with a chemosensitizer) for locally advanced rectal cancer (LARC), 28% following SCRT and neoadjuvant systemic therapy for LARC in the RAPIDO trial, 28% following CRT and neoadjuvant systemic therapy in the PRODIGE23 trial and even 60% of organ preservation at 3 years following CRT and neoadjuvant systemic consolidation therapy in the OPRA trial [16–19].

Besides addition of systemic therapy, escalation of the irradiation dose could well be another viable strategy to render more patients eligible for organ preservation after SCRT. The positive relationship between irradiation dose and tumour response is well recognized [20]. Meta-analysis demonstrated that dose-escalated CRT (with a total dose of ≥ 54 Gy) is associated with a relatively high pooled pCR rate of 24% in LARC [21]. Dose-escalated SCRT has been investigated by only four trials (Table 1) [22–25]. An important limiting factor for dose-escalating SCRT is the risk of radiation-induced toxicity

Table 1: overview of previous studies on dose-escalated short course radiotherapy (SCRT) for rectal cancer.

Study + design	Design	Patients	Treatment	Acute radiation-induced toxicity	Postoperative complications	Tumour response	Comments
Guckenberger, Radonc 2009.[22]	One-arm phase II, 2000-2007	cT2-T4N0-2M0-1 (n=118)	SCRT of total 29 Gy in twice daily fractions of 2.9 Gy followed by immediate TME and adjuvant chemotherapy if pathology UICC stage ≥II	Maximum grade 1	Any complication: 27/118 (23%) Reoperation: n=18/118 (15%) Postoperative mortality: n=4/118 (3%)	ypT1 n=8/118 (7%) ypN0 n=53/118 (45%)	
Bujko, Radonc 2013.[23]	Semi-randomized two-arm phase II, 2003-2010	cT1-3N0M0 and maximum tumour diameter ≤ 4 cm (n=89)	SCRT plus 4 Gy boost (n=64) vs. CRT of 50 Gy in 31 fractions plus 5 Gy boost with 5-FU and leucovorin (n=25) followed by LE. ypT2 or higher proceeded to TME.	Grade 3: n=1/64 (2%) vs. n=2/25 (8%)	Any complication following LE: n=12/64 (19%) vs. n=8/25 (32%)	pCR*: n=23/64 (36%) vs. n=16/25 (64%) ypT0-1: n=43/64 (67%) vs. n=20/25 (80%)	Study was terminated early due to poor accrual. Patients with poor performance status were only eligible for SCRT arm. 17 patients (27%) did not receive the boost in the SCRT arm.
Faria, Col Dis 2014. [24]	One-arm phase II. 2008-2011	cT3-4N0-2 or cT2N0-2 (n=52)	SCRT with integrated boost up to a total of 30 Gy and TME at 8 weeks	Grade 3: n=4/52 (8%)	Reoperation: 1/52 (2%) Postoperative mortality: 1/52 (2%)	pCR: 5/52 (10%)	
Chakrabarti, AoO 2020. [25]	One-arm phase II, 2018-2018.	UICC stage II-II (n=43)	SCRT of 30 Gy in 6 fractions and two cycles of CapOx followed by TME at 7 weeks	Grade 3-4: n=5/43 (12%)		pCR n=8/43 (18%)	

SCRT = short course radiotherapy. Gy = Gray. TME = total mesorectal excision. UICC = Union for International Cancer Control. cTNM: clinical tumor, nodal and metastasis stage. ypTN = pathological tumor and nodal stage following neoadjuvant treatment. CRT = chemoradiation. 5-FU = 5-fluoro-uracil based chemotherapy. LE = local excision. pCR = pathological complete response. * = significant at $p < 0.05$. CapOx = capecitabine and oxaliplatin

Recently, online adaptive magnetic resonance guided radiotherapy (MRgRT) on a magnetic resonance linear accelerator (MR-Linac) has been implemented in clinical care [26,27]. In contrast to conventional radiotherapy, MRgRT allows for online visualization of the tumour and surrounding organs at risk (OAR) on MRI during treatment and adaptation of the treatment plan to the current anatomy at each treatment fraction. This technique has unprecedented accuracy and lowers the dose to the healthy tissues [28–30]. As a consequence, online adaptive MRgRT is anticipated to reduce radiation-induced toxicity and enable dose-escalated SCRT.

Adequate patient selection for dose-escalation is important, as some patients will experience radiation-induced toxicity and delay of surgery without the benefit of achieving a cCR. No biomarkers are currently clinically available for prediction of the response to radiotherapy. However, predictive value for the response to radiotherapy has been demonstrated for several biomarkers in blood, tissue, faeces and MRI [31–33]. These biomarkers could potentially aid in response-based adaptation of the treatment plan. The current trial includes exploratory analyses of blood, faecal and tissue samples and (quantitative) MRI, in order to prepare for a response adaptive dose-escalation strategy.

In conclusion, the rationale for the current trial is to offer intermediate risk rectal cancer patients a higher chance of organ preservation using dose-escalated, online adaptive MRgRT on an MR-Linac. We designed a phase I trial to determine the maximum tolerated dose (MTD) of dose-escalated SCRT. The MTD is based on the incidence of dose-limiting toxicity (DLT), i.e. acute radiation-induced toxicity and postoperative complications. The MTD will be the recommended dose for a subsequent phase II trial that will evaluate the efficacy of dose-escalated SCRT on the organ preservation rate. Meanwhile, imaging and laboratory biomarkers are explored for early prediction of the response to radiotherapy. This trial is the first step towards Response ADAptive Radiotherapy for organ preservation for rectal cancer: the preRADAR trial.

METHODS AND ANALYSIS

Study design

The preRADAR trial is a phase I multicentre trial that follows the 6+3 dose-escalation design (Figure 1). The trial is conducted in the University Medical Centre Utrecht and the Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, both in the Netherlands. A minimum of six and a maximum of 45 patients will be recruited. Participant enrolment has started in November 2021 and is expected to finish by February 2024.

Figure 1: study flow according to dose limiting toxicity (DLT) per dose level in the 6 + 3 design.

Objectives

The primary objective is to establish the MTD of dose-escalated SCRT in intermediate risk rectal cancer patients. Secondary objectives are to determine non-dose limiting acute radiation-induced toxicity, the 30- and 90-day postoperative complication rate, organ preservation rate at 6, 12 and 24 months, oncological outcomes at 24 months, patient-reported QoL and functional outcomes at 3, 6, 12, 18 and 24 months. Exploratory objectives are to seek imaging and laboratory biomarkers that are predictive for the response to radiotherapy at an early stage of treatment.

Study population

Adult patients (≥ 18 years old) presenting to the participating centres with (1) biopsy proven rectal adenocarcinoma, (2) classified as intermediate risk according to the Dutch guideline (cT3c-d(MRF-)N0M0 or cT1-3(MRF-)N1M0 based on the AJCC 8th edition) [14], (3) referred for neoadjuvant SCRT, (4) distal or midrectal tumour location: the upper border of the rectal tumour below the sigmoid take-off and lower border below the peritoneal fold [34], (5) judged fit for multimodal treatment by multidisciplinary tumour board meeting and (6) interest in organ preservation, are eligible.

Exclusion criteria are mucinous carcinoma or neuroendocrine neoplasms, indication for additional SCRT and TME following LE, recurrent tumour or regrowth after previous treatment, extramesorectal pathological lymph nodes, extramural venous invasion (EMVI+), planned systemic therapy, history of inflammatory bowel disease, prior pelvic radiotherapy, concurrent pregnancy, orthopaedic hip implants or absolute contraindication for MRI.

Patient inclusion

Eligible patients are identified during multidisciplinary tumour board meetings. Patients are informed about the preRADAR trial by their treating radiation-oncologist, in both an oral and a written manner. Patients are free to accept or decline the intervention and have at least three days to consider their decision and sign the informed consent form. Trial participation includes consent to undergo the intervention and to participate in acute toxicity monitoring. Consent to collect blood, faeces, tumour tissue, additional MR sequences, MR sequences with intravenous contrast (i.e. dynamic contrast enhanced (DCE) MRI) and filling out QoL questionnaires is

optional. Additionally, patients are asked to share their medical data within the Prospective Dutch ColoRectal Cancer cohort (PLCRC) and the Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-Linac study (MOMENTUM) [35,36].

Treatment

The study treatment consists of a radiotherapy boost of 2 x 5 Gy (dose level 0), 3 x 5 Gy (dose level 1), 4 x 5 Gy (dose level 2) or 5 x 5 Gy (dose level 3) on the gross tumour volume (GTV) in the week following standard SCRT (Table 2). SCRT is administered on the conventional elective volumes, consisting of the mesorectum, presacral lymph nodes and internal iliac lymph nodes [37]. Uniform planning target volume (PTV) margins of 4 mm are applied during SCRT, except for 6 mm in the ventral direction. The boost is delivered on the GTV consisting of the tumour and suspicious lymph nodes, if present. Lymph nodes are classified as suspicious if they are (1) ≥ 9 mm, (2) 5-9 mm and have two out of three malignant characteristics (irregular border, heterogeneous texture or round shape), (3) < 5 mm and have all three malignant characteristics (measurements are of the short axis diameter) [14]. During the boost fractions, a uniform PTV margin of 5 mm is applied. The bowel cavity, bowel loops, bladder, left and right femoral head and lumbosacral plexus are considered organs at risk (OAR, constraints in Supplementary File A). Delineation of the target volumes and OARs of both SCRT and the boost is performed on a 3D T2-weighted MRI and administered with online adaptive MRgRT on a 1.5 Tesla MR-Linac.

Table 2: dose scheme and biologic equivalent doses compared for the current standard of short course radiotherapy and the dose levels of the preRADAR trial.

	Dose scheme	Physical dose (Gy)	Tumour dose (EQD2 α/β = 10, Gy)	Normal tissue dose (EQD2 α/β = 3, Gy)
Current standard	5 x 5 Gy	25.00	31.25	40.00
Dose level 0	5 x 5 Gy + 2 x 5 Gy boost	35.00	43.75	56.00
Dose level 1	5 x 5 Gy + 3 x 5 Gy boost	40.00	50.00	64.00
Dose level 2	5 x 5 Gy + 4 x 5 Gy boost	45.00	56.25	72.00
Dose level 3	5 x 5 Gy + 5 x 5 Gy boost	50.00	62.50	80.00

The trial starts at dose level 1 (5 x 5 Gy + 3 x 5 Gy boost). When, after the treatment of six patients, no radiation-induced DLT and less than one in three postoperative DLT has occurred, the study progresses to the next dose level (see primary endpoint and Figure 1). When one in six radiation-induced DLT and/or one in three postoperative DLT has occurred, three additional patients are added to the current dose level and adverse events are reassessed accordingly. Whenever more than one radiation-induced DLT or more than one in three postoperative DLT occurs, the trial is stopped and the previous dose level is considered the MTD. While awaiting the occurrence of DLT in six (or nine) patients of the current dose level, newly presenting eligible patients are included to the previous dose level. Since dose level 0 (5 x 5 Gy + 2 x 5 Gy boost) has the same biological effective dose as chemoradiation, we consider it safe without testing. If less than one in six patients had radiation-induced DLT and less than three patients have been treated with TME, additional patients are added to the current dose level until at least three patients have been treated with TME.

Patients will not proceed to the boost if treatment-related grade ≥ 3 radiation-induced toxicity or signs of sacral plexopathy are present at the end of SCRT, nor when ≥ 80% GTV coverage for

the boost is not achievable due to nearby OARs. When a patient does not proceed to the boost , the patient is replaced by a new inclusion.

Acute toxicity monitoring

Patients are consulted before the start of treatment (baseline), at end of SCRT (week 1), after the administration of the boost (week 2), at week 3, week 4, week 5 and every other week thereafter up to surgery or week 20 (Figure 2). Toxicity is registered at each consultation for proctitis, rectal pain, rectal haemorrhage, non-infective cystitis, urinary obstruction, fatigue, radiation dermatitis and other non-prespecified toxicity according to the CTCAE version 5.0 [38]. Simultaneously, patients are asked to fill out a low anterior resection syndrome (LARS) score questionnaire online or in a paper diary to monitor bowel function [39].

Figure 2: patient timeline in the preRADAR trial

SCRT: short course radiotherapy. LARS: low anterior resection syndrome score. DCE-MRI: dynamic contrast enhanced magnetic resonance imaging. QoL: quality of life.

Response evaluation

The first response assessment is performed at 11-13 weeks following the start of treatment, using T2-weighted MRI, diffusion weighted imaging (DWI) and endoscopy (Figure 2) [14]. Insufficient responders are planned for TME. An insufficient response is defined as downsizing of less than 50% of the maximum diameter of the primary tumour, residual tumour of more than 2cm and/or

persistent suspicious lymph nodes. All other patients are considered good responders and proceed to the second response assessment at 16-20 weeks, using T2-weighted MRI, DWI and/or endoscopy. Insufficient responders at the second response evaluation, i.e. residual disease not amenable for LE or progressive disease, are planned for TME. Good, yet incomplete responders are offered LE that might be followed by TME in case of irradical resection or >ypT1, and otherwise active surveillance. Complete responders enter active surveillance. All patients treated with active surveillance are asked to participate in the Dutch Watch & Wait registry.

Follow-up

Patients are followed up according to local practice. In the Netherlands, follow-up after TME commonly exists of clinical consultation and CEA measurement every 4-6 months and thoraco-abdominal computed tomography (CT) after the first year and on indication thereafter. For patients treated with active surveillance, this follow-up scheme is complemented with endoscopy and MRI at each consultation for the first 2-3 years [14].

Primary endpoint

The primary endpoint is the MTD based on the incidence of DLT per dose level. A maximum of either one in nine severe acute radiation-induced toxicity or one in three severe postoperative complications per dose level is considered safe (Figure 1).

Severe acute radiation-induced toxicity is defined as:

- Treatment-related (Supplementary File B) grade ≥ 4 radiation-induced toxicity according the Common Toxicity Criteria for Adverse Events (CTCAE version 5.0), occurring within 20 weeks after start of radiotherapy and before surgery [38];
- Treatment-related grade 3 radiation-induced toxicity persisting beyond 12 weeks after start of radiotherapy;
- Postponing of surgery > 20 weeks after start of radiotherapy due to any grade of treatment-related toxicity, in patients with an insufficient response at the first and/or second response evaluation;
- In case of grade 3-4 radiation-induced toxicity that was not prespecified, or grade 3 radiation-induced toxicity newly occurring between 12-20 weeks after start of radiotherapy, the trial management group will judge if this classifies as a DLT on a case-to-case basis.

Severe postoperative complications are defined as Clavien-Dindo grade 3b-4 complications occurring within 30 days postoperative, in patients treated with TME or LE within 26 weeks following the start of treatment [40].

Secondary endpoints

The most important secondary endpoint is the organ preservation rate at 24 months, which is defined as an in situ rectum, no ostomy and no residual or recurrent locoregional disease [41]. Other secondary endpoints include:

- feasibility of delivery of the boost based on GTV coverage,
- non-dose limiting acute radiation-induced toxicity as measured by the CTCAE assessments and LARS diaries up to 20 weeks following the start of treatment or, if planned earlier, up to TME [38,39],

- non-dose limiting 30- and 90-day complications according to Clavien-Dindo in patients treated with TME or LE within 26 weeks following the start of treatment [40],
- tumour regression grade on pathology according to Mandard in patients treated with TME and LE within 26 weeks following the start of treatment [42],
- type and radicality of salvage surgery in patients with a local regrowth during watch & wait up to 24 months,
- overall survival (OS) and disease-free survival (DFS) at 24 months [43],
- late radiation-induced toxicity grade ≥3 according to CTCAE version 5.0 presenting after 90 days up to 24 months, and,
- patient-reported quality of life and functional outcome as measured by the European Organisation of Research and Treatment of Cancer Quality of life Core and ColoRectal specific Questionnaire (EORTC QLQ-C30 and QLQ-CR29), Low Anterior Resection Syndrome (LARS) score, the International Index of Erectile Function (IIEF), Urinary Distress Inventory (UDI-6), Incontinence Impact Questionnaire (IIQ-7) and McCoy Female Sexuality Questionnaire (MFSQ) at baseline and at 3, 6, 12, 18 and 24 months following the start of treatment (Figure 2) [39,44–48].

Translational research

Blood and faeces are collected at baseline, after the second radiotherapy fraction and at the second response evaluation (Figure 2). Blood is additionally collected at 6, 12, 18 and 24 months of follow-up. Blood is analysed for haematology, carcinoembryonic antigen (CEA), kidney function, albumin, c-reactive protein, lactate dehydrogenase and circulating tumour (ct)DNA [31,32]. Faeces is analysed for the microbiome [33]. Tumour tissue is collected at diagnosis and at surgery. An MRI is routinely acquired pre-treatment and additional sequences are acquired during idle time

of each radiotherapy fraction. In some centres, an extra MR scan is performed on an MR-Linac pre-treatment and a DCE MRI is performed pre-treatment and after the second radiotherapy fraction.

Data management and analysis

Clinical data are collected from the medical files and captured in an electronic case report form (eCRF) in Castor EDC. Data management details are reported in a separate data management plan. Technical treatment data are collected within the Multiple Outcome Evaluation of Radiotherapy Using the MR-Linac cohort (MOMENTUM) [36]. PROs are collected within the Prospective Dutch ColoRectal Cancer Cohort (PLCRC) [35]. Human samples for translational research are stored at the Netherlands Cancer Institute.

The incidence of DLT will be calculated per dose level, excluding patients who did not proceed to the boost. Secondary toxicity outcomes are described in the same per-protocol population (i.e. non-dose limiting radiation-induced toxicity and postoperative complications, PROs and late radiation-induced toxicity). Secondary efficacy outcomes are described in the intention-to-treat population (i.e. organ preservation rate, feasibility of the boost, tumour regression grade, salvage surgery, OS, DFS). Outcomes will be analysed using descriptive statistics, a mixed-effects model (for PROs) or Kaplan-Meier method (for time-to-event data). Data of this phase I trial might be reused for data analysis of the subsequent phase II trial.

Patient and public involvement

The Dutch patient federation for colorectal cancer (*Stichting Darmkanker)* was involved during the design phase of this trial. The definition of the primary outcome (DLT), the burden of the intervention and follow-up and the patient information leaflet were discussed with two patients. The patient federation officially declared their support for the current trial. They will remain involved during the evaluation of the results and designing the subsequent phase II trial. Patient information on the trial is displayed on the website www.kanker.nl/trials.

Safety

A trial management group has been appointed, consisting of an independent colorectal surgeon and radiation-oncologist per centre. They have the right to temporarily stop the trial if any non-prespecified safety issues are of concern. If a patient dies within 20 weeks following the start of treatment or within thirty days postoperatively (in patients treated with TME or LE in 26 weeks following the start of treatment), the trial will be temporarily stopped to investigate if the event is related to the trial intervention.

Serious adverse events (SAE's) that occur within 20 weeks following the start of treatment or within 30 days postoperatively, in patients treated with TME or LE within 26 weeks following the start of treatment, will be reported within 7 days of first knowledge through an online form to the medical ethics committee of the UMC Utrecht. SAE's that occur after this period, will be reported in the same manner if the local principal investigator considers the event to be related to the intervention.

Ethics and dissemination

This trial is designed in accordance with 18th version of the World Medical Association Declaration of Helsinki, Good Clinical Practice and the Dutch Law. The trial protocol has been approved by the medical ethics committee of the UMC Utrecht in March 2021. The trial is registered at https://www.trialregister.nl/, trial number NL8997. To ensure adequate data collection and confirmation to the trial protocol, an external monitor of the Netherlands Comprehensive Cancer Organisation will audit the trial twice yearly. The primary and secondary trial results will be published in international peer-reviewed journals. After consent of both participating centres, sharing of pseudonymized data with other researchers within the scope of the current project is possible.

DISCUSSION

The phase I preRADAR trial aims to establish the MTD of dose-escalated SCRT using online adaptive MRgRT in intermediate risk rectal cancer patients, following a 6 + 3 dose-escalation design. Patients are treated with a boost of 2 x 5 Gy, 3 x 5 Gy, 4 x 5 Gy or 5 x 5 Gy in the week following standard SCRT on an MR-Linac. Maximum one in nine severe acute radiation-induced toxicity and one in three severe postoperative complications are accepted for a dose level to be considered safe. The MTD will be the recommended dose for the subsequent phase II RADAR trial that will evaluate the efficacy of dose-escalated SCRT using online adaptive MRgRT on the organ preservation rate.

Dose-escalated SCRT is administered as neoadjuvant *monotherapy* in the preRADAR trial. SCRT is the standard neoadjuvant treatment for intermediate risk rectal cancer in the Netherlands, since it is associated with similar survival and local recurrence rates as CRT, but significantly lower grade 3-4 acute toxicity rates (risk ratio = 0.13, 95%CI [0.06, 0.28], P < 0.00001) [49]. The favourable

toxicity profile of SCRT is also illustrated by two recent trials on organ preservation for early rectal cancer: SCRT in the TREC trial was associated with 15% grade ≥ 3 acute toxicity, while CRT in the CARTS trial came with 42% grade ≥ 3 toxicity [50,51]. The two trials reported comparable organ preservation rates (64% vs. 59%), although it should be acknowledged that the CARTS trial included slightly bigger tumours. The earlier GRECCAR2 and ACOSOG Z6041 trials reported acute radiation-induced toxicity grade ≥ 3 rates of 20% and 39%, respectively, following CRT for organ preservation [52,53]. Based on these numbers, CRT might be considered overtreatment for inducing a cCR in intermediate risk rectal cancer.

Besides radiotherapy dose-escalation, the addition of neoadjuvant systemic therapy to (chemo)radiotherapy has been shown to achieve high complete response rates in the RAPIDO, PRODIGE23 and OPRA trials [17–19]. The study schedules came with 48%, 46% and 34% grade ≥ 3 toxicity, respectively [54]. The RAPIDO and PRODIGE23 trials demonstrated improved DFS compared to CRT only as neoadjuvant strategy for LARC, but no OS benefit mc (yet). In the Netherlands, rectal cancer is not treated with adjuvant systemic therapy because an OS benefit never has been demonstrated following adequate TME [55]. Since patients with intermediate risk rectal cancer are at substantially lower risk of distant metastases than LARC, the toxicity of neoadjuvant systemic therapy may not outweigh the benefits for this patient group [56]. Dose-escalated SCRT might become a more *proportional* strategy for improving organ-sparing probability in intermediate risk rectal cancer patients.

The maximum incidence of DLT in the preRADAR trial was defined while thinking of the additional toxicity that patients would 'trade off' for averting TME. We believe that patients would accept mild-moderate complaints (grade 1-2) and transient, severe complaints that limit self-care (grade 3) in the weeks following radiotherapy as a 'trade-off' for a higher probability of organ preservation. However, long-lasting complaints that limit self-care (persisting grade 3) as well as severe

complaints that warrant hospital admission and an acute intervention (grade 4) might outweigh the benefits of possibly omitting TME. We therefore defined DLT as acute radiation-induced toxicity grade 4, long-lasting grade 3, or the postponement of surgery > 20 weeks due to any grade of radiation-induced toxicity. Based on the low toxicity rate of dose-escalated SCRT in previous studies (Table 1), a 6 + 3 design was chosen over the classic 3 + 3 dose-escalation design, allowing a lower maximum incidence of radiation-induced DLT of one in nine patients instead of one in six. Furthermore, we deem it unacceptable if the intervention would significantly increase the probability of reoperation or ICU admittance (Clavien-Dindo 3b-4) in patients who are treated with TME despite the study intervention. Based on an incidence of 10-15% complications requiring reoperation following TME, plus a sampling error (that may be bigger if fewer patients are operated upon), a dose level is considered safe when a maximum of one in three operated patients experiences postoperative complication grade 3b-4 [57,58]. This subjective measure for DLT was formulated in collaboration with patients.

A possible limitation might be that late radiation-induced toxicity is not included as a DLT. Radiation-induced toxicity may newly occur for several years after treatment [59]. It is not feasible to include such long-term outcomes as DLT in a dose-finding trial. Studies in prostate and gynaecological cancer have shown acceptable levels of severe late radiation-induced toxicity with dosages of 80 Gy. The maximum biologically equivalent dose to late responding healthy tissue (EQD2, α/β = 3 Gy) in the preRADAR therefore does not exceed 80 Gy (Table 2) [60–62].

The number of patients in the current phase I trial will not be sufficient to answer the explorative questions. For these purposes, data will be merged with the subsequent phase II trial and possibly other rectal cancer trials of participating institutes.

Conclusion

In conclusion, the preRADAR trial will determine the MTD of dose-escalated SCRT using online adaptive MRgRT for intermediate risk rectal cancer, based on the incidence of acute radiation-induced toxicity and postoperative complications. Dose-escalated SCRT is administered as neoadjuvant monotherapy since it has a favourable toxicity profile compared to CRT and SCRT followed by systemic therapy. The maximum incidence of DLT is defined as the additional toxicity that patients would 'trade off' for averting TME.

Authors' contributions:

MEV: conceptualization, methodology, software (design of eCRF), investigation, data curation, writing- original draft, visualization, project administration. MDT: investigation, recourses, data curation, writing – reviewing & editing, project administration. CMK: software (technique of intervention), writing – reviewing & editing. UAvdH: software (technique of intervention), writing – reviewing & editing. CAMM: methodology, software (technique of intervention), resources, supervision, funding acquisition. TJ: software (technique of intervention), writing – reviewing & editing. TV: software (technique of intervention). WMUvG: methodology, resources, supervision. LMGM: resources. MK: resources, writing – reviewing & editing. MML: resources. MNGJAB: resources, writing – reviewing & editing. MC: resources. MM: resources, writing – reviewing & editing. ILH: resources, writing – reviewing & editing. PS: methodology, resources, writing – reviewing & editing. BAG: methodology, resources, writing – reviewing & editing. RJAF: methodology, resources, writing – reviewing & editing. ECJC: resources. AP: resources. ABS: resources. JTH: resources. SGE: methodology, writing – reviewing & editing. HMV: conceptualization, methodology, supervision, funding acquisition. MMC: software (technique of

intervention). GJM: software (technique of intervention), writing – reviewing & editing. MPW: conceptualization, methodology, software (technique of intervention), investigation, resources, writing – reviewing & editing, supervision, funding acquisition. FPP: conceptualization, methodology, software (technique of intervention), investigation, resources, writing – reviewing & editing, supervision, funding acquisition.

Competing interest statement: The department of radiotherapy of both the UMC Utrecht and the Netherlands Cancer Institute have received funding from Elekta AB, Sweden and Philips Healthcare. PS reports consulting fees from MSD and Bayer and fees for MEDtalks educational presentations. RJAF reports grants for Personal Genome Diagnostics, Delfi Diagnostics, Cergentis BV and MERCK BV. HMV is a member of the European Commission and The Netherlands Organization of Health Research and Development and reports grants for the Dutch Cancer Foundation. MPWI has received personal fees from Elekta AB, Sweden.

Funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data statement: After consent of both participating centres, sharing of pseudonymized data with other researchers within the scope of the current project is possible.

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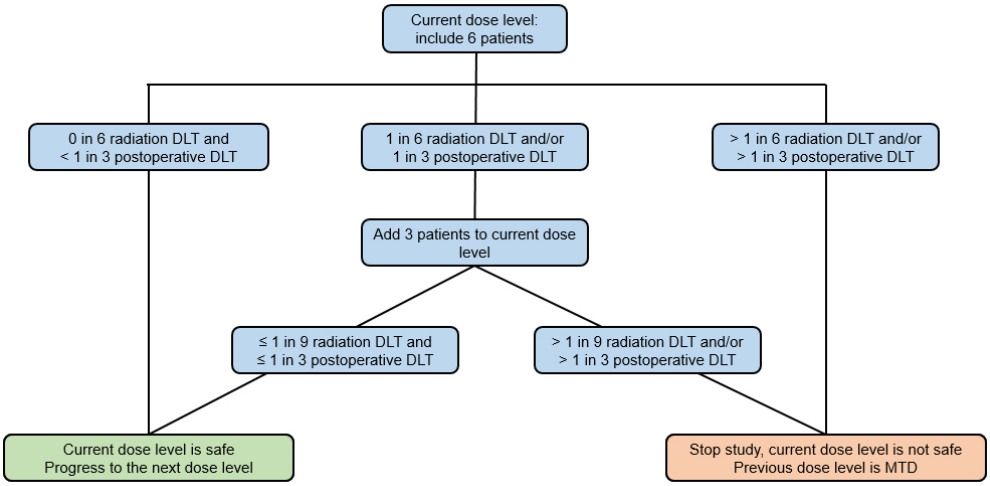

Figure 1: study flow according to dose limiting toxicity (DLT) per dose level in the 6 + 3 design.

665x346mm (38 x 38 DPI)

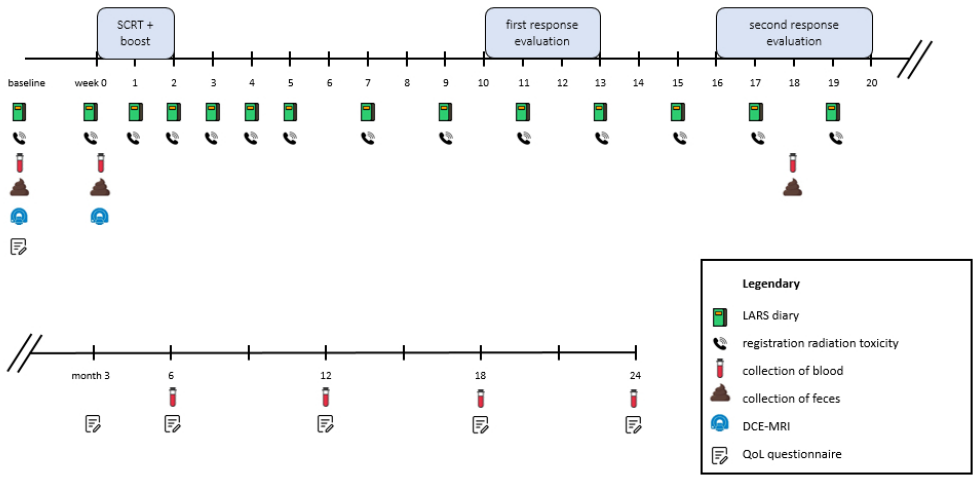

Figure 2: patient timeline in the preRADAR trial

SCRT: short course radiotherapy. LARS: low anterior resection syndrome score. DCE-MRI: dynamic contrast enhanced magnetic resonance imaging. QoL: quality of life.

651x320mm (38 x 38 DPI)

SUPPLEMENTARY FILES

Supplementary File A: equivalent dose limits for organs at risk

Structure	Volume (cc)	EQD2 α/β = 3 (Gy)	Comments
Small Bowel (loops) [1,2,3]	0.5	70	Constraint
	10	40	Aim
Large Bowel (loops)	0.5	60.16	Constraint, excluding the sigmoid lying in the course of the bowel within 2 cm of GTV
Bladder [1,4]	0.5	80.56	Constraint
Plexus Sacral [1,4]	0.1	60.16	Constraint
	5	54	Constraint

For the vagina no formal constraints exists. Patients will receive instructions for the use of dilators after radiotherapy.

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Supplementary File B: possible treatment-related toxicity, adapted from the CTCAE v5.0 and the STAR-TREC trial

Category	Toxicity
Gastrointestinal disorders	Abdominal pain
	Anal/rectal fistula
	Anal/rectal hemorrhage
	Anal mucositis
	Anal/rectal necrosis
	Anal/rectal pain
	Anal/rectal stenosis
	Anal/rectal ulcer
	Colonic/small intestinal fistula
	Lower gastrointestinal hemorrhage
	Colonic/small intestinal obstruction
	Colonic/small intestinal perforation
	Colonic/small intestinal stenosis
	Colonic/small intestinal ulcer
	Constipation
	Diarrhea
	Enterocolitis
	Enterovesical fistula
	Fecal incontinence
	Hemorrhoids
	Hemorrhoidal hemorrhage
	Ileus
	Intra-abdominal hemorrhage

	Proctitis
	Rectal obstruction
	Rectal perforation
Renal and urinary disorders	Bladder perforation
	Bladder spasm
	Cystitis noninfective
	Hematuria
	Urinary fistula
	Urinary incontinence
	Urinary retention
	Urinary tract obstruction
	Urinary tract pain
Injury, poisoning and procedural complications	Dermatitis radiation (if in radiation field)
Reproductive system and breast disorders	Prostatic pain
	Uterine fistula
	Uterine hemorrhage
	Vaginal fistula
	Vaginal hemorrhage
	Vaginal perforation
	Vaginal stricture
General disorders	Fatigue
	Malaise
	Pain
Infections and infestations	Abdominal infection
	Anorectal infection
	Bladder infection
	Enterocolitis infectious

	Prostate infection
	Vaginal infection
	Uterine infection
	Wound infection (if in radiation field)
Musculoskeletal and connective tissue disorders	Abdominal soft tissue necrosis
	Pelvic soft tissue necrosis
	Osteonecrosis
Nervous system disorders	Neuralgia
	Peripheral motor/sensory neuropathy

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	7
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-3
Roles and	#5b	Name and contact information for the trial sponsor	n/a

responsibilities: sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	9-11
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	11-12
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	11
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	12

		eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-18
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	38
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17-19
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data	18-19, data management

		entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	plan
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20, full protocol
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20, monitoring plan
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial	20, full protocol

		participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13, full protocol
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	data management plan
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	4
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	data management plan
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if	19

applicable

Notes:

- 19: 18-19, data management plan
- 21a: 20, full protocol
- 23: 20, monitoring plan
- 25: 20, full protocol
- 26a: 13, full protocol
- 27: data management plan
- 29: data management plan This checklist was completed on 20. May 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Towards Response ADAptive Radiotherapy for organ preservation for intermediate risk rectal cancer (preRADAR): protocol of a phase I dose-escalation trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065010.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Mar-2023
Complete List of Authors:	Verweij, Maaike; University Medical Centre Utrecht, Radiation-Oncology; University Medical Centre Utrecht, Surgery Tanaka, Max; Netherlands Cancer Institute, Radiation-Oncology Kensen, Chavelli; Netherlands Cancer Institute, Radiation-Oncology van der Heide, Uulke ; Netherlands Cancer Institute, Radiation-Oncology Marijnen, Corrie A. M.; Netherlands Cancer Institute, Radiation-Oncology Janssen, Tomas; Netherlands Cancer Institute, Radiation-Oncology Vijlbrief, Tineke; Netherlands Cancer Institute, Radiation-Oncology van Grevenstein, Wilhelmina; University Medical Centre Utrecht, Surgery Moons, Leon; University Medical Centre Utrecht, Gastroenterology Koopman , M ; University Medical Centre Utrecht, Medical Oncology Lacle, MM; University Medical Centre Utrecht, Pathology Braat, Manon; University Medical Centre Utrecht, Radiology Chalabi, Myriam; Netherlands Cancer Institute, Medical Oncology Maas, Monique; Netherlands Cancer Institute, Radiology Huibregtse, Inge; Netherlands Cancer Institute, Gastroenterology Snaebjornsson, Petur; Netherlands Cancer Institute, Pathology Grotenhuis, Brechtje; Netherlands Cancer Institute, Surgery Fijneman, Remond; Netherlands Cancer Institute, Pathology Consten, Esther; Meander Medical Centre, Surgery; University Medical Centre Groningen, Surgery Pronk, Apollo; Diakonessenhuis Utrecht Zeist Doorn, Surgery Smits, Anke; Sint Antonius Hospital, Surgery Heikens, Joost; Hospital Rivierenland, Department of Surgery Eijkelenkamp, Hidde; University Medical Centre Utrecht, Radiation-Oncology Elias, Sjoerd; Julius Center for Health Sciences and Primary Care, Epidemiology Verkooijen, Helena; University Medical Centre Utrecht, Radiation-Oncology Schoenmakers, Maartje; University Medical Centre Utrecht, Radiation-Oncology Meijer, Gert ; University Medical Centre Utrecht, Radiation-Oncology Intven, Martijn; University Medical Centre Utrecht, Radiation-Oncology Peters, Femke; Netherlands Cancer Institute, Radiation-Oncology
Primary Subject Heading:	Oncology

Secondary Subject Heading:	Gastroenterology and hepatology, Surgery, Radiology and imaging
Keywords:	RADIOTHERAPY, Colorectal surgery < SURGERY, Gastrointestinal tumours < ONCOLOGY, Magnetic resonance imaging < RADIOTHERAPY, Clinical trials < THERAPEUTICS

Towards Response ADAptive Radiotherapy for organ preservation for intermediate risk rectal cancer (preRADAR): protocol of a phase I dose-escalation trial

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Key words: rectal cancer, radiotherapy, dose-escalation, clinical trial, organ preservation.

Word count: 4011/4000

ABSTRACT (301 words)

Introduction Organ preservation is associated with superior functional outcome and quality of life (QoL) compared to total mesorectal excision (TME) for rectal cancer. Only 10% of patients are eligible for organ preservation following short course radiotherapy (SCRT, 25Gy in 5 fractions) and a prolonged interval (4-8 weeks) to response evaluation. The organ preservation rate could potentially be increased by dose-escalated radiotherapy. Online adaptive magnetic resonance-guided radiotherapy (MRgRT) is anticipated to reduce radiation-induced toxicity and enable radiotherapy dose-escalation. This trial aims to establish the maximum tolerated dose (MTD) of dose-escalated SCRT using online adaptive MRgRT.

Methods and analysis The preRADAR is a multicentre phase I trial with a 6+3 dose-escalation design. Intermediate risk rectal cancer patients (cT3c-d(MRF-)N1M0 or cT1-3(MRF-)N1M0) interested in organ preservation are eligible. Patients are treated with a radiotherapy boost of 2x5Gy (level 0), 3x5Gy (level 1), 4x5Gy (level 2) or 5x5Gy (level 3) on the gross tumour volume in the week following standard SCRT using online adaptive MRgRT. The trial starts on dose level 1. The primary endpoint is the MTD based on the incidence of dose limiting toxicity (DLT) per dose level. DLT is a composite of maximum one in nine severe radiation-induced toxicity and maximum one in three severe postoperative complications, in patients treated with TME or local excision (LE) within 26 weeks following start of treatment. Secondary endpoints include the organ preservation rate, non-dose limiting toxicity, oncological outcomes, patient-reported QoL and functional outcomes up to two years following start of treatment. Imaging and laboratory biomarkers are explored for early response prediction.

Ethics and dissemination The trial protocol has been approved by the medical ethics committee of the UMC Utrecht. The primary and secondary trial results will be published in international peer-reviewed journals.

Registration details NL8997 at the World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int)

ARTICLE SUMMARY

Strengths and limitations of the study (5/5)

- Dose-escalated short course radiotherapy (SCRT) is expected to increase the probability of organ preservation compared to standard-dose SCRT.
- The new technique of online adaptive magnetic resonance guided radiotherapy (MRgRT) is anticipated to reduce radiation-induced toxicity and enable dose-escalated SCRT.
- Dose-escalated SCRT is administered as neoadjuvant monotherapy since it has a favourable toxicity profile compared to chemoradiation (CRT) and SCRT followed by systemic therapy.
- The definition of dose-limiting toxicity (DLT) is based on what patients would 'trade off' for a higher probability of organ preservation.
- Since late toxicity can occur for several years after radiotherapy, it cannot be included as DLT in this dose-finding trial.

INTRODUCTION

Introduction of multimodal treatment consisting of neoadjuvant (chemo)radiotherapy and total mesorectal excision (TME) has improved oncological outcomes for patients with rectal cancer in the previous decades [1,2]. Multimodal treatment unfortunately is associated with long-term impaired quality of life (QoL) and bowel, urinary and sexual dysfunction [3,4]. In recent years, organ preservation has become possible for rectal cancer patients who reach a (near) clinical complete response (cCR) after neoadjuvant (chemo)radiotherapy: patients with minimal or no residual tumour on physical examination, endoscopy and magnetic resonance imaging (MRI) after neoadjuvant treatment can be managed by local excision (LE) and/or active surveillance instead of TME [5]. When performed in appropriately selected patients, organ preservation has similar oncological outcomes as TME [6]. Since the morbidity of TME is averted, including the formation of an ostomy, organ preservation is associated with superior QoL and functional outcome [7,8].

The majority of patients with rectal cancer would rather opt for organ preservation than TME [9,10]. The chance of reaching a cCR and therewith eligibility for organ preservation depends on the neoadjuvant treatment schedule and the timing of response evaluation, among other clinical factors [11–13]. The standard neoadjuvant treatment for intermediate risk rectal cancer according to the Dutch guideline (cT3c-d(MRF-)N0M0 and cT1-3(MRF-)N1M0) is short course radiotherapy (SCRT, 25 Gy in 5 fractions) [14]. After SCRT and a 4-8 weeks interval, the complete response rate is approximately 10% [15]. This rate is low compared to complete response rates of approximately 16% following chemoradiation (CRT, 50 Gy in 25 fractions with a chemosensitizer) for locally advanced rectal cancer (LARC), 28% following SCRT and neoadjuvant systemic therapy for LARC in the RAPIDO trial, 28% following CRT and neoadjuvant systemic therapy in the PRODIGE23 trial and even 60% of organ preservation at 3 years following CRT and neoadjuvant systemic consolidation therapy in the OPRA trial [16–19].

Besides addition of systemic therapy, escalation of the irradiation dose could well be another viable strategy to render more patients eligible for organ preservation after SCRT. The positive relationship between irradiation dose and tumour response is well recognized [20]. Meta-analysis demonstrated that dose-escalated CRT (with a total dose of ≥ 54 Gy) is associated with a relatively high pooled pCR rate of 24% in LARC [21]. Dose-escalated SCRT has been investigated by only four trials (Table 1) [22–25]. An important limiting factor for dose-escalating SCRT is the risk of radiation-induced toxicity.

Recently, online adaptive magnetic resonance guided radiotherapy (MRgRT) on a magnetic resonance linear accelerator (MR-Linac) has been implemented in clinical care [26,27]. In contrast to conventional radiotherapy, MRgRT allows for online visualization of the tumour and surrounding organs at risk (OAR) on MRI during treatment and adaptation of the treatment plan to the current anatomy at each treatment fraction. This technique has unprecedented accuracy and lowers the dose to the healthy tissues [28–30]. As a consequence, online adaptive MRgRT is anticipated to reduce radiation-induced toxicity and enable dose-escalated SCRT.

Adequate patient selection for dose-escalation is important, as some patients will experience radiation-induced toxicity and delay of surgery without the benefit of achieving a cCR. No biomarkers are currently clinically available for prediction of the response to radiotherapy. However, predictive value for the response to radiotherapy has been demonstrated for several biomarkers in blood, tissue, faeces and MRI [31–33]. These biomarkers could potentially aid in response-based adaptation of the treatment plan. The current trial includes exploratory analyses of blood, faecal and tissue samples and (quantitative) MRI, in order to prepare for a response adaptive dose-escalation strategy.

In conclusion, the rationale for the current trial is to offer intermediate risk rectal cancer patients a higher chance of organ preservation using dose-escalated, online adaptive MRgRT on an MR-Linac. We designed a phase I trial to determine the maximum tolerated dose (MTD) of dose-escalated SCRT. The MTD is based on the incidence of dose-limiting toxicity (DLT), i.e. acute radiation-induced toxicity and postoperative complications. The MTD will be the recommended dose for a subsequent phase II trial that will evaluate the efficacy of dose-escalated SCRT on the organ preservation rate. Meanwhile, imaging and laboratory biomarkers are explored for early prediction of the response to radiotherapy. This trial is the first step towards Response ADAptive Radiotherapy for organ preservation for rectal cancer: the preRADAR trial.

METHODS AND ANALYSIS

Study design

The preRADAR trial is a phase I multicentre trial that follows the 6+3 dose-escalation design. The trial is conducted in the University Medical Centre Utrecht and the Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, both in the Netherlands. A minimum of six and a maximum of 45 patients will be recruited. Participant enrolment has started in November 2021 and is expected to finish by February 2024. Follow up for the primary endpoint is expected to finish by August 2024.

Objectives

The primary objective is to establish the MTD of dose-escalated SCRT in intermediate risk rectal cancer patients. Secondary objectives are to determine non-dose limiting acute radiation-induced toxicity, the 30- and 90-day postoperative complication rate, organ preservation rate at 6, 12 and 24 months, oncological outcomes at 24 months, patient-reported QoL and functional outcomes at 3, 6, 12, 18 and 24 months. Exploratory objectives are to seek imaging and laboratory biomarkers that are predictive for the response to radiotherapy at an early stage of treatment.

Study population

Adult patients (≥ 18 years old) presenting to the participating centres with (1) biopsy proven rectal adenocarcinoma, (2) classified as intermediate risk according to the Dutch guideline (cT3c-d(MRF-)N0M0 or cT1-3(MRF-)N1M0 based on the AJCC 8th edition) [14], (3) referred for neoadjuvant SCRT, (4) distal or midrectal tumour location: the upper border of the rectal tumour below the sigmoid take-off and lower border below the peritoneal fold [34], (5) judged fit for multimodal treatment by multidisciplinary tumour board meeting and (6) interest in organ preservation, are eligible.

Exclusion criteria are mucinous carcinoma or neuroendocrine neoplasms, indication for additional SCRT and TME following LE, recurrent tumour or regrowth after previous treatment, extramesorectal pathological lymph nodes, extramural venous invasion (EMVI+), planned systemic therapy, history of inflammatory bowel disease, prior pelvic radiotherapy, concurrent pregnancy, orthopaedic hip implants or absolute contraindication for MRI.

Patient inclusion

Eligible patients are identified during multidisciplinary tumour board meetings. Patients are informed about the preRADAR trial by their treating radiation-oncologist, in both an oral and a written manner. Patients are free to accept or decline the intervention and have at least three days to consider their decision and sign the informed consent form. Trial participation includes consent to undergo the intervention and to participate in acute toxicity monitoring. Consent to collect blood, faeces, tumour tissue, additional MR sequences, MR sequences with intravenous contrast (i.e. dynamic contrast enhanced (DCE) MRI) and filling out QoL questionnaires is optional. Additionally, patients are asked to share their medical data within the Prospective Dutch ColoRectal Cancer cohort (PLCRC) and the Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-Linac study (MOMENTUM) [35,36].

Treatment

The study treatment consists of a radiotherapy boost of 2 x 5 Gy (dose level 0), 3 x 5 Gy (dose level 1), 4 x 5 Gy (dose level 2) or 5 x 5 Gy (dose level 3) on the gross tumour volume (GTV) in the week following standard SCRT (Table 2). SCRT is administered on the conventional elective volumes, consisting of the mesorectum, presacral lymph nodes and internal iliac lymph nodes [37]. Uniform planning target volume (PTV) margins of 4 mm are applied during SCRT, except for 6 mm in the ventral direction. The boost is delivered on the GTV consisting of the tumour and suspicious lymph nodes, if present. Lymph nodes are classified as suspicious if they are (1) ≥ 9 mm, (2) 5-9 mm and have two out of three malignant characteristics (irregular border, heterogeneous texture or round shape), (3) < 5 mm and have all three malignant characteristics (measurements are of the short axis diameter) [14]. During the boost fractions, a uniform PTV margin of 5 mm is applied. The bowel cavity, bowel loops, bladder, left and right femoral head

and lumbosacral plexus are considered organs at risk (OAR, constraints in Supplementary File A). Delineation of the target volumes and OARs of both SCRT and the boost is performed on a 3D T2-weighted MRI and administered with online adaptive MRgRT on a 1.5 Tesla MR-Linac.

The trial starts at dose level 1 (5 x 5 Gy + 3 x 5 Gy boost). When, after the treatment of six patients, no radiation-induced DLT and less than one in three postoperative DLT has occurred, the study progresses to the next dose level (see primary endpoint and Figure 1). When one in six radiation-induced DLT and/or one in three postoperative DLT has occurred, three additional patients are added to the current dose level and adverse events are reassessed accordingly. Whenever more than one radiation-induced DLT or more than one in three postoperative DLT occurs, the trial is stopped and the previous dose level is considered the MTD. While awaiting the occurrence of DLT in six (or nine) patients of the current dose level, newly presenting eligible patients are included to the previous dose level. Since dose level 0 (5 x 5 Gy + 2 x 5 Gy boost) has the same biological effective dose as chemoradiation, we consider it safe without testing. If less than one in six patients had radiation-induced DLT and less than three patients have been treated with TME, additional patients are added to the current dose level until at least three patients have been treated with TME.

Patients will not proceed to the boost if treatment-related grade ≥ 3 radiation-induced toxicity or signs of sacral plexopathy are present at the end of SCRT, nor when ≥ 80% GTV coverage for the boost is not achievable due to nearby OARs. When a patient does not proceed to the boost, an additional patient is included to the current dose level.

Acute toxicity monitoring

Patients are consulted before the start of treatment (baseline), at end of SCRT (week 1), after the administration of the boost (week 2), at week 3, week 4, week 5 and every other week thereafter up to surgery or week 20 (Figure 2). Toxicity is registered at each consultation for proctitis, rectal pain, rectal haemorrhage, non-infective cystitis, urinary obstruction, fatigue, radiation dermatitis and other non-prespecified toxicity according to the CTCAE version 5.0 [38]. Simultaneously, patients are asked to fill out a low anterior resection syndrome (LARS) score questionnaire online or in a paper diary to monitor bowel function [39].

Response evaluation

The first response evaluation is performed at 11-13 weeks following the start of treatment, using T2-weighted MRI, diffusion weighted imaging (DWI) and endoscopy. A poor response at the first response evaluation is defined as downsizing of less than 50% of the maximum diameter of the primary tumour, residual tumour of more than 2cm and/or persistent suspicious lymph nodes. Poor responders at the first response evaluation are planned for TME. All other patients proceed to the second response evaluation at 16-20 weeks, using T2-weighted MRI, DWI and/or endoscopy. A near complete response is defined as minimal residual tumour without any signs of residual pathological lymph nodes, amenable for LE (ycT1N0). Near complete responders are offered LE followed by active surveillance, or TME in case of irradical resection or >ypT1. A complete response is defined as no signs of residual tumour. Complete responders enter active surveillance. All other patients (i.e. patients with diseasee progression or a residual tumour not amenable for LE) are planned for TME. All patients treated with active surveillance are asked to participate in the Dutch Watch & Wait registry.

Follow-up

Patients are followed up according to local practice. In the Netherlands, follow-up after TME commonly exists of clinical consultation and CEA measurement every 3-6 months during the first two years after start of treatment and every 6-12 months for the three years thereafter. Thoraco-abdominal computed tomography (CT) is performed at one year after start of treatment and on indication thereafter. For patients treated with active surveillance, the follow-up scheme consists of endoscopy and MRI every 3 months during the first year, every 6 months during the second year and every 6-12 months during year 3-5 after start of treatment.

Primary endpoint

The primary endpoint is the MTD based on the incidence of DLT per dose level. A maximum of either one in nine severe acute radiation-induced toxicity or one in three severe postoperative complications per dose level is considered safe.

Severe acute radiation-induced toxicity is defined as:

- Treatment-related (Supplementary File B) grade ≥ 4 radiation-induced toxicity according the Common Toxicity Criteria for Adverse Events (CTCAE version 5.0), occurring within 20 weeks after start of radiotherapy and before surgery [38];
- Treatment-related grade 3 radiation-induced toxicity persisting beyond 12 weeks after start of radiotherapy;
- Postponing of surgery > 20 weeks after start of radiotherapy due to any grade of treatment-related toxicity, in patients with an insufficient response at the first and/or second response evaluation;

- In case of grade 3-4 radiation-induced toxicity that was not prespecified, or grade 3 radiation-induced toxicity newly occurring between 12-20 weeks after start of radiotherapy, the trial management team will judge if this classifies as a DLT on a case-to-case basis.

Severe postoperative complications are defined as Clavien-Dindo grade 3b-4 complications occurring within 30 days postoperative, in patients treated with TME or LE within 26 weeks following the start of treatment [40].

Secondary endpoints

The most important secondary endpoint is the organ preservation rate at 24 months, which is defined as an in situ rectum, no ostomy and no residual or recurrent locoregional disease [41]. Other secondary endpoints include:

- feasibility of delivery of the boost based on GTV coverage,
- non-dose limiting acute radiation-induced toxicity as measured by the CTCAE assessments and LARS diaries up to 20 weeks following the start of treatment or, if planned earlier, up to TME [38,39],
- non-dose limiting 30- and 90-day complications according to Clavien-Dindo, length of hospital stay and hospital readmittance in patients treated with TME or LE within 26 weeks following the start of treatment 40,
- clinical complete response (cCR) and clinical near complete response (near cCR) at the first and the second response evaluation,

- tumour regression grade on pathology according to Mandard and type and radicality of surgery in patients treated with TME and LE within 26 weeks following the start of treatment [42],
- type and radicality of salvage surgery in patients with a local regrowth during watch & wait up to 24 months,
- overall survival (OS) and disease-free survival (DFS) at 24 months [43],
- late radiation-induced toxicity grade ≥3 according to CTCAE version 5.0 presenting after 90 days up to 24 months, and,
- patient-reported quality of life and functional outcome as measured by the European Organisation of Research and Treatment of Cancer Quality of life Core and ColoRectal specific Questionnaire (EORTC QLQ-C30 and QLQ-CR29), Low Anterior Resection Syndrome (LARS) score, the International Index of Erectile Function (IIEF), Urinary Distress Inventory (UDI-6), Incontinence Impact Questionnaire (IIQ-7) and McCoy Female Sexuality Questionnaire (MFSQ) at baseline and at 3, 6, 12, 18 and 24 months following the start of treatment [39,44–48].

Translational research

Blood and faeces are collected at baseline, after the second radiotherapy fraction and at the second response evaluation. Blood is additionally collected at 6, 12, 18 and 24 months of follow-up. Blood is analysed for haematology, carcinoembryonic antigen (CEA), kidney function, albumin, c-reactive protein, lactate dehydrogenase and circulating tumour (ct)DNA [31,32]. Faeces is analysed for the microbiome [33]. Tumour tissue is collected at diagnosis and at surgery. An MRI is routinely acquired pre-treatment and additional sequences are acquired during

idle time of each radiotherapy fraction. In some centres, an extra MR scan is performed on an MR-Linac pre-treatment and a DCE MRI is performed pre-treatment and after the second radiotherapy fraction. The specific methodology for the translational part of the preRADAR trial is yet to be determined.

Data management and analysis

Clinical data are collected from the medical files and captured in an electronic case report form (eCRF) in Castor EDC. Data management details are reported in a separate data management plan. Technical treatment data are collected within the Multiple Outcome Evaluation of Radiotherapy Using the MR-Linac cohort (MOMENTUM) [36]. PROs are collected within the Prospective Dutch ColoRectal Cancer Cohort (PLCRC) [35]. Human samples for translational research are stored at the Netherlands Cancer Institute.

The incidence of DLT will be calculated per dose level, excluding patients who did not proceed to the boost. Secondary toxicity outcomes are described in the same per-protocol population (i.e. non-dose limiting radiation-induced toxicity and postoperative complications, PROs and late radiation-induced toxicity). Secondary efficacy outcomes are described in the intention-to-treat population (i.e. organ preservation rate, feasibility of the boost, tumour regression grade, salvage surgery, OS, DFS). Outcomes will be analysed using descriptive statistics, a mixed-effects model (for PROs) or Kaplan-Meier method (for time-to-event data). Data of this phase I trial might be reused for data analysis of the subsequent phase II trial.

Patient and public involvement statement

The Dutch patient federation for colorectal cancer (*Stichting Darmkanker)* was involved during the design phase of this trial. The definition of the primary outcome (DLT), the burden of the intervention and follow-up and the patient information leaflet were discussed with two patients. The patient federation officially declared their support for the current trial. They will remain involved during the evaluation of the results and designing the subsequent phase II trial. Patient information on the trial is displayed on the website www.kanker.nl/trials.

Safety

A trial safety committee has been appointed, consisting of an independent colorectal surgeon and radiation-oncologist per centre. They have the right to temporarily stop the trial if any non-prespecified safety issues are of concern. If a patient dies within 20 weeks following the start of treatment or within thirty days postoperatively (in patients treated with TME or LE in 26 weeks following the start of treatment), the trial will be temporarily stopped to investigate if the event is related to the trial intervention.

Serious adverse events (SAE's) that occur within 20 weeks following the start of treatment or within 30 days postoperatively, in patients treated with TME or LE within 26 weeks following the start of treatment, will be reported within 7 days of first knowledge through an online form to the medical ethics committee of the UMC Utrecht. SAE's that occur after this period, will be reported in the same manner if the local principal investigator considers the event to be related to the intervention.

Ethics and dissemination

This trial is designed in accordance with 18th version of the World Medical Association Declaration of Helsinki, Good Clinical Practice and the Dutch Law. The trial protocol has been approved by the medical ethics committee of the UMC Utrecht in March 2021. The trial is registered at https://www.trialregister.nl/, trial number NL8997. To ensure adequate data collection and confirmation to the trial protocol, an external monitor of the Netherlands Comprehensive Cancer Organisation will audit the trial twice yearly. The primary and secondary trial results will be published in international peer-reviewed journals. After consent of both participating centres, sharing of pseudonymized data with other researchers within the scope of the current project is possible.

DISCUSSION

The phase I preRADAR trial aims to establish the MTD of dose-escalated SCRT using online adaptive MRgRT in intermediate risk rectal cancer patients, following a 6 + 3 dose-escalation design. Patients are treated with a boost of 2 x 5 Gy, 3 x 5 Gy, 4 x 5 Gy or 5 x 5 Gy in the week following standard SCRT on an MR-Linac. Maximum one in nine severe acute radiation-induced toxicity and one in three severe postoperative complications are accepted for a dose level to be considered safe. The MTD will be the recommended dose for the subsequent phase II RADAR trial that will evaluate the efficacy of dose-escalated SCRT using online adaptive MRgRT on the organ preservation rate.

Dose-escalated SCRT is administered as neoadjuvant *monotherapy* in the preRADAR trial. SCRT is the standard neoadjuvant treatment for intermediate risk rectal cancer in the Netherlands, since it is associated with similar survival and local recurrence rates as CRT, but significantly lower grade 3-4 acute toxicity rates (risk ratio = 0.13, 95%CI [0.06, 0.28], P < 0.00001) [49]. The

favourable toxicity profile of SCRT is also illustrated by two recent trials on organ preservation for early rectal cancer: SCRT in the TREC trial was associated with 15% grade ≥ 3 acute toxicity, while CRT in the CARTS trial came with 42% grade ≥ 3 toxicity [50,51]. The two trials reported comparable organ preservation rates (64% vs. 59%), although it should be acknowledged that the CARTS trial included slightly bigger tumours. The earlier GRECCAR2 and ACOSOG Z6041 trials reported acute radiation-induced toxicity grade ≥ 3 rates of 20% and 39%, respectively, following CRT for organ preservation [52,53]. Based on these numbers, CRT might be considered overtreatment for inducing a cCR in intermediate risk rectal cancer.

Besides radiotherapy dose-escalation, the addition of neoadjuvant systemic therapy to (chemo)radiotherapy has been shown to achieve high complete response rates in the RAPIDO, PRODIGE23 and OPRA trials [17–19]. The study schedules came with 48%, 46% and 34% grade ≥ 3 toxicity, respectively [54]. The RAPIDO and PRODIGE23 trials demonstrated improved DFS compared to CRT only as neoadjuvant strategy for LARC, but no OS benefit (yet). In the Netherlands, rectal cancer is not treated with adjuvant systemic therapy because an OS benefit never has been demonstrated following adequate TME [55]. Since patients with intermediate risk rectal cancer are at substantially lower risk of distant metastases than LARC, the toxicity of neoadjuvant systemic therapy may not outweigh the benefits for this patient group [56]. Dose-escalated SCRT might become a more *proportional* strategy for improving organ-sparing probability in intermediate risk rectal cancer patients.

The maximum incidence of DLT in the preRADAR trial was defined while thinking of the additional toxicity that patients would 'trade off' for averting TME. We believe that patients would accept mild-moderate complaints (grade 1-2) and transient, severe complaints that limit self-care (grade 3) in the weeks following radiotherapy as a 'trade-off' for a higher probability of organ preservation. However, long-lasting complaints that limit self-care (persisting grade 3) as well as severe

complaints that warrant hospital admission and an acute intervention (grade 4) might outweigh the benefits of possibly omitting TME. We therefore defined DLT as acute radiation-induced toxicity grade 4, long-lasting grade 3, or the postponement of surgery > 20 weeks due to any grade of radiation-induced toxicity. Based on the low toxicity rate of dose-escalated SCRT in previous studies (Table 1), a 6 + 3 design was chosen over the classic 3 + 3 dose-escalation design, allowing a lower maximum incidence of radiation-induced DLT of one in nine patients instead of one in six. Furthermore, we deem it unacceptable if the intervention would significantly increase the probability of reoperation or ICU admittance (Clavien-Dindo 3b-4) in patients who are treated with TME despite the study intervention. Based on an incidence of 10-15% complications requiring reoperation following TME, plus a sampling error (that may be bigger if fewer patients are operated upon), a dose level is considered safe when a maximum of one in three operated patients experiences postoperative complication grade 3b-4 [57,58]. This subjective measure for DLT was formulated in collaboration with patients.

A possible limitation might be that late radiation-induced toxicity is not included as a DLT. Radiation-induced toxicity may newly occur for several years after treatment [59]. It is not feasible to include such long-term outcomes as DLT in a dose-finding trial. Studies in prostate and gynaecological cancer have shown acceptable levels of severe late radiation-induced toxicity with dosages of 80 Gy. The maximum biologically equivalent dose to late responding healthy tissue (EQD2, α/β = 3 Gy) in the preRADAR therefore does not exceed 80 Gy (Table 2) [60–62].

The number of patients in the current phase I trial will not be sufficient to answer the explorative questions. For these purposes, data will be merged with the subsequent phase II trial and possibly other rectal cancer trials of participating institutes.

Contributorship:

MEV: conceptualization, methodology, software (design of eCRF), investigation, data curation, writing- original draft, visualization, project administration. MDT: investigation, recourses, data curation, writing – reviewing & editing, project administration. CMK: software (technique of intervention), writing – reviewing & editing. UAvdH: software (technique of intervention), writing – reviewing & editing. CAMM: methodology, software (technique of intervention), resources, supervision, funding acquisition. TJ: software (technique of intervention), writing – reviewing & editing. TV: software (technique of intervention). WMUvG: methodology, resources, supervision. LMGM: resources. MK: resources, writing – reviewing & editing. MML: resources. MNGJAB: resources, writing – reviewing & editing. MC: resources. MM: resources, writing – reviewing & editing. ILH: resources, writing – reviewing & editing. PS: methodology, resources, writing – reviewing & editing. BAG: methodology, resources, writing – reviewing & editing. RJAF: methodology, resources, writing – reviewing & editing. ECJC: resources. AP: resources. ABS: resources. JTH: resources. HE: investigation, data curation, writing – reviewing & editing, project administration. SGE: methodology, writing – reviewing & editing. HMV: conceptualization, methodology, supervision, funding acquisition. MMC: software (technique of intervention). GJM: software (technique of intervention), writing – reviewing & editing. MPWI: conceptualization, methodology, software (technique of intervention), investigation, resources, writing – reviewing & editing, supervision, funding acquisition. FPP: conceptualization, methodology, software (technique of intervention), investigation, resources, writing – reviewing & editing, supervision, funding acquisition.

Funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing of interests: The department of radiotherapy of both the UMC Utrecht and the Netherlands Cancer Institute have received funding from Elekta AB, Sweden and Philips Healthcare. PS reports consulting fees from MSD and Bayer and fees for MEDtalks educational presentations. RJAF reports grants for Personal Genome Diagnostics, Delfi Diagnostics, Cergentis BV and MERCK BV. HMV is a member of the European Commission and The Netherlands Organization of Health Research and Development and reports grants for the Dutch Cancer Foundation. MPWI has received personal fees from Elekta AB, Sweden.

Ethics approval: The trial protocol has been approved by the medical ethics committee of the UMC Utrecht.

Data statement: After completion of the trial, data will be shared upon reasonable request.

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FIGURES AND TABLES

Table 1: overview of previous studies on dose-escalated short course radiotherapy (SCRT) for rectal cancer.

Study + design	Design	Patients	Treatment	Acute radiation-induced toxicity	Postoperative complications	Tumour response	Comments
Guckenberger, Radonc 2009.[22]	One-arm phase II, 2000-2007	cT2-T4N0-2M0-1 (n=118)	SCRT of total 29 Gy in twice daily fractions of 2.9 Gy followed by immediate TME and adjuvant chemotherapy if pathology UICC stage ≥II	Maximum grade 1	Any complication: 27/118 (23%) Reoperation: n=18/118 (15%) Postoperative mortality: n=4/118 (3%)	ypT1 n=8/118 (7%) ypN0 n=53/118 (45%)	
Bujko, Radonc 2013.[23]	Semi-randomized two-arm phase II, 2003-2010	cT1-3N0M0 and maximum tumour diameter ≤ 4 cm (n=89)	SCRT plus 4 Gy boost (n=64) vs. CRT of 50 Gy in 31 fractions plus 5 Gy boost with 5-FU and leucovorin (n=25) followed by LE. ypT2 or higher proceeded to TME.	Grade 3: n=1/64 (2%) vs. n=2/25 (8%)	Any complication following LE: n=12/64 (19%) vs. n=8/25 (32%)	pCR*: n=23/64 (36%) vs. n=16/25 (64%) ypT0-1: n=43/64 (67%) vs. n=20/25 (80%)	Study was terminated early due to poor accrual. Patients with poor performance status were only eligible for SCRT arm. 17 patients (27%) did not receive the boost in the SCRT arm.
Faria, Col Dis 2014. [24]	One-arm phase II. 2008-2011	cT3-4N0-2 or cT2N0-2 (n=52)	SCRT with integrated boost up to a total of 30 Gy and TME at 8 weeks	Grade 3: n=4/52 (8%)	Reoperation: 1/52 (2%) Postoperative mortality: 1/52 (2%)	pCR: 5/52 (10%)	
Chakrabarti, AoO 2020. [25]	One-arm phase II, 2018-2018.	UICC stage II-II (n=43)	SCRT of 30 Gy in 6 fractions and two cycles of CapOx followed by TME at 7 weeks	Grade 3-4: n=5/43 (12%)		pCR n=8/43 (18%)	

SCRT = short course radiotherapy. Gy = Gray. TME = total mesorectal excision. UICC = Union for International Cancer Control. cTNM: clinical tumor, nodal and metastasis stage. ypTN = pathological tumor and nodal stage following neoadjuvant treatment. CRT = chemoradiation. 5-FU = 5-fluoro-uracil based chemotherapy. LE = local excision. pCR = pathological complete response. * = significant at $p < 0.05$. CapOx = capecitabine and oxaliplatin.

Figure 1: study flow according to dose limiting toxicity (DLT) per dose level in the 6 + 3 design.

Table 2: dose scheme and biologic equivalent doses compared for the current standard of short course radiotherapy and the dose levels of the preRADAR trial.

	Dose scheme	Physical dose (Gy)	Tumour dose (EQD2 α/β = 10, Gy)	Normal tissue dose (EQD2 α/β = 3, Gy)
Current standard	5 x 5 Gy	25.00	31.25	40.00
Dose level 0	5 x 5 Gy + 2 x 5 Gy boost	35.00	43.75	56.00
Dose level 1	5 x 5 Gy + 3 x 5 Gy boost	40.00	50.00	64.00
Dose level 2	5 x 5 Gy + 4 x 5 Gy boost	45.00	56.25	72.00
Dose level 3	5 x 5 Gy + 5 x 5 Gy boost	50.00	62.50	80.00

Figure 2: patient timeline in the preRADAR trial

SCRT: short course radiotherapy. LARS: low anterior resection syndrome score. DCE-MRI: dynamic contrast enhanced magnetic resonance imaging. QoL: quality of life.

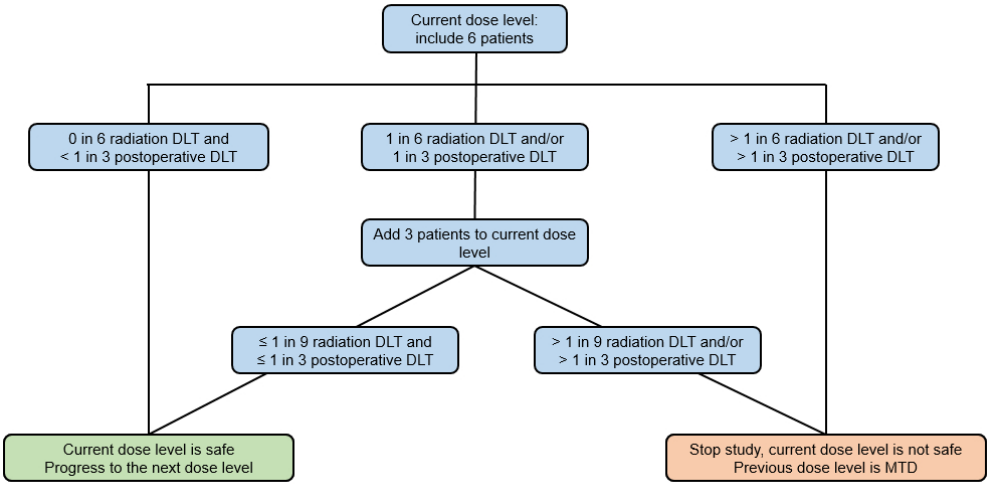


Figure 1: study flow according to dose limiting toxicity (DLT) per dose level in the 6 + 3 design.

665x346mm (38 x 38 DPI)

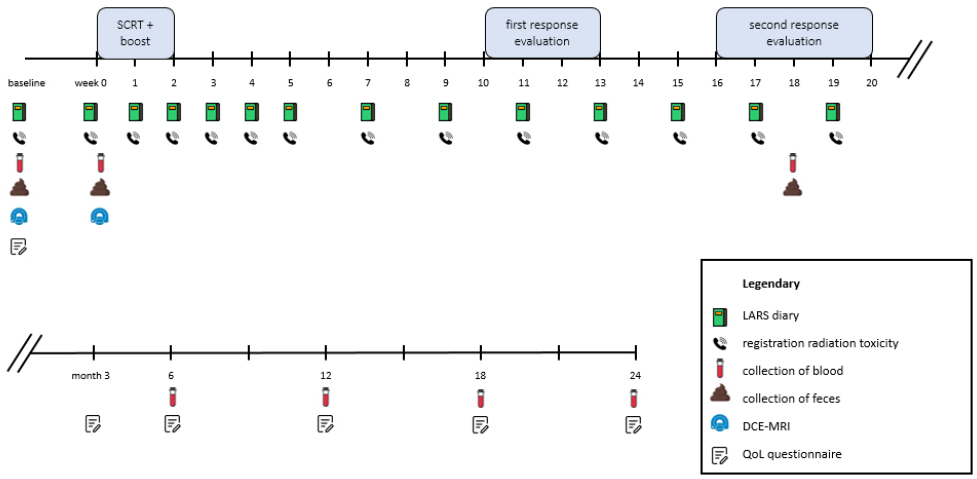


Figure 2: patient timeline in the preRADAR trial

SCRT: short course radiotherapy. LARS: low anterior resection syndrome score. DCE-MRI: dynamic contrast enhanced magnetic resonance imaging. QoL: quality of life.

651x320mm (38 x 38 DPI)

SUPPLEMENTARY FILES

Supplementary File A: equivalent dose limits for organs at risk

Structure	Volume (cc)	EQD2 α/β = 3 (Gy)	Comments
Small Bowel (loops) [1,2,3]	0.5	70	Constraint
	10	40	Aim
Large Bowel (loops)	0.5	60.16	Constraint, excluding the sigmoid lying in the course of the bowel within 2 cm of GTV
Bladder [1,4]	0.5	80.56	Constraint
Plexus Sacral [1,4]	0.1	60.16	Constraint
	5	54	Constraint

For the vagina no formal constraints exists. Patients will receive instructions for the use of dilators after radiotherapy.

[1] UK SABR consortium 2019. Stereotactic Ablative Body Radiation Therapy (SABR): A Resource version 6.1

[2] ABC-07 Addition of stereotactic body radiotherapy to systemic chemotherapy in locally advanced biliary tract. Cancer Research UK. [Accessed: 06.01.16]; Available from: http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-chemotherapy-stereotactic-radiotherapy-people-locally-advanced-bile-duct-cancer-abc-07 -undefined.

[3] A trial looking at stereotactic body radiotherapy before surgery for pancreatic cancer (SPARC). Cancer Research UK. [Accessed: 14.12.16]; Available from: http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-stereotactic-body-radiotherapy-before-surgery-for-pancreatic-cancer-sparc -undefined.

[4] Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys. 2010;37(8):4078-101

Supplementary File B: possible treatment-related toxicity, adapted from the CTCAE v5.0 and the STAR-TREC trial

Category	Toxicity
Gastrointestinal disorders	Abdominal pain
	Anal/rectal fistula
	Anal/rectal hemorrhage
	Anal mucositis
	Anal/rectal necrosis
	Anal/rectal pain
	Anal/rectal stenosis
	Anal/rectal ulcer
	Colonic/small intestinal fistula
	Lower gastrointestinal hemorrhage
	Colonic/small intestinal obstruction
	Colonic/small intestinal perforation
	Colonic/small intestinal stenosis
	Colonic/small intestinal ulcer
	Constipation
	Diarrhea
	Enterocolitis
	Enterovesical fistula
	Fecal incontinence
	Hemorrhoids
	Hemorrhoidal hemorrhage
	Ileus
	Intra-abdominal hemorrhage

	Proctitis
	Rectal obstruction
	Rectal perforation
Renal and urinary disorders	Bladder perforation
	Bladder spasm
	Cystitis noninfective
	Hematuria
	Urinary fistula
	Urinary incontinence
	Urinary retention
	Urinary tract obstruction
	Urinary tract pain
Injury, poisoning and procedural complications	Dermatitis radiation (if in radiation field)
Reproductive system and breast disorders	Prostatic pain
	Uterine fistula
	Uterine hemorrhage
	Vaginal fistula
	Vaginal hemorrhage
	Vaginal perforation
	Vaginal stricture
General disorders	Fatigue
	Malaise
	Pain
Infections and infestations	Abdominal infection
	Anorectal infection
	Bladder infection
	Enterocolitis infectious

	Prostate infection
	Vaginal infection
	Uterine infection
	Wound infection (if in radiation field)
Musculoskeletal and connective tissue disorders	Abdominal soft tissue necrosis
	Pelvic soft tissue necrosis
	Osteonecrosis
Nervous system disorders	Neuralgia
	Peripheral motor/sensory neuropathy

UMC Utrecht

Proefpersoneninformatie voor deelname aan medisch-wetenschappelijk onderzoek

Hogere dosis bestraling voor niet-operatieve behandeling van endeldarmkanker: het preRADAR onderzoek

Officiële titel: Respons ADAptieve Radiotherapie voor orgaansparende behandeling van intermediair risico rectumcarcinoom: een fase I dosisescalatie onderzoek

Inleiding

Geachte heer/mevrouw,

Met deze informatiebrief willen wij u vragen om mee te doen aan medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig. U ontvangt deze brief omdat u binnenkort bestralingen *(radiotherapie)* voor endeldarmkanker ondergaat.

U leest hier om wat voor onderzoek het gaat, wat het voor u betekent, en wat de voordelen en nadelen zijn. Het is veel informatie. Wilt u de informatie doorlezen en beslissen of u wilt meedoen? Als u wilt meedoen, kunt u het formulier invullen dat u vindt in bijlage D.

Stel uw vragen

U kunt uw beslissing nemen met de informatie die u in deze informatiebrief vindt. Daarnaast raden we u aan om dit te doen:

- Stel vragen aan de onderzoeker die u deze informatie geeft.
- Praat met uw partner, familie, vrienden of de huisarts over dit onderzoek.
- Stel vragen aan de onafhankelijk deskundige, dr. Jochem van der Voort-van Zijp, bijlage A.
- Lees de informatie op www.rijksoverheid.nl/mensenonderzoek.

1. Algemene informatie

Het Universitair Medisch Centrum (UMC) Utrecht en het Antoni Van Leeuwenhoek (AVL) hebben dit onderzoek opgezet. Bestralingsartsen (*radiotherapeut-oncologen)* in beide ziekenhuizen voeren dit onderzoek uit. Voor dit onderzoek zijn tussen de 6 en 45 proefpersonen nodig. Het aantal benodigde proefpersonen hangt af van de bevindingen tijdens het onderzoek. De medisch-ethische toetsingscommissie van het UMC Utrecht heeft dit onderzoek goedgekeurd.

2. Wat is het doel van het onderzoek?

In dit onderzoek kijken we tot welke hoogte de dosis van bestraling bij endeldarmkanker veilig gegeven kan worden. De laagste bestralingsdosis is 2 extra bestralingen. De bestralingsdosis wordt opgehoogd tot maximaal 5 extra bestralingen. Of totdat een bestralingsdosis niet meer veilig lijkt. 'Veilig' betekent in dit onderzoek dat maximaal 1 op de 9 deelnemers ernstige bijwerkingen van de bestraling heeft. Uiteindelijk hopen we dat bestraling met een hogere dosis bij meer patiënten met endeldarmkanker een operatie kan voorkomen.

Daarnaast kijken we in dit onderzoek welke bepalingen in bloed, tumorweefsel of ontlasting en welk type MR-scans voorspellen of de bestralingen goed bij u werken. Zo'n voorspelling kan bijdragen aan op maat gemaakte behandeling voor iedere patiënt.

3. Wat is de achtergrond van het onderzoek?

Voor patiënten met middelhoog risico endeldarmkanker is het al twintig jaar standaardzorg om vijf bestralingen voor de operatie te doen. Bij ongeveer 1 op de 10 patiënten lijkt de tumor weg na de bestralingen *(*zie Afbeelding 1). Sinds een paar jaar weten we dat we deze mensen veilig kunnen behandelen zonder een operatie waarbij de endeldarm wordt verwijderd. Wij denken dat we meer mensen met endeldarmkanker zonder operatie kunnen behandelen door met een hogere dosis te bestralen. We verwachten dat de hoogste bestralingsdosis van dit onderzoek bij ongeveer 4 op de 10 patiënten een behandeling zonder operatie mogelijk kan maken. Omdat we gerichter kunnen bestralen op een nieuw bestralingsapparaat (*de MR-Linac*), denken we dat deze hogere dosis niet zo veel extra bijwerkingen geeft. Dat de hoogte van de bestralingsdosis in verband staat met de kans dat de tumor weg is, is al aangetoond in eerder onderzoek.

Afbeelding 1: bij ongeveer 1 op de 10 patiënten lijkt de tumor helemaal weg na de bestralingen.

Voordat we kunnen uitzoeken of bestralen met een hogere dosis inderdaad vaker leidt tot behandeling zonder operatie, moeten we eerst weten wat een veilige, hogere dosis is van die bestralingen. De hoogste, veilige dosis willen we daarom in dit onderzoek vaststellen.

Ten tweede willen we onderzoeken of we vroeg tijdens de behandeling kunnen voorspellen of de tumor weg zal zijn na de bestralingen. Dan kunnen we in de toekomst de hoogte van de bestralingsdosis per persoon aanpassen. Op dit moment weten we dat een paar eiwitten en

cellen in bloed, tumorweefsel en ontlasting verband houden met de kans dat de tumor weg is na de bestraling. Dit geldt ook voor bepaald type MRI-scans. Maar die kennis is nog onvoldoende om de behandeling hierop aan te passen. Daarom vragen we u of we uw bloed, tumorweefsel en ontlasting mogen gebruiken voor onderzoek. En of we extra MRI-scans mogen maken. U kunt ook meedoen aan dit onderzoek zonder de extra afnames en MRI-scans.

4. Hoe verloopt het onderzoek?

Hoelang duurt het onderzoek?

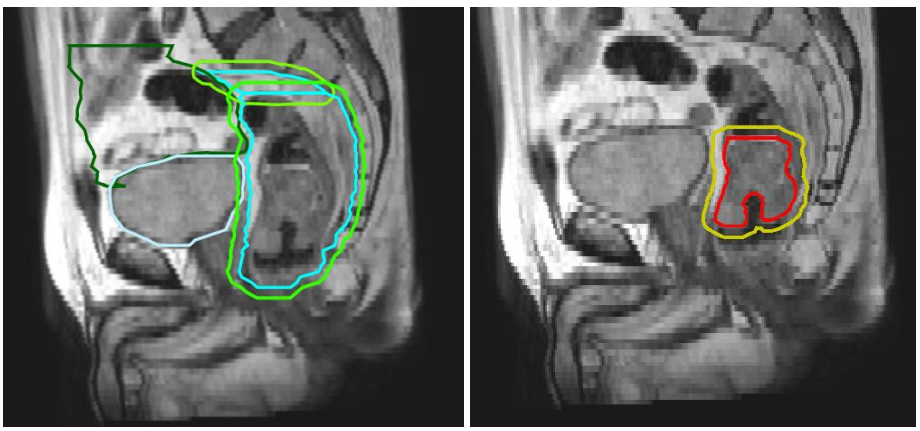
Als u beslist om mee te doen aan dit onderzoek, duurt dat in totaal ongeveer 3 maanden.

Stap 1: bent u geschikt om mee te doen?

Uw behandelend radiotherapeut heeft in overleg met andere medisch specialisten, zoals de chirurg en internist-oncoloog, en de onderzoekers besloten dat u geschikt lijkt om mee te doen.

Stap 2: de behandeling

De behandeling start net zoals de standaardbehandeling met 5 bestralingen op 5 achtereenvolgende werkdagen. De standaardbestralingen zijn gericht op de gehele endeldarm en lymfekliergebieden, inclusief de tumor en de aangedane lymfeklieren (afbeelding 2, links). U komt de 2, 3, 4 of 5 werkdagen daarna extra naar het UMC Utrecht voor de bestralingen van het onderzoek. Deze extra bestralingen worden alleen op de tumor en de aangedane lymfeklieren gegeven (afbeelding 2, rechts). Of u 2, 3, 4 of 5 extra bestralingen krijgt, hoort u van de onderzoeker voor start van de behandeling. Dit aantal hangt af van de bevindingen bij de proefpersonen die eerder dan u hebben deelgenomen aan dit onderzoek.



Afbeelding 2: Twee MRI-opnames van het kleine bekken van een man met endeldarmkanker. Links is de buikzijde en rechts is de rugzijde. Op de linker afbeelding geeft het helderblauwe lijntje de gehele endeldarm aan, die bestraald wordt tijdens de vijf standaard bestralingen. Op de rechter afbeelding geeft het rode lijntje de tumor aan, die extra bestraald wordt op de extra bestralingsdagen.

Stap 3: controles en metingen

In de weken na de behandeling is het niet nodig dat u extra naar het ziekenhuis komt. Wel vinden controles plaats door:

- Telefoongesprekken. De onderzoeker belt u 8—12x in de weken na de bestraling om te horen hoe het gaat. Deze gesprekken duren ongeveer 10 minuten per keer.
- Bijhouden van een dagboek. We vragen u om 8-12x een dagboek in te vullen. Per keer stellen we u 5 vragen over uw darmfunctie. Invullen kan digitaal of op papier en kost u ongeveer 5 minuten per keer.

De telefoongesprekken en het bijhouden van het dagboek stoppen als u geopereerd wordt, of na 20 weken als u zonder operatie behandeld wordt.

Stap 4: wel of niet opereren?

Na 11-13 weken komt u naar UMC Utrecht voor een MRI-scan en een kijkonderzoek van de darm (*endoscopie).* Daarmee kijken we hoe de tumor heeft gereageerd op de bestralingen. Als de tumor nog groot is, wordt u ingepland voor een endeldarmoperatie bij de chirurg in uw eigen ziekenhuis. Als de tumor (bijna) weg is, krijgt u 5-8 weken later nog een keer een MRI-scan en/of kijkonderzoek. Daarna wordt met u gekozen voor de uiteindelijke behandeling: geen operatie, een kleine ingreep onder narcose waarbij de resttumor oppervlakkig uit de endeldarm wordt gesneden (*lokale excisie)* of toch een endeldarmoperatie.

Extra onderdelen van dit onderzoek zijn:

- Afname van uw bloed. Dit doen we zo veel mogelijk wanneer we toch al bloed moeten prikken. Voor het onderzoek nemen we totaal 7 keer bloed af, per keer 20-50 ml. Ter vergelijking: iemand die bloed geeft bij de bloedbank, geeft per keer 500 ml bloed. Met het bloedonderzoek kijken we bijvoorbeeld naar afweercellen (witte bloedcellen) en naar stukjes genetisch materiaal van de tumor (*circulerend tumor DNA)* in het bloed.
- Opslag van tumorweefsel. Dit gaat om tumorweefsel dat toch al wordt afgenomen tijdens het kijkonderzoek in de darm of tijdens de endeldarmoperatie. Met het weefselonderzoek kijken we bijvoorbeeld naar de opbouw van de tumor op celniveau.
- Afname van ontlasting. We vragen u 3 keer een buisje met ontlasting op te sturen, inclusief een korte vragenlijst over de ontlasting. In de ontlasting kijken we bijvoorbeeld naar het type bacteriën.
- Extra MRI-opnames. Deze MRI-opnames vinden zo veel mogelijk plaats wanneer u toch al onder het bestralingsapparaat (*MR-Linac)* ligt voor de bestraling. We vragen of u het goed vindt om deze technische gegevens te delen in het internationale onderzoek naar de MR-Linac (*MOMENTUM).* Daarnaast vragen we uw toestemming voor een extra, losse scan voor start van de bestraling. En voor scans met contrastvloeistof dat in een bloedvat gespoten wordt.
- Invullen van vragenlijsten. We vinden het belangrijk om te weten wat de invloed van de ziekte en behandeling is op uw dagelijks leven en functioneren. Daarom vragen we

u om vragenlijsten in te vullen via het landelijk darmkanker onderzoek *(PLCRC).* De vragenlijsten gaan over kwaliteit van leven, darm- en blaasfunctie en seksualiteit. U krijgt deze vragenlijsten voor start van de behandeling en na 3, 6, 12, 18 en 24 maanden.

Wat is er anders dan bij gewone zorg?

In bijlage C staat een overzicht van de behandelingen en controles van dit onderzoek.

5. Welke afspraken maken we met u?

We willen graag dat het onderzoek goed verloopt. Daarom maken we de volgende afspraken met u:

- U houdt mogelijke bijwerkingen bij;
- U komt de afspraken voor bezoeken na;
- U neemt contact op met de onderzoeker in deze situaties:
    - U wordt in een ziekenhuis opgenomen of behandeld.
    - U krijgt plotseling problemen met uw gezondheid.
    - U wilt niet meer meedoen met het onderzoek.
    - Uw telefoonnummer, adres of e-mailadres verandert.

Mag u of uw partner zwanger worden tijdens het onderzoek?

Vrouwen die zwanger zijn, kunnen niet meedoen aan dit onderzoek. Vrouwen mogen ook niet zwanger worden tijdens het onderzoek. Bent u een man, en heeft u een vrouwelijke partner? Dan moet u ervoor zorgen dat zij niet zwanger kan worden van u. Bestralingen kunnen namelijk schadelijke gevolgen hebben voor een ongeboren kind.

6. Van welke bijwerkingen, nadelige effecten of ongemakken kunt u last krijgen?

Bijwerkingen tijdens en in de weken na de bestraling

Bestralen op de endeldarm geeft bij alle patiënten in meer of mindere mate bijwerkingen. Tijdens de eerste 2-4 weken na de vijf standaardbestralingen zien we de meeste bijwerkingen. Na deze periode herstellen de bijwerkingen geleidelijk. We verwachten dat de hogere dosis bestraling van dit onderzoek kan leiden tot vaker, langer of ernstiger bijwerkingen dan de standaardbestralingen in de eerste weken na de bestraling.

Deze bijwerkingen komen heel vaak voor in de 2-4 weken na bestralingen op de endeldarm (bij 5 op de 10 mensen of meer):

- Vermoeidheid;
- Frequente aandrang voor ontlasting;
- Moeite met ophouden van de ontlasting;
- Bloed- en/of slijmverlies bij de ontlasting.

Deze bijwerkingen komen vaak voor in de 2-4 weken na bestraling op de endeldarm (bij 1 op de 10 mensen of meer):

- Pijn bij de ontlasting;
- Buikkrampen;
- Gebrek aan eetlust en misselijkheid;
- Frequente aandrang voor plassen;
- Branderig gevoel bij het plassen.

Deze bijwerkingen komen soms voor in de 2-4 weken na bestraling op de endeldarm (bij 1 op de 100 mensen of meer):

- Bloedverlies bij de urine;
- Moeite met ophouden van de urine;
- Moeite met uitplassen;
- Beschadigde huid aan de billen.

U moet onmiddellijk contact opnemen met de onderzoeker als u last krijgt van:

- Ernstige diarree (> 7x /dag) tegelijkertijd met onvoldoende vochtinname (< 1,5 L / dag);
- Onhoudbare pijn;
- Beschadigde huid op het zitvlak met tekenen van infectie;
- Veranderd gevoel, pijn of tintelingen rondom het zitvlak of in de benen;
- Moeite met voor u zelf te zorgen door welke klachten dan ook.

Complicaties na de operatie

Het is mogelijk dat een hogere dosis bestraling op de endeldarm een grotere kans geeft op complicaties na de operatie. Dit risico geldt alleen als het bij u toch nodig blijkt om de endeldarm te verwijderen. Mogelijke complicaties na de operatie zijn een lekkage van een nieuwe verbinding tussen darmen *(naadlekkage)*, of een ontsteking van het operatiegebied *(wondinfectie)*. Soms is het nodig dat een complicatie na de operatie behandeld wordt met bijvoorbeeld een nieuwe operatie, het aanleggen van een stoma of met opname op de Intensive Care. Het is niet zeker in welke mate een hogere dosis bestraling kan bijdragen aan complicaties na de operatie. Als we tijdens het onderzoek zien dat ernstige complicaties vaker optreden na een hogere dosis bestraling, zullen we met een lagere dosis gaan bestralen.

Lange termijn bijwerkingen

In de jaren na bestraling en operatie voor endeldarmkanker krijgt een deel van de patiënten darmklachten, moeite met ophouden van de urine *(urine-incontinentie)* of problemen met seks. Het is mogelijk dat de hogere dosis bestraling van dit onderzoek een grotere kans geeft op deze lange termijn bijwerkingen. Maar wij verwachten dit niet, op basis van eerdere onderzoeken naar bestraling in het bekkengebied met een net zo hoge dosis. Als de hogere

dosis bestraling ervoor zorgt dat een operatie bij u niet nodig is, heeft u juist minder kans op lange termijn bijwerkingen.

7. Mogelijke voor- en nadelen

Meedoen aan het onderzoek kan voordelen en nadelen hebben. Hieronder zetten we ze op een rij. Denk hier goed over na, en praat erover met anderen.

Mogelijke nadelen:
- Korte en lange termijn bijwerkingen van hogere dosis bestraling
- Kans op complicaties na de operatie
- Verplichtingen van dit onderzoek

Mogelijk voordeel:
- Kans op behandeling zonder operatie waarbij de endeldarm verwijderd wordt (en zonder stoma)

Afbeelding 3: het is belangrijk dat u de mogelijke voor- en nadelen goed afweegt voordat u besluit mee te doen aan dit onderzoek.

Wat zijn de voordelen?

Meedoen aan dit onderzoek kan u een grotere kans bieden om zonder endeldarmoperatie behandeld te worden. Maar zeker is dat niet. Als u zonder operatie behandeld kan worden, heeft u:

- geen pijn en ongemakken door de operatie (zoals een stoma);
- geen kans op complicaties na de operatie;
- minder kans op lange termijn bijwerkingen van de operatie zoals urine-incontinentie, problemen met seks of darmklachten.

Wat zijn de nadelen?

Meedoen aan dit onderzoek kan deze nadelen hebben:

- U kunt last krijgen van bijwerkingen of nadelige effecten van de extra bestralingen, zoals beschreven in hoofdstuk 6. Als u langdurig last houdt van matig-ernstige bijwerkingen in de weken na de bestraling, kan het zijn dat uitstel van de endeldarmoperatie nodig is;
- U bent extra tijd kwijt aan 2-5 extra ziekenhuisbezoeken voor bestraling, telefoongesprekken met de onderzoeker, het invullen van het dagboek over darmklachten en het invullen van vragenlijsten over kwaliteit van leven (zie bijlage C).

- Geeft u toestemming voor afname en opslag van bloed, tumorweefsel en ontlasting en/of extra MRI-opnames? Dan bent u hier mogelijk ook extra tijd aan kwijt. Daarnaast kan een bloedafname of het inspuiten van contrastvloeistof wat pijn doen;
- U moet zich aan de afspraken houden die horen bij dit onderzoek (zie hoofdstuk 5).

Wilt u niet meedoen?

U beslist zelf of u meedoet aan het onderzoek. Wilt u niet meedoen? Dan krijgt u de gewone behandeling voor endeldarmkanker. De gewone behandeling voor middelgrote endeldarmtumoren is vijf bestralingen, in principe gevolgd door een operatie waarbij de endeldarm wordt verwijderd. Uw arts kan u meer vertellen over de behandelingsmogelijkheden die er zijn. En over de voor- en nadelen daarvan.

8. Wanneer stopt het onderzoek?

De onderzoeker laat het u weten als er nieuwe informatie over het onderzoek komt die belangrijk voor u is. De onderzoeker vraagt u daarna of u blijft meedoen.

In deze situaties stopt voor u het onderzoek:

- Alle onderzoeken volgens het schema zijn voorbij (20 weken na start van de bestralingen, of als u eerder geopereerd wordt);
- U wilt zelf stoppen met het onderzoek. Dat mag op ieder moment. Meld dit dan meteen bij de onderzoeker. U hoeft er niet bij te vertellen waarom u stopt. U krijgt dan weer de gewone behandeling voor endeldarmkanker. De onderzoeker kan voor uw veiligheid nog een of meer controles afspreken;
- De onderzoeker vindt het beter voor u om te stoppen;
- Het UMC Utrecht, de overheid of de beoordelende medisch-ethische toetsingscommissie, besluit om het onderzoek te stoppen.

Wat gebeurt er als u stopt met het onderzoek?

De onderzoekers gebruiken de gegevens die tot het moment van stoppen zijn verzameld.

9. Wat gebeurt er na het onderzoek?

Krijgt u de resultaten van het onderzoek?

Ongeveer 1 jaar na deelname van de laatste patiënt laat de onderzoeker u per brief of email weten wat de belangrijkste uitkomsten van het onderzoek zijn.

10. Wat doen we met uw gegevens en lichaamsmateriaal?

Doet u mee met het onderzoek? Dan geeft u ook toestemming om uw gegevens te verzamelen, gebruiken en bewaren. Daarnaast kunt u extra toestemming geven om uw lichaamsmateriaal te verzamelen, gebruiken en bewaren.

Welke gegevens bewaren we?

We bewaren deze gegevens:

- uw naam
- uw geslacht
- uw adres
- uw geboortedatum
- gegevens over uw gezondheid
- (medische) gegevens die we tijdens het onderzoek verzamelen

Welk lichaamsmateriaal bewaren we?

We bewaren buisjes bloed, tumorweefsel en ontlasting.

Waarom verzamelen, gebruiken en bewaren we uw gegevens (en lichaamsmateriaal)?

We verzamelen, gebruiken en bewaren uw gegevens (en als u toestemming geeft, ook uw lichaamsmateriaal) om de vragen van dit onderzoek te kunnen beantwoorden. En om de resultaten te kunnen publiceren.

Hoe beschermen we uw privacy?

Om uw privacy te beschermen geven wij uw gegevens een code. Op al uw gegevens zetten we alleen deze code. De sleutel van de code bewaren we op een beveiligde plek in het UMC Utrecht. Als we uw gegevens verwerken, gebruiken we steeds alleen die code. Ook in rapporten en publicaties over het onderzoek kan niemand terughalen dat het over u ging.

Wie kunnen uw gegevens zien?

Sommige personen kunnen wel uw naam en andere persoonlijke gegevens zonder code inzien. Dit zijn mensen die controleren of de onderzoekers het onderzoek goed en betrouwbaar uitvoeren. Deze personen kunnen bij uw gegevens komen:

- De onderzoekers.
- Een controleur die voor het UMC Utrecht werkt.
- Nationale autoriteiten zoals de Inspectie Gezondheidszorg en Jeugd.

Deze personen houden uw gegevens geheim. Wij vragen u voor deze inzage toestemming te geven.

Hoelang bewaren we uw gegevens?

We bewaren uw gegevens 15 jaar in het UMC Utrecht.

Hoelang bewaren we uw lichaamsmateriaal?

Uw bloed, tumorweefsel en ontlasting versturen we naar het Antoni van Leeuwenhoek. Daar wordt het onderzocht en bewaard. Het lichaamsmateriaal wordt maximaal 30 jaar bewaard om nieuwe bepalingen te kunnen doen die te maken hebben met dit onderzoek. Zodra dit niet meer nodig is, vernietigen we uw lichaamsmateriaal.

Wat gebeurt er bij onverwachte ontdekkingen?
Tijdens het onderzoek kunnen we toevallig iets vinden dat belangrijk is voor uw gezondheid. Uw behandelend arts neemt dan contact op met u. U kunt met uw huisarts of specialist bespreken wat er moet gebeuren. U geeft met het formulier toestemming voor het informeren van uw huisarts of specialist.

Kunt u uw toestemming voor het gebruik van uw gegevens weer intrekken?
U kunt uw toestemming voor het gebruik van uw gegevens op ieder moment intrekken. Maar let op: trekt u uw toestemming in, en hebben onderzoekers dan al gegevens verzameld voor een onderzoek? Dan mogen zij deze gegevens nog wel gebruiken.

Voor uw lichaamsmateriaal geldt dat de onderzoekers dit vernietigen nadat u uw toestemming intrekt. Maar zijn er dan al metingen gedaan met uw lichaamsmateriaal? Dan mag de onderzoeker de resultaten daarvan blijven gebruiken.

Wilt u meer weten over uw privacy?

- Wilt u meer weten over uw rechten bij de verwerking van persoonsgegevens? Kijk dan op www.autoriteitpersoonsgegevens.nl.
- Heeft u vragen over uw rechten? Kijk dan op https://www.umcutrecht.nl/nl/rechten-in-de-zorg
- Als u klachten heeft over de verwerking van uw persoonsgegevens, raden we u aan om deze eerst te bespreken met het onderzoeksteam. U kunt ook naar de Functionaris Gegevensbescherming van het UMC Utrecht gaan. Of u dient een klacht in bij de Autoriteit Persoonsgegevens (bijlage A).

Waar vindt u meer informatie over het onderzoek?
Op de volgende website(s) vindt u meer informatie over het onderzoek: https://trialsearch.who.int/. Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek tonen. U vindt het onderzoek door te zoeken op ID: NL8997.

11. Krijgt u een vergoeding als u meedoet aan het onderzoek?

De extra bestralingsdagen en controlemomenten voor het onderzoek kosten u niets. U krijgt ook geen vergoeding als u meedoet aan dit onderzoek. Wel krijgt u een vergoeding voor uw (extra) reiskosten

12. Bent u verzekerd tijdens het onderzoek?

Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. De verzekering betaalt voor schade door het onderzoek. Maar niet voor alle schade. In bijlage B vindt u meer informatie over de verzekering en de uitzonderingen. Daar staat ook aan wie u schade kunt melden.

13. We informeren uw huisarts en behandelend specialist

De onderzoeker stuurt uw huisarts en behandelend chirurg een bericht om te laten weten dat u meedoet aan het onderzoek. Dit is voor uw eigen veiligheid. Indien u bijwerkingen krijgt van de extra bestralingen, kunnen we contact opnemen met uw huisarts.

14. Heeft u vragen?

Vragen over het onderzoek kunt u stellen aan de onderzoekers. Wilt u advies van iemand die er geen belang bij heeft? Ga dan naar dr. van der Voort-van Zijp (radiotherapeut-oncoloog, UMC Utrecht). Hij weet veel over het onderzoek, maar werkt niet mee aan dit onderzoek.

Heeft u een klacht?

Bespreek dit dan met de onderzoeker of de arts die u behandelt. Wilt u dit liever niet? Ga dan naar de klachtenbemiddelaars van het UMC Utrecht. In bijlage A staat waar u die kunt vinden.

15. Hoe geeft u toestemming voor het onderzoek?

U kunt eerst rustig nadenken over dit onderzoek. Daarna vertelt u de onderzoeker of u de informatie begrijpt. Wilt u meedoen? Dan vult u het toestemmingsformulier in, Bijlage D. U en de onderzoeker krijgen allebei een getekende versie van deze toestemmingsverklaring.

Dank voor uw tijd.

16. Bijlagen bij deze informatie

A. Contactgegevens
B. Informatie over de verzekering
C. Overzicht onderzoekshandelingen en controles
D. Toestemmingsformulieren

Bijlage A: contactgegevens

Contactpersoon:
Drs. Hidde Eijkelenkamp, arts-onderzoeker
Afdeling radiotherapie, UMC Utrecht
Huispostnummer Q.00.311
Antwoordnummer 8419
3508 GA Utrecht
Direct bereikbaar op werkdagen 8:00-16.30u:
T: 088-75559112
E: preradar@umcutrecht.nl

Hoofdonderzoeker UMC Utrecht:
Dr. Martijn P.W. Intven, radiotherapeut-oncoloog
Bereikbaar op werkdagen 8:00-16.30u via afdeling radiotherapie, UMC Utrecht:
T: 088–7558800

Noodgevallen buiten kantooruren :
Dienstdoende radiotherapeut-oncoloog, bereikbaar via afdeling radiotherapie, UMC Utrecht
T : 088-7558800

Onafhankelijk arts:
Dr. Jochem van der Voort-van Zijp, radiotherapeut-oncoloog
Bereikbaar op werkdagen 8:00-16.30u via afdeling radiotherapie, UMC Utrecht:
T: 088–7558800

Heeft u een klacht?
Bespreek dit dan met de onderzoeker of de arts die u behandelt. Wilt u dit liever niet? Ga dan naar de klachtenbemiddelaars van het UMC Utrecht.
T: 088 75 562 08
https://www.umcutrecht.nl/nl/een-klacht-indienen

Functionaris voor de Gegevensbescherming van het UMC Utrecht:
T: 088 75 555 55
E: privacy@umcutrecht.nl
https://www.umcutrecht.nl/nl/privacy

Voor meer informatie over uw rechten:
https://www.umcutrecht.nl/nl/rechten-in-de-zorg
https://autoriteitpersoonsgegevens.nl/

Bijlage B: informatie over de verzekering

Het UMC Utrecht heeft een verzekering afgesloten voor iedereen die meedoet aan het onderzoek. De verzekering betaalt de schade die u heeft doordat u aan het onderzoek meedeed. Het gaat om schade die u krijgt tijdens het onderzoek, of binnen 4 jaar na het onderzoek. U moet schade binnen 4 jaar melden bij de verzekeraar.

Bij schade kunt u direct contact leggen met de verzekeraar.

De verzekeraar van het onderzoek is:	
Naam:	CNA Insurance Company Ltd
Contactpersoon:	mevrouw Esther van Herk
Adres:	Strawinskylaan 703, 1077 XX Amsterdam
Telefoonnummer:	020 5737274
E-mail:	Esther.Vanherk@cnahardy.com
Polisnummer:	10201366

De verzekering biedt een dekking van € 650.000 per proefpersoon en € 5.000.000 voor het hele onderzoek en € 7.500.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever.
Let op: de verzekering dekt de volgende schade **niet**:

- Schade door een risico waarover we u informatie hebben gegeven in deze brief. Maar dit geldt niet als het risico groter bleek te zijn dan we van tevoren dachten. Of als het risico heel onwaarschijnlijk was.
- Schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan.
- Schade die ontstaat doordat u aanwijzingen of instructies niet of niet goed opvolgde.
- Schade aan de gezondheid van uw kinderen of kleinkinderen.
- Schade door een behandelmethode die al bestaat. Of door onderzoek naar een behandelmethode die al bestaat.

Deze bepalingen staan in het 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015'. Dit besluit staat in de Wettenbank van de overheid (https://wetten.overheid.nl).

Bijlage C: overzicht onderzoekshandelingen en controles

WEEK	IN HET ZIEKENHUIS	THUIS
-x	Gesprek over behandeling met bestralingsarts. Na ten minste 3 dagen bedenktijd kunt u het toestemmingsformulier voor dit onderzoek tekenen met de onderzoeker.	
1	5 standaardbestralingen, op de tweede dag :	
2	2-5 extra bestralingen voor het onderzoek	
3		
4		
5		
6		
7		
8		
9		
10		
11	Eerste controle met MRI-scan en kijkonderzoek. (a) Is de tumor nog groot? Dan wordt u ingepland voor een operatie om de endeldarm te verwijderen. (b) Is de tumor klein of weg? Dan zien we u terug bij de tweede controle.	
12		
13		
14		
15		
16	Tweede controle met kijkonderzoek en/of MRI-scan om te zien of de tumor helemaal weg is. U kiest met uw arts tussen (a) een endeldarmoperatie, (b) een kleine ingreep of (c) behandeling zonder operatie.	
17		
18		
19		
20		
½ jaar		
1 jaar		
1½ jaar		
2 jaar		

U beantwoordt 5 vragen over uw darmfunctie in het dagboek (papier of online).

U wordt gebeld door de arts-onderzoeker om te horen hoe het gaat.

U gaat naar het UMC Utrecht voor bloedafname.

U stuurt uw ontlasting op per post naar het Antoni van Leeuwenhoek.

U ondergaat een extra MRI-scan (met contrast).

U ontvangt vragenlijsten over kwaliteit van leven, darm- en blaasfunctie en seksualiteit.

Bloedafname

1. Voor start van de behandeling
2. Na de 2e bestraling
3. Bij de tweede controle (16-20 weken na start bestraling)
4. Bij de controle na 6 maanden
5. Bij de controle na 12 maanden
6. Bij de controle na 18 maanden
7. Bij de controle na 24 maanden

Weefsel

1. Van het kijkonderzoek in de darm
2. Als u geopereerd wordt aan de endeldarm

Ontlasting

1. Voor start van de behandeling
2. Na de 2e bestraling
3. Bij de tweede controle (16-20 weken na start bestraling)

Extra MRI opnames

1. Voor start van de behandeling, dit gebeurt 1x wanneer u toch al in het UMC Utrecht bent en kost ongeveer 30 minuten
2. Met contrastvloeistof in het bloedvat, dit gebeurt 2x en kost 5 minuten extra per keer
    a. Voor start van de behandeling
    b. Tijdens de 2e bestraling

Vragenlijsten over kwaliteit van leven, darm- en blaasfunctie en seksualiteit

1. Voor start van de behandeling
2. Na 3 maanden
3. Na 6 maanden
4. Na 12 maanden
5. Na 18 maanden
6. Na 24 maanden

Bijlage D: toestemmingsformulier proefpersoon

Behorende bij 'Hogere dosis bestraling voor niet-operatieve behandeling van endeldarmkanker: het preRADAR onderzoek'

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn huisarts en specialisten die mij behandelen te laten weten dat ik meedoe aan dit onderzoek.
- Ik geef de onderzoeker toestemming om informatie op te vragen bij mijn huisarts en specialisten die mij behandelen.
- Ik geef de onderzoeker toestemming om mijn huisarts of specialist informatie te geven over onverwachte bevindingen uit het onderzoek die van belang zijn voor mijn gezondheid.
- Ik geef de onderzoekers toestemming om mijn gegevens (en lichaamsmateriaal) te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksvraag van dit onderzoek te beantwoorden.
- Ik geef de onderzoekers toestemming om mij vragenlijsten over kwaliteit van leven, darm- en blaasfunctie en seksualiteit te sturen.
- Ik geef de onderzoekers toestemming om mij een eetdagboek te sturen.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.
- Ik weet dat ik niet zwanger mag worden/mijn partner niet zwanger mag maken tijdens het onderzoek.
- Ik wil meedoen aan dit onderzoek.
- Wilt u ja of nee aankruisen voor de extra onderdelen van dit onderzoek (zie bijlage C)?

Ik geef toestemming voor extra bloedafnames.	□ Ja	□ Nee
Ik geef toestemming voor opslag van tumorweefsel.	□ Ja	□ Nee
Ik geef toestemming voor onderzoek van mijn ontlasting.	□ Ja	□ Nee
Ik geef toestemming voor eenmalig een extra MRI-scan voor start van de behandeling.	□ Ja	□ Nee
Ik geef toestemming voor MRI-opnames met contrastvloeistof.	□ Ja	□ Nee

Op de volgende bladzijde kunt u uw handtekening zetten.

Proefpersoneninformatie preRADAR

UMC Utrecht

Mijn naam is (proefpersoon): ……..

Handtekening: …… **Datum : __ / __ / __**

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek. Wordt er tijdens het onderzoek informatie bekend die die de toestemming van de proefpersoon kan beïnvloeden? Dan laat ik dit op tijd weten aan deze proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger):……

Handtekening:…… **Datum: __ / __ / __**

Bijlage D: toestemmingsformulier proefpersoon

Behorende bij 'Hogere dosis bestraling voor niet-operatieve behandeling van endeldarmkanker: het preRADAR onderzoek'

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn huisarts en specialisten die mij behandelen te laten weten dat ik meedoe aan dit onderzoek.
- Ik geef de onderzoeker toestemming om informatie op te vragen bij mijn huisarts en specialisten die mij behandelen.
- Ik geef de onderzoeker toestemming om mijn huisarts of specialist informatie te geven over onverwachte bevindingen uit het onderzoek die van belang zijn voor mijn gezondheid.
- Ik geef de onderzoekers toestemming om mijn gegevens (en lichaamsmateriaal) te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksvraag van dit onderzoek te beantwoorden.
- Ik geef de onderzoekers toestemming om mij vragenlijsten over kwaliteit van leven, darm- en blaasfunctie en seksualiteit te sturen.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.
- Ik weet dat ik niet zwanger mag worden/mijn partner niet zwanger mag maken tijdens het onderzoek.
- Ik wil meedoen aan dit onderzoek.
- Wilt u ja of nee aankruisen voor de extra onderdelen van dit onderzoek (zie bijlage C)?

Ik geef toestemming voor extra bloedafnames.	□ Ja	□ Nee
Ik geef toestemming voor opslag van tumorweefsel.	□ Ja	□ Nee
Ik geef toestemming voor onderzoek van mijn ontlasting.	□ Ja	□ Nee
Ik geef toestemming voor eenmalig een extra MRI-scan voor start van de behandeling.	□ Ja	□ Nee
Ik geef toestemming voor MRI-opnames met contrastvloeistof.	□ Ja	□ Nee

Op de volgende bladzijde kunt u uw handtekening zetten.

Proefpersoneninformatie preRADAR

Mijn naam is (proefpersoon): ……..

Handtekening: …… **Datum : __ / __ / __**

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek. Wordt er tijdens het onderzoek informatie bekend die die de toestemming van de proefpersoon kan beïnvloeden? Dan laat ik dit op tijd weten aan deze proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger):…….

Handtekening:…… **Datum: __ / __ / __**

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	7
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-3
Roles and	#5b	Name and contact information for the trial sponsor	n/a

responsibilities: sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	9-11
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	11-12
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	11
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	12

		eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-18
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	38
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17-19
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data	18-19, data management

		entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	plan
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20, full protocol
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20, monitoring plan
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial	20, full protocol

		participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13, full protocol
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	data management plan
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	4
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	data management plan
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if	19

applicable

Notes:

- 19: 18-19, data management plan
- 21a: 20, full protocol
- 23: 20, monitoring plan
- 25: 20, full protocol
- 26a: 13, full protocol
- 27: data management plan
- 29: data management plan This checklist was completed on 20. May 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Towards Response ADAptive Radiotherapy for organ preservation for intermediate risk rectal cancer (preRADAR): protocol of a phase I dose-escalation trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-065010.R2
Article Type:	Protocol
Date Submitted by the Author:	22-Apr-2023
Complete List of Authors:	Verweij, Maaike; University Medical Centre Utrecht, Radiation-Oncology; University Medical Centre Utrecht, Surgery Tanaka, Max; Netherlands Cancer Institute, Radiation-Oncology Kensen, Chavelli; Netherlands Cancer Institute, Radiation-Oncology van der Heide, Uulke ; Netherlands Cancer Institute, Radiation-Oncology Marijnen, Corrie A. M.; Netherlands Cancer Institute, Radiation-Oncology Janssen, Tomas; Netherlands Cancer Institute, Radiation-Oncology Vijlbrief, Tineke; Netherlands Cancer Institute, Radiation-Oncology van Grevenstein, Wilhelmina; University Medical Centre Utrecht, Surgery Moons, Leon; University Medical Centre Utrecht, Gastroenterology Koopman , M ; University Medical Centre Utrecht, Medical Oncology Lacle, MM; University Medical Centre Utrecht, Pathology Braat, Manon; University Medical Centre Utrecht, Radiology Chalabi, Myriam; Netherlands Cancer Institute, Medical Oncology Maas, Monique; Netherlands Cancer Institute, Radiology Huibregtse, Inge; Netherlands Cancer Institute, Gastroenterology Snaebjornsson, Petur; Netherlands Cancer Institute, Pathology Grotenhuis, Brechtje; Netherlands Cancer Institute, Surgery Fijneman, Remond; Netherlands Cancer Institute, Pathology Consten, Esther; Meander Medical Centre, Surgery; University Medical Centre Groningen, Surgery Pronk, Apollo; Diakonessenhuis Utrecht Zeist Doorn, Surgery Smits, Anke; Sint Antonius Hospital, Surgery Heikens, Joost; Hospital Rivierenland, Department of Surgery Eijkelenkamp, Hidde; University Medical Centre Utrecht, Radiation-Oncology Elias, Sjoerd; Julius Center for Health Sciences and Primary Care, Epidemiology Verkooijen, Helena; University Medical Centre Utrecht, Radiation-Oncology Schoenmakers, Maartje; University Medical Centre Utrecht, Radiation-Oncology Meijer, Gert ; University Medical Centre Utrecht, Radiation-Oncology Intven, Martijn; University Medical Centre Utrecht, Radiation-Oncology Peters, Femke; Netherlands Cancer Institute, Radiation-Oncology
Primary Subject Heading:	Oncology

Secondary Subject Heading:	Gastroenterology and hepatology, Surgery, Radiology and imaging
Keywords:	RADIOTHERAPY, Colorectal surgery < SURGERY, Gastrointestinal tumours < ONCOLOGY, Magnetic resonance imaging < RADIOTHERAPY, Clinical trials < THERAPEUTICS

Towards Response ADAptive Radiotherapy for organ preservation for intermediate risk rectal cancer (preRADAR): protocol of a phase I dose-escalation trial

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Key words: rectal cancer, radiotherapy, dose-escalation, clinical trial, organ preservation.

Word count: 4011/4000

ABSTRACT (301 words)

Introduction Organ preservation is associated with superior functional outcome and quality of life (QoL) compared to total mesorectal excision (TME) for rectal cancer. Only 10% of patients are eligible for organ preservation following short course radiotherapy (SCRT, 25Gy in 5 fractions) and a prolonged interval (4-8 weeks) to response evaluation. The organ preservation rate could potentially be increased by dose-escalated radiotherapy. Online adaptive magnetic resonance-guided radiotherapy (MRgRT) is anticipated to reduce radiation-induced toxicity and enable radiotherapy dose-escalation. This trial aims to establish the maximum tolerated dose (MTD) of dose-escalated SCRT using online adaptive MRgRT.

Methods and analysis The preRADAR is a multicentre phase I trial with a 6+3 dose-escalation design. Intermediate risk rectal cancer patients (cT3c-d(MRF-)N1M0 or cT1-3(MRF-)N1M0) interested in organ preservation are eligible. Patients are treated with a radiotherapy boost of 2x5Gy (level 0), 3x5Gy (level 1), 4x5Gy (level 2) or 5x5Gy (level 3) on the gross tumour volume in the week following standard SCRT using online adaptive MRgRT. The trial starts on dose level 1. The primary endpoint is the MTD based on the incidence of dose limiting toxicity (DLT) per dose level. DLT is a composite of maximum one in nine severe radiation-induced toxicity and maximum one in three severe postoperative complications, in patients treated with TME or local excision (LE) within 26 weeks following start of treatment. Secondary endpoints include the organ preservation rate, non-dose limiting toxicity, oncological outcomes, patient-reported QoL and functional outcomes up to two years following start of treatment. Imaging and laboratory biomarkers are explored for early response prediction.

Ethics and dissemination The trial protocol has been approved by the medical ethics committee of the UMC Utrecht. The primary and secondary trial results will be published in international peer-reviewed journals.

Registration details NL8997 at the World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int)

ARTICLE SUMMARY

Strengths and limitations of the study (5/5)

- Dose-escalated short course radiotherapy (SCRT) is expected to increase the probability of organ preservation compared to standard-dose SCRT.
- The new technique of online adaptive magnetic resonance guided radiotherapy (MRgRT) is anticipated to reduce radiation-induced toxicity and enable dose-escalated SCRT.
- Dose-escalated SCRT is administered as neoadjuvant monotherapy since it has a favourable toxicity profile compared to chemoradiation (CRT) and SCRT followed by systemic therapy.
- The definition of dose-limiting toxicity (DLT) is based on what patients would 'trade off' for a higher probability of organ preservation.
- Since late toxicity can occur for several years after radiotherapy, it cannot be included as DLT in this dose-finding trial.

INTRODUCTION

Introduction of multimodal treatment consisting of neoadjuvant (chemo)radiotherapy and total mesorectal excision (TME) has improved oncological outcomes for patients with rectal cancer in the previous decades [1,2]. Multimodal treatment unfortunately is associated with long-term impaired quality of life (QoL) and bowel, urinary and sexual dysfunction [3,4]. In recent years, organ preservation has become possible for rectal cancer patients who reach a (near) clinical complete response (cCR) after neoadjuvant (chemo)radiotherapy: patients with minimal or no residual tumour on physical examination, endoscopy and magnetic resonance imaging (MRI) after neoadjuvant treatment can be managed by local excision (LE) and/or active surveillance instead of TME [5]. When performed in appropriately selected patients, organ preservation has similar oncological outcomes as TME [6]. Since the morbidity of TME is averted, including the formation of an ostomy, organ preservation is associated with superior QoL and functional outcome [7,8].

The majority of patients with rectal cancer would rather opt for organ preservation than TME [9,10]. The chance of reaching a cCR and therewith eligibility for organ preservation depends on the neoadjuvant treatment schedule and the timing of response evaluation, among other clinical factors [11–13]. The standard neoadjuvant treatment for intermediate risk rectal cancer according to the Dutch guideline (cT3c-d(MRF-)N0M0 and cT1-3(MRF-)N1M0) is short course radiotherapy (SCRT, 25 Gy in 5 fractions) [14]. After SCRT and a 4-8 weeks interval, the complete response rate is approximately 10% [15]. This rate is low compared to complete response rates of approximately 16% following chemoradiation (CRT, 50 Gy in 25 fractions with a chemosensitizer) for locally advanced rectal cancer (LARC), 28% following SCRT and neoadjuvant systemic therapy for LARC in the RAPIDO trial, 28% following CRT and neoadjuvant systemic therapy in the PRODIGE23 trial and even 60% of organ preservation at 3 years following CRT and neoadjuvant systemic consolidation therapy in the OPRA trial [16–19].

Besides addition of systemic therapy, escalation of the irradiation dose could well be another viable strategy to render more patients eligible for organ preservation after SCRT. The positive relationship between irradiation dose and tumour response is well recognized [20]. Meta-analysis demonstrated that dose-escalated CRT (with a total dose of ≥ 54 Gy) is associated with a relatively high pooled pCR rate of 24% in LARC [21]. Dose-escalated SCRT has been investigated by only four trials (Table 1) [22–25]. An important limiting factor for dose-escalating SCRT is the risk of radiation-induced toxicity.

Recently, online adaptive magnetic resonance guided radiotherapy (MRgRT) on a magnetic resonance linear accelerator (MR-Linac) has been implemented in clinical care [26,27]. In contrast to conventional radiotherapy, MRgRT allows for online visualization of the tumour and surrounding organs at risk (OAR) on MRI during treatment and adaptation of the treatment plan to the current anatomy at each treatment fraction. This technique has unprecedented accuracy and lowers the dose to the healthy tissues [28–30]. As a consequence, online adaptive MRgRT is anticipated to reduce radiation-induced toxicity and enable dose-escalated SCRT.

Adequate patient selection for dose-escalation is important, as some patients will experience radiation-induced toxicity and delay of surgery without the benefit of achieving a cCR. No biomarkers are currently clinically available for prediction of the response to radiotherapy. However, predictive value for the response to radiotherapy has been demonstrated for several biomarkers in blood, tissue, faeces and MRI [31–33]. These biomarkers could potentially aid in response-based adaptation of the treatment plan. The current trial includes exploratory analyses of blood, faecal and tissue samples and (quantitative) MRI, in order to prepare for a response adaptive dose-escalation strategy.

In conclusion, the rationale for the current trial is to offer intermediate risk rectal cancer patients a higher chance of organ preservation using dose-escalated, online adaptive MRgRT on an MR-Linac. We designed a phase I trial to determine the maximum tolerated dose (MTD) of dose-escalated SCRT. The MTD is based on the incidence of dose-limiting toxicity (DLT), i.e. acute radiation-induced toxicity and postoperative complications. The MTD will be the recommended dose for a subsequent phase II trial that will evaluate the efficacy of dose-escalated SCRT on the organ preservation rate. Meanwhile, imaging and laboratory biomarkers are explored for early prediction of the response to radiotherapy. This trial is the first step towards Response ADAptive Radiotherapy for organ preservation for rectal cancer: the preRADAR trial.

METHODS AND ANALYSIS

Study design

The preRADAR trial is a phase I multicentre trial that follows the 6+3 dose-escalation design. The trial is conducted in the University Medical Centre Utrecht and the Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, both in the Netherlands. A minimum of six and a maximum of 45 patients will be recruited. Participant enrolment has started in November 2021 and is expected to finish by February 2024. Follow up for the primary endpoint is expected to finish by August 2024.

Objectives

The primary objective is to establish the MTD of dose-escalated SCRT in intermediate risk rectal cancer patients. Secondary objectives are to determine non-dose limiting acute radiation-induced toxicity, the 30- and 90-day postoperative complication rate, organ preservation rate at 6, 12 and 24 months, oncological outcomes at 24 months, patient-reported QoL and functional outcomes at 3, 6, 12, 18 and 24 months. Exploratory objectives are to seek imaging and laboratory biomarkers that are predictive for the response to radiotherapy at an early stage of treatment.

Study population

Adult patients (≥ 18 years old) presenting to the participating centres with (1) biopsy proven rectal adenocarcinoma, (2) classified as intermediate risk according to the Dutch guideline (cT3c-d(MRF-)N0M0 or cT1-3(MRF-)N1M0 based on the AJCC 8th edition) [14], (3) referred for neoadjuvant SCRT, (4) distal or midrectal tumour location: the upper border of the rectal tumour below the sigmoid take-off and lower border below the peritoneal fold [34], (5) judged fit for multimodal treatment by multidisciplinary tumour board meeting and (6) interest in organ preservation, are eligible.

Exclusion criteria are mucinous carcinoma or neuroendocrine neoplasms, indication for additional SCRT and TME following LE, recurrent tumour or regrowth after previous treatment, extramesorectal pathological lymph nodes, extramural venous invasion (EMVI+), planned systemic therapy, history of inflammatory bowel disease, prior pelvic radiotherapy, concurrent pregnancy, orthopaedic hip implants or absolute contraindication for MRI.

Patient inclusion

Eligible patients are identified during multidisciplinary tumour board meetings. Patients are informed about the preRADAR trial by their treating radiation-oncologist, in both an oral and a written manner (Supplementary File 1). Patients are free to accept or decline the intervention and have at least three days to consider their decision and sign the informed consent form. Trial participation includes consent to undergo the intervention and to participate in acute toxicity monitoring. Consent to collect blood, faeces, tumour tissue, additional MR sequences, MR sequences with intravenous contrast (i.e. dynamic contrast enhanced (DCE) MRI) and filling out QoL questionnaires is optional. Additionally, patients are asked to share their medical data within the Prospective Dutch ColoRectal Cancer cohort (PLCRC) and the Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-Linac study (MOMENTUM) [35,36].

Treatment

The study treatment consists of a radiotherapy boost of 2 x 5 Gy (dose level 0), 3 x 5 Gy (dose level 1), 4 x 5 Gy (dose level 2) or 5 x 5 Gy (dose level 3) on the gross tumour volume (GTV) in the week following standard SCRT (Table 2). SCRT is administered on the conventional elective volumes, consisting of the mesorectum, presacral lymph nodes and internal iliac lymph nodes [37]. Uniform planning target volume (PTV) margins of 4 mm are applied during SCRT, except for 6 mm in the ventral direction. The boost is delivered on the GTV consisting of the tumour and suspicious lymph nodes, if present. Lymph nodes are classified as suspicious if they are (1) ≥ 9 mm, (2) 5-9 mm and have two out of three malignant characteristics (irregular border, heterogeneous texture or round shape), (3) < 5 mm and have all three malignant characteristics (measurements are of the short axis diameter) [14]. During the boost fractions, a uniform PTV margin of 5 mm is applied. The bowel cavity, bowel loops, bladder, left and right femoral head,

the vagina and lumbosacral plexus are considered organs at risk (OAR, constraints in Supplementary File 2). Delineation of the target volumes and OARs of both SCRT and the boost is performed on a 3D T2-weighted MRI and administered with online adaptive MRgRT on a 1.5 Tesla MR-Linac.

The trial starts at dose level 1 (5 x 5 Gy + 3 x 5 Gy boost). When, after the treatment of six patients, no radiation-induced DLT and less than one in three postoperative DLT has occurred, the study progresses to the next dose level (see primary endpoint and Figure 1). When one in six radiation-induced DLT and/or one in three postoperative DLT has occurred, three additional patients are added to the current dose level and adverse events are reassessed accordingly. Whenever more than one radiation-induced DLT or more than one in three postoperative DLT occurs, the trial is stopped and the previous dose level is considered the MTD. While awaiting the occurrence of DLT in six (or nine) patients of the current dose level, newly presenting eligible patients are included to the previous dose level. Dose level 0 has been added to the preRADAR trial so that patient inclusion can continue while awaiting whether dose level 1 is safe. Since dose level 0 (5 x 5 Gy + 2 x 5 Gy boost) has the same biological effective dose as chemoradiation, we consider it safe without testing. If less than one in six patients had radiation-induced DLT and less than three patients have been treated with TME, additional patients are added to the current dose level until at least three patients have been treated with TME.

Patients will not proceed to the boost if treatment-related grade ≥ 3 radiation-induced toxicity or signs of sacral plexopathy are present at the end of SCRT, nor when ≥ 80% GTV coverage for the boost is not achievable due to nearby OARs. When a patient does not proceed to the boost, an additional patient is included to the current dose level.

Acute toxicity monitoring

Patients are consulted before the start of treatment (baseline), at end of SCRT (week 1), after the administration of the boost (week 2), at week 3, week 4, week 5 and every other week thereafter up to surgery or week 20 (Figure 2). Toxicity is registered at each consultation for proctitis, rectal pain, rectal haemorrhage, non-infective cystitis, urinary obstruction, fatigue, radiation dermatitis and other non-prespecified toxicity according to the CTCAE version 5.0 [38]. Simultaneously, patients are asked to fill out a low anterior resection syndrome (LARS) score questionnaire online or in a paper diary to monitor bowel function [39].

Response evaluation

The first response evaluation is performed at 11-13 weeks following the start of treatment, using T2-weighted MRI, diffusion weighted imaging (DWI) and endoscopy. A poor response at the first response evaluation is defined as downsizing of less than 50% of the maximum diameter of the primary tumour, residual tumour of more than 2cm and/or persistent suspicious lymph nodes. Poor responders at the first response evaluation are planned for TME. All other patients proceed to the second response evaluation at 16-20 weeks, using T2-weighted MRI, DWI and/or endoscopy. When patients show a poor response on MRI, they may not proceed to endoscopy to avert this more invasive examination. A near complete response is defined as minimal residual tumour without any signs of residual pathological lymph nodes, amenable for LE (ycT1N0). Near complete responders are offered LE followed by active surveillance, or TME in case of irradical resection or >ypT1. A complete response is defined as no signs of residual tumour. Complete responders enter active surveillance. All other patients (i.e. patients with diseasee progression or

a residual tumour not amenable for LE) are planned for TME. All patients treated with active surveillance are asked to participate in the Dutch Watch & Wait registry.

Follow-up

Patients are followed up according to local practice. In the Netherlands, follow-up after TME commonly exists of clinical consultation and CEA measurement every 3-6 months during the first two years after start of treatment and every 6-12 months for the three years thereafter. Thoraco-abdominal computed tomography (CT) is performed at one year after start of treatment and on indication thereafter. For patients treated with active surveillance, the follow-up scheme consists of endoscopy and MRI every 3 months during the first year, every 6 months during the second year and every 6-12 months during year 3-5 after start of treatment.

Primary endpoint

The primary endpoint is the MTD based on the incidence of DLT per dose level. A maximum of either one in nine severe acute radiation-induced toxicity or one in three severe postoperative complications per dose level is considered safe.

Severe acute radiation-induced toxicity is defined as:

- Treatment-related (Supplementary File 3) grade ≥ 4 radiation-induced toxicity according the Common Toxicity Criteria for Adverse Events (CTCAE version 5.0), occurring within 20 weeks after start of radiotherapy and before surgery [38];

- Treatment-related grade 3 radiation-induced toxicity persisting beyond 12 weeks after start of radiotherapy;
- Postponing of surgery > 20 weeks after start of radiotherapy due to any grade of treatment-related toxicity, in patients with an insufficient response at the first and/or second response evaluation;
- In case of grade 3-4 radiation-induced toxicity that was not prespecified, or grade 3 radiation-induced toxicity newly occurring between 12-20 weeks after start of radiotherapy, the trial management team will judge if this classifies as a DLT on a case-to-case basis.

Severe postoperative complications are defined as Clavien-Dindo grade 3b-4 complications occurring within 30 days postoperative, in patients treated with TME or LE within 26 weeks following the start of treatment [40].

Secondary endpoints

The most important secondary endpoint is the organ preservation rate at 24 months, which is defined as an in situ rectum, no ostomy and no residual or recurrent locoregional disease [41]. We chose this follow up duration because 88% of local regrowths occur within the first 24 months of organ preservation [6]. Other secondary endpoints include:

- feasibility of delivery of the boost based on GTV coverage,
- non-dose limiting acute radiation-induced toxicity as measured by the CTCAE assessments and LARS diaries up to 20 weeks following the start of treatment or, if planned earlier, up to TME [38,39],

- non-dose limiting 30- and 90-day complications according to Clavien-Dindo, length of hospital stay and hospital readmittance in patients treated with TME or LE within 26 weeks following the start of treatment 40,
- clinical complete response (cCR) and clinical near complete response (near cCR) at the first and the second response evaluation,
- tumour regression grade on pathology according to Mandard and type and radicality of surgery in patients treated with TME and LE within 26 weeks following the start of treatment [42],
- type and radicality of salvage surgery in patients with a local regrowth during watch & wait up to 24 months,
- overall survival (OS) and disease-free survival (DFS) at 24 months [43],
- late radiation-induced toxicity grade ≥3 according to CTCAE version 5.0 presenting after 90 days up to 24 months, and,
- patient-reported quality of life and functional outcome as measured by the European Organisation of Research and Treatment of Cancer Quality of life Core and ColoRectal specific Questionnaire (EORTC QLQ-C30 and QLQ-CR29), Low Anterior Resection Syndrome (LARS) score, the International Index of Erectile Function (IIEF), Urinary Distress Inventory (UDI-6), Incontinence Impact Questionnaire (IIQ-7) and McCoy Female Sexuality Questionnaire (MFSQ) at baseline and at 3, 6, 12, 18 and 24 months following the start of treatment [39,44–48].

Translational research

Blood and faeces are collected at baseline, after the second radiotherapy fraction and at the second response evaluation. Blood is additionally collected at 6, 12, 18 and 24 months of follow-up. Blood is analysed for haematology, carcinoembryonic antigen (CEA), kidney function, albumin, c-reactive protein, lactate dehydrogenase and circulating tumour (ct)DNA [31,32]. Faeces is analysed for the microbiome [33]. Tumour tissue is collected at diagnosis and at surgery. An MRI is routinely acquired pre-treatment and additional sequences are acquired during idle time of each radiotherapy fraction. In some centres, an extra MR scan is performed on an MR-Linac pre-treatment and a DCE MRI is performed pre-treatment and after the second radiotherapy fraction. The specific methodology for the translational part of the preRADAR trial is yet to be determined.

Data management and analysis

Clinical data are collected from the medical files and captured in an electronic case report form (eCRF) in Castor EDC. Data management details are reported in a separate data management plan. Technical treatment data are collected within the Multiple Outcome Evaluation of Radiotherapy Using the MR-Linac cohort (MOMENTUM) [36]. PROs are collected within the Prospective Dutch ColoRectal Cancer Cohort (PLCRC) [35]. Human samples for translational research are stored at the Netherlands Cancer Institute.

The incidence of DLT will be calculated per dose level, excluding patients who did not proceed to the boost. Secondary toxicity outcomes are described in the same per-protocol population (i.e. non-dose limiting radiation-induced toxicity and postoperative complications, PROs and late radiation-induced toxicity). Secondary efficacy outcomes are described in the intention-to-treat population (i.e. organ preservation rate, feasibility of the boost, tumour regression grade, salvage

surgery, OS, DFS). Outcomes will be analysed using descriptive statistics, a mixed-effects model (for PROs) or Kaplan-Meier method (for time-to-event data). Data of this phase I trial might be reused for data analysis of the subsequent phase II trial.

Patient and public involvement statement

The Dutch patient federation for colorectal cancer (*Stichting Darmkanker)* was involved during the design phase of this trial. The definition of the primary outcome (DLT), the burden of the intervention and follow-up and the patient information leaflet were discussed with two patients. The patient federation officially declared their support for the current trial. They will remain involved during the evaluation of the results and designing the subsequent phase II trial. Patient information on the trial is displayed on the website www.kanker.nl/trials.

Safety

A trial safety committee has been appointed, consisting of an independent colorectal surgeon and radiation-oncologist per centre. They have the right to temporarily stop the trial if any non-prespecified safety issues are of concern. If a patient dies within 20 weeks following the start of treatment or within thirty days postoperatively (in patients treated with TME or LE in 26 weeks following the start of treatment), the trial will be temporarily stopped to investigate if the event is related to the trial intervention.

Serious adverse events (SAE's) that occur within 20 weeks following the start of treatment or within 30 days postoperatively, in patients treated with TME or LE within 26 weeks following the

start of treatment, will be reported within 7 days of first knowledge through an online form to the medical ethics committee of the UMC Utrecht. SAE's that occur after this period, will be reported in the same manner if the local principal investigator considers the event to be related to the intervention.

Ethics and dissemination

This trial is designed in accordance with 18th version of the World Medical Association Declaration of Helsinki, Good Clinical Practice and the Dutch Law. The trial protocol has been approved by the medical ethics committee of the UMC Utrecht in March 2021. The trial is registered at https://www.trialregister.nl/, trial number NL8997. To ensure adequate data collection and confirmation to the trial protocol, an external monitor of the Netherlands Comprehensive Cancer Organisation will audit the trial twice yearly. The primary and secondary trial results will be published in international peer-reviewed journals. After consent of both participating centres, sharing of pseudonymized data with other researchers within the scope of the current project is possible.

DISCUSSION

The phase I preRADAR trial aims to establish the MTD of dose-escalated SCRT using online adaptive MRgRT in intermediate risk rectal cancer patients, following a 6 + 3 dose-escalation design. Patients are treated with a boost of 2 x 5 Gy, 3 x 5 Gy, 4 x 5 Gy or 5 x 5 Gy in the week following standard SCRT on an MR-Linac. Maximum one in nine severe acute radiation-induced toxicity and one in three severe postoperative complications are accepted for a dose level to be

considered safe. The MTD will be the recommended dose for the subsequent phase II RADAR trial that will evaluate the efficacy of dose-escalated SCRT using online adaptive MRgRT on the organ preservation rate.

Dose-escalated SCRT is administered as neoadjuvant *monotherapy* in the preRADAR trial. SCRT is the standard neoadjuvant treatment for intermediate risk rectal cancer in the Netherlands, since it is associated with similar survival and local recurrence rates as CRT, but significantly lower grade 3-4 acute toxicity rates (risk ratio = 0.13, 95%CI [0.06, 0.28], P < 0.00001) [49]. The favourable toxicity profile of SCRT is also illustrated by two recent trials on organ preservation for early rectal cancer: SCRT in the TREC trial was associated with 15% grade ≥ 3 acute toxicity, while CRT in the CARTS trial came with 42% grade ≥ 3 toxicity [50,51]. The two trials reported comparable organ preservation rates (64% vs. 59%), although it should be acknowledged that the CARTS trial included slightly bigger tumours. The earlier GRECCAR2 and ACOSOG Z6041 trials reported acute radiation-induced toxicity grade ≥ 3 rates of 20% and 39%, respectively, following CRT for organ preservation [52,53]. Based on these numbers, CRT might be considered overtreatment for inducing a cCR in intermediate risk rectal cancer.

Besides radiotherapy dose-escalation, the addition of neoadjuvant systemic therapy to (chemo)radiotherapy has been shown to achieve high complete response rates in the RAPIDO, PRODIGE23 and OPRA trials [17–19]. The study schedules came with 48%, 46% and 34% grade ≥ 3 toxicity, respectively [54]. The RAPIDO and PRODIGE23 trials demonstrated improved DFS compared to CRT only as neoadjuvant strategy for LARC, but no OS benefit (yet). In the Netherlands, rectal cancer is not treated with adjuvant systemic therapy because an OS benefit never has been demonstrated following adequate TME [55]. Since patients with intermediate risk rectal cancer are at substantially lower risk of distant metastases than LARC, the toxicity of neoadjuvant systemic therapy may not outweigh the benefits for this patient group [56]. Dose-

escalated SCRT might become a more *proportional* strategy for improving organ-sparing probability in intermediate risk rectal cancer patients.

The maximum incidence of DLT in the preRADAR trial was defined while thinking of the additional toxicity that patients would 'trade off' for averting TME. We believe that patients would accept mild-moderate complaints (grade 1-2) and transient, severe complaints that limit self-care (grade 3) in the weeks following radiotherapy as a 'trade-off' for a higher probability of organ preservation. However, long-lasting complaints that limit self-care (persisting grade 3) as well as severe complaints that warrant hospital admission and an acute intervention (grade 4) might outweigh the benefits of possibly omitting TME. We therefore defined DLT as acute radiation-induced toxicity grade 4, long-lasting grade 3, or the postponement of surgery > 20 weeks due to any grade of radiation-induced toxicity. Based on the low toxicity rate of dose-escalated SCRT in previous studies (Table 1), a 6 + 3 design was chosen over the classic 3 + 3 dose-escalation design, allowing a lower maximum incidence of radiation-induced DLT of one in nine patients instead of one in six. Furthermore, we deem it unacceptable if the intervention would significantly increase the probability of reoperation or ICU admittance (Clavien-Dindo 3b-4) in patients who are treated with TME despite the study intervention. Based on an incidence of 10-15% complications requiring reoperation following TME, plus a sampling error (that may be bigger if fewer patients are operated upon), a dose level is considered safe when a maximum of one in three operated patients experiences postoperative complication grade 3b-4 [57,58]. This subjective measure for DLT was formulated in collaboration with patients.

A possible limitation might be that late radiation-induced toxicity is not included as a DLT. Radiation-induced toxicity may newly occur for several years after treatment [59]. It is not feasible to include such long-term outcomes as DLT in a dose-finding trial. Studies in prostate and gynaecological cancer have shown acceptable levels of severe late radiation-induced toxicity with

dosages of 80 Gy. The maximum biologically equivalent dose to late responding healthy tissue (EQD2, α/β = 3 Gy) in the preRADAR therefore does not exceed 80 Gy (Table 2) [60–62].

The number of patients in the current phase I trial will not be sufficient to answer the explorative questions. For these purposes, data will be merged with the subsequent phase II trial and possibly other rectal cancer trials of participating institutes.

Contributorship:

MEV: conceptualization, methodology, software (design of eCRF), investigation, data curation, writing- original draft, visualization, project administration. MDT: investigation, recourses, data curation, writing – reviewing & editing, project administration. CMK: software (technique of intervention), writing – reviewing & editing. UAvdH: software (technique of intervention), writing – reviewing & editing. CAMM: methodology, software (technique of intervention), resources, supervision, funding acquisition. TJ: software (technique of intervention), writing – reviewing & editing. TV: software (technique of intervention). WMUvG: methodology, resources, supervision. LMGM: resources. MK: resources, writing – reviewing & editing. MML: resources. MNGJAB: resources, writing – reviewing & editing. MC: resources. MM: resources, writing – reviewing & editing. ILH: resources, writing – reviewing & editing. PS: methodology, resources, writing – reviewing & editing. BAG: methodology, resources, writing – reviewing & editing. RJAF: methodology, resources, writing – reviewing & editing. ECJC: resources. AP: resources. ABS: resources. JTH: resources. HE: investigation, data curation, writing – reviewing & editing, project administration. SGE: methodology, writing – reviewing & editing. HMV: conceptualization, methodology, supervision, funding acquisition. MMC: software (technique of intervention). GJM: software (technique of intervention), writing – reviewing & editing. MPWI: conceptualization, methodology, software (technique of intervention), investigation, resources, writing – reviewing & editing, supervision, funding acquisition. FPP: conceptualization, methodology, software (technique of intervention), investigation, resources, writing – reviewing & editing, supervision, funding acquisition.

Funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing of interests: The department of radiotherapy of both the UMC Utrecht and the Netherlands Cancer Institute have received funding from Elekta AB, Sweden and Philips Healthcare. PS reports consulting fees from MSD and Bayer and fees for MEDtalks educational presentations. RJAF reports grants for Personal Genome Diagnostics, Delfi Diagnostics, Cergentis BV and MERCK BV. HMV is a member of the European Commission and The Netherlands Organization of Health Research and Development and reports grants for the Dutch Cancer Foundation. MPWI has received personal fees from Elekta AB, Sweden.

Ethics approval: The trial protocol has been approved by the medical ethics committee of the UMC Utrecht.

Data statement: After completion of the trial, data will be shared upon reasonable request.

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FIGURES AND TABLES

Table 1: overview of previous studies on dose-escalated short course radiotherapy (SCRT) for rectal cancer.

Study + design	Design	Patients	Treatment	Acute radiation-induced toxicity	Postoperative complications	Tumour response	Comments
Guckenberger, Radonc 2009.[22]	One-arm phase II, 2000-2007	cT2-T4N0-2M0-1 (n=118)	SCRT of total 29 Gy in twice daily fractions of 2.9 Gy followed by immediate TME and adjuvant chemotherapy if pathology UICC stage ≥II	Maximum grade 1	Any complication: 27/118 (23%) Reoperation: n=18/118 (15%) Postoperative mortality: n=4/118 (3%)	ypT1 n=8/118 (7%) ypN0 n=53/118 (45%)	
Bujko, Radonc 2013.[23]	Semi-randomized two-arm phase II, 2003-2010	cT1-3N0M0 and maximum tumour diameter ≤ 4 cm (n=89)	SCRT plus 4 Gy boost (n=64) vs. CRT of 50 Gy in 31 fractions plus 5 Gy boost with 5-FU and leucovorin (n=25) followed by LE. ypT2 or higher proceeded to TME.	Grade 3: n=1/64 (2%) vs. n=2/25 (8%)	Any complication following LE: n=12/64 (19%) vs. n=8/25 (32%)	pCR*: n=23/64 (36%) vs. n=16/25 (64%) ypT0-1: n=43/64 (67%) vs. n=20/25 (80%)	Study was terminated early due to poor accrual. Patients with poor performance status were only eligible for SCRT arm. 17 patients (27%) did not receive the boost in the SCRT arm.
Faria, Col Dis 2014. [24]	One-arm phase II. 2008-2011	cT3-4N0-2 or cT2N0-2 (n=52)	SCRT with integrated boost up to a total of 30 Gy and TME at 8 weeks	Grade 3: n=4/52 (8%)	Reoperation: 1/52 (2%) Postoperative mortality: 1/52 (2%)	pCR: 5/52 (10%)	
Chakrabarti, AoO 2020. [25]	One-arm phase II, 2018-2018.	UICC stage II-II (n=43)	SCRT of 30 Gy in 6 fractions and two cycles of CapOx followed by TME at 7 weeks	Grade 3-4: n=5/43 (12%)		pCR n=8/43 (18%)	

SCRT = short course radiotherapy. Gy = Gray. TME = total mesorectal excision. UICC = Union for International Cancer Control. cTNM: clinical tumor, nodal and metastasis stage. ypTN = pathological tumor and nodal stage following neoadjuvant treatment. CRT = chemoradiation. 5-FU = 5-fluoro-uracil based chemotherapy. LE = local excision. pCR = pathological complete response. * = significant at $p < 0.05$. CapOx = capecitabine and oxaliplatin.

Figure 1: study flow according to dose limiting toxicity (DLT) per dose level in the 6 + 3 design.

Table 2: dose scheme and biologic equivalent doses compared for the current standard of short course radiotherapy and the dose levels of the preRADAR trial.

	Dose scheme	Physical dose (Gy)	Tumour dose (EQD2 α/β = 10, Gy)	Normal tissue dose (EQD2 α/β = 3, Gy)
Current standard	5 x 5 Gy	25.00	31.25	40.00
Dose level 0	5 x 5 Gy + 2 x 5 Gy boost	35.00	43.75	56.00
Dose level 1	5 x 5 Gy + 3 x 5 Gy boost	40.00	50.00	64.00
Dose level 2	5 x 5 Gy + 4 x 5 Gy boost	45.00	56.25	72.00
Dose level 3	5 x 5 Gy + 5 x 5 Gy boost	50.00	62.50	80.00

Figure 2: patient timeline in the preRADAR trial

SCRT: short course radiotherapy. LARS: low anterior resection syndrome score. DCE-MRI: dynamic contrast enhanced magnetic resonance imaging. QoL: quality of life.

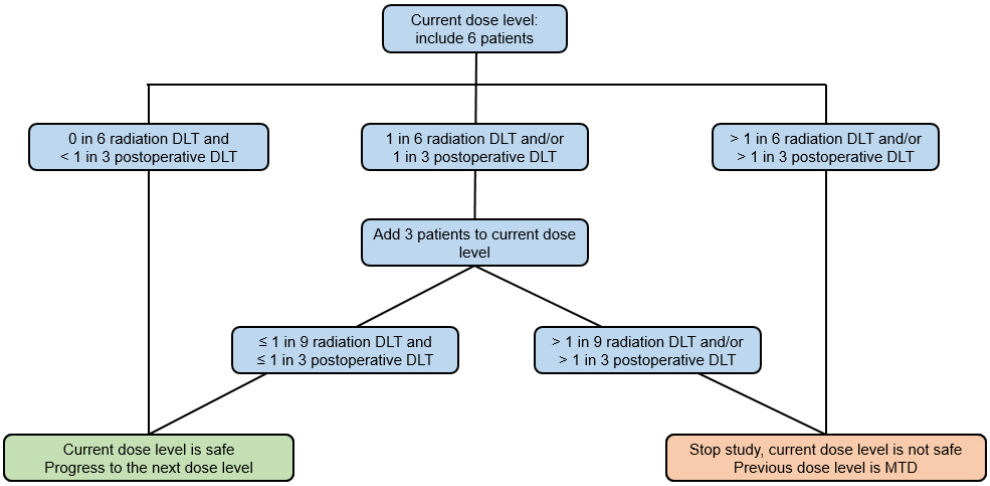

Figure 1: study flow according to dose limiting toxicity (DLT) per dose level in the 6 + 3 design.

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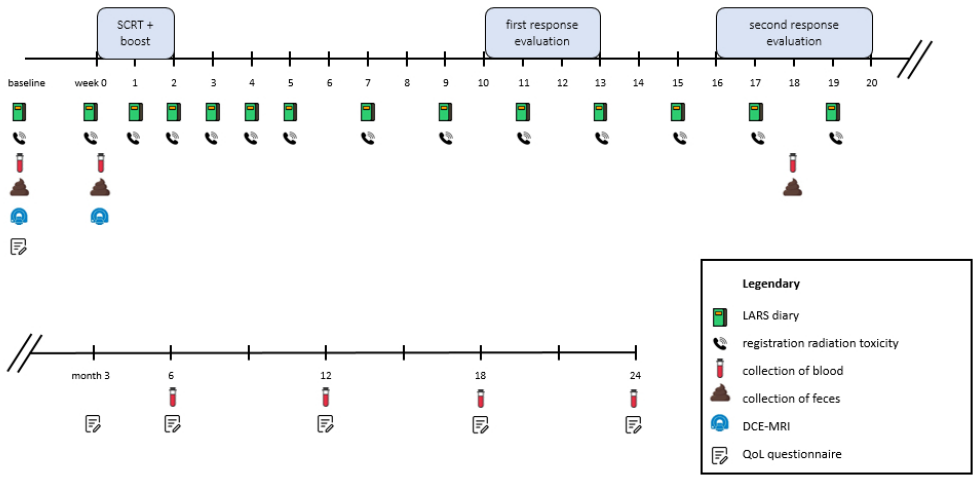


Figure 2: patient timeline in the preRADAR trial

SCRT: short course radiotherapy. LARS: low anterior resection syndrome score. DCE-MRI: dynamic contrast enhanced magnetic resonance imaging. QoL: quality of life.

651x320mm (38 x 38 DPI)

Proefpersoneninformatie voor deelname aan medisch-wetenschappelijk onderzoek

Hogere dosis bestraling voor niet-operatieve behandeling van endeldarmkanker: het preRADAR onderzoek

Officiële titel: Respons ADAptieve Radiotherapie voor orgaansparende behandeling van intermediair risico rectumcarcinoom: een fase I dosisescalatie onderzoek

Inleiding

Geachte heer/mevrouw,

Met deze informatiebrief willen wij u vragen om mee te doen aan medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig. U ontvangt deze brief omdat u binnenkort bestralingen *(radiotherapie)* voor endeldarmkanker ondergaat.

U leest hier om wat voor onderzoek het gaat, wat het voor u betekent, en wat de voordelen en nadelen zijn. Het is veel informatie. Wilt u de informatie doorlezen en beslissen of u wilt meedoen? Als u wilt meedoen, kunt u het formulier invullen dat u vindt in bijlage D.

Stel uw vragen

U kunt uw beslissing nemen met de informatie die u in deze informatiebrief vindt. Daarnaast raden we u aan om dit te doen:

- Stel vragen aan de onderzoeker die u deze informatie geeft.
- Praat met uw partner, familie, vrienden of de huisarts over dit onderzoek.
- Stel vragen aan de onafhankelijk deskundige, dr. Jochem van der Voort-van Zijp, bijlage A.
- Lees de informatie op www.rijksoverheid.nl/mensenonderzoek.

1. Algemene informatie

Het Universitair Medisch Centrum (UMC) Utrecht en het Antoni Van Leeuwenhoek (AVL) hebben dit onderzoek opgezet. Bestralingsartsen (*radiotherapeut-oncologen)* in beide ziekenhuizen voeren dit onderzoek uit. Voor dit onderzoek zijn tussen de 6 en 45 proefpersonen nodig. Het aantal benodigde proefpersonen hangt af van de bevindingen tijdens het onderzoek. De medisch-ethische toetsingscommissie van het UMC Utrecht heeft dit onderzoek goedgekeurd.

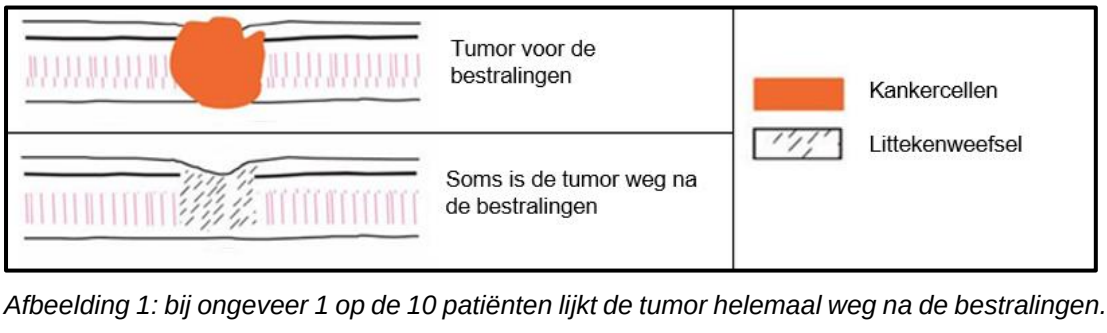
2. Wat is het doel van het onderzoek?

In dit onderzoek kijken we tot welke hoogte de dosis van bestraling bij endeldarmkanker veilig gegeven kan worden. De laagste bestralingsdosis is 2 extra bestralingen. De bestralingsdosis wordt opgehoogd tot maximaal 5 extra bestralingen. Of totdat een bestralingsdosis niet meer veilig lijkt. 'Veilig' betekent in dit onderzoek dat maximaal 1 op de 9 deelnemers ernstige bijwerkingen van de bestraling heeft. Uiteindelijk hopen we dat bestraling met een hogere dosis bij meer patiënten met endeldarmkanker een operatie kan voorkomen.

Daarnaast kijken we in dit onderzoek welke bepalingen in bloed, tumorweefsel of ontlasting en welk type MR-scans voorspellen of de bestralingen goed bij u werken. Zo'n voorspelling kan bijdragen aan op maat gemaakte behandeling voor iedere patiënt.

3. Wat is de achtergrond van het onderzoek?

Voor patiënten met middelhoog risico endeldarmkanker is het al twintig jaar standaardzorg om vijf bestralingen voor de operatie te doen. Bij ongeveer 1 op de 10 patiënten lijkt de tumor weg na de bestralingen *(*zie Afbeelding 1). Sinds een paar jaar weten we dat we deze mensen veilig kunnen behandelen zonder een operatie waarbij de endeldarm wordt verwijderd. Wij denken dat we meer mensen met endeldarmkanker zonder operatie kunnen behandelen door met een hogere dosis te bestralen. We verwachten dat de hoogste bestralingsdosis van dit onderzoek bij ongeveer 4 op de 10 patiënten een behandeling zonder operatie mogelijk kan maken. Omdat we gerichter kunnen bestralen op een nieuw bestralingsapparaat (*de MR-Linac*), denken we dat deze hogere dosis niet zo veel extra bijwerkingen geeft. Dat de hoogte van de bestralingsdosis in verband staat met de kans dat de tumor weg is, is al aangetoond in eerder onderzoek.



Afbeelding 1: bij ongeveer 1 op de 10 patiënten lijkt de tumor helemaal weg na de bestralingen.

Voordat we kunnen uitzoeken of bestralen met een hogere dosis inderdaad vaker leidt tot behandeling zonder operatie, moeten we eerst weten wat een veilige, hogere dosis is van die bestralingen. De hoogste, veilige dosis willen we daarom in dit onderzoek vaststellen.

Ten tweede willen we onderzoeken of we vroeg tijdens de behandeling kunnen voorspellen of de tumor weg zal zijn na de bestralingen. Dan kunnen we in de toekomst de hoogte van de bestralingsdosis per persoon aanpassen. Op dit moment weten we dat een paar eiwitten en

cellen in bloed, tumorweefsel en ontlasting verband houden met de kans dat de tumor weg is na de bestraling. Dit geldt ook voor bepaald type MRI-scans. Maar die kennis is nog onvoldoende om de behandeling hierop aan te passen. Daarom vragen we u of we uw bloed, tumorweefsel en ontlasting mogen gebruiken voor onderzoek. En of we extra MRI-scans mogen maken. U kunt ook meedoen aan dit onderzoek zonder de extra afnames en MRI-scans.

4. Hoe verloopt het onderzoek?

Hoelang duurt het onderzoek?

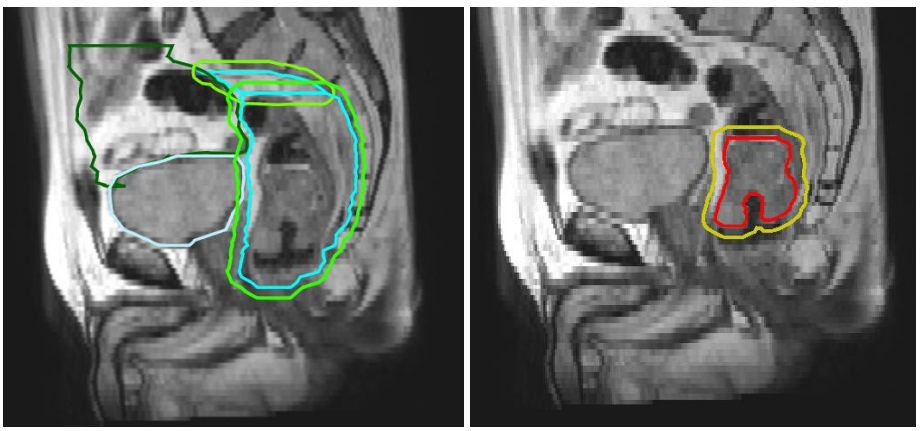
Als u beslist om mee te doen aan dit onderzoek, duurt dat in totaal ongeveer 3 maanden.

Stap 1: bent u geschikt om mee te doen?

Uw behandelend radiotherapeut heeft in overleg met andere medisch specialisten, zoals de chirurg en internist-oncoloog, en de onderzoekers besloten dat u geschikt lijkt om mee te doen.

Stap 2: de behandeling

De behandeling start net zoals de standaardbehandeling met 5 bestralingen op 5 achtereenvolgende werkdagen. De standaardbestralingen zijn gericht op de gehele endeldarm en lymfekliergebieden, inclusief de tumor en de aangedane lymfeklieren (afbeelding 2, links). U komt de 2, 3, 4 of 5 werkdagen daarna extra naar het UMC Utrecht voor de bestralingen van het onderzoek. Deze extra bestralingen worden alleen op de tumor en de aangedane lymfeklieren gegeven (afbeelding 2, rechts). Of u 2, 3, 4 of 5 extra bestralingen krijgt, hoort u van de onderzoeker voor start van de behandeling. Dit aantal hangt af van de bevindingen bij de proefpersonen die eerder dan u hebben deelgenomen aan dit onderzoek.



Afbeelding 2: Twee MRI-opnames van het kleine bekken van een man met endeldarmkanker. Links is de buikzijde en rechts is de rugzijde. Op de linker afbeelding geeft het helderblauwe lijntje de gehele endeldarm aan, die bestraald wordt tijdens de vijf standaard bestralingen. Op de rechter afbeelding geeft het rode lijntje de tumor aan, die extra bestraald wordt op de extra bestralingsdagen.

Stap 3: controles en metingen

In de weken na de behandeling is het niet nodig dat u extra naar het ziekenhuis komt. Wel vinden controles plaats door:

- Telefoongesprekken. De onderzoeker belt u 8—12x in de weken na de bestraling om te horen hoe het gaat. Deze gesprekken duren ongeveer 10 minuten per keer.
- Bijhouden van een dagboek. We vragen u om 8-12x een dagboek in te vullen. Per keer stellen we u 5 vragen over uw darmfunctie. Invullen kan digitaal of op papier en kost u ongeveer 5 minuten per keer.

De telefoongesprekken en het bijhouden van het dagboek stoppen als u geopereerd wordt, of na 20 weken als u zonder operatie behandeld wordt.

Stap 4: wel of niet opereren?

Na 11-13 weken komt u naar UMC Utrecht voor een MRI-scan en een kijkonderzoek van de darm (*endoscopie).* Daarmee kijken we hoe de tumor heeft gereageerd op de bestralingen. Als de tumor nog groot is, wordt u ingepland voor een endeldarmoperatie bij de chirurg in uw eigen ziekenhuis. Als de tumor (bijna) weg is, krijgt u 5-8 weken later nog een keer een MRI-scan en/of kijkonderzoek. Daarna wordt met u gekozen voor de uiteindelijke behandeling: geen operatie, een kleine ingreep onder narcose waarbij de resttumor oppervlakkig uit de endeldarm wordt gesneden (*lokale excisie)* of toch een endeldarmoperatie.

Extra onderdelen van dit onderzoek zijn:

- Afname van uw bloed. Dit doen we zo veel mogelijk wanneer we toch al bloed moeten prikken. Voor het onderzoek nemen we totaal 7 keer bloed af, per keer 20-50 ml. Ter vergelijking: iemand die bloed geeft bij de bloedbank, geeft per keer 500 ml bloed. Met het bloedonderzoek kijken we bijvoorbeeld naar afweercellen (witte bloedcellen) en naar stukjes genetisch materiaal van de tumor (*circulerend tumor DNA)* in het bloed.
- Opslag van tumorweefsel. Dit gaat om tumorweefsel dat toch al wordt afgenomen tijdens het kijkonderzoek in de darm of tijdens de endeldarmoperatie. Met het weefselonderzoek kijken we bijvoorbeeld naar de opbouw van de tumor op celniveau.
- Afname van ontlasting. We vragen u 3 keer een buisje met ontlasting op te sturen, inclusief een korte vragenlijst over de ontlasting. In de ontlasting kijken we bijvoorbeeld naar het type bacteriën.
- Extra MRI-opnames. Deze MRI-opnames vinden zo veel mogelijk plaats wanneer u toch al onder het bestralingsapparaat (*MR-Linac)* ligt voor de bestraling. We vragen of u het goed vindt om deze technische gegevens te delen in het internationale onderzoek naar de MR-Linac (*MOMENTUM).* Daarnaast vragen we uw toestemming voor een extra, losse scan voor start van de bestraling. En voor scans met contrastvloeistof dat in een bloedvat gespoten wordt.
- Invullen van vragenlijsten. We vinden het belangrijk om te weten wat de invloed van de ziekte en behandeling is op uw dagelijks leven en functioneren. Daarom vragen we

u om vragenlijsten in te vullen via het landelijk darmkanker onderzoek *(PLCRC).* De vragenlijsten gaan over kwaliteit van leven, darm- en blaasfunctie en seksualiteit. U krijgt deze vragenlijsten voor start van de behandeling en na 3, 6, 12, 18 en 24 maanden.

Wat is er anders dan bij gewone zorg?

In bijlage C staat een overzicht van de behandelingen en controles van dit onderzoek.

5. Welke afspraken maken we met u?

We willen graag dat het onderzoek goed verloopt. Daarom maken we de volgende afspraken met u:

- U houdt mogelijke bijwerkingen bij;
- U komt de afspraken voor bezoeken na;
- U neemt contact op met de onderzoeker in deze situaties:
    - U wordt in een ziekenhuis opgenomen of behandeld.
    - U krijgt plotseling problemen met uw gezondheid.
    - U wilt niet meer meedoen met het onderzoek.
    - Uw telefoonnummer, adres of e-mailadres verandert.

Mag u of uw partner zwanger worden tijdens het onderzoek?

Vrouwen die zwanger zijn, kunnen niet meedoen aan dit onderzoek. Vrouwen mogen ook niet zwanger worden tijdens het onderzoek. Bent u een man, en heeft u een vrouwelijke partner? Dan moet u ervoor zorgen dat zij niet zwanger kan worden van u. Bestralingen kunnen namelijk schadelijke gevolgen hebben voor een ongeboren kind.

6. Van welke bijwerkingen, nadelige effecten of ongemakken kunt u last krijgen?

Bijwerkingen tijdens en in de weken na de bestraling

Bestralen op de endeldarm geeft bij alle patiënten in meer of mindere mate bijwerkingen. Tijdens de eerste 2-4 weken na de vijf standaardbestralingen zien we de meeste bijwerkingen. Na deze periode herstellen de bijwerkingen geleidelijk. We verwachten dat de hogere dosis bestraling van dit onderzoek kan leiden tot vaker, langer of ernstiger bijwerkingen dan de standaardbestralingen in de eerste weken na de bestraling.

Deze bijwerkingen komen heel vaak voor in de 2-4 weken na bestralingen op de endeldarm (bij 5 op de 10 mensen of meer):

- Vermoeidheid;
- Frequente aandrang voor ontlasting;
- Moeite met ophouden van de ontlasting;
- Bloed- en/of slijmverlies bij de ontlasting.

Deze bijwerkingen komen vaak voor in de 2-4 weken na bestraling op de endeldarm (bij 1 op de 10 mensen of meer):

- Pijn bij de ontlasting;
- Buikkrampen;
- Gebrek aan eetlust en misselijkheid;
- Frequente aandrang voor plassen;
- Branderig gevoel bij het plassen.

Deze bijwerkingen komen soms voor in de 2-4 weken na bestraling op de endeldarm (bij 1 op de 100 mensen of meer):

- Bloedverlies bij de urine;
- Moeite met ophouden van de urine;
- Moeite met uitplassen;
- Beschadigde huid aan de billen.

U moet onmiddellijk contact opnemen met de onderzoeker als u last krijgt van:

- Ernstige diarree (> 7x /dag) tegelijkertijd met onvoldoende vochtinname (< 1,5 L / dag);
- Onhoudbare pijn;
- Beschadigde huid op het zitvlak met tekenen van infectie;
- Veranderd gevoel, pijn of tintelingen rondom het zitvlak of in de benen;
- Moeite met voor u zelf te zorgen door welke klachten dan ook.

Complicaties na de operatie

Het is mogelijk dat een hogere dosis bestraling op de endeldarm een grotere kans geeft op complicaties na de operatie. Dit risico geldt alleen als het bij u toch nodig blijkt om de endeldarm te verwijderen. Mogelijke complicaties na de operatie zijn een lekkage van een nieuwe verbinding tussen darmen *(naadlekkage)*, of een ontsteking van het operatiegebied *(wondinfectie)*. Soms is het nodig dat een complicatie na de operatie behandeld wordt met bijvoorbeeld een nieuwe operatie, het aanleggen van een stoma of met opname op de Intensive Care. Het is niet zeker in welke mate een hogere dosis bestraling kan bijdragen aan complicaties na de operatie. Als we tijdens het onderzoek zien dat ernstige complicaties vaker optreden na een hogere dosis bestraling, zullen we met een lagere dosis gaan bestralen.

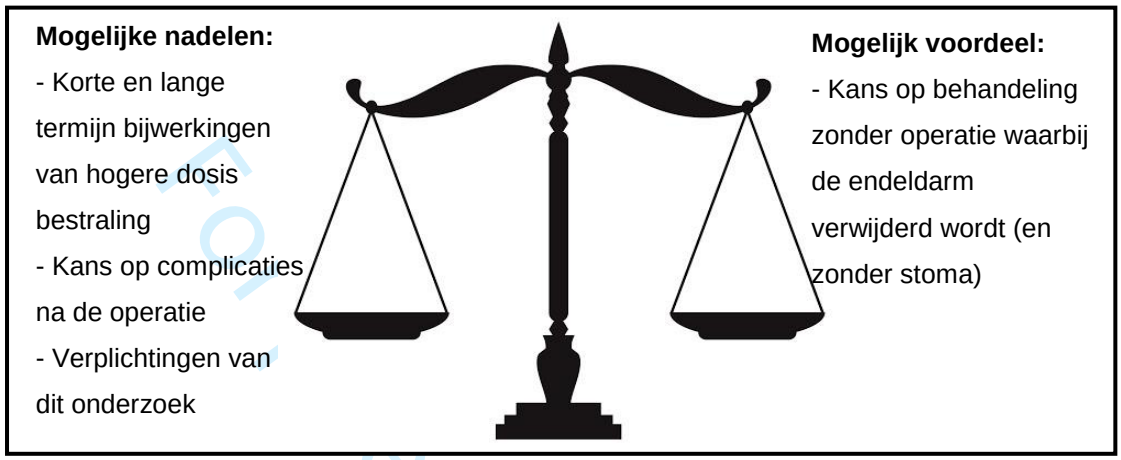
Lange termijn bijwerkingen

In de jaren na bestraling en operatie voor endeldarmkanker krijgt een deel van de patiënten darmklachten, moeite met ophouden van de urine *(urine-incontinentie)* of problemen met seks. Het is mogelijk dat de hogere dosis bestraling van dit onderzoek een grotere kans geeft op deze lange termijn bijwerkingen. Maar wij verwachten dit niet, op basis van eerdere onderzoeken naar bestraling in het bekkengebied met een net zo hoge dosis. Als de hogere

dosis bestraling ervoor zorgt dat een operatie bij u niet nodig is, heeft u juist minder kans op lange termijn bijwerkingen.

7. Mogelijke voor- en nadelen

Meedoen aan het onderzoek kan voordelen en nadelen hebben. Hieronder zetten we ze op een rij. Denk hier goed over na, en praat erover met anderen.



Afbeelding 3: het is belangrijk dat u de mogelijke voor- en nadelen goed afweegt voordat u besluit mee te doen aan dit onderzoek.

Wat zijn de voordelen?

Meedoen aan dit onderzoek kan u een grotere kans bieden om zonder endeldarmoperatie behandeld te worden. Maar zeker is dat niet. Als u zonder operatie behandeld kan worden, heeft u:

- geen pijn en ongemakken door de operatie (zoals een stoma);
- geen kans op complicaties na de operatie;
- minder kans op lange termijn bijwerkingen van de operatie zoals urine-incontinentie, problemen met seks of darmklachten.

Wat zijn de nadelen?

Meedoen aan dit onderzoek kan deze nadelen hebben:

- U kunt last krijgen van bijwerkingen of nadelige effecten van de extra bestralingen, zoals beschreven in hoofdstuk 6. Als u langdurig last houdt van matig-ernstige bijwerkingen in de weken na de bestraling, kan het zijn dat uitstel van de endeldarmoperatie nodig is;
- U bent extra tijd kwijt aan 2-5 extra ziekenhuisbezoeken voor bestraling, telefoongesprekken met de onderzoeker, het invullen van het dagboek over darmklachten en het invullen van vragenlijsten over kwaliteit van leven (zie bijlage C).

- Geeft u toestemming voor afname en opslag van bloed, tumorweefsel en ontlasting en/of extra MRI-opnames? Dan bent u hier mogelijk ook extra tijd aan kwijt. Daarnaast kan een bloedafname of het inspuiten van contrastvloeistof wat pijn doen;
- U moet zich aan de afspraken houden die horen bij dit onderzoek (zie hoofdstuk 5).

Wilt u niet meedoen?

U beslist zelf of u meedoet aan het onderzoek. Wilt u niet meedoen? Dan krijgt u de gewone behandeling voor endeldarmkanker. De gewone behandeling voor middelgrote endeldarmtumoren is vijf bestralingen, in principe gevolgd door een operatie waarbij de endeldarm wordt verwijderd. Uw arts kan u meer vertellen over de behandelingsmogelijkheden die er zijn. En over de voor- en nadelen daarvan.

8. Wanneer stopt het onderzoek?

De onderzoeker laat het u weten als er nieuwe informatie over het onderzoek komt die belangrijk voor u is. De onderzoeker vraagt u daarna of u blijft meedoen.

In deze situaties stopt voor u het onderzoek:

- Alle onderzoeken volgens het schema zijn voorbij (20 weken na start van de bestralingen, of als u eerder geopereerd wordt);
- U wilt zelf stoppen met het onderzoek. Dat mag op ieder moment. Meld dit dan meteen bij de onderzoeker. U hoeft er niet bij te vertellen waarom u stopt. U krijgt dan weer de gewone behandeling voor endeldarmkanker. De onderzoeker kan voor uw veiligheid nog een of meer controles afspreken;
- De onderzoeker vindt het beter voor u om te stoppen;
- Het UMC Utrecht, de overheid of de beoordelende medisch-ethische toetsingscommissie, besluit om het onderzoek te stoppen.

Wat gebeurt er als u stopt met het onderzoek?

De onderzoekers gebruiken de gegevens die tot het moment van stoppen zijn verzameld.

9. Wat gebeurt er na het onderzoek?

Krijgt u de resultaten van het onderzoek?

Ongeveer 1 jaar na deelname van de laatste patiënt laat de onderzoeker u per brief of email weten wat de belangrijkste uitkomsten van het onderzoek zijn.

10. Wat doen we met uw gegevens en lichaamsmateriaal?

Doet u mee met het onderzoek? Dan geeft u ook toestemming om uw gegevens te verzamelen, gebruiken en bewaren. Daarnaast kunt u extra toestemming geven om uw lichaamsmateriaal te verzamelen, gebruiken en bewaren.

Welke gegevens bewaren we?

We bewaren deze gegevens:

- uw naam
- uw geslacht
- uw adres
- uw geboortedatum
- gegevens over uw gezondheid
- (medische) gegevens die we tijdens het onderzoek verzamelen

Welk lichaamsmateriaal bewaren we?

We bewaren buisjes bloed, tumorweefsel en ontlasting.

Waarom verzamelen, gebruiken en bewaren we uw gegevens (en lichaamsmateriaal)?

We verzamelen, gebruiken en bewaren uw gegevens (en als u toestemming geeft, ook uw lichaamsmateriaal) om de vragen van dit onderzoek te kunnen beantwoorden. En om de resultaten te kunnen publiceren.

Hoe beschermen we uw privacy?

Om uw privacy te beschermen geven wij uw gegevens een code. Op al uw gegevens zetten we alleen deze code. De sleutel van de code bewaren we op een beveiligde plek in het UMC Utrecht. Als we uw gegevens verwerken, gebruiken we steeds alleen die code. Ook in rapporten en publicaties over het onderzoek kan niemand terughalen dat het over u ging.

Wie kunnen uw gegevens zien?

Sommige personen kunnen wel uw naam en andere persoonlijke gegevens zonder code inzien. Dit zijn mensen die controleren of de onderzoekers het onderzoek goed en betrouwbaar uitvoeren. Deze personen kunnen bij uw gegevens komen:

- De onderzoekers.
- Een controleur die voor het UMC Utrecht werkt.
- Nationale autoriteiten zoals de Inspectie Gezondheidszorg en Jeugd.

Deze personen houden uw gegevens geheim. Wij vragen u voor deze inzage toestemming te geven.

Hoelang bewaren we uw gegevens?

We bewaren uw gegevens 15 jaar in het UMC Utrecht.

Hoelang bewaren we uw lichaamsmateriaal?

Uw bloed, tumorweefsel en ontlasting versturen we naar het Antoni van Leeuwenhoek. Daar wordt het onderzocht en bewaard. Het lichaamsmateriaal wordt maximaal 30 jaar bewaard om nieuwe bepalingen te kunnen doen die te maken hebben met dit onderzoek. Zodra dit niet meer nodig is, vernietigen we uw lichaamsmateriaal.

Wat gebeurt er bij onverwachte ontdekkingen?
Tijdens het onderzoek kunnen we toevallig iets vinden dat belangrijk is voor uw gezondheid. Uw behandelend arts neemt dan contact op met u. U kunt met uw huisarts of specialist bespreken wat er moet gebeuren. U geeft met het formulier toestemming voor het informeren van uw huisarts of specialist.

Kunt u uw toestemming voor het gebruik van uw gegevens weer intrekken?
U kunt uw toestemming voor het gebruik van uw gegevens op ieder moment intrekken. Maar let op: trekt u uw toestemming in, en hebben onderzoekers dan al gegevens verzameld voor een onderzoek? Dan mogen zij deze gegevens nog wel gebruiken.

Voor uw lichaamsmateriaal geldt dat de onderzoekers dit vernietigen nadat u uw toestemming intrekt. Maar zijn er dan al metingen gedaan met uw lichaamsmateriaal? Dan mag de onderzoeker de resultaten daarvan blijven gebruiken.

Wilt u meer weten over uw privacy?

- Wilt u meer weten over uw rechten bij de verwerking van persoonsgegevens? Kijk dan op www.autoriteitpersoonsgegevens.nl.
- Heeft u vragen over uw rechten? Kijk dan op https://www.umcutrecht.nl/nl/rechten-in-de-zorg
- Als u klachten heeft over de verwerking van uw persoonsgegevens, raden we u aan om deze eerst te bespreken met het onderzoeksteam. U kunt ook naar de Functionaris Gegevensbescherming van het UMC Utrecht gaan. Of u dient een klacht in bij de Autoriteit Persoonsgegevens (bijlage A).

Waar vindt u meer informatie over het onderzoek?
Op de volgende website(s) vindt u meer informatie over het onderzoek: https://trialsearch.who.int/. Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek tonen. U vindt het onderzoek door te zoeken op ID: NL8997.

11. Krijgt u een vergoeding als u meedoet aan het onderzoek?

De extra bestralingsdagen en controlemomenten voor het onderzoek kosten u niets. U krijgt ook geen vergoeding als u meedoet aan dit onderzoek. Wel krijgt u een vergoeding voor uw (extra) reiskosten

12. Bent u verzekerd tijdens het onderzoek?

Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. De verzekering betaalt voor schade door het onderzoek. Maar niet voor alle schade. In bijlage B vindt u meer informatie over de verzekering en de uitzonderingen. Daar staat ook aan wie u schade kunt melden.

13. We informeren uw huisarts en behandelend specialist

De onderzoeker stuurt uw huisarts en behandelend chirurg een bericht om te laten weten dat u meedoet aan het onderzoek. Dit is voor uw eigen veiligheid. Indien u bijwerkingen krijgt van de extra bestralingen, kunnen we contact opnemen met uw huisarts.

14. Heeft u vragen?

Vragen over het onderzoek kunt u stellen aan de onderzoekers. Wilt u advies van iemand die er geen belang bij heeft? Ga dan naar dr. van der Voort-van Zijp (radiotherapeut-oncoloog, UMC Utrecht). Hij weet veel over het onderzoek, maar werkt niet mee aan dit onderzoek.

Heeft u een klacht?

Bespreek dit dan met de onderzoeker of de arts die u behandelt. Wilt u dit liever niet? Ga dan naar de klachtenbemiddelaars van het UMC Utrecht. In bijlage A staat waar u die kunt vinden.

15. Hoe geeft u toestemming voor het onderzoek?

U kunt eerst rustig nadenken over dit onderzoek. Daarna vertelt u de onderzoeker of u de informatie begrijpt. Wilt u meedoen? Dan vult u het toestemmingsformulier in, Bijlage D. U en de onderzoeker krijgen allebei een getekende versie van deze toestemmingsverklaring.

Dank voor uw tijd.

16. Bijlagen bij deze informatie

A. Contactgegevens
B. Informatie over de verzekering
C. Overzicht onderzoekshandelingen en controles
D. Toestemmingsformulieren

Bijlage A: contactgegevens

Contactpersoon:
Drs. Hidde Eijkelenkamp, arts-onderzoeker
Afdeling radiotherapie, UMC Utrecht
Huispostnummer Q.00.311
Antwoordnummer 8419
3508 GA Utrecht
Direct bereikbaar op werkdagen 8:00-16.30u:
T: 088-75559112
E: preradar@umcutrecht.nl

Hoofdonderzoeker UMC Utrecht:
Dr. Martijn P.W. Intven, radiotherapeut-oncoloog
Bereikbaar op werkdagen 8:00-16.30u via afdeling radiotherapie, UMC Utrecht:
T: 088–7558800

Noodgevallen buiten kantooruren :
Dienstdoende radiotherapeut-oncoloog, bereikbaar via afdeling radiotherapie, UMC Utrecht
T : 088-7558800

Onafhankelijk arts:
Dr. Jochem van der Voort-van Zijp, radiotherapeut-oncoloog
Bereikbaar op werkdagen 8:00-16.30u via afdeling radiotherapie, UMC Utrecht:
T: 088–7558800

Heeft u een klacht?
Bespreek dit dan met de onderzoeker of de arts die u behandelt. Wilt u dit liever niet? Ga dan naar de klachtenbemiddelaars van het UMC Utrecht.
T: 088 75 562 08
https://www.umcutrecht.nl/nl/een-klacht-indienen

Functionaris voor de Gegevensbescherming van het UMC Utrecht:
T: 088 75 555 55
E: privacy@umcutrecht.nl
https://www.umcutrecht.nl/nl/privacy

Voor meer informatie over uw rechten:
https://www.umcutrecht.nl/nl/rechten-in-de-zorg
https://autoriteitpersoonsgegevens.nl/

Bijlage B: informatie over de verzekering

Het UMC Utrecht heeft een verzekering afgesloten voor iedereen die meedoet aan het onderzoek. De verzekering betaalt de schade die u heeft doordat u aan het onderzoek meedeed. Het gaat om schade die u krijgt tijdens het onderzoek, of binnen 4 jaar na het onderzoek. U moet schade binnen 4 jaar melden bij de verzekeraar.

Bij schade kunt u direct contact leggen met de verzekeraar.

De verzekeraar van het onderzoek is:

Naam:	CNA Insurance Company Ltd
Contactpersoon:	mevrouw Esther van Herk
Adres:	Strawinskylaan 703, 1077 XX Amsterdam
Telefoonnummer:	020 5737274
E-mail:	Esther.Vanherk@cnahardy.com
Polisnummer:	10201366

De verzekering biedt een dekking van € 650.000 per proefpersoon en € 5.000.000 voor het hele onderzoek en € 7.500.000 per jaar voor alle onderzoeken van dezelfde opdrachtgever.
Let op: de verzekering dekt de volgende schade **niet**:

- Schade door een risico waarover we u informatie hebben gegeven in deze brief. Maar dit geldt niet als het risico groter bleek te zijn dan we van tevoren dachten. Of als het risico heel onwaarschijnlijk was.
- Schade aan uw gezondheid die ook zou zijn ontstaan als u niet aan het onderzoek had meegedaan.
- Schade die ontstaat doordat u aanwijzingen of instructies niet of niet goed opvolgde.
- Schade aan de gezondheid van uw kinderen of kleinkinderen.
- Schade door een behandelmethode die al bestaat. Of door onderzoek naar een behandelmethode die al bestaat.

Deze bepalingen staan in het 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015'. Dit besluit staat in de Wettenbank van de overheid (https://wetten.overheid.nl).

Bijlage C: overzicht onderzoekshandelingen en controles

WEEK	IN HET ZIEKENHUIS	THUIS
-x	Gesprek over behandeling met bestralingsarts. Na ten minste 3 dagen bedenktijd kunt u het toestemmingsformulier voor dit onderzoek tekenen met de onderzoeker. + +	
1	5 standaardbestralingen, op de tweede dag : + +	
2	2-5 extra bestralingen voor het onderzoek	
3		
4		
5		
6		
7		
8		
9		
10		
11	Eerste controle met MRI-scan en kijkonderzoek. (a) Is de tumor nog groot? Dan wordt u ingepland voor een operatie om de endeldarm te verwijderen. (b) Is de tumor klein of weg? Dan zien we u terug bij de tweede controle.	
12		
13		
14		
15		
16	Tweede controle met kijkonderzoek en/of MRI-scan om te zien of de tumor helemaal weg is. U kiest met uw arts tussen (a) een endeldarmoperatie, (b) een kleine ingreep of (c) behandeling zonder operatie. +	
17		
18		
19		
20		
½ jaar		
1 jaar		
1½ jaar		
2 jaar		

U beantwoordt 5 vragen over uw darmfunctie in het dagboek (papier of online).

U wordt gebeld door de arts-onderzoeker om te horen hoe het gaat.

U gaat naar het UMC Utrecht voor bloedafname.

U stuurt uw ontlasting op per post naar het Antoni van Leeuwenhoek.

U ondergaat een extra MRI-scan (met contrast).

U ontvangt vragenlijsten over kwaliteit van leven, darm- en blaasfunctie en seksualiteit.

Bloedafname

1. Voor start van de behandeling
2. Na de 2e bestraling
3. Bij de tweede controle (16-20 weken na start bestraling)
4. Bij de controle na 6 maanden
5. Bij de controle na 12 maanden
6. Bij de controle na 18 maanden
7. Bij de controle na 24 maanden

Weefsel

1. Van het kijkonderzoek in de darm
2. Als u geopereerd wordt aan de endeldarm

Ontlasting

1. Voor start van de behandeling
2. Na de 2e bestraling
3. Bij de tweede controle (16-20 weken na start bestraling)

Extra MRI opnames

1. Voor start van de behandeling, dit gebeurt 1x wanneer u toch al in het UMC Utrecht bent en kost ongeveer 30 minuten
2. Met contrastvloeistof in het bloedvat, dit gebeurt 2x en kost 5 minuten extra per keer
    a. Voor start van de behandeling
    b. Tijdens de 2e bestraling

Vragenlijsten over kwaliteit van leven, darm- en blaasfunctie en seksualiteit

1. Voor start van de behandeling
2. Na 3 maanden
3. Na 6 maanden
4. Na 12 maanden
5. Na 18 maanden
6. Na 24 maanden

Bijlage D: toestemmingsformulier proefpersoon

Behorende bij 'Hogere dosis bestraling voor niet-operatieve behandeling van endeldarmkanker: het preRADAR onderzoek'

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn huisarts en specialisten die mij behandelen te laten weten dat ik meedoe aan dit onderzoek.
- Ik geef de onderzoeker toestemming om informatie op te vragen bij mijn huisarts en specialisten die mij behandelen.
- Ik geef de onderzoeker toestemming om mijn huisarts of specialist informatie te geven over onverwachte bevindingen uit het onderzoek die van belang zijn voor mijn gezondheid.
- Ik geef de onderzoekers toestemming om mijn gegevens (en lichaamsmateriaal) te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksvraag van dit onderzoek te beantwoorden.
- Ik geef de onderzoekers toestemming om mij vragenlijsten over kwaliteit van leven, darm- en blaasfunctie en seksualiteit te sturen.
- Ik geef de onderzoekers toestemming om mij een eetdagboek te sturen.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.
- Ik weet dat ik niet zwanger mag worden/mijn partner niet zwanger mag maken tijdens het onderzoek.
- Ik wil meedoen aan dit onderzoek.
- Wilt u ja of nee aankruisen voor de extra onderdelen van dit onderzoek (zie bijlage C)?

Ik geef toestemming voor extra bloedafnames.	□ Ja	□ Nee
Ik geef toestemming voor opslag van tumorweefsel.	□ Ja	□ Nee
Ik geef toestemming voor onderzoek van mijn ontlasting.	□ Ja	□ Nee
Ik geef toestemming voor eenmalig een extra MRI-scan voor start van de behandeling.	□ Ja	□ Nee
Ik geef toestemming voor MRI-opnames met contrastvloeistof.	□ Ja	□ Nee

Op de volgende bladzijde kunt u uw handtekening zetten.

Mijn naam is (proefpersoon): ……..

Handtekening: …… **Datum : __ / __ / __**

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek. Wordt er tijdens het onderzoek informatie bekend die die de toestemming van de proefpersoon kan beïnvloeden? Dan laat ik dit op tijd weten aan deze proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger):……

Handtekening:…… **Datum: __ / __ / __**

Bijlage D: toestemmingsformulier proefpersoon

Behorende bij 'Hogere dosis bestraling voor niet-operatieve behandeling van endeldarmkanker: het preRADAR onderzoek'

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn huisarts en specialisten die mij behandelen te laten weten dat ik meedoe aan dit onderzoek.
- Ik geef de onderzoeker toestemming om informatie op te vragen bij mijn huisarts en specialisten die mij behandelen.
- Ik geef de onderzoeker toestemming om mijn huisarts of specialist informatie te geven over onverwachte bevindingen uit het onderzoek die van belang zijn voor mijn gezondheid.
- Ik geef de onderzoekers toestemming om mijn gegevens (en lichaamsmateriaal) te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksvraag van dit onderzoek te beantwoorden.
- Ik geef de onderzoekers toestemming om mij vragenlijsten over kwaliteit van leven, darm- en blaasfunctie en seksualiteit te sturen.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.
- Ik weet dat ik niet zwanger mag worden/mijn partner niet zwanger mag maken tijdens het onderzoek.
- Ik wil meedoen aan dit onderzoek.
- Wilt u ja of nee aankruisen voor de extra onderdelen van dit onderzoek (zie bijlage C)?

Ik geef toestemming voor extra bloedafnames.	□ Ja	□ Nee
Ik geef toestemming voor opslag van tumorweefsel.	□ Ja	□ Nee
Ik geef toestemming voor onderzoek van mijn ontlasting.	□ Ja	□ Nee
Ik geef toestemming voor eenmalig een extra MRI-scan voor start van de behandeling.	□ Ja	□ Nee
Ik geef toestemming voor MRI-opnames met contrastvloeistof.	□ Ja	□ Nee

Op de volgende bladzijde kunt u uw handtekening zetten.

Mijn naam is (proefpersoon): ……..

Handtekening: …… **Datum : __ / __ / __**

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek. Wordt er tijdens het onderzoek informatie bekend die die de toestemming van de proefpersoon kan beïnvloeden? Dan laat ik dit op tijd weten aan deze proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger):…….

Handtekening:…… **Datum: __ / __ / __**

Supplementary File 2: equivalent dose limits for organs at risk

Structure	Volume (cc)	EQD2 α/β = 3 (Gy)	Comments
Small Bowel (loops) [1,2,3]	0.5	70	Constraint
	10	40	Aim
Large Bowel (loops)	0.5	60.16	Constraint, excluding the sigmoid lying in the course of the bowel within 2 cm of GTV
Bladder [1,4]	0.5	80.56	Constraint
Plexus Sacral [1,4]	0.1	60.16	Constraint
	5	54	Constraint

For the vagina no formal constraints exists, though we will try to limit the dose to this organ. Patients will receive instructions for the use of dilators after radiotherapy.

[1] UK SABR consortium 2019. Stereotactic Ablative Body Radiation Therapy (SABR): A Resource version 6.1

[2] ABC-07 Addition of stereotactic body radiotherapy to systemic chemotherapy in locally advanced biliary tract. Cancer Research UK. [Accessed: 06.01.16]; Available from: http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-chemotherapy-stereotactic-radiotherapy-people-locally-advanced-bile-duct-cancer-abc-07 -undefined.

[3] A trial looking at stereotactic body radiotherapy before surgery for pancreatic cancer (SPARC). Cancer Research UK. [Accessed: 14.12.16]; Available from: http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-stereotactic-body-radiotherapy-before-surgery-for-pancreatic-cancer-sparc -undefined.

[4] Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys. 2010;37(8):4078-101

Supplementary File 3: possible treatment-related toxicity, adapted from the CTCAE v5.0 and the STAR-TREC trial

Category	Toxicity
Gastrointestinal disorders	Abdominal pain
	Anal/rectal fistula
	Anal/rectal hemorrhage
	Anal mucositis
	Anal/rectal necrosis
	Anal/rectal pain
	Anal/rectal stenosis
	Anal/rectal ulcer
	Colonic/small intestinal fistula
	Lower gastrointestinal hemorrhage
	Colonic/small intestinal obstruction
	Colonic/small intestinal perforation
	Colonic/small intestinal stenosis
	Colonic/small intestinal ulcer
	Constipation
	Diarrhea
	Enterocolitis
	Enterovesical fistula
	Fecal incontinence
	Hemorrhoids
	Hemorrhoidal hemorrhage
	Ileus
	Intra-abdominal hemorrhage

	Proctitis
	Rectal obstruction
	Rectal perforation
Renal and urinary disorders	Bladder perforation
	Bladder spasm
	Cystitis noninfective
	Hematuria
	Urinary fistula
	Urinary incontinence
	Urinary retention
	Urinary tract obstruction
	Urinary tract pain
Injury, poisoning and procedural complications	Dermatitis radiation (if in radiation field)
Reproductive system and breast disorders	Prostatic pain
	Uterine fistula
	Uterine hemorrhage
	Vaginal fistula
	Vaginal hemorrhage
	Vaginal perforation
	Vaginal stricture
General disorders	Fatigue
	Malaise
	Pain
Infections and infestations	Abdominal infection
	Anorectal infection
	Bladder infection
	Enterocolitis infectious

	Prostate infection
	Vaginal infection
	Uterine infection
	Wound infection (if in radiation field)
Musculoskeletal and connective tissue disorders	Abdominal soft tissue necrosis
	Pelvic soft tissue necrosis
	Osteonecrosis
Nervous system disorders	Neuralgia
	Peripheral motor/sensory neuropathy

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	7
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-3
Roles and	#5b	Name and contact information for the trial sponsor	n/a

responsibilities: sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	9-11
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	11-12
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	11
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	12

		eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-18
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	38
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17-19
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data	18-19, data management

		entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	plan
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20, full protocol
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20, monitoring plan
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial	20, full protocol

		participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13, full protocol
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	data management plan
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	4
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	data management plan
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if	19

applicable

Notes:

- 19: 18-19, data management plan
- 21a: 20, full protocol
- 23: 20, monitoring plan
- 25: 20, full protocol
- 26a: 13, full protocol
- 27: data management plan
- 29: data management plan This checklist was completed on 20. May 2022 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai