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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ABSTRACT

Introduction Organ preservation is associated with superior functional outcome and quality of life (QoL) compared with total mesorectal excision (TME) for rectal cancer. Only 10% of patients are eligible for organ preservation following short-course radiotherapy (SCRT, 25 Gy in five 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. Patients with intermediate-risk rectal cancer (cT3c-d(MRF-)N1M0 or cT1-3(MRF-)N1M0) interested in organ preservation are eligible. Patients are treated with a radiotherapy boost of 2×5 Gy (level 0), 3×5 Gy (level 1), 4×5 Gy (level 2) or 5×5 Gy (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 toxicities and maximum one in three severe postoperative complications, in patients treated with TME or local excision within 26 weeks following start of treatment. Secondary endpoints include the organ preservation rate, non-DLT, oncological outcomes, patient-reported QoL and functional outcomes up to 2 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 University Medical Centre Utrecht. The primary and secondary trial results will be published in international peer-reviewed journals.

Trial registration number WHO International Clinical Trials Registry (NL8997; https://trialsearch.who.int).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Dose-escalated short-course radiotherapy (SCRT) is expected to increase the probability of organ preservation compared with standard-dose SCRT.
⇒ The new technique of online adaptive magnetic resonance-guided radiotherapy 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 with chemoradiation 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 patients with rectal cancer who reach a (near) clinical complete response (cCR) after neoadjuvant (chemo)radiotherapy: patients with minimal or no residual tumour on physical examination, endoscopy and 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 five fractions).[14] After SCRT and an interval of 4–8 weeks, the complete response rate is approximately 10%.[15] This rate is low compared with complete response rates of approximately 16% following chemoradiation (CRT, 50 Gy in 25 fractions with a chemosensitiser) 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 recognised.[20] Meta-analysis demonstrated that dose-escalated CRT (with a total dose of ≥54 Gy) is associated with a relatively high pooled pathological complete response 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 visualisation of the tumour and surrounding organs at risk (OARs) 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.

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

Study	Design	Patients	Treatment	Acute radiation-induced toxicity	Postoperative complications	Tumour response	Comments
Guckenberger *et al*[22]	One-arm phase II, 2000–2007	cT2-T4N0-2M0-1 (n=118)	SCRT of total 29 Gy in two times a day 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 *et al*[23]	Semirandomised 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 *et al*[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 *et al*[25]	One-arm phase II, 2018–2019	UICC stage II–III (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%)	

*Significant at p<0.05.
CapOx, capecitabine and oxaliplatin; CRT, chemoradiation; cTNM, clinical tumour, nodal and metastasis stage; 5-FU, 5-fluorouracil-based chemotherapy; LE, local excision; pCR, pathological complete response; TME, total mesorectal excision; UICC, Union for International Cancer Control; ypTN, pathological tumour and nodal stage following neoadjuvant treatment.

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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 patients with intermediate-risk rectal cancer 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), that is, 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 (UMC) Utrecht and the Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, both in the Netherlands. A minimum of 6 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 patients with intermediate-risk rectal cancer. Secondary objectives are to determine non-dose-limiting acute radiation-induced toxicity, the 30-day 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 objective is 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 American Joint Committee on Cancer eighth 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, 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 (online supplemental file 1). Patients are free to accept or decline the intervention and have at least 3 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 MRI sequences, MRI sequences with intravenous contrast (ie, dynamic contrast-enhanced (DCE)-MRI) and filling out QoL questionnaires are 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 (MOMENTUM) Study.[35 36]

Treatment

The study treatment consists of a radiotherapy boost of 2×5 Gy (dose level 0), 3×5 Gy (dose level 1), 4×5 Gy (dose level 2) or 5×5 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

Table 2 Dose scheme and biological 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	5×5 Gy	25.00	31.25	40.00
Dose level 0	5×5 Gy+2×5 Gy boost	35.00	43.75	56.00
Dose level 1	5×5 Gy+3×5 Gy boost	40.00	50.00	64.00
Dose level 2	5×5 Gy+4×5 Gy boost	45.00	56.25	72.00
Dose level 3	5×5 Gy+5×5 Gy boost	50.00	62.50	80.00

plexus are considered OARs (constraints in online supplemental file 2). Delineation of the target volumes and OARs of both SCRT and the boost is performed on a three-dimensional T2-weighted MRI and administered with online adaptive MRgRT on a 1.5 Tesla MR-Linac.

The trial starts at dose level 1 (5×5 Gy+3×5 Gy boost). When, after the treatment of six patients, no radiation-induced DLT and less than one in three postoperative DLTs have occurred, the study progresses to the next dose level (see the Primary endpoint section and figure 1). When one in six radiation-induced DLTs and/or one in three postoperative DLTs 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 DLTs 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 (5×5 Gy+2×5 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

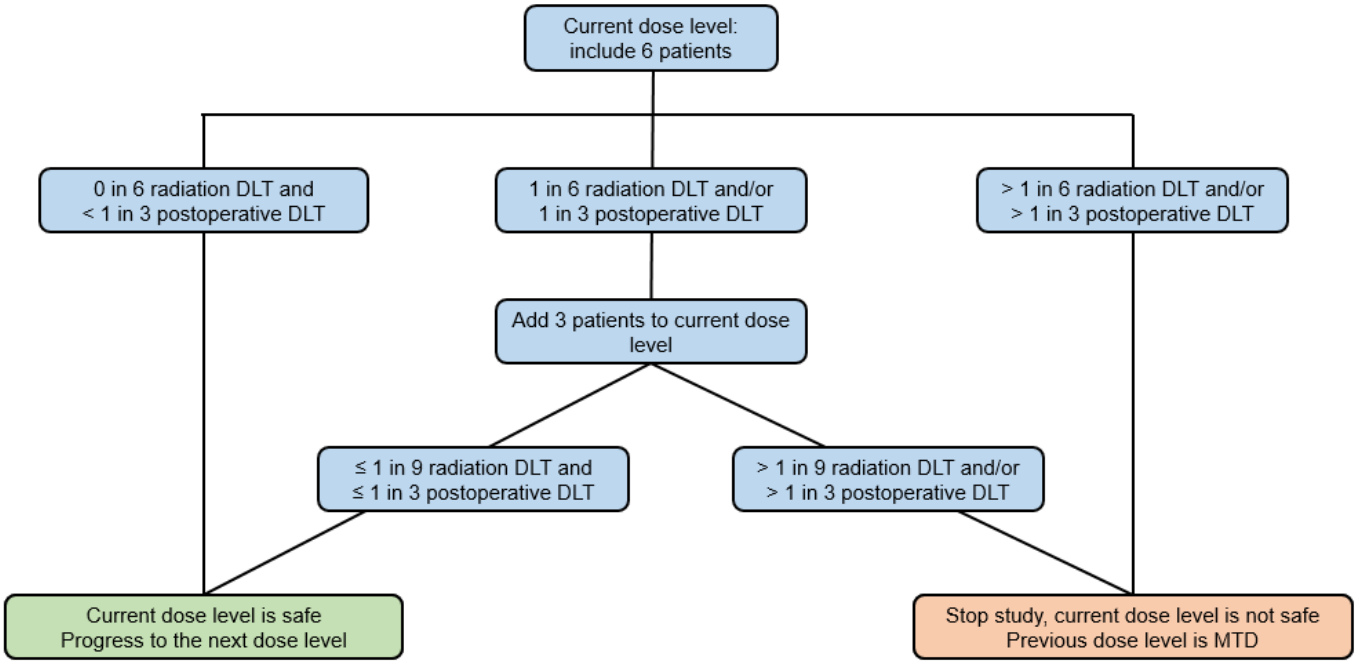

Figure 1 Study flow according to dose-limiting toxicity (DLT) per dose level in the 6+3 design. MTD, maximum tolerated dose.

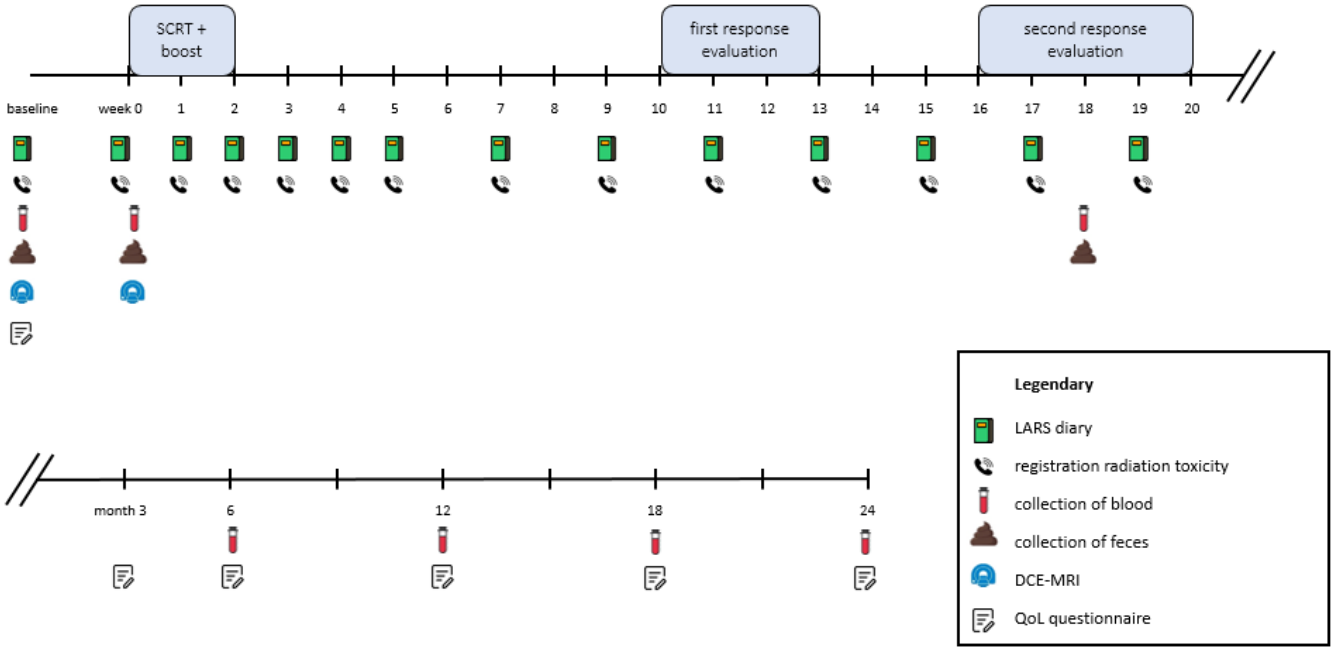

Figure 2 Patient timeline in the preRADAR trial. DCE-MRI, dynamic contrast-enhanced MRI; LARS, low anterior resection syndrome; QoL, quality of life; SCRT, short-course radiotherapy.

(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 toxicities according to the Common Toxicity Criteria for Adverse Events (CTCAE) V.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 2 cm 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 (ie, patients with disease 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 consists of clinical consultation and carcinoembryonic antigen (CEA) measurement every 3–6 months during the first 2 years after start of treatment and every 6–12 months for the 3 years thereafter. Thoracoabdominal CT is performed at 1 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 toxicities or one in three severe postoperative complications per dose level is considered safe.

Severe acute radiation-induced toxicity is defined as:

- Treatment-related (online supplemental file 3) grade ≥4 radiation-induced toxicity according to the CTCAE V.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 and 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 postoperatively, 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-day 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]
- cCR and clinical near-complete response 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 V.5.0 presenting after 90 days up to 24 months.
- Patient-reported QoL and functional outcome as measured by the European Organisation of Research and Treatment of Cancer Quality of life Core and ColoRectal specific Questionnaire, LARS score, the International Index of Erectile Function, Urinary Distress Inventory, Incontinence Impact Questionnaire and McCoy Female Sexuality Questionnaire 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, CEA, kidney function, albumin, C reactive protein, lactate dehydrogenase and circulating tumour DNA.[31 32] Faeces is analysed for the microbiome.[33] Tumour tissue is collected at diagnosis and at surgery. An MRI is routinely acquired pretreatment and additional sequences are acquired during idle time of each radiotherapy fraction. In some centres, an extra MRI scan is performed on an MR-Linac pretreatment and a DCE-MRI is performed pretreatment 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 in Castor EDC. Data management details are reported in a separate data management plan. Technical treatment data are collected within the MOMENTUM cohort.[36] Patient-reported outcomes (PROs) are collected within the 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 (ie, 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 (ie, 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 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 30 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 (SAEs) 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. SAEs 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 the 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 two times per year. The primary and secondary trial results will be published in international peer-reviewed journals. After consent of both participating centres, sharing of pseudonymised 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 patients with intermediate-risk rectal cancer, following a 6+3 dose-escalation design. Patients are treated with a boost of 2×5 Gy, 3×5 Gy, 4×5 Gy or 5×5 Gy in the week following standard SCRT on an MR-Linac. Maximum one in nine severe acute radiation-induced toxicities 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 with 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 has never 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 patients with intermediate-risk rectal cancer.

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 intensive care unit 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 on), 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.

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