STEP-UP STUDY

Multicentre, Prospective, Open-Label Feasibility Study of Radiotherapy Dose Escalation for the Non-Operative Management of Patients with Unresectable Locally Recurrent Rectal Cancer

PROTOCOL TITLE: 'Multicentre, prospective, open-label feasibility study of radiotherapy dose escalation for the non-operative management of patients with unresectable locally recurrent rectal cancer' (STEP-UP STUDY).

Protocol ID	NL-011150
Short title	STEP-UP
Version	1.2
Date	06-05-2026
Project leader	H.M.U. Peulen, MD, PhD Department of Radiation Oncology Catharina Hospital, Eindhoven, The Netherlands E: heike.peulen@catharinaziekenhuis.nl
Coordinating investigator	H.M.U. Peulen, MD, PhD Department of Radiation Oncology Catharina Hospital, Eindhoven, The Netherlands E: heike.peulen@catharinaziekenhuis.nl
Principal investigator(s) per site	H.M.U. Peulen, MD, PhD Department of Radiation Oncology Catharina Hospital, Eindhoven, The Netherlands E: heike.peulen@catharinaziekenhuis.nl M.P.W. Intven, MD, PhD Department of Radiation Oncology University Medical Centre Utrecht, Utrecht, The Netherlands E: m.intven@umcutrecht.nl C.S.E.W. Schuurhuizen, MD, PhD Department of Radiation Oncology Erasmus Medical Centre, Rotterdam, The Netherlands E: c.schuurhuizen@erasmusmc.nl

	M.D. den Hartogh, MD, PhD Department of Radiation Oncology Radiotherapiegroep, Arnhem, The Netherlands E: m.denhartogh@radiotherapiegroep.nl I.M. Werter, MD Department of Medical Oncology Rijnstate Hospital, Arnhem, The Netherlands E: iwerter@rijnstate.nl
Local investigators	J.W.A. Burger, MD, PhD Department of Surgery Catharina Hospital, Eindhoven, The Netherlands E: pim.burger@catharinaziekenhuis.nl J.G. Bloemen, MD, PhD Department of Surgery Catharina Hospital, Eindhoven, The Netherlands E: johanne.bloemen@catharinaziekenhuis.nl. A.E. Verrijssen, MD, PhD Department of Radiation Oncology Catharina Hospital, Eindhoven, The Netherlands E: an-sofie.verrijssen@catharinaziekenhuis.nl I.E.G. van Hellemond, MD, PhD Department of Medical Oncology Catharina Hospital, Eindhoven, The Netherlands E: irene.v.hellemond@catharinaziekenhuis.nl S.G. van Ravensteijn, MD, PhD Department of Medical Oncology Catharina Hospital, Eindhoven, The Netherlands E: stefan.v.ravensteijn@catharinaziekenhuis.nl

	R.H.N. Tijssen, Ir, PhD Department of Radiation Oncology Catharina Hospital, Eindhoven, The Netherlands E: rob.tijssen@catharinaziekenhuis.nl B. Hupkens, MD, PhD Department of Radiation Oncology MAASTRO Clinic, Maastricht, The Netherlands E: britt.hupkens@maastro.nl J. Buijsen, MD, PhD Department of Radiation Oncology MAASTRO Clinic, Maastricht, The Netherlands E: jeroen.buijsen@maastro.nl
Sponsor (in Dutch: verrichter/opdrachtgever)	Catharina Hospital Eindhoven, The Netherlands
Subsidising party	ZonMW The Hague, The Netherlands
Independent expert	L.J.C. van Warmerdam, MD, PhD Department of Medical Oncology Catharina Hospital, Eindhoven, The Netherlands
Laboratory sites and pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Department: D. Rijkaart, MD, PhD Department of Radiation Oncology Catharina Hospital, Eindhoven		**06-05-2026**
Project leader: H.M.U. Peulen, MD, PhD Department of Radiation Oncology Catharina Hospital, Eindhoven		**06-05-2026**
Coordinating investigator: H.M.U. Peulen, MD, PhD Department of Radiation Oncology Catharina Hospital, Eindhoven		**06-05-2026**

TABLE OF CONTENTS

1. INTRODUCTION AND RATIONALE 13
1.1 Therapeutic condition and current treatment status 13
1.2 Current evidence regarding radiotherapy dose escalation 15
1.3 Rationale for the study 17
2. OBJECTIVES 20
3. STUDY DESIGN 21
3.1 Design 21
3.2 Duration 21
3.3 Setting 22
4. STUDY POPULATION 23
4.1 Population (base) 23
4.2 Inclusion criteria 23
4.3 Exclusion criteria 24
4.4 Sample size calculation 24
5. TREATMENT OF SUBJECTS 25
5.1 Diagnostic work-up 25
5.2 General radiotherapeutic conditions 27
5.2.1 Stereotactic Body Radiation Therapy (SBRT) 34
5.2.2 Hyperfractionated chemo-reirradiation 36
5.2.3 Full-course chemoradiotherapy 36
5.3 Follow-up: radiation-related toxicity 37
5.4 Follow-up: radiology 37
5.5 Questionnaires 37
5.6 Use of co-intervention 38
5.7 Escape medication 38
6. METHODS 39
6.1 Study parameters/endpoints 39
6.1.1 Main study parameter/endpoint 39
6.1.2 Secondary study parameters/endpoints 39
6.2 Data collection 40
6.3 Study procedures 40
6.4 Withdrawal of individual research participants 40
6.5 Replacement of individual research participants after withdrawal 41
6.6 Follow-up of research participants withdrawn from treatment 41
6.7 Premature termination of the study 41
7. SAFETY REPORTING 42
7.1 Temporary halt for reasons of research participant safety 42
7.2 AEs, SAEs 42
7.2.1 Adverse events (AEs) 42
7.2.2 Serious adverse events (SAEs) 42
7.2.3 List of acute toxicities excluded from feasibility stopping rule 43

7.3 Follow-up of adverse events....44
7.4 Data Safety Monitoring Board (DSMB)....44
8. STATISTICAL ANALYSIS....45
8.1 Primary study parameter....45
8.2 Secondary study parameters....45
7.3 Interim analysis (if applicable)....46
9. ETHICAL CONSIDERATIONS....46
9.1 Regulation statement....46
9.2 Recruitment and consent....46
9.3 Objection by minors or incapacitated subjects....46
9.4 Benefits and risks assessment....46
9.5 Compensation for injury....47
9.6 Incentives....47
10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION....48
10.1 Handling and storage of data and documents....48
10.2 Monitoring and Quality Assurance....48
10.3 Amendments....48
10.4 Annual progress report....48
10.5 Temporary halt and (prematurely) end of study report....48
10.6 Public disclosure and publication policy....49
11. REFERENCES....50
12. APPENDICES....54
12.1 Common toxicity criteria of adverse events (CTCAE) version 5.0....55
12.2 Overall quality of life and well-being....57
12.3 Structured MRI report template....62

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
AR	**Adverse Reaction**
ATMP	**Advanced Therapy Medicinal Product**
AxMP	**Auxiliary Medicinal Product**
BD	**Bidaily**
BID	**Twice daily radiation therapy**
CA	**Competent Authority**
CAPOX	**Capecitabine, oxaliplatin**
CBCT	**Cone beam computed tomography**
CCMO	**Centrale Commissie Mensgebonden Onderzoek (Central Committee on Research Involving Human Subjects)**
CRA	**Clinical Research Associate**
CRF	**Case Report Form**
CRO	**Contract Research Organisation**
CT	**Clinical Trial**
CTA	**Clinical Trial Authorisation**
CTCAE	**Common Terminology Criteria for Adverse Events**
CTV	**Clinical Target Volume**
DSMB	**Data Safety Monitoring Board**
EC	**Ethics Committee**
e-CRF	**Electronic Case Report Form**
EMA	**European Medicines Agency**
EORTC	**European Organisation for Research and Treatment of Cancer**
EQD2Gy	**Equivalent dose in 2 Gy fractions (Gy)**
ESTRO	**European Society for Therapeutic Radiology and Oncology**
EU	**European Union**

FOLFOXIRI	**Leucovorin, fluorouracil, oxaliplatin, irinotecan**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation**
GTV	**Gross tumour volume**
Gy	**Gray**
IB	**Investigator's Brochure**
IC	**Informed Consent**
ICF	**Informed Consent Form**
ICH	**International Conference on Harmonisation**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
LLRC	**Locally recurrent rectal cancer**
MS	**Member State**
OOI	**Organs of Interest**
pCR	**Pathological complete response**
PI	**Principal Investigator**
PTV	**Planning Target Volume**
RSI	**Reference Safety Information**
SAE	**Serious Adverse Event**
SAR	**Serious Adverse Reaction**
SBRT	**Stereotactic Body Radiation Therapy**
SIB	**Simultaneous integrated boost**
SmPC	**Summary of Product Characteristics**
SOP	**Standard Operating Procedure**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
TME	**Total mesorectal excision**

SUMMARY

Rationale: The optimal curative-intent management of locally recurrent rectal cancer (LRRC) typically involves multimodality therapy, comprising neoadjuvant therapy and subsequent salvage surgery. However, in patients with unresectable LRRC, where surgical intervention is not feasible, management is limited to non-operative bimodality therapy with systemic therapy and radiotherapy. For this patient group, evidence guiding the optimisation of non-operative management remains limited, particularly regarding strategies to optimise radiotherapy and achieve durable control. In this context, the therapeutic goal is to achieve prolonged local control while minimising treatment-related toxicity. Radiotherapy dose escalation has been proposed as a potential strategy to achieve this balance. However, its feasibility and safety in the non-operative management of unresectable LRRC have not yet been established. As such, this study aims to evaluate the feasibility and safety of this radiotherapeutic approach, and to determine its impact on both symptomatic control and oncological outcomes.

Objective: The primary objective of this study is to assess the feasibility of radiotherapy dose escalation in the non-operative treatment of previously irradiated and radiotherapy naïve patients with unresectable LRRC. Feasibility is defined as ≤7 participants with acute grade 3-5 radiation-induced toxicities (CTCAE version 5.0). Radiotherapy dose escalation is offered in a feasibility trial at a predefined dose level in two settings:

(1) (Chemo-)reirradiation: previously irradiated patients with unresectable LRRC undergo stereotactic body radiation therapy (SBRT) (daily adaptive magnetic resonance (MR) or cone beam computed tomography (CBCT)-guided) reirradiation (5 x 9 Gy) when feasible or, alternatively, hyperfractionated chemoreirradiation (50.4 Gy in 1.2 Gy BID fractions with concurrent capecitabine 825mg/m^2 bidaily (BD)). SBRT feasibility is dependent on specific tumour criteria (i.e., <6 cm in tumour diameter, and tumour not infiltrating the lumen of the bowel- or bladder wall, as in accordance with the *UK SABR consortium guidance*[1]).

(2) Full-course chemoradiotherapy: radiotherapy naïve patients undergo full-course chemoradiotherapy with a simultaneous integrated boost (SIB; 25 × 2.6 Gy; EQD2Gy = 71 Gy, α/β = 5 Gy)[2] with concurrent capecitabine 825mg/m^2 BD.

We anticipate a safe toxicity profile, and potentially improved oncological outcomes. The secondary objectives are to determine symptomatic control, quality of life, local control, progression-free survival and overall survival.

Study design: This is a prospective, single-arm feasibility study. Eligible patients receive radiotherapy dose escalation at one predefined dose level in either a (chemo-)reirradiation or full-course radiotherapy setting.

Study population: A total of 30 patients will be included in the study. Eligible patients are divided in two treatment groups:

(1) (Chemo-)reirradiation: Previously irradiated patients with unresectable LRRC (without distant metastases, or, with (oligo)metastatic disease that does not require imminent start of systematic therapy) treated with non-operative management.

(2) Full-course chemoradiotherapy: Radiotherapy-naïve patients with unresectable LRRC (without distant metastases, or, with (oligo)metastatic disease that does not require imminent start of systematic therapy) treated with non-operative management.

Intervention study: All cases are reviewed in a multidisciplinary tumour board before enrolment. Interventions are defined as follows:

(1) (Chemo-)reirradiation: SBRT (daily adaptive MR or CBCT-guided) will be delivered when feasible, depending on tumour characteristics (i.e., <6 cm in tumour diameter, and tumour not infiltrating the lumen of the bowel- or bladder wall, as in accordance with the *UK SABR consortium guidance*). The SBRT regimen consists of 5 fractions of 9 Gy. Alternatively, hyperfractionated chemo-reirradiation will be delivered, consisting of 50.4 Gy in 1.2 Gy twice-daily fractions (BID), in combination with concurrent capecitabine 825mg/m^2 BD.

(2) Full-course chemoradiotherapy: delivered with a simultaneous integrated boost (SIB) technique (25x2.6 Gy), corresponding to an EQD2Gy (α/β = 5 Gy, rectum) of 71 Gy, with concurrent capecitabine 825mg/m^2 BD.

Main study parameters/endpoints: The primary objective is to evaluate the feasibility of radiotherapy dose escalation, as defined by the incidence of acute (<3 months) grade 3-5 radiation-induced toxicities ≤7 participants (CTCAE version 5.0). Secondary objectives include acute and late radiation-induced toxicity stratified per fractionation schedule, quality of life and symptomatic control (using validated patient-reported outcome questionnaires), and 1- and 3-year (infield and outfield) progression-free survival (PFS), disease-free survival (DFS) and overall survival (OS).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The potential benefit of radiotherapy dose escalation in the non-operative management of patients with unresectable LRRC has to be weighed against the associated burden and risks of toxicity. Importantly, this study addresses a patient population in which treatment is primarily palliative, aimed at achieving local disease control and symptom relief, with otherwise limited therapeutic options. The primary risks of this study are related to treatment-associated toxicity and morbidity. Radiotherapy dose escalation may result in both

acute and late adverse effects. Acute and late toxicity may include gastro-intestinal disorders (ileus, diarrhoea, gastroparesis, nausea/weight loss, perforation, fistula), abdominal infections (intra-abdominal abscess, presacral abscess), renal and urinary disorders (urinary tract obstruction, urinary retention, urinary incontinence, acute kidney injury and ureter stenosis), delayed wound healing, erectile dysfunction and peripheral neuropathy. These toxicities may negatively impact quality of life. The extent and severity of these effects may vary between patients. Toxicity related to radiotherapy will be closely monitored as the primary outcome, with continuous evaluation throughout the study. Preliminary results of radiotherapy dose escalation in locally advanced rectal cancer and curative setting in LRRC have demonstrated to be safe and feasible. Nevertheless, uncertainty remains regarding the balance between potential benefits and risks in this specific patient group with unresectable LRRC.

For patients receiving hyperfractionated chemo-reirradiation, the total duration of radiotherapy will be 4 weeks. For those undergoing full-course chemoradiotherapy, the treatment will last 5 weeks. For patients treated with SBRT, the treatment duration is shortened to 2 weeks. In addition, to carefully monitor radiation-related toxicity within the study, patients will be consulted before and after start of treatment (both out-patient clinic visits or follow up by telephone is allowed to minimize burden on participants). Lastly, patients will be asked to complete patient-reported outcome questionnaires, which are brief, intuitive, and tailored to the study population, thereby minimizing the burden on participants. Participation of the questionnaires is optional.

Radiotherapy dose escalation may induce local tumour response and thereby contribute to symptom relief, which in turn, could enhance quality of life. Overall, given the treatment intent and limited therapeutic alternatives to provide symptomatic relief to this patient group, the investigators believe that the expected benefits of participation in this study outweigh the potential risks and burden associated with the treatment.

1. INTRODUCTION AND RATIONALE

1.1 Therapeutic condition and current treatment status

Over the past two decades, advances in the management of primary rectal cancer, including the introduction of total mesorectal excision (TME) and the integration of neoadjuvant therapy, have led to substantial improvements in overall survival and a reduction in local recurrence rates from 20-30% to 5-11%.[3-8] Despite these developments, management of locally recurrent rectal cancer (LRRC), remains a clinical challenge characterised by poor prognosis and a considerable symptomatic burden. Reported overall survival among patients with LRRC treated with curative intent, comprising neoadjuvant therapy followed by salvage surgery, is approximately 73% at 3 years[9] and 30% at 5 years.[10-14] In contrast, among patients managed with non-operative treatment, 3-year overall survival is approximately 27%.[9]

For patients with LRRC, curative-intent management consists of multimodality therapy, comprising neoadjuvant (chemo)radiotherapy followed by salvage surgery, given its association with improved oncological outcomes, as recommended in current international guidelines.[5, 6, 14-20] The role of neoadjuvant induction chemotherapy as part of trimodality treatment is currently being investigated in the prospective PelvEx II randomised controlled trial [NCT04389086]. However, at diagnosis, approximately 40-60% of patients with LRRC are ineligible for curative intent treatment due to unresectable local disease, distant metastases, comorbidity, frailty and/or patient preference.[9, 13, 21-23] In approximately 86% of patients, the disease is symptomatic, with clinical complaints including pain, mucous or faecal discharge, rectal bleeding, fistula and abscess formation, and obstructive or lymphatic complications, leading to a considerable reduction in health-related quality of life.[24, 25] In this setting, non-operative management is a crucial aspect of LRRC treatment, with highly individualised strategies tailored to achieve locoregional control, symptom relief, preservation of quality of life, and extend overall survival where possible. Nevertheless, evidence regarding the effectiveness of non-operative modalities remain limited. In The Netherlands, as in most European countries, non-operative care for LRRC is not centralised in expert centres unlike curative intent treatment for LRRC. Consequently, robust data regarding its impact on oncological outcomes, symptomatic burden, and quality of life remain scarce.

Non-operative treatment strategies vary considerably depending on the extent and distribution of disease. In LRRC patients with extensive synchronous distant metastases (M1), systemic palliative chemotherapy (typically using regimens as CAPOX, FOLFOX, FOLFIRI, FOLFOXIRI, often with agents targeting the VEGF en EGFR receptors) remain the standard of care, contingent upon the patient's functional status and ability to tolerate treatment.[9, 15, 17,

[18] In clinical settings where patients with LRRC present with unresectable local disease and/or local symptoms (such as pain, bowel obstruction, bleeding, or tenesmus), radiotherapy is often prioritized prior to systemic therapy initiation to achieve rapid symptomatic relief. In such clinical scenarios, short-course regimens (e.g., 5 x 4-5 Gy or 1x8 Gy) are often employed to minimize treatment delays in commencing systemic therapy. Lastly, for patients who are not candidates for systemic treatment due to poor performance status or comorbidities, best supportive care remains the preferred approach, focusing on symptom palliation and quality of life.

Conversely, among patients without extensive distant metastases (M0, or with (oligo)metastatic disease that does not require imminent start of systematic therapy), upfront (chemo)radiotherapy is often preferred to optimize locoregional control.[15, 17, 18] In radiotherapy-naïve patients, full-course chemoradiotherapy with capecitabine is typically administered, mirroring curative intent protocols.[15] However, approximately 62-70% of patients with LRRC have previously received radiotherapy in the pelvis, necessitating type 1 reirradiation strategies, in which full geometric overlap with irradiated volumes of previous courses occur.[26-28] Currently, a wide range of chemo-reirradiation regimens are employed in this setting, including 15x2 Gy regimens or hyperfractionated radiotherapy regimens such as 40-50 Gy in 1.2 BID fractions or 1.8 Gy once daily.[29, 30] Although several non-operative studies are outdated and more modern radiotherapy techniques are increasingly employed, reported overall palliative effects range from 57 to 100%, with median duration of symptom relief lasting approximately 9 months. Nevertheless, local control rates following (chemo-)reirradiation remain variable (25-70%), reflecting heterogeneity in patient selection and treatment strategies across centres.[15]

For a selected subgroup of patients with unresectable LRRC, particularly those without extensive distant metastases, there is a rationale to pursue intensified local therapy to achieve prolonged local control. However, evidence-based strategies in this setting remain limited. In a national survey conducted by our research team (unpublished data) among members of the Dutch Society of Radiation Oncology (NVRO), we identified significant clinical heterogeneity and lack of consensus in the radiotherapeutic management of unresectable LRRC. Variability in treatment approaches, including dose and fractionation schedules and target volume delineation, highlighted the need for prospective studies and systematic outcome evaluations. Dose-escalated radiotherapy has been proposed as a potential means of addressing this therapeutic gap and opportunity to improve outcomes. For example, at a median EQD2Gy dose >30 Gy, an efficacy of (chemo-)reirradiation of 83-94% has been reported for symptom relief in LRRC.[3, 29, 31] Nonetheless, in the non-operative management where organs remain in

situ, treatment-related toxicity remains a critical consideration. Particularly (chemo-)reirradiation of previously irradiated pelvic tissues and organs poses a risk of increased cumulative toxicity, which may offset clinical benefit. Overall, a key unresolved question remains whether dose escalated radiotherapy in the non-operative management can achieve prolonged local control without compromising toxicity within this population. Given the limited evidence to date regarding the feasibility (in terms of toxicity) of dose-escalated radiotherapy, further investigation is warranted.

1.2 Current evidence regarding radiotherapy dose escalation

In patients with locally advanced rectal cancer (LARC), prior studies have demonstrated that radiotherapy dose escalation may enhance tumour response without a corresponding increase in acute toxicity. Appelt et al. reported a significant dose-response relationship with tumour regression across dose levels of 50.4-70 Gy.[32] Furthermore, systematic reviews by Burbach et al. and Hearn et al. demonstrated higher pooled pathological complete response (pCR) estimates of 20.4-24.1% with radiation doses of 54-60 Gy, alongside acceptable rates of grade ≥3 acute toxicity of 10.3-11.2%.[33, 34] Lastly, the RECTAL-BOOST trial demonstrated higher rates of near-complete or complete tumour regression with an external radiation boost followed by standard pelvic chemoradiation, combared to no boost.[35] Collectively, these findings suggest a dose-effect relationship in the primary rectal cancer setting. However, it remains unknown whether similar benefits can be achieved in the setting of LRRC, highlighting the need for further evaluation.

(Chemo-)reirradiation setting

Considering the favourable outcomes of radiotherapy dose escalation in primary LARC patients, current research is focusing on its potential application in the curative-intent treatment of LRRC. However, as aforementioned, a key challenge in the LRRC population is that approximately 62-70% have previously received pelvic radiotherapy and are thus candidate for type 1 reirradiation. Currently, with respect to dose-escalated (chemo)(re)irradiation for LRRC, only a limited number of cohorts have been published to date. A retrospective study by Chung et al. demonstrated that higher reirradiation doses (median 50 Gy, range 30-60 Gy) using mostly conventional fractionation (n=38 normofractionated, n=2 hypofractionated and n=1 hyperfractionated regimen) were associated with improved 2-year in-field progression-free survival (PFS) of 49.4% and 2-year overall survival (OS) of 55.3%.[36] However, this approach was associated with a substantial high rate of overall severe late toxicity (42% grade 3 or higher) with a median time from reirradiation to severe late toxicity of 10.5 months (range 2.3-33.3 months).[36] The 2-year severe late toxicity-free rate was 55.5%.[36] A meta-analysis by Lee et al. further demonstrated rates of 11.7% (95% CI 6.7-19.5%) and 25.5% (95% CI

16.7-40.0%) for overall grade ≥3 late toxicities, with an odds ratio of 6.39 (95% CI 3.2-12.7).[29] Most relevant late toxicities observed as a result of reirradiation were perforation, obstruction, bleeding and fistula formation.[28] Compared to patients undergoing curative-intent trimodality treatment for LRRC (chemo-reirradiation followed by surgery and intraoperative electron radiotherapy), acute cumulative treatment-related grade 3 toxicities are observed in 38% and late grade 3 toxicities in 43% (with no grade 4-5 toxicities).[37]

In this context, hyperfractionated chemo-reirradiation has emerged as a promising strategy, associated with lower rates of both acute toxicity and late complications. As the biological rationale for hyperfractionation leverages the differential sensitivity of tumour and late-reacting normal tissues with lower α/β ratios, a potentially more favourable therapeutic ratio can be achieved. In reirradiation, this approach may be particularly beneficial to mitigate late toxicity. For example, Cai et al. demonstrated that hyperfractionated intensity-modulated reirradiation up to 39 Gy in 30 fractions resulted in significant improvement of local symptoms (complete symptomatic relief in 59.1% and partial symptomatic relief in 27.3%), local response (40.9%) and acceptable toxicity rates (no grade 4 acute toxicity or treatment related deaths, and in total 23% acute grade 3 toxicities including diarrhoea, cystitis, dermatitis and intestinal obstruction).[38] Late toxicities observed were infrequent (chronic severe diarrhoea in 9.1%, small bowel obstruction in 4.5% and dysuria in 9.1%).Lastly, a multicentre phase II study by Valentini et al. employing hyperfractionated chemo-reirradiation in previously irradiated LRRC patients demonstrated acceptable acute CTCEA grade ≥3 toxicity rate of 5.1% and acceptable incidence of late complications (11.9%, including skin fibrosis, urinary complications requiring nephrostomy and a bowel fistula).[30] Overall, these findings suggest that hyperfractionated dose escalation is a viable and well-tolerated approach for LRRC management, though current evidence is largely limited to retrospective series and limited prospective data.

Stereotactic body radiation therapy (SBRT) is a high precision technique, delivering high-dose radiation in a limited number of fractions generally to tumours < 5 cm in diameter. In recurrent pelvic disease, this technique has emerged as a feasible treatment option for patients with otherwise limited treatment options.[39] A systematic review by Murray et al. from 2017, demonstrated that reirradiation SBRT prescription doses ranged from 15 Gy in 3 fractions to 60 Gy in 3 fractions.[39] The median physical delivered dose was 30 Gy in a median of 4.5 fractions.[39] Currently, in accordance with to the UK consortium guidance for SBRT reirradiation, an isotoxic dose-escalation approach up to 45 Gy in 5 fractions is recommended primarily for rectal cancer patients who are not eligible for exenterative surgery or patient preference.[1, 40-42] Nonetheless, a limitation of SBRT is the sensitivity of the bowel to high fraction doses, raising concerns about increased toxicity. Studies have demonstrated that, with

appropriate patient selection, SBRT can achieve 2-year local control rates of 60-70% and overall survival rates of up to 78% with acceptable toxicity rates.[43, 44] The *Pelvic SBRT reirradiation Commissioning through Evaluation Programme* (United Kingdom) demonstrated a 1-year local control rate of 76%, with grade 3 toxicity of 3.8% and no documented grade 4-5 toxicities.[45] To further mitigate toxicity, MRI or CBCT-guided adaptive radiotherapy has emerged as a promising strategy, further reducing Planning Target Volume (PTV) margins.[46] This technique enables daily plan adaptation based on real-time anatomical changes, thereby enhancing precision and sparing of surrounding healthy tissue.[46] In recent years, the clinical implementation of daily online adaptive radiotherapy has advanced rapidly, offering new opportunities for safe and effective treatment in complex cases.

Full-course chemoradiotherapy

Lastly, in the radiotherapy-naïve setting, full-course chemoradiotherapy may also be a promising radiotherapy strategy in the non-operative management of unresectable local recurrent disease. For example, in radiotherapy-naïve LRRC patients, Watanabe et al. has demonstrated a clinical complete response rate achieved in 17% following treatment with chemoradiotherapy (50 to 60 Gy), with a 5-year progression-free survival of 34.8% and a 5-year OS of 54.4% without surgery.[47] Another study, delivering a biologically effective dose (BED) 48.0-95.2 Gy in radiotherapy-naïve LRRC patients, demonstrated a 1-year local control rate of 51.5% and 3-year local control rate of 19.6%, with a higher local control rate in patients treated with a higher BED than patients treated with a lower BED (threshold of ≥75 Gy_{10} p = 0.07).[48] Lastly, dose-escalation with external radiation therapy boost to the tumour in patients with locally advanced rectal cancer demonstrated acceptable acute grade ≥3 toxicities of 9.4%, which was comparable to standard pelvic chemoradiation (7.8%).[35]

1.3 Rationale for the study

While emerging data on dose-escalated radiotherapy for unresectable recurrent rectal disease suggest promising feasibility and oncological outcomes, current available literature remains limited and primarily consists of small retrospective cohorts and a few prospective studies. Currently, the ongoing Danish phase II non-randomized prospective ReRAD II trial [NCT04695782] is investigating dose-escalated pencil beam proton therapy for reirradiation in LRRC. Interim results demonstrate manageable acute toxicity (treatment-related grade ≥3 acute toxicity in 2/25 patients) and preserved quality of life.[49] Nonetheless, in the Netherlands, proton therapy is currently not considered standard of care and is only available for model-based indications, limiting its broad clinical applicability. Additionally, the Italian RETRY study [NCT05984576], a multicentre prospective observational study, is currently investigating multiple treatment modalities for LRRC, including conventional normofractionated

chemoradiotherapy (≥40 Gy), proton and photon therapies, SBRT or carbon ion radiotherapy with consolidation chemotherapy for high-risk/borderline resectable or unresectable LRRC patients. The available retrospective cohorts and prospective studies further highlight the heterogeneity in patient populations and variety in treatment approaches inherent to this disease setting.

Patients with unresectable LRRC represent a clinically heterogeneous group (radiotherapy-naïve and previously irradiation patients) with currently limited therapeutic options to achieve (prolonged) local tumour control and symptom relief. In this setting, individualised treatment strategies constitute a central component of care. Notably, if inadequately treated, the local recurrence may lead to substantial, often debilitating symptom burden with profound impairment of quality of life without necessarily shortening survival. To our knowledge, no other prospective studies or registries have addressed the role of dose-escalated radiotherapy in the non-operative management of unresectable tumours for patients in whom the primary aim is to maximise prolonged local control and limit treatment-induced toxicity.

Given the current scarcity of data and heterogeneity in radiotherapy dose escalation strategies, there is a clear need for a feasibility study to evaluate the safety of dose-escalated radiotherapy in LRRC in the non-operative setting, for both settings of previously irradiated patients and radiotherapy naïve patients. Based on the aforementioned available literature, the expected incidence of acute grade ≥3 toxicity will vary by treatment modality. For hyperfractionated (chemo)-reirradiation (50.4 Gy in 1.2 Gy twice-daily fractions), expected rates of acute toxicity are approximately 20% for grade 3 toxicity, up to 10% for grade 4 toxicity, and <5% for grade 5 toxicity. For SBRT (5x9 Gy) and full-course chemoradiotherapy (simultaneous integrated boost (SIB) technique (25x2.6 Gy)) lower rates are expected, with approximately 10% grade 3 toxicity, 5% grade 4 toxicity, and no grade 5 toxicity. Taking these data together, the anticipated overall incidence of acute grade ≥3 radiation-induced toxicity in the total study population is estimated to be approximately 20%. Given the small sample size and expected heterogeneity in both patient characteristics and treatment allocation, the following safety boundary has been defined: feasibility will be considered unacceptable if more than 7 of 30 patients (23.3%) experience grade 3-5 toxicity. This threshold is set marginally above the expected rate to account for statistical variability in a small cohort and to reduce the risk of chance variation or imbalanced distribution of higher-risk patients across treatment subgroups. As subgroup sizes cannot be predefined and are expected to remain small, toxicity rates within individual strata may not reliably reflect overall safety. Patient safety will be closely monitored throughout the study by high frequency of independent expert Data Safety Monitoring Board (DSMB) reviews, enabling early identification of unexpected toxicity.

To conclude, we hypothesize that dose-escalated radiotherapy would achieve acceptable acute toxicity rates (grade 3-5 ≤7 participants) and compliance, across two radiotherapy settings:

- *(Chemo-)reirradiation*: for patients with unresectable LRRC (without distant metastases, or with (oligo)metastatic disease that does not require imminent start of systematic therapy). Consisting of dose-escalation with (MRI/CBCT) daily online adaptive SBRT where feasible, or otherwise as hyperfractionated chemo-reirradiation.
- *Full-course chemoradiotherapy*: for radiotherapy-naïve patients with unresectable LRRC (without distant metastases, or with (oligo)metastatic disease that does not require imminent start of systematic therapy). Consisting of dose escalation with a simultaneous integrated boost (SIB).

If feasible, this approach could establish the foundation for subsequent studies evaluating improvements in locoregional control, symptom burden reduction, and ultimately, quality of life for patients undergoing non-operative treatment for LRRC.

2. OBJECTIVES

Primary Objective:

- To determine the feasibility of radiotherapy dose-escalation in the non-operative management of patients with unresectable locally recurrent rectal cancer.
    - Outcome measure: the number of subjects with acute grade 3-5 radiation-induced toxicity (<3 months), according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.
    - Feasibility-maximum: defined as ≤7 participants with acute grade 3-5 radiation-induced toxicity (<3 months), according to CTCAE, version 5.0.

Secondary Objective(s):

- To determine acute (<3 months) and late (presenting after 90 days up to 36 months) grade 3-5 radiation-induced toxicity or date of death, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, stratified per fractionation schedule.
- To determine patient-reported quality of life and duration of symptomatic control following treatment with radiotherapy dose escalation.
    - Generic and cancer-specific quality of life assessments are assessed with QLQ-C15-PAL, QLQ-CR29 and EQ-5D-5L at inclusion, and at 3-, 6-, 12-, 24-, and 36- months post radiotherapy treatment. The questionnaires will be sent either by mail of digitally, according to the patient's preference.
- To determine 1-, 2- and 3-year infield progression-free survival.
    - Defined as the time interval from start of radiotherapy dose escalation to radiological or clinical confirmed infield progression (defined as recurrence or disease progression within the PTV). Infield progression is registered by the treating physician in the patient file during follow-up.
- To determine 1-, 2- and 3-year outfield progression-free survival.
    - Defined as the time interval from start of radiotherapy dose escalation to radiological or clinical confirmed outfield progression (defined as recurrence or disease progression outside the PTV). Outfield progression is registered by the treating physician in the patient file during follow-up.
- To determine 1-, 2- and 3-year progression-free survival.
    - Defined as the time interval from start of radiotherapy dose escalation to radiological or clinical confirmed locoregional progression. Progression is registered by the treating physician in the patient file during follow-up.
- To determine 1, 2-, and 3-year disease-free survival.

  - Defined as the time interval from start of radiotherapy dose escalation to first documented sign of disease progression (including locoregional progression or distant metastases) or death from any course. Disease progression is registered by the treating physician in the patient file during follow-up.
- To determine 1-, 2- and 3-year overall survival.
  - Defined as the time interval from date of inclusion to date of death. Mortality is registered in the patient file which is linked to municipal personal records database.
- To determine the compliance of treatment with radiotherapy dose escalation.
  - Information on the completion of radiotherapy dose escalation is registered by the treating radiation oncologist.

3. STUDY DESIGN

3.1 Design

This is a prospective, open-label, multi-centre, single-arm feasibility study established for eligible for radiotherapy dose escalation with one predefined dose level, in the non-operative management of LRRC (Figure 1). For unresectable LRRC patients with a prior history of radiotherapy, (chemo-)reirradiation dose-escalation will be delivered either using SBRT or hyperfractionated chemoreirradiation, depending on specific tumour criteria. For radiotherapy-naïve patients, radiotherapy dose escalation will be delivered with a simultaneous integrated boost (SIB).

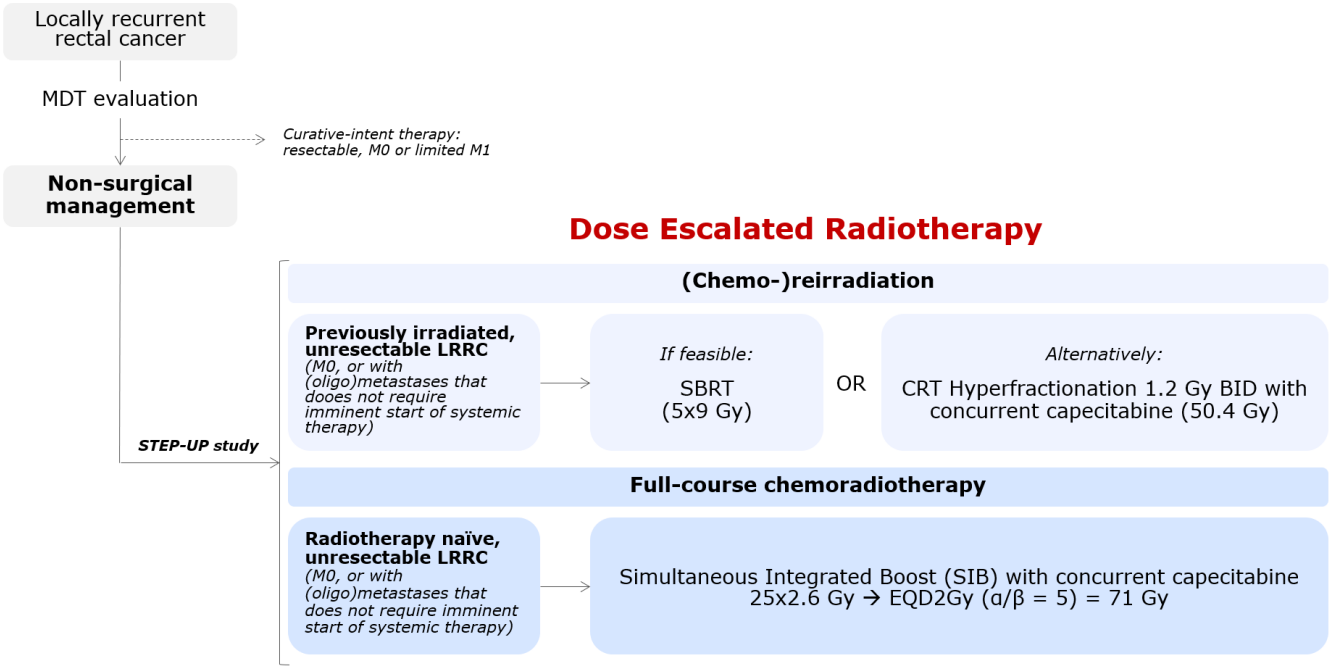
3.2 Duration

An inclusion of 30 patients eligible for radiotherapy dose escalation, fulfilling the inclusion criteria of the present study, in seven high-volume radiotherapeutic centres across the Netherlands is estimated to be completed in approximately 36 months. The total treatment duration is dependent on the radiotherapeutic modality: SBRT 2 weeks, chemo-reirradiation hyperfractionation 4 weeks and full-course chemoradiotherapy 5 weeks. It is expected that all participants will be ready for evaluation of the primary endpoint (acute radiation-induced toxicity) 3 months after the completion of radiotherapy dose escalation. No later than three to four months after the last included patients completed radiotherapeutic treatment, an evaluation of the primary endpoint is available. The duration of follow-up will be 36 months (or until date of death) to assess primary and secondary outcomes, and 60 months for overall survival status.

3.3 Setting

The study is conducted by the Catharina Hospital Eindhoven, University Medical Centre Utrecht, Erasmus Medical Centre, Radiotherapiegroep and Rijnstate Hospital who are responsible for inclusion, radiotherapeutic intervention and follow-up.

Figure 1. STUDY FLOWCHART



MDT = multidisciplinary tumour board, M0 = absence of distant metastasis; M1 = presence of distant metastasis; SBRT = stereotactic body radiation therapy; Gy = Gray; CRT = chemo-reirradiation; BID = twice-daily; EQD2Gy = equivalent dose in 2 Gy fractions.

4. STUDY POPULATION

4.1 Population (base)

Yearly, 3500 patients are diagnosed with primary rectal cancer in the Netherlands. With a recurrence rate of 6-12%, approximately 315 patients per year present with LRRC in the Netherlands. Approximately 200 patients with LRRC are referred each year to the Catharina Hospital Eindhoven, of which approximately half are treated with non-operative management due to unresectable local disease, distant metastases or frailty[9, 10, 21-23], totalling 100-110 patients per year. It is estimated that in the participating centres, the majority of patients will have diffuse metastatic disease and will start with systemic treatment. Approximately 20 patients per year are expected to receive radiotherapy upfront for symptom control of which approximately 6 will be eligible for radiotherapy dose escalation. After discussion in the multidisciplinary tumour board, patients will be recruited and selected by the local treating radiation oncologist, referring surgeon or medical oncologist. Given the participation of the specialized, high-volume hospitals, inclusion of the required 30 patients in 36 months is considered realistic.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

- Age ≥ 18 years old.
- Diagnosis of locally recurrent rectal cancer, defined as recurrent disease within the pelvis after surgical excision for primary rectal or distal sigmoidal cancer, diagnosed either by histopathology or clinically proven (evidence on imaging in combination with clinical findings, with consensus in MDT). A second recurrence is eligible if (chemo-)reirradiation is considered feasible, with consensus in MDT.
- Recurrent disease is determined as unresectable where surgery has been ruled out by clinicians (or refused by patient), with consensus in MDT.
    - *Unresectable is defined as: expected gross incomplete resection with overt tumour remaining in the patient after resection, encasement of the ischiadic nerve and invasion of the cortex and/or neuroforamina from S2 and upwards.*
- Either radiological absence of distant metastatic disease (M0), *or*, with (oligo)metastatic disease that does not require imminent start of systematic therapy at time of inclusion.
    - *If systematic chemotherapy was previously administered prior to inclusion, and there is a current indication for local treatment with radiotherapy, patients are still eligible.*
- WHO/ECOG performance score 0-2.
- MR pelvis and thoracoabdominal CT with interpretation no longer than 6 weeks prior to inclusion.
- Written informed consent according to the ICH-GCP and national/local regulations.

4.3 Exclusion criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

- Radiological evidence of extensive metastatic disease (e.g., extensive liver or lung metastases) at time of inclusion, that requires imminent start of systemic therapy, with consensus in MDT.
- Radiotherapy in the past 6 months.
- Any contraindication for planned radiotherapy dose escalation, as determined by the radiation oncologist (e.g., residual grade 3 toxicity from previous radiotherapy).
- Administration of bevacizumab/panitumumab/cetuximab <6 weeks prior to start radiotherapy dose escalation.
- Severe active morbidity, concomitant disease or active infections.
- dMMR/MSI status

4.4 Sample size calculation

The sample size for this feasibility study has been determined based on expected accrual rates and feasibility constraints. According to the sample size estimation method described by Viechtbauer et al., a toxicity event with an expected prevalence of approximately 20% can be detected with 95% confidence in a pilot study including a minimum of 14 participants.[50] Importantly, given the exploratory and feasibility-oriented nature of the study, as well as the anticipated patient heterogeneity and subgroups in treatment modalities of radiotherapy dose escalation (SBRT, hyperfractionated chemoreirradiation and full-course chemoradiotherapy), a larger sample size is considered appropriate within the bounds of feasible recruitment. In particular, defining minimum numbers per treatment arm is necessary to avoid very small subgroup sizes that would preclude meaningful interpretation of toxicity and feasibility outcomes. Accordingly, the total study population will be 30 patients, with a predefined minimum inclusion target of 10 patients per treatment arm (SBRT, hyperfractionated chemoreirradiation and full-course chemoradiotherapy). Based on institutional referral patterns and expected accrual, this is considered feasible. The sample size is considered adequate to evaluate feasibility while allowing sufficient monitoring of acute toxicity rates and treatment compliance. Furthermore, it will provide valuable preliminary data to inform the design of subsequent larger-scale trials. The chosen sample size is also consistent with comparable feasibility studies, which have typically included between 6 and 22 patients.[51-55]

5. TREATMENT OF SUBJECTS

Trial entry

All participants will be discussed and screened during one of the multidisciplinary team meetings (MDTs). Patients are informed about the feasibility study by their treating physician, in both an oral and a written manner. Patients are free to accept or decline the study intervention and have sufficient time consider their decision and sign the informed consent form. Screening of the eligibility criteria and review of the MR images will be performed by the initial treating centre. A standardised structured MRI report template is employed during assessment to ensure uniform assessment of involvement pelvic compartments (Appendix 12.3). To maintain quality of data, central review of all imaging of participating patients will be performed in a multidisciplinary meeting between the participating centres on a scheduled time base. Trial participation includes consent to undergo the intervention and to participate in acute toxicity monitoring. Consent to filling out quality of life questionnaires during the study are optional.

In case of inclusion:

(1) (Chemo-)reirradiation: SBRT (daily adaptive MR or CBCT-guided) will be delivered when feasible, depending on tumour characteristics (i.e., <6 cm in tumour diameter, and tumour not infiltrating the lumen of the bowel- or bladder wall, as in accordance with the *UK SABR consortium guidance*). The SBRT regimen consists of 5 fractions of 9 Gy. Alternatively, hyperfractionated chemo-reirradiation will be delivered, consisting of 50.4 Gy in 1.2 Gy twice-daily fractions (BID), with concurrent capecitabine 825mg/m^2 bidaily.

(2) Full-course chemoradiotherapy: Treatment will be delivered with a simultaneous integrated boost (SIB) technique (25x2.6 Gy), corresponding to an EQD2Gy (α/β = 5 Gy, rectum) of 71 Gy, with concurrent capecitabine 825mg/m^2 bidaily.

5.1 Diagnostic work-up

The work-up described below is standard of care in the Netherlands, and therefore not considered as study interventions.

If a patient is referred to the participating hospitals, the completeness of the work-up will be determined. Work-up should at least include a high-dose thoracoabdominal CT-scan to detect distant metastases and a pelvic MRI to assess resectability of the local tumour. Molecular diagnostics of the primary tumour (including MMR status, RAS and BRAF mutations and Her2 amplification) should be documented, as current standard of care. An additional FDG-PET/CT-scan is optional. CT-scan and MRI must be performed no longer than 6 weeks prior to inclusion. In case of incomplete or insufficient work-up, radiological imaging will be repeated.

MRI acquisition should adhere to the following minimal requirements:

- 1.5T or 3T MR equipment.
- Phased-array receiver coil for pelvic-/body imaging.
- T2-weighted high-resolution sequences in 3 standard planes (true sagittal, coronal, transverse). Minimal slice thickness of ≤ 3 mm. No fat suppression.
- Diffusion-weighted imaging (DWI): axial plane, b-value ≥ b800, including ADC maps.
- Field of view (FOV) of both T2 and DWI needs to cover the entire tumour area.

Optionally, but not routinely required are:

- Angulated sequences
- T1-weighted sequences
- Fat suppressed sequences
- (Dynamic) Post-contrast sequences
- Patient preparation (e.g., spasmolytic agents, endorectal filling)

Minimal requirements for assessment and reporting are described in a Standard Operating Procedure (Appendix 12.3).

After complete work-up is performed patients will be discussed in the multidisciplinary tumour board (MDT) in the including centres. The MDT consists of at least one surgical oncologist, one medical oncologist, one radiation oncologist, and one radiologist who are experienced in the diagnosis and treatment of LRRC. Only if there is consensus in the MDT about whether or not a patient meets the inclusion and exclusion criteria, the patient will be included. Following inclusion and treatment planning, a multi-professional team (MPT) including a radiation oncologist, medical physicist, radiographer/radiation therapist and if available a radiobiologist will be involved in determining the technical suitability of dose escalation by SBRT or hyperfractionated chemo-reirradiation or SIB in RT naïve patients. Radiotherapy dose escalation starts within 4 weeks after inclusion. Concomitant chemotherapy should be prescribed as current standard of care, which is capecitabine, administered orally with a dose of 825mg/m^2 bidaily on radiotherapy days. For patients with a DPD deficiency, the dose of concomitant chemotherapy should be reduced by 25-50%, based on the specific type of DPD deficiency, in accordance with current standard of care guidelines. The treating radiation oncologist is responsible for the counselling, administration and follow-up with regard to the treatment.

To ensure uniform delivery of radiotherapy, a quality assurance (QA) procedure with central assessment of individual cases will be performed for all patients. The QA procedure is described in more detail in a Radiotherapy Treatment Planning and Quality Assurance Guideline.

5.2 General radiotherapeutic conditions

General considerations and reirradiation specific details are based on the ESTRO guideline (under review) regarding the use, planning and delivery of reirradiation in rectal cancer.[56]

Previous radiotherapy plans

An essential part of the pre-treatment workup includes sourcing/requesting previous treatment details, including complete radiotherapy data. This data should preferably include full 3D imaging, structures, and dose distributions. If complete 3D data is not available, efforts should be made to gather as much as information as possible to recreate the spatial dose distributions.[56] At the very least the full list of clinical goals, including (near) maximum dose levels for all OOI, should be present. One should verify that this information is complete and corresponds to the actual delivered treatment (e.g., all scheduled fractions were delivered and no additional fractions, like sequential boost fractions, were added).

Image acquisitions

A reference CT (either a native CT or synthetic CT from MRI) with ≤3 mm slice-thickness is acquired in supine treatment position, maximally 7-10 days before the start of radiotherapy. The scan limits are 5 cm above the os ilium and 5 cm below the os ischii. Appropriate and reproducible immobilisation such as knee fix is applied according to local policies. A vacuum bag is not recommended. Bladder preparation (filling/emptying) and rectal emptying should be determined on an individual patient basis, taking into account organs of interest during prior treatment as well as the proximity of the organs of interest to the new target volume. An intravenous agent for CT is optional and may be administered, to enhance target volume delineation and will be decided by the local treating radiation oncologist. This should align with local centre policy. Additionally, other modality scans (MRI and/or PET-CT) may be acquired to aid the delineation, preferably in treatment position and with the appropriate image acquisition parameters to classify as RT simulation scan (e.g., flat couch, sufficient resolution, and high appropriate bandwidth in case of MRI).[57] It is advised to acquire the additional data sets just prior or immediately after the acquisition of the reference CT to aid the registration of the images.

Image registration

Multi-modality scans e.g., MRI and/or PET should be registered to the reference CT using a rigid registration with a focus region around the region of interest. The delineation is performed either on the reference CT (with the MRI and/or PET as guidance) or directly on the MRI if an MRI in treatment position is performed.

Target volumes

Target volumes and organs of interest (OOI) nomenclature is based on the recommendations in the American Association of Physicists in Medicine (AAPM) report TG-263 including a gross tumour volume (GTV), a clinical target volume (CTV) where appropriate and a planning target volume (PTV). Every delineation will undergo a review prior to the start of treatment by the central study team in a quality assurance (QA) meeting. A QA manual will be provided and updated if necessary. The QA manual has been instated, similarly to the PelvEx II study.[58, 59] Unlike the PelvEx II trial, the aim of the current study is not to properly treat the area at risk for an irradical resection (R1), but to increase local control and minimize toxicity. Hence the major difference will be a smaller and cropped CTV margin.

Table 1: Organs of interest (OOI) which should be delineated in the pelvis, when applicable (e.g., OOI are within 2 cm of the PTV).

Organ	Nomenclature	Description
Bladder	Bladder	Entire bladder should be contoured in its entirety (from base to dome) including bladder wall.
Femoral heads	Femur_Head_L/R	As according to Kronborg et al[60]: outer contour of the bones (cranially first slice with visible caput; caudally last slice with visible minor trochanter).
Os sacrum	Os_sacrum	As according to Kronborg et al[60]: outer contour of the sacral bone (cranially first slice with S1 including alae of the sacral bone; caudally last slice with S5. The neural foramina are included, the coccygeal bone is not included).
Anus	Anus	Including in and outer sphincter from the level of the anorectal junction. The anorectal junction is easiest recognised on coronal images, at the insertion of the levator ani into the puborectalis (continuous with the external sphincter).
Rectum	Rectum	With the with the cranial border at the sigmoid take-off where the rectum bends ventrally to the sigmoid. If LAR was performed only delineation the remnant of the rectum.
Sacral plexus	SacralPlexus	As according to Yi et al.[61] including identifiable anatomic structures from the L4-5 interspace to the level of the sciatic nerve.

Spinal Canal	SpinalCanal	As surrogate for of the cauda equina for spine lesions below the level of the spinal cord (on CT only).
Cauda Equina	CaudaEquina	Defined as the sac within the spinal canal. Cranial border is located at the caudal limit of the spinal cord, usually at the level of L1-2 vertebral bodies (only MRI only).
Small bowel loops	Bowel_Small	Loops will be delineated separately in case of an online adaptive procedure.
Sigmoid/colon	SigmoidColon	Colon_Sigmoid +/- Bowel_Large depending on adaptive strategy or not.
Large vessels		Internal and external iliac vessels.
Skin	Skin	5 mm inner rind of the external body contour.
Ureter	Ureter_right Ureter_left	Delineation from renal pelvis down to the insertion point into the bladder.
Penile bulb	Penile bulb	Delineation will start inferior to the apex of the prostate down to the level where it branches into the corpus spongiosum (contouring superior on T2 MRI).
Vagina	Vagina	Cranially below cervix until labia (on MR only).
Urethra	Urethra	From bladder to genitals (on MR only).

Some OOI will not have specific dose guidance but will be contoured for dose accumulation purposes.

Margins

In short, a CTV margin will be used in non-SBRT treatments. The CTV is a numerical expansion of the GTV (CTV margin provided below), but will be manually edited to exclude organs that are not involved. The edited CTV will be expanded to a PTV according to local policies. In general, the PTV margin will be smaller for online-adaptive procedures compared to non-adaptive treatments. Further details regarding the volume delineations and margins are provided in treatment sub paragraphs and in detail in the Radiotherapy Treatment Planning and Quality Assurance Guideline.

Evaluation of previous and cumulative dose evaluation

The method for dose summation is heavily dependent on the amount of information available and the anatomical variations between the primary and current treatment. To obtain the best estimate, all participating centres should follow the recommendations as described by the ESTRO Reirradiation Physics Working Group et al. for detailed, site-agnostic recommendations for cumulative dose evaluation for reirradiation.[62] Full 3D dose summation is preferable but not always feasible. If full DICOM RT information is available a dose summation should be performed using image registration unless an appropriate registration is not feasible (e.g., after major surgery this can be challenging). In that case, one should revert back to point dose estimated. In all cases, previous dose distributions should be rescaled to equieffective dose (typically equieffective dose EQD2Gy with α/β=3Gy) for normal tissue cumulative dose evaluation.[63]

Treatment planning and dose guidance

In general, radiation therapy should be delivered with photon energies ≥ 6 MV using external beam radiotherapy (EBRT). The use of IMRT or dynamic arc radiotherapy is mandated. Previous dose distributions should be accounted for as much as possible. Depending on the amount of information from the previous delivered dose that is available, one of the approaches as presented in Table 2 should be taken. The choice of approach and the resulting treatment plan will be discussed in the QA meeting prior to the start of treatment.

Dose planning

Treatment margins (CTV and PTV) for all radiation interventions are listed in detail the QA manual, whereas the constraints are given in the sections below (Table 3 and 4).

Dose process of treatment planning for reirradiation of LCCR is inherently challenging and difficult to standardise. Non-standard pelvic anatomy (due to surgical intervention(s)), recurrence location in organs without clear boundaries, significant variation in target position and shape, and the need to account for and evaluate previous radiation dose in treatment planning all add to the complexity. IMRT allows selection of gantry angles to utilise sharp beam penumbras, whereas VMAT is optimally delivered using half or quarter arcs to avoid unnecessary dose to previously irradiated tissues. The planning approach will therefore depend on the exact position of the new target relative to the original target and high dose volumes to OOI. When the volume is completely within the previous treatment volume (e.g., local recurrence in anastomosis), optimisation should proceed as for ‘de novo’ treatments with subsequent evaluation of cumulative equieffective dose to OOI. If no high dose overlap in critical OOI exists (e.g., inguinal node recurrence in exit dose of previous pelvic beams), careful field/arc arrangements

are required to avoid entry/exit dose through previously irradiated volumes. A partial overlap with previous targets or high dose volumes (e.g., recurrence in external iliac node on edge of previous PTV) may make it challenging to achieve full target coverage while keeping OOI doses within tolerance, particularly if cumulative doses of EQD2Gy α/β=3Gy >90Gy are planned. For the purpose of the trial, a certain underdosage of the PTV is allowed to meet OOI constraints.

A number of different strategies can routinely be employed to take the previous dose into account during the optimisation process, as summarised in Table 2.[1, 40, 64-68]

Table 2: Treatment plan optimization strategies actively taking previous dose into account as part of the treatment planning process[56]

1) Optimization structures from previous isodose levels	Up-front generation of isodose structures from previous dose distribution, representing relevant dose levels (e.g., 100%, 85%, 70% of previous prescription dose, or clinically relevant normal tissue dose levels in equieffective dose); mapped to the current imaging and included as avoidance or optimization volumes in plan optimization.
2) Optimization constraints based on previous max OOI doses	Previous maximum point dose to OOI (or sub-volume of OOI in vicinity of new target) subtracted from OOI cumulative maximum dose constraint to establish 'remaining' safe dose (in EQD2Gy). This is subsequently rescaled into current fractionation regime to establish max dose constraint for current plan optimization.
3) High dose overlap volumes	Initial standard plan optimization; followed by cumulative equieffective dose evaluation and identification of high dose overlap areas, for which new optimisation structures are generated to aid further optimization.
4) Background / bias dose for plan optimization	Use of the full previous dose distributions as a 'background' or 'bias' dose directly in plan optimization. This is not straightforward, as it requires iterative evaluation of cumulative equieffective dose, and although reported in the literature, this approach is not commonly available.[69, 70]

Chemotherapy

The incorporation of neoadjuvant concomitant or systemic chemotherapy as described below is standard of care in the Netherlands, and therefore are not considered as study interventions.

Radiotherapy for radiotherapy-naïve and previously irradiated patients will be combined with capecitabine administered orally in a dose of 825 mg/m^2 twice daily on radiotherapy treatment days, as in accordance with current national standard of care.[15] In case of unacceptable toxicity of capecitabine during induction chemotherapy (physician's discretion) Teysuno may be administered orally in a dose of 25 mg/m^2 twice daily on radiotherapy days.

Neoadjuvant chemotherapy is not subject of this study, but may be incorporated into the treatment strategy as in concordance with the current national standard of care.[15] Possible options are FOLFOX, FOLFOXIRI, FOLFIRI or CAPOX with or without bevacizumab/panitumumab/cetuximab. Radiotherapy should start within 3-6 weeks after the first day of the last cycle of neoadjuvant chemotherapy. Due to limited available data on the toxicity risks associated with reirradiation and concurrent administration of monoclonal antibodies[71, 72], it is recommended that bevacizumab/panitumumab/cetuximab should be stopped at least 6 weeks prior to start radiotherapy to minimize radio sensitization, and may be resumed at least one week after completion of radiotherapy.[71, 72] Laboratory tests (complete blood count, liver function, and kidney function), and an evaluation MRI and CT within 4-6 weeks of the start of radiotherapy are obliged as tumour regression may influence target volume delineation.

Online imaging

Treatment verification should be performed according to local protocol, with daily cone beam CT imaging as a minimum for the fractionated treatment regimens. Adaptive treatment is allowed including both MR or CBCT guided adaptive treatment. For SBRT adaptive treatment is mandatory.

Organs of interest constraints

There is no evidence regarding the optimal dose guidance for OOI in rectal (chemo)reirradiation. Patients receiving repeat reirradiation may accept a higher adverse effects risk, when the alternative is poor QoL with uncontrolled pelvic disease. In table 3 an overview of published data is summarized.[56] OOI constraints are provided per treatment arm separately. There is a range of α/β values per OOI published.[28] For practical purposes an α/β=3 Gy will be used for all late toxicity, with the exception of spinal cord (canal), sacral plexus and cauda equina where an α/β=2 Gy will be applied.

Since there is no consensus about the degree of tissue repair, some report cumulative dose and others do incorporate a tissue recovery factor. The initial constraints of Abusaris et al. were maximal EQD2Gy α/β=3Gy of 110 Gy for rectum and bowel and EQD2Gy α/β=3Gy of 120 Gy for bladder (Dmax was not further specified).[40] A maximum of 10 cc bowel, rectum and bladder was allowed to receive a higher Dmax. If the tumour was located in the bladder, rectum or colon than a higher volume of Dmax was allowed. The *UK SABR consortium guidance* does incorporate tissue recovery.[1] This prospective registry is ongoing and collects data from patients that receive reirradiation for oligometastatic/oligorecurrent disease in the pelvis. They use standard constraints, corrected for tissue recovery.

Table 3. Details of reirradiation publications suggesting constraints[56]

Reference	**Published constraints**
Cai et al.[38]	OOI constraints with no reference to cumulative doses therefore not relevant.
GRECCAR 15[73]	Trial protocol: • Cumulative bladder dose, (no α/β given) = <80Gy • Cumulative rectal dose, (no α/β given) = <76Gy • V40Gy to small bowel of <200cc, no α/β given (optimal constraint)
PelvEx II[68]	Trial protocol: • Optimise dose to PTV with no compromise for OOI
Abusaris et al[40]	Retrospective SBRT cohort delivered as per below with no grade 3-5 toxicity: • Median cumulative rectal EQD2Gyα/β=3Gy <104Gy (65-129Gy) • Median cumulative bowel EQD2Gyα/β=3Gy <98Gy (range 56-144Gy) • Median cumulative bladder EQD2Gyα/β=3Gy <113Gy (range 79-235Gy)
TORCH-R[64]	SBRT Trial protocol: • Cumulative constraints for each organ from standard UK SABR consortium guidance[1] plus 15% recovery per year from primary irradiation
UK SABR Consortium Guidance[1]	Guidance document: • Cumulative constraints for each organ using standard UK SABR consortium guidance[1]plus 30% recovery if primary irradiation 6-18 months ago, 50% if >18 months. Please refer to Table 4 for OOI constraints.

5.2.1 Stereotactic Body Radiation Therapy (SBRT)

In accordance with the *UK SABR consortium guidance* for Stereotactic ablative body radiotherapy (SBRT) reirradiation for oligometastatic / oligorecurrent disease in the pelvis[(1)], patients are eligible for stereotactic radiotherapy if the tumour is:

- <6 cm in diameter
- is not infiltrating the lumen of the bowel- or bladder wall.

SBRT reirradiation is not appropriate in case of:

- Direct invasion of a luminal organ at risk
- In the presence of moderate (e.g., CTCAE grade 2) or severe (e.g., CTCAE grade 3 or greater) previous/persistent late radiotherapy-induced toxicity

In general, no CTV is used in well demarcated tumours, e.g., lateral lymph nodes. In case of OOI involvement such as bone a CTV margin of 3 mm is suggested, keeping in mind the balance between improved local control versus higher risk of adverse event(s).[(1)] The primary goal of SBRT in this setting is to maximise local control. Hence, a high dose of 5x9 Gy will be delivered, prescribed to the 100% isodose line. Maximum dose will be D0.1cc >110% and <130% of prescription and must be within the PTV (according to the *UK SABR consortium guidance*).[(1)] A minimum coverage criterion of 70% of the PTV covered by the prescription isodose (D100%) is applied in circumstances where compromise of the PTV coverage is necessary to meet OOI constraints as suggested by the Re-irradiation Delphi consensus.[(74)] In case of less coverage it is recommended to change to a hyperfractionated regimen.

Based on the UK consortium guidance[(1)], a 30% recovery will be incorporated into the original dose delivered, when performing calculations for OOI constraints for patients with 6 – 18 months from their previous radiation therapy treatment.

For patients with >18 months from their previous radiation therapy treatment, a 50% recovery will be incorporated into the original dose delivered, when performing calculations for OOI constraints. To aid dose calculations an excel file is available.

The SBRT consortium constraints are similar to the AAPM constraints. The Catharina Hospital Eindhoven (CZE) is a bit more lenient in the lower dose higher volume constraints (Table 4). However, for the purpose of this study, the stricter constraints of the SABR consortium will be applied.

Table 4: SBRT UK consortium guidance SBRT reirradiation pelvis[1]. Except for colon from APPM. Also CZE and AAPM as comparison.[56]

OOI (organ of interest) or PTV	UK SABR-consortium	CZE (LN01 MR guided)	AAPM
Small bowel	D0.1cc<35 Gy D10cc<25 Gy	D0.1cc<35 Gy D1cc<33 Gy D5cc<26Gy	D0.035cc<35Gy D5cc<19.5
Large bowel/rectum	D0.1cc<38 Gy	D0.1cc<38 Gy D1cc<36.25 Gy D5cc<34.44 Gy D10cc<32.63Gy D20cc<25Gy	D0.035cc<38Gy D20cc<25Gy
Bladder	D0.1cc<38 Gy	D0.1cc<38Gy D1cc<37 Gy D5cc<36.25 Gy D15cc<32.63 Gy	D0.035cc<38Gy D15cc<18.3 Gy
Femoral Head	D10cc<30 Gy	D10cc<30Gy	D10cc<30 Gy
Skin	D0.5cc<39.5 Gy D10cc<36.5	N/A	D0.035cc<39.5 Gy D10cc<36.5 Gy
Cauda equina / lumbosacral plexus	D0.1cc<32 Gy D5cc<30 Gy	N/A	D0.035cc<32 Gy D10cc<30 Gy
Ureter	D0.5cc<45 Gy	N/A	N/A
Penile bulb	D0.5cc<50 Gy D3cc<30 Gy	N/A	D0.035<50 Gy D3cc<30 Gy
PTV PTV	V100%≥70% D0.1cc 110% and <130%	V95% > 97% D0.5cc<125%	

5.2.2 Hyperfractionated chemo-reirradiation

Patients that have a large recurrence where re-SBRT constraints cannot be met, will be treated with hyperfractionated reirradiation. The GTV will be delineated based on baseline pelvic MRI and CT or RT-simulation imaging. If neoadjuvant chemotherapy was given prior to inclusion, a new diagnostic MRI should be made to aid tumour delineation. A CTV tumour margin of 5 mm will be used, cropped for non-involved OOI. Depending on whether there is an online adaptive procedure, PTV margins will be 7 – 10 mm for non-adaptive procedures, and 4 – 6 mm for adaptive procedures. The tumour without elective lymph nodes will be treated with a dose of 50.4 Gy, delivered in 42 fractions of 1.2 Gy BID with a least 6 hours in between fractions. As the cumulative physical dose of 100.4 Gy does not exceed the re-SBRT constraints in EQD2Gy α/β=3 Gy, there will be no other OOI constraints than that there should be no hotspots, i.e., the D0.5cc is maximum 107% of the prescribed dose, preferably maximum 100% within OOI.
PTV coverage should be:

PTVtot-Skin05	V95% > 98%
PTVtot-Skin05	V90% > 99%
PTVtot-Skin05	D0.5cc <107%

As standard of care, concomitant capecitabine will be administered orally with a dose of 825 mg/m^2 on radiotherapy days.

5.2.3 Full-course chemoradiotherapy

Full-course chemoreirradiation will be the study treatment for radiotherapy-naïve patients with unresectable LRRC (without distant metastases, or with (oligo)metastatic disease that does not require imminent start of systematic therapy). Treatment will be delivered with a simultaneous integrated boost (SIB) technique. As current standard of care, concomitant capecitabine will be administered orally with a dose of 825 mg/m^2 on radiotherapy days as radiosensitizer. After pelvic surgery small bowel may have moved to the small pelvis, limiting dose escalation or elective fields in general. This will have to be judged per patient, i.e., during a QA meeting. Nevertheless, invasion of luminal organs such as the small bowel and bladder will be a contra-indication for a boost arm.

The elective volume will be delineated according to the national guidelines. The prescribed dose will be 25 fractions of 2 Gy to the elective volume and 25 fractions of 2.6 Gy up to 65 Gy corresponding to an equieffective EQD2Gy α/β=3Gy of 72.8 Gy and EQD2Gy α/β=10Gy of 68.25 Gy using a SIB technique to the primary tumour. Lymph nodes will not receive a boost dosis, but standard elective dose of 50 Gy. There will be a CTV tumour margin of 5 mm cropped

for uninvolved OOI. The PTV tumour boost margin will be preferably 3 - 5 mm depending on tumour location and position verification protocol. The elective PTV will be 7-15 mm depending on local policies. PTV coverage will be the same as in reirradiation setting (Table page 36). Dose constraints for the bowel bag will be according to the EMBRACE protocol with D2cc<75 Gy with α/β=3Gy (2, 75). Further details will be provided in the QA manual.

Target	**D90 CTV_{HR} $EQD2_{10}$**	**D98 CTV_{HR} $EQD2_{10}$**	**D98 GTV_{res} $EQD2_{10}$**	**D98 GTV_{IR} $EQD2_{10}$**	**Point A $EQD2_{10}$**
OOI	Bladder D_{2cm^3} $EQD2_3$	Rectum D_{2cm^3} $EQD2_3$	Recto-vaginal point $EQD2_3$	Sigmoid D_{2cm^3} $EQD2_3$	Bowel D_{2cm^3} $EQD2_3$
Planning aims	< 80 Gy	< 65 Gy	< 65 Gy	< 70 Gy	< 70 Gy
Limits for prescribed dose	< 90 Gy	< 75 Gy	< 75 Gy	< 75 Gy	< 75 Gy

5.3 Follow-up: radiation-related toxicity

Patients are consulted before the start of treatment (baseline) and after completion of radiotherapy dose escalation (last week of radiotherapy, at 2 weeks after radiotherapy (at 6 weeks only required if toxicity is present, as indicated), thereafter at 3, 6, 12, 24 and 36 months). Both out-patient clinic visits or follow up by telephone is allowed. Toxicity is registered at each consultation for rectal pain, rectal haemorrhage, dermatitis reaction, diarrhoea, weight loss, urinary obstruction, neuropathy and other non-prespecified toxicities according to the Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0. Simultaneously, patients are asked to fill out the quality-of-life questionnaires at baseline and 3-, 6-, 12-, 24- and 36-months post radiotherapy treatment.

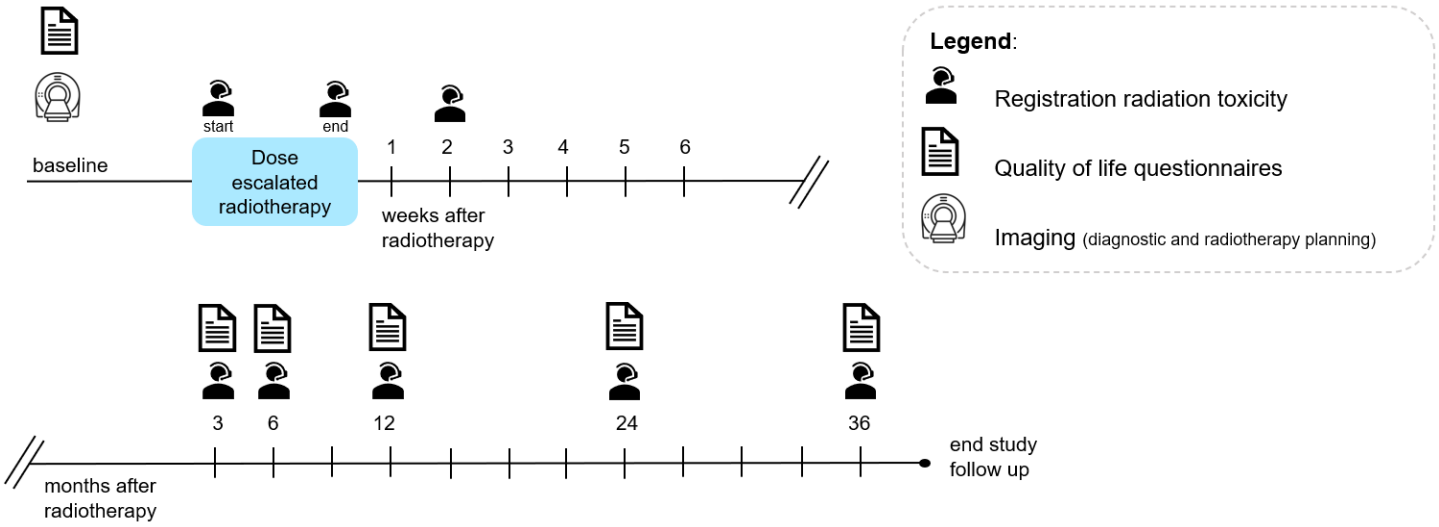
5.4 Follow-up: radiology

Figure 2 presents schedules of all interventions and follow-up assessments patients undergo in the radiotherapy dose escalation intervention. Radiological follow-up is performed according to local practice. A high-dose thoracoabdominal CT-scan should be performed three months after completion of radiotherapy, every six months for the first two years, and annually thereafter. An MRI or FDG-PET/CT-scan should be performed to assess local and distant control, in line with local protocols.

5.5 Questionnaires

All patients participating in the study receive validated quality of life questionnaires. Patients are asked to complete QLQ-C30, QLQ-CR29 and EQ-5D-5L at inclusion, 3-, 6-, 12- and 24 and 36-months post radiotherapy treatment. Patients receive questionnaires either by mail or digitally, according to their own preference.

FIGURE 2. TIMELINE OF STUDY INTERVENTION AND FOLLOW-UP ASSESSMENTS



6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

The main study parameter is to determine the feasibility of radiotherapy dose escalation in LRRC patients undergoing non-operative management, defined as ≤7 participants grade 3-5 acute radiation-induced toxicity (<3 months) *, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

6.1.2 Secondary study parameters/endpoints

Secondary analyses will focus on oncological and symptomatic outcomes. The following secondary parameters have been defined:

(1) Acute and late radiation-induced toxicity (stratified per arm)
(2) overall quality of life and well-being**
(3) one-, two- and three-year local control
(4) one-, two- and three-year progression-free survival
(5) one-, two- and three-year disease-free survival
(6) one-, two- and three-year overall survival
(7) compliance of treatment with radiotherapy dose escalation

**Treatment toxicity is defined as:*

- acute radiation-induced toxicity grade 3-5 presenting within 3 months post radiotherapy treatment, according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. (Appendix 12.1);
- late radiation-induced related toxicity grade 3 and 4 radiotherapy toxicity occurring after 3 months until 36 months post radiotherapy treatment or until date of death, defined by the common toxicity criteria of adverse events (CTCAE) version 5.0 (Appendix 12.1).

***Overall quality of life and well-being:*

Quality of life of patients undergoing radiotherapy dose escalation will be evaluated with a composite questionnaire using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL and QLQ-CR29 (Appendix 12.2) as well as the EuroQol EQ-5D-5L questionnaire. The use of this composite questionnaire is approved by the EORTC. The quality of life will be assessed at baseline (within two weeks of the inclusion), at 3 months, 6 months, 12 months, 24 months and 36 months post radiotherapy treatment. The questionnaires will be sent either by mail of digitally, according to the patient's preference.

6.2 Data collection

The following data are registered from all patients in the study:

- Patient characteristics (e.g., age, sex, WHO performance score, comorbidities)
- Tumour characteristics of primary tumour (e.g., tumour type and differentiation, location, abscess/fistulae, TNM stage of primary tumour, molecular diagnostics (MRR status, RAS and BRAF mutation and Her2 amplification), synchronous or metachronous metastases)
- Treatment of primary tumour (e.g., neoadjuvant therapy (radiotherapy, chemotherapy, chemoradiotherapy), surgical procedure, radicality of primary resection)
- Tumour characteristics of the recurrent tumour (e.g., tumour type, location, abscess/fistulae, M-stage, time to LRRC and reirradiation)
- Aetiology of the LRRC (e.g., complicated treatment course of the primary tumour, anastomotic leakage, lymph node recurrence etc.)
- Radiotherapy related toxicity (according to CTCEA v5.0)
- Locoregional control, progression-free survival, disease-free survival and overall survival
- Radiological and/or radiotherapeutic data from MRI- and CT scans
- All radiotherapy details of previous and current treatment (including full 3D imaging, structures and dose distributions)

6.3 Study procedures

Figure 1 (chapter 3) shows a flowchart of the study. *Figure 2* (chapter 5) presents schedules of all interventions and assessments patients undergo in the radiotherapy dose escalation intervention.

6.4 Withdrawal of individual research participants

Participants can leave the study at any time for any reason without any consequences if they wish to do so. The investigator can decide to withdraw a participant from the study for urgent medical reasons. In the specific case patients have already been included for the feasibility study, however, radiotherapy dose escalation appears not feasible due to tumour characteristics or clinical condition, patient will be excluded from the feasibility study and labelled as “screening failure”. These patients do not count as failures of treatment in the feasibility study, but will receive alternative non-operative treatment options.

6.5 Replacement of individual research participants after withdrawal

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The withdrawal of the informed consent shall not affect the activities already carried out and the use of data obtained based on informed consent before its withdrawal. The investigator can decide to withdraw a subject from the study for urgent medical reasons or in case of a screenings-failure or major protocol violation. If a study subject withdraws from the study after commencement of radiotherapy, no replacement will be performed. If a study subject withdraws from the study before commencement of radiotherapy, the subject will be replaced by another patient.

6.6 Follow-up of research participants withdrawn from treatment

Patients withdrawn from the treatment will be followed-up and analyzed for all major outcomes.

6.7 Premature termination of the study

Premature termination of the study will take place when the risk-benefit ratio becomes unacceptable based on safety findings of any interim analysis from this study or upcoming information from other clinical studies. After premature termination of the study, the investigators must contact all participating subjects within 4 weeks. No new patients are included in the trial. Follow-up of participating subjects will continue, following the study protocol. In case of premature termination of the study, this will not have a direct consequence for the treatment or follow-up of the study patients.

7. SAFETY REPORTING

7.1 Temporary halt for reasons of research participant safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise participant health or safety. The sponsor will notify the review committee without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the review committee. The investigator will take care that all participants are kept informed.

A predefined safety stopping rule will be applied for each treatment arm separately: inclusion within a fractionation arm will be suspended if ≥2 treatment-related CTCAE v5.0 grade 5 toxicities (treatment-related deaths) are observed in that arm.

7.2 AEs, SAEs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a participant during the study, when related to the radiotherapy intervention of the study. All grade ≥3 non-haematological adverse events determined by CTCAE v5.0, all grade ≥4 haematological adverse events determined by CTCAE v5.0 reported spontaneously by the participant or observed by the investigator or his/her staff will be recorded. The time window for recording (S)AEs is from inclusion till 12 months after the last day of radiotherapy treatment. Remaining late toxicities will be registered until 36 months after the last day of radiotherapy treatment or until date of death. Information on all AEs is recorded in the eCRF.

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator shall report serious adverse events to the sponsor without undue delay after obtaining knowledge of the events, unless, for certain serious adverse events (SAE's not related to the radiotherapy dose escalation), the protocol provides that no immediate reporting is required. SAE's occurring in the participating centres will be communicated and reported to the initiating centre (Catharina Hospital, Eindhoven) using a standardized SAE reporting form. The decision regarding relationship to radiotherapy dose escalation will be recorded on the SAE report. The assessment of causality to radiotherapy treatment is made by the local investigator using the following criteria: unrelated, unlikely related, possibly related, probably related and definitely related.

The sponsor will report the SAEs through the web portal *Research Portal* to the review committee that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

7.2.3 List of acute toxicities excluded from feasibility stopping rule

For feasibility assessment, certain expected acute toxicities that are commonly observed with both chemotherapy and (chemo)radiotherapy will not be counted toward the feasibility stopping criterion and will not independently trigger premature study closure.

The following acute toxicities are excluded from the feasibility endpoint:

- Fatigue (CTCAE v5.0 grade 3)
- Diarrhoea (CTCAE v5.0 grade 3)
- Nausea/vomiting (CTCAE v5.0 grade 3)
- Radiation dermatitis (CTCAE v5.0 grade 3)
- Hand-foot syndrome (CTCAE v5.0 grade 3)
- Proctitis (CTCAE v5.0 grade 3)
- Mucositis (CTCAE v5.0 grade 3)
- Haematological (CTCAE v5.0 grade 3 or higher)

Relevant acute toxicities included in the feasibility endpoint include, but are not limited to:

- Ileus (CTCAE v5.0 grade ≥3)
- Gastro-intestinal perforation (CTCAE v5.0 grade ≥3)

- Gastro-intestinal fistula (CTCAE v5.0 grade ≥3)
- Ureter tract obstruction (CTCAE v5.0 grade ≥3)

All abovementioned (serious) adverse events must be reported according to the protocol. The investigator must provide an assessment of the relationship to radiotherapy and/or chemotherapy. All reported SAE's, irrespectively of their potential attribution and relationship to treatment, will be presented to the DSMB to allow full safety profile evaluation.

If a patient presents with toxicities at baseline, any worsening during radiation treatment should be reviewed by the central study team and DSMB to determine whether the event represents treatment-related toxicity, or progression of a pre-existing condition. SAE's that are attributable to disease progression do not require expedited reporting.

7.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

7.4 Data Safety Monitoring Board (DSMB)

The central DSMB consists of two radiation oncologists with relevant expertise, a medical physicist, and a research methodologist (e.g., epidemiologist or statistician), all of whom are independent of the study and have no competing interests. All relevant data is made available to the DSMB by the central datamanager and the study statistician. The DSMB meetings will take place before the start of the study and upon completion of the primary endpoint following every three patients, with the option to increase the frequency of review if required. In addition, explicit safety stopping rules have been defined for severe grade 5 toxicity. In the event of a treatment-related CTCAE v5.0 grade 5 toxicity (treatment-related death), inclusion in the corresponding treatment arm will be temporarily suspended and an expedited DSMB meeting will be convened within one week to evaluate the event and provide recommendations regarding study continuation. Permanent closure of a treatment arm will occur if ≥2 treatment-related CTCAE v5.0 grade 5 toxicities are observed within that arm. Cessation of the study is warranted if the criteria for termination as described in section 6.7 have been met. In all other situations, the DSMB advices the study steering committee on study continuation or termination based on the available data and their expertise. The advice(s) of the DSMB will

only be sent to the study steering committee. The study steering committee will send the advice to the reviewing METC. Should the study steering committee decide not to fully implement the advice of the DSMB, the study steering committee should include a note to substantiate why (part of) the advice of the DSMB will not be followed.

8. STATISTICAL ANALYSIS

Before the official lock of an export from the database, a detailed Statistical Analysis Plan (SAP) will be prepared. Demographics, patient and tumour characteristics will be summarized. Continuous data are reported as mean with standard deviation or as median with interquartile range, as appropriate depending on the distribution. Categorical data are reported as count with percentage. All statistical tests will be two-sided and a p-value of less than 0.05 will be classified as statistically significant. Patients initially randomised but considered ineligible afterwards based on information that should have been available before inclusion, will be excluded from all analysis. Outcomes will be analysed using descriptive statistics, a mixed-effects models (for patient-reported outcomes) or Kaplan-Meier method (for time-to-event data).

8.1 Primary study parameter

The primary endpoint of this study is the incidence of grade 3-5 acute radiation-induced toxicity (<3 months) from the start of radiotherapy, graded according to the CTCAE, version 5.0. This will be presented as count with exact 95% confidence interval.

8.2 Secondary study parameters

Acute grade 3-5 (<3 months) and late (90 days up to 36 months) radiation-induced toxicity grade 3 and 4, according to the CTCAE version 5.0 will be analysed descriptively and stratified per arm. All survival curves will be constructed using the Kaplan-Meier method. Infield progression-free survival will be calculated from the date of start radiotherapy until the date of radiological or clinical confirmed infield progression. Death as first event will be censored as well as patients without any infield progression at last follow-up. Outfield progression-free survival will be calculated from the date of start radiotherapy until the date of radiological or clinical confirmed outfield progression. Progression-free survival will be calculated from the date of start radiotherapy until the date of radiological or clinical confirmed locoregional progression. Disease-free survival will be calculated from the date of start radiotherapy until the date of first documented signs of locoregional progression, the date of distant metastases or the date of death from any cause, whichever occurs first. Patients who are still alive at last follow-up will be censored. Overall survival will be calculated from the date of inclusion until the date of death from any cause, censoring patients who are still alive at last follow-up. The reported mean level of health-related quality of life will be analysed per time interval with 95%

confidence interval. To appropriately account for repeated measurements within patients over time, a repeated measures analysis will be performed. For normally distributed data, a Linear Mixed-Effects Model will be used. If the normality assumption of the residuals is violated, robust standard errors will be estimated using the sandwich estimator.

7.3 Interim analysis (if applicable)

Not applicable considering intensive safety monitoring and frequent review and evaluation by DSMB.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent

Patient's pathway is presented in section 5. In case of an indication for radiotherapy as part of non-operative management for LRRC, the potential radiotherapy dose escalation strategies are explored in case patient is interested and the treating physician will briefly inform the patient about the study. If the patient is interested in study participation, permission will be asked for a member of the research team to approach the patient. If patient agrees, a member of the research team will provide detailed written and oral information regarding the study. Each patient has sufficient time (minimum of 48 hours) to consider participation. Written informed consent will be obtained by the researcher at the outpatient clinic. Important is that inclusion will take place after extensive informing (about risks and benefits) of the patient and obtaining written informed consent.

9.3 Objection by minors or incapacitated subjects

Minors and incapacitated patients are not eligible for the study.

9.4 Benefits and risks assessment

The potential benefit of radiotherapy dose escalation in the non-operative management of patients with unresectable LRRC has to be weighed against the associated burden and risks of toxicity. Importantly, this study addresses a patient population in which treatment is primarily palliative, aimed at achieving local disease control and symptom relief, with otherwise limited therapeutic options. The primary risks of this study are related to treatment-associated toxicity and morbidity. Radiotherapy dose escalation may result in both acute and late adverse effects. Acute and late toxicity may include gastro-intestinal disorders (ileus, diarrhoea, gastroparesis, nausea/weight loss), abdominal infections (intra-abdominal abscess, presacral abscess), renal and urinary disorders (urinary tract obstruction, urinary retention, urinary incontinence, acute

kidney injury), delayed wound healing, erectile dysfunction and peripheral neuropathy. These toxicities may negatively impact quality of life. The extent and severity of these effects may vary between patients. Toxicity related to radiotherapy will be closely monitored as the primary outcome, with continuous evaluation throughout the study. Preliminary results of radiotherapy dose escalation in locally advanced rectal cancer and curative setting in LRRC have demonstrated to be safe and feasible. Nevertheless, uncertainty remains regarding the balance between potential benefits and risks in this specific patient group with unresectable LRRC.

For patients receiving hyperfractionated chemo-reirradiation, the total duration of radiotherapy will be 4 weeks. For those undergoing full-course chemoradiotherapy, the treatment will last 5 weeks. For patients treated with SBRT, the treatment duration is shortened to 2 weeks. In addition, to carefully monitor radiation-related toxicity within the study, patients will be consulted before and after start of treatment (both out-patient clinic visits or follow up by telephone is allowed to minimize burden on participants). Lastly, patients will be asked to complete patient-reported outcome questionnaires, which are brief, intuitive, and tailored to the study population, thereby minimizing the burden on participants. Participation of the questionnaires is optional.

Radiotherapy dose escalation may induce local tumour response and thereby contribute to symptom relief, which in turn, could enhance quality of life. Overall, given the treatment intent and limited therapeutic alternatives to provide symptomatic relief to this patient group, the investigators believe that the expected benefits of participation in this study outweigh the potential risks and burden associated with the treatment.

9.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research participants through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9.6 Incentives

This study has no special incentives, compensation, or treatment for participating patients.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Privacy of the patients will be protected by giving all patients a unique anonymized study number. This number does not include details derived from participant's details. The key-document that links the patient's identification code to the participants details will be safe-guarded by a password, known only by the responsible local study coordinators of the study centre. Hereby, outsiders cannot relate any results or data back to the participant. All radiotherapeutic, imaging and questionnaire data will be encoded to ensure an anonymous data collection. Castor database management will be used for electronic Case Report Forms. Archiving of documents will be continued until the project has finished. These documents will be stored for a maximum duration of 15 years after completion of the study. These data will be accessible to the current and future members of the research team. Patients who do not agree with these terms, are excluded from participation.

10.2 Monitoring and Quality Assurance

The study will be monitored based on the recommendations as described in the brochure "Kwaliteitsborging mensgebonden onderzoek 2.0", published in October 2012 by the Dutch Federation of University Medical Centres (NFU). The monitor plan is based on the judgement of the project leader that the study treatment takes high risk for the participating patients. In the Netherlands, the study will be monitored by independent qualified monitors. Further detail on the aspects and frequency of monitoring and quality assurance can be found in a separate monitoring plan.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the review committee has been given. All amendments will be notified to the review committee that gave a favourable opinion.

Non-substantial amendments will not be notified to the review committee, but will be recorded and filed by the sponsor.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the review committee once a year. Information will be provided on the date of inclusion of the first participant, numbers of participants included and numbers of participants that have completed the trial, serious adverse events, other problems, and amendments.

10.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the review committee of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the review committee immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the review committee within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the review committee.

10.6 Public disclosure and publication policy

The publication policy according to the CCMO is being followed, meaning that positive as well as negative results will be published. The publication policy is established in the clinical trial agreement between sponsor and participating centres. We have aimed to acquire multiple publications in various international journals and to give presentations at congresses. The order of other authors will be determined at time of submission of any abstracts or papers. The registration policy of The International Committee of Medical Journal Editors (ICMJE) is followed. For (prospective) clinical trials the ICMJE requires, as a condition for consideration for publication, registration of clinical trials in a public trials' registry at or before the time of first patient enrolment as a condition of consideration for publication.

11. REFERENCES

1. Moreno-Olmedo E, Owczarczyk K, Chadwick E, Dickinson P, Duffton A, Jones B, et al. Pelvic stereotactic ablative body radiotherapy (SABR) reirradiation: UK SABR consortium guidance for use in routine clinical care. Tech Innov Patient Support Radiat Oncol. 2025;35:100326.
2. Suwinski R, Wzietek I, Tarnawski R, Namysl-Kaletka A, Kryj M, Chmielarz A, Wydmanski J. Moderately low alpha/beta ratio for rectal cancer may best explain the outcome of three fractionation schedules of preoperative radiotherapy. Int J Radiat Oncol Biol Phys. 2007;69(3):793-9.
3. Guren MG, Undseth C, Rekstad BL, Braendengen M, Dueland S, Spindler KL, et al. Reirradiation of locally recurrent rectal cancer: a systematic review. Radiother Oncol. 2014;113(2):151-7.
4. Gao Z, Gu J. Surgical treatment of locally recurrent rectal cancer: a narrative review. Ann Transl Med. 2021;9(12):1026.
5. Tanis PJ, Doeksen A, van Lanschot JJ. Intentionally curative treatment of locally recurrent rectal cancer: a systematic review. Can J Surg. 2013;56(2):135-44.
6. van der Meij W, Rombouts AJ, Rutten H, Bremers AJ, de Wilt JH. Treatment of Locally Recurrent Rectal Carcinoma in Previously (Chemo)Irradiated Patients: A Review. Dis Colon Rectum. 2016;59(2):148-56.
7. Dijkstra EA, Nilsson PJ, Hospers GAP, Bahadoer RR, Meershoek-Klein Kranenbarg E, Roodvoets AGH, et al. Locoregional Failure During and After Short-course Radiotherapy Followed by Chemotherapy and Surgery Compared With Long-course Chemoradiotherapy and Surgery: A 5-Year Follow-up of the RAPIDO Trial. Ann Surg. 2023;278(4):e766-e72.
8. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. 2011;12(6):575-82.
9. Banken E, Creemers DMJ, Kerckhove F, Ketelaers SHJ, van Hellemond IEG, Peulen HMU, et al. Palliative management of patients with locally recurrent rectal cancer: Clinical presentation, treatment strategies, and overall survival. Eur J Surg Oncol. 2025;51(7):109758.
10. Nielsen MB, Laurberg S, Holm T. Current management of locally recurrent rectal cancer. Colorectal Dis. 2011;13(7):732-42.
11. Kusters M, Dresen RC, Martijn H, Nieuwenhuijzen GA, van de Velde CJ, van den Berg HA, et al. Radicality of resection and survival after multimodality treatment is influenced by subsite of locally recurrent rectal cancer. Int J Radiat Oncol Biol Phys. 2009;75(5):1444-9.
12. Westberg K, Palmer G, Hjern F, Holm T, Martling A. Population-based study of surgical treatment with and without tumour resection in patients with locally recurrent rectal cancer. Br J Surg. 2019;106(6):790-8.
13. Nielsen M, Rasmussen P, Pedersen B, Hagemann-Madsen R, Lindegaard J, Laurberg S. Early and Late Outcomes of Surgery for Locally Recurrent Rectal Cancer: A Prospective 10-Year Study in the Total Mesorectal Excision Era. Ann Surg Oncol. 2015;22(8):2677-84.
14. Hagemans JAW, van Rees JM, Alberda WJ, Rothbarth J, Nuyttens J, van Meerten E, et al. Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre. Eur J Surg Oncol. 2020;46(3):448-54.
15. Piqeur F, Creemers DMJ, Banken E, Coolen L, Tanis PJ, Maas M, et al. Dutch national guidelines for locally recurrent rectal cancer. Cancer Treat Rev. 2024;127:102736.
16. PelvEx C. Contemporary Management of Locally Advanced and Recurrent Rectal Cancer: Views from the PelvEx Collaborative. Cancers (Basel). 2022;14(5).
17. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rodel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv263.
18. Beyond TMEC. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. Br J Surg. 2013;100(8):1009-14.
19. Bhangu A, Ali SM, Darzi A, Brown G, Tekkis P. Meta-analysis of survival based on resection margin status following surgery for recurrent rectal cancer. Colorectal Dis. 2012;14(12):1457-66.
20. Gould LE, Pring ET, Drami I, Moorghen M, Naghibi M, Jenkins JT, et al. A systematic review of the pathological determinants of outcome following resection by pelvic exenteration of locally advanced and locally recurrent rectal cancer. Int J Surg. 2022;104:106738.
21. Palmer G, Martling A, Cedermark B, Holm T. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. Ann Surg Oncol. 2007;14(2):447-54.

22. Detering R, Karthaus EG, Borstlap WAA, Marijnen CAM, van de Velde CJH, Bemelman WA, et al. Treatment and survival of locally recurrent rectal cancer: A cross-sectional population study 15 years after the Dutch TME trial. Eur J Surg Oncol. 2019;45(11):2059-69.
23. Swartjes H, van Rees JM, van Erning FN, Verheij M, Verhoef C, de Wilt JHW, et al. Locally Recurrent Rectal Cancer: Toward a Second Chance at Cure? A Population-Based, Retrospective Cohort Study. Ann Surg Oncol. 2023;30(7):3915-24.
24. Kodeda K, Derwinger K, Gustavsson B, Nordgren S. Local recurrence of rectal cancer: a population-based cohort study of diagnosis, treatment and outcome. Colorectal Dis. 2012;14(5):e230-7.
25. Camilleri-Brennan J, Steele RJ. The impact of recurrent rectal cancer on quality of life. Eur J Surg Oncol. 2001;27(4):349-53.
26. Nordkamp S, Piqeur F, van den Berg K, Tolenaar JL, van Hellemond IEG, Creemers GJ, et al. Locally recurrent rectal cancer: Oncological outcomes for patients with a pathological complete response after neoadjuvant therapy. Br J Surg. 2023;110(8):950-7.
27. Nordkamp S, Voogt ELK, van Zoggel D, Martling A, Holm T, Jansson Palmer G, et al. Locally recurrent rectal cancer: oncological outcomes with different treatment strategies in two tertiary referral units. Br J Surg. 2022;109(7):623-31.
28. Andratschke N, Willmann J, Appelt AL, Alyamani N, Balermpas P, Baumert BG, et al. European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus on re-irradiation: definition, reporting, and clinical decision making. Lancet Oncol. 2022;23(10):e469-e78.
29. Lee J, Kim CY, Koom WS, Rim CH. Practical effectiveness of re-irradiation with or without surgery for locoregional recurrence of rectal cancer: A meta-analysis and systematic review. Radiother Oncol. 2019;140:10-9.
30. Valentini V, Morganti AG, Gambacorta MA, Mohiuddin M, Doglietto GB, Coco C, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. Int J Radiat Oncol Biol Phys. 2006;64(4):1129-39.
31. Tao R, Tsai CJ, Jensen G, Eng C, Kopetz S, Overman MJ, et al. Hyperfractionated accelerated reirradiation for rectal cancer: An analysis of outcomes and toxicity. Radiother Oncol. 2017;122(1):146-51.
32. Appelt AL, Ploen J, Vogelius IR, Bentzen SM, Jakobsen A. Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. Int J Radiat Oncol Biol Phys. 2013;85(1):74-80.
33. Burbach JP, den Harder AM, Intven M, van Vulpen M, Verkooijen HM, Reerink O. Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: a systematic review and meta-analysis. Radiother Oncol. 2014;113(1):1-9.
34. Hearn N, Atwell D, Cahill K, Elks J, Vignarajah D, Lagopoulos J, Min M. Neoadjuvant Radiotherapy Dose Escalation in Locally Advanced Rectal Cancer: a Systematic Review and Meta-analysis of Modern Treatment Approaches and Outcomes. Clin Oncol (R Coll Radiol). 2021;33(1):e1-e14.
35. Couwenberg AM, Burbach JPM, Berbee M, Lacle MM, Arensman R, Raicu MG, et al. Efficacy of Dose-Escalated Chemoradiation on Complete Tumor Response in Patients with Locally Advanced Rectal Cancer (RECTAL-BOOST): A Phase 2 Randomized Controlled Trial. Int J Radiat Oncol Biol Phys. 2020;108(4):1008-18.
36. Chung SY, Koom WS, Keum KC, Chang JS, Shin SJ, Ahn JB, et al. Treatment Outcomes of Re-irradiation in Locoregionally Recurrent Rectal Cancer and Clinical Significance of Proper Patient Selection. Front Oncol. 2019;9:529.
37. Vande Kerckhove FEC, Piqeur F, Banken E, Morsink NC, Rijkaart DC, Cnossen JS, et al. Neoadjuvant chemo-reirradiation followed by resection and intraoperative electron beam radiotherapy: outcomes of multimodality treatment for locally recurrent rectal cancer. Radiat Oncol. 2025;21(1):21.
38. Cai G, Zhu J, Hu W, Zhang Z. Accelerated hyperfractionated intensity-modulated radiotherapy for recurrent/unresectable rectal cancer in patients with previous pelvic irradiation: results of a phase II study. Radiat Oncol. 2014;9:278.
39. Murray LJ, Lilley J, Hawkins MA, Henry AM, Dickinson P, Sebag-Montefiore D. Pelvic re-irradiation using stereotactic ablative radiotherapy (SABR): A systematic review. Radiother Oncol. 2017;125(2):213-22.
40. Abusaris H, Hoogeman M, Nuyttens JJ. Re-irradiation: outcome, cumulative dose and toxicity in patients retreated with stereotactic radiotherapy in the abdominal or pelvic region. Technol Cancer Res Treat. 2012;11(6):591-7.
41. Kim MS, Choi C, Yoo S, Cho C, Seo Y, Ji Y, et al. Stereotactic body radiation therapy in patients with pelvic recurrence from rectal carcinoma. Jpn J Clin Oncol. 2008;38(10):695-700.

42. Defoe SG, Bernard ME, Rwigema JC, Heron DE, Ozhasoglu C, Burton S. Stereotactic body radiotherapy for the treatment of presacral recurrences from rectal cancers. J Cancer Res Ther. 2011;7(4):408-11.
43. Johnstone P, Okonta L, Aitken K, Holmes J, Harrison M, Harji D, et al. A multicentre retrospective review of SABR reirradiation in rectal cancer recurrence. Radiother Oncol. 2021;162:1-6.
44. Robinson M, O'Cathail S, Duffton A, Aitken K, Muirhead R. Potential for Isotoxic Re-irradiation Stereotactic Ablative Body Radiotherapy in Locally Recurrent Rectal Cancer. Clin Oncol (R Coll Radiol). 2022;34(9):571-7.
45. Muirhead R, Dean C, Diez P, Williams M, McDonald F. Launch of the UK SABR Consortium Pelvic Stereotactic Ablative Radiotherapy Re-irradiation Guidelines and National Audit. Clin Oncol (R Coll Radiol). 2023;35(1):29-32.
46. Leeman JE, Shin KY, Chen YH, Mak RH, Nguyen PL, D'Amico AV, Martin NE. Acute toxicity comparison of magnetic resonance-guided adaptive versus fiducial or computed tomography-guided non-adaptive prostate stereotactic body radiotherapy: A systematic review and meta-analysis. Cancer. 2023;129(19):3044-52.
47. Watanabe J, Shoji H, Hamaguchi T, Miyamoto T, Hirano H, Iwasa S, et al. Chemoradiotherapy for Local Recurrence of Rectal Cancer: A Single Center Study of 18 Patients. In Vivo. 2019;33(4):1363-8.
48. Tanaka H, Yamaguchi T, Hachiya K, Okada S, Kitahara M, Matsuyama K, Matsuo M. Radiotherapy for locally recurrent rectal cancer treated with surgery alone as the initial treatment. Radiat Oncol J. 2017;35(1):71-7.
49. Truelsen CG, Ronde HS, Kallehauge JF, Szpejewska JE, Bahij R, Diness LV, et al. Acute toxicity and quality of life in dose-escalated proton reirradiation for locally recurrent rectal cancer: The prospective ReRad II trial. Clin Transl Radiat Oncol. 2025;54:100999.
50. Viechtbauer W, Smits L, Kotz D, Bude L, Spigt M, Serroyen J, Crutzen R. A simple formula for the calculation of sample size in pilot studies. J Clin Epidemiol. 2015;68(11):1375-9.
51. Wittenstein O, Krause F, Fischer M, Domschikowski J, Nitsche M, Henkenberens C, et al. The tumor core boost study: A feasibility study of radical dose escalation to the central part of large tumors with an integrated boost in the palliative treatment setting. Strahlenther Onkol. 2023;199(3):258-67.
52. Adjogatse D, Michaelidou A, Sanchez Nieto B, Kozarski R, Sassoon I, Evans M, et al. Protocol letter: Intra-treatment Image Guided Adaptive Radiotherapy Dose-escalation Study (InGReS) - A Phase 1 multicentre feasibility study. Radiother Oncol. 2023;183:109645.
53. Zwart K, Braat M, van der Baan FH, May AM, Roodhart JML, Al-Toma D, et al. Feasibility and safety of single-fraction sub-ablative radiotherapy with systemic therapy in colorectal cancer patients with </= 10 metastases: A multicenter pilot study (NCT05375708). Clin Transl Radiat Oncol. 2024;49:100874.
54. Fields EC, Kaplan BJ, Karlin J, Myers JL, Mukhopadhyay N, Deng X, et al. Phase 1 Study of Neoadjuvant Short-Course Radiation Therapy Concurrent With Infusional 5-Fluorouracil for the Treatment of Locally Advanced Rectal Cancer. Adv Radiat Oncol. 2019;4(4):605-12.
55. Baak R, Willemssen F, van Norden Y, Eskens F, Milder MTW, Heijmen BJM, et al. Stereotactic Body Radiation Therapy after Chemotherapy for Unresectable Perihilar Cholangiocarcinoma: The STRONG Trial, a Phase I Safety and Feasibility Study. Cancers (Basel). 2021;13(16).
56. Peulen H. ESTRO guideline for the use, planning and delivery of reirradiation in rectal cancer. Radiother Oncol. 2026.
57. van Kesteren Z PS, Tijssen RH, de Smet M, Philippens M, Kuijer J, Brunenberg E. . Quality assurance of magnetic resonance imaging for use in radiotherapy. NCS report 36. 2023.
58. Piqeur F, Hupkens BJP, Nordkamp S, Witte MG, Meijnen P, Ceha HM, et al. Development of a consensus-based delineation guideline for locally recurrent rectal cancer. Radiother Oncol. 2022;177:214-21.
59. Piqeur F, Hupkens BJP, Creemers DMJ, Nordkamp S, Berbee M, Buijsen J, et al. Prospective radiotherapy quality Assurance leads to delineation guideline refinements for recurrent rectal cancer: Experience from the PelvEx II study. Clin Transl Radiat Oncol. 2025;52:100934.
60. Kronborg CJ, Pedersen BG, Klemmensen J, Lefevre AC, Wind KL, Spindler KG. Pelvic Insufficiency Fractures and Bone Pain after Radiation Therapy for Anal Cancer: Relation to Pelvic Bone Dose-Volume Parameters. Adv Radiat Oncol. 2023;8(1):101110.
61. Yi SK, Mak W, Yang CC, Liu T, Cui J, Chen AM, et al. Development of a standardized method for contouring the lumbosacral plexus: a preliminary dosimetric analysis of this organ at risk among 15 patients treated with intensity-modulated radiotherapy for lower gastrointestinal cancers and the incidence of radiation-induced lumbosacral plexopathy. Int J Radiat Oncol Biol Phys. 2012;84(2):376-82.

62. Appelt AL, Andrzejewski P, Hoffmann L, Kelly C, Michailidou C, Murrell DH, et al. Cumulative dose evaluation in clinical reirradiation - Consensus guidance on technical considerations by the ESTRO reirradiation focus group. Radiother Oncol. 2026;214:111313.
63. Bentzen SM, Dorr W, Gahbauer R, Howell RW, Joiner MC, Jones B, et al. Bioeffect modeling and equieffective dose concepts in radiation oncology--terminology, quantities and units. Radiother Oncol. 2012;105(2):266-8.
64. Wan J, Wu R, Fu M, Shen L, Zhang H, Wang Y, et al. TORCH-R trial protocol: hypofractionated radiotherapy combined with chemotherapy and toripalimab for locally recurrent rectal cancer: a prospective, single-arm, two-cohort, phase II trial. Front Oncol. 2023;13:1304767.
65. Murray L, Thompson C, Pagett C, Lilley J, Al-Qaisieh B, Svensson S, et al. Treatment plan optimisation for reirradiation. Radiother Oncol. 2023;182:109545.
66. Garcia-Alvarez JA, Paulson E, Kainz K, Puckett L, Shukla ME, Zhu F, et al. Radiobiologically equivalent deformable dose mapping for re-irradiation planning: Implementation, robustness, and dosimetric benefits. Radiother Oncol. 2025;205:110741.
67. Hanna GG, McDonald F, Murray L, Harrow S, Landau D, Ahmed M, Franks KN. UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy: Reply to Ghafoor et al. Clin Oncol (R Coll Radiol). 2018;30(7):456.
68. PelvEx C. Induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as neoadjuvant treatment for locally recurrent rectal cancer: study protocol of a multicentre, open-label, parallel-arms, randomized controlled study (PelvEx II). BJS Open. 2021;5(3).
69. Takiyama H, Yamada S, Isozaki T, Ikawa H, Shinoto M, Imai R, Koto M. Carbon-Ion Radiation Therapy for Unresectable Locally Recurrent Colorectal Cancer: A Promising Curative Treatment for Both Radiation Therapy: Naive Cases and Reirradiation Cases. Int J Radiat Oncol Biol Phys. 2024;118(3):734-42.
70. Yamada S, Kamada T, Ebner DK, Shinoto M, Terashima K, Isozaki Y, et al. Carbon-Ion Radiation Therapy for Pelvic Recurrence of Rectal Cancer. Int J Radiat Oncol Biol Phys. 2016;96(1):93-101.
71. Barney BM, Markovic SN, Laack NN, Miller RC, Sarkaria JN, Macdonald OK, et al. Increased bowel toxicity in patients treated with a vascular endothelial growth factor inhibitor (VEGFI) after stereotactic body radiation therapy (SBRT). Int J Radiat Oncol Biol Phys. 2013;87(1):73-80.
72. Kroeze SGC, Pavic M, Stellamans K, Lievens Y, Becherini C, Scorsetti M, et al. Metastases-directed stereotactic body radiotherapy in combination with targeted therapy or immunotherapy: systematic review and consensus recommendations by the EORTC-ESTRO OligoCare consortium. Lancet Oncol. 2023;24(3):e121-e32.
73. Denost Q, Frison E, Salut C, Sitta R, Rullier A, Harji D, et al. A phase III randomized trial evaluating chemotherapy followed by pelvic reirradiation versus chemotherapy alone as preoperative treatment for locally recurrent rectal cancer - GRECCAR 15 trial protocol. Colorectal Dis. 2021;23(7):1909-18.
74. Slevin F, Aitken K, Alongi F, Arcangeli S, Chadwick E, Chang AR, et al. An international Delphi consensus for pelvic stereotactic ablative radiotherapy re-irradiation. Radiother Oncol. 2021;164:104-14.
75. Potter R, Tanderup K, Kirisits C, de Leeuw A, Kirchheiner K, Nout R, et al. The EMBRACE II study: The outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. Clin Transl Radiat Oncol. 2018;9:48-60.

12. APPENDICES

1. Common toxicity criteria of adverse events (CTCAE) version 5.0

2. Questionnaires: overall quality of life, symptomatic control and well-being

3. Structured MRI report templates

5. Patient information letter and Informed Consent

12.1 Common toxicity criteria of adverse events (CTCAE) version 5.0

Grades	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

**ADL: Activities of daily living: Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

Possible treatment-related toxicity, adapted from the CTCAE version 5.0 and the STAR-TREC trial

Category	Toxicity
Gastrointestinal disorders	Abdominal pain, anal/rectal fistula, anal/rectal haemorrhage, anal mucositis, anal/rectos necrosis, anal/rectal pain, anal/rectal stenosis, anal/rectal ulcer, colon/small intestinal fistula, lower gastrointestinal haemorrhage, colonic/small intestinal obstruction, colonic/small intestinal perforation, colonic/small intestinal stenosis, colonic/small intestinal ulcer, constipation, diarrhoea, enterocolitis, enterovesical fistula, faecal incontinence, haemorrhoids, hemorrhoidal haemorrhage, ileus, intra-abdominal haemorrhage, proctitis, rectal obstruction, rectal perforation
Renal and urinary disorders	Bladder perforation, bladder spasm, cystitis noninfective, haematuria, urinary fistula, urinary incontinence, urinary retention, urinary tract obstruction and urinary tract pain
Injury, poisoning and procedural complications	Dermatitis reaction (if in radiation field)
Reproductive system and breast disorder	Prostatic pain, uterine fistula, uterine haemorrhage, vaginal fistula, vaginal haemorrhage, 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 disorder	Abdominal soft tissue necrosis, pelvic soft tissue necrosis, osteonecrosis
Nervous system disorders	Neuralgia, peripheral moto/sensory neuropathy

12.2 Overall quality of life and well-being

Kwaliteit van leven (EORTC C15-PAL & CR29 & EQ-5D-5L)

Wij zijn geïnteresseerd in bepaalde dingen over u en uw gezondheid. Wilt u alle vragen zelf beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is. Er zijn geen "juiste" of "onjuiste" antwoorden. De informatie die u geeft zal strikt vertrouwelijk worden behandeld.

		Helemaal niet	**Een beetje**	**Nogal**	**Heel erg**
1	Heeft u moeite met het maken van een korte wandeling buitenshuis?	1	2	3	4
2	Moet u overdag in bed of op een stoel blijven?	1	2	3	4
3	Heeft u hulp nodig met eten, aankleden, uzelf wassen of naar het toilet gaan?	1	2	3	4

Gedurende de afgelopen week:

4	Was u kortademig?	1	2	3	4
5	Heeft u pijn gehad?	1	2	3	4
6	Heeft u moeite met slapen gehad?	1	2	3	4
7	Heeft u zich slap gevoeld?	1	2	3	4
8	Heeft u gebrek aan eetlust gehad?	1	2	3	4
9	Heeft u zich misselijk gevoeld?	1	2	3	4
10	Had u last van obstipatie? (was u verstopt?)	1	2	3	4
11	Was u moe?	1	2	3	4
12	Heeft pijn u gehinderd bij uw dagelijkse bezigheden?	1	2	3	4
13	Voelde u zich gespannen?	1	2	3	4
14	Voelde u zich neerslachtig?	1	2	3	4

Wilt u voor de volgende vragen het getal tussen 1 en 7 omcirkelen dat het meest op u van toepassing is?

15. Hoe zou u uw algehele 'kwaliteit van leven' gedurende de afgelopen week beoordelen?

1 2 3 4 5 6 7

Erg slecht *Uitstekend*

Soms zeggen patiënten dat de volgende klachten of problemen hebben. Wilt u aangeven in welke mate u deze klachten of problemen gedurende de afgelopen week heeft ervaren? Wilt u de vragen beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is?

		Helemaal niet	**Een beetje**	**Nogal**	**Heel erg**
15	Heeft u overdag vaak geplast?	1	2	3	4
16	Heeft u 's nachts vaak geplast?	1	2	3	4
17	Heeft u ongewild urine verloren?	1	2	3	4
18	Heeft u pijn gehad bij het plassen?	1	2	3	4
19	Heeft u buikpijn gehad?	1	2	3	4
20	Heeft u pijn gehad in uw zitvlak of bij uw anus?	1	2	3	4
21	Heeft u een opgeblazen gevoel gehad in uw buik?	1	2	3	4
22	Heeft u bloed in uw ontlasting gehad?	1	2	3	4
23	Heeft u slijm in uw ontlasting gehad?	1	2	3	4
24	Heeft u een droge mond gehad?	1	2	3	4
25	Heeft u haaruitval gehad ten gevolge van uw behandeling?	1	2	3	4
26	Heeft u problemen met uw smaak gehad?	1	2	3	4

Gedurende **<u>de afgelopen week</u>**:

		Helemaal niet	**Een beetje**	**Nogal**	**Heel erg**
27	Heeft u zich zorgen gemaakt over uw gezondheid in de toekomst?	1	2	3	4
28	Heeft u zich zorgen gemaakt over uw gewicht?	1	2	3	4
29	Voelde u zich lichamelijk minder aantrekkelijk ten gevolge van uw ziekte of behandeling?	1	2	3	4
30	Was u ontevreden met uw lichaam?	1	2	3	4
31	Heeft u een stoma? (dunnedarm-stoma of dikkedarm-stoma)			**Ja**	**Nee**

<u>Beantwoord deze vragen ALLEEN ALS U EEN STOMA HEBT, zo niet, ga dan naar het volgende vak</u>

	Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
32	Heeft u last gehad van het ongewild vrijkomen van gas (winderigheid) uit uw stoma?	1	2	3	4
33	Was er lekkage van ontlasting uit uw stomazakje?	1	2	3	4
34	Heeft u een pijnlijke huid gehad rond uw stoma?	1	2	3	4
35	Heeft u overdag vaak het stomazakje moeten vervangen?	1	2	3	4

36	Heeft u ’s nachts vaak het stomazakje moeten vervangen?	1	2	3	4
37	Voelde u zich opgelaten door uw stoma?	1	2	3	4
38	Heeft u problemen gehad met de verzorging van uw stoma?	1	2	3	4

Alleen voor patiënten **zonder stoma:**

	Gedurende de afgelopen week:	**Helemaal niet**	**Een beetje**	**Nogal**	**Heel erg**
39	Heeft u last gehad van ongewild vrijkomen van gas (winderigheid)?	1	2	3	4
40	Heeft u ongewild ontlasting verloren?	1	2	3	4
41	Heeft u een pijnlijke huid gehad rondom uw anus?	1	2	3	4
42	Heeft u overdag vaak ontlasting gehad?	1	2	3	4
43	Heeft u ’s nachts vaak ontlasting gehad?	1	2	3	4
44	Voelde u zich opgelaten door uw ontlastingspatroon?	1	2	3	4

Alleen voor **mannelijke patiënten**:

Gedurende de afgelopen 4 weken:

		Helemaal niet	**Een beetje**	**Nogal**	**Heel erg**
34	In hoeverre had u zin in seks?	1	2	3	4
35	Indien u seksueel actief was (met of zonder geslachtsgemeenschap): Had u moeite met het stijf worden of blijven van uw penis?	1	2	3	4

Alleen voor **vrouwelijke patiënten:**

Gedurende de afgelopen 4 weken:

		Helemaal niet	**Een beetje**	**Nogal**	**Heel erg**
34	In hoeverre had u zin in seks?	1	2	3	4
35	Indien u geslachtsgemeenschap hebt gehad: Had u pijn of ongemak tijdens de gemeenschap?	1	2	3	4

Zet bij iedere groep in de lijst hieronder een kruisje in het hokje dat het best past bij uw gezondheid VANDAAG.

MOBILITEIT

Ik heb geen problemen met lopen ❑
Ik heb een beetje problemen met lopen ❑
Ik heb matige problemen met lopen ❑
Ik heb ernstige problemen met lopen ❑
Ik ben niet in staat om te lopen ❑

ZELFZORG

Ik heb geen problemen met mijzelf wassen of aankleden ❑
Ik heb een beetje problemen met mijzelf wassen of aankleden ❑
Ik heb matige problemen met mijzelf wassen of aankleden ❑
Ik heb ernstige problemen met mijzelf wassen of aankleden ❑
Ik ben niet in staat mijzelf te wassen of aan te kleden ❑

DAGELIJKSE ACTIVITEITEN *(bijv. werk, studie, huishouden, gezins- en vrijetijdsactiviteiten)*

Ik heb geen problemen met mijn dagelijkse activiteiten ❑
Ik heb een beetje problemen met mijn dagelijkse activiteiten ❑
Ik heb matige problemen met mijn dagelijkse activiteiten ❑
Ik heb ernstige problemen met mijn dagelijkse activiteiten ❑
Ik ben niet in staat mijn dagelijkse activiteiten uit te voeren ❑

PIJN / ONGEMAK

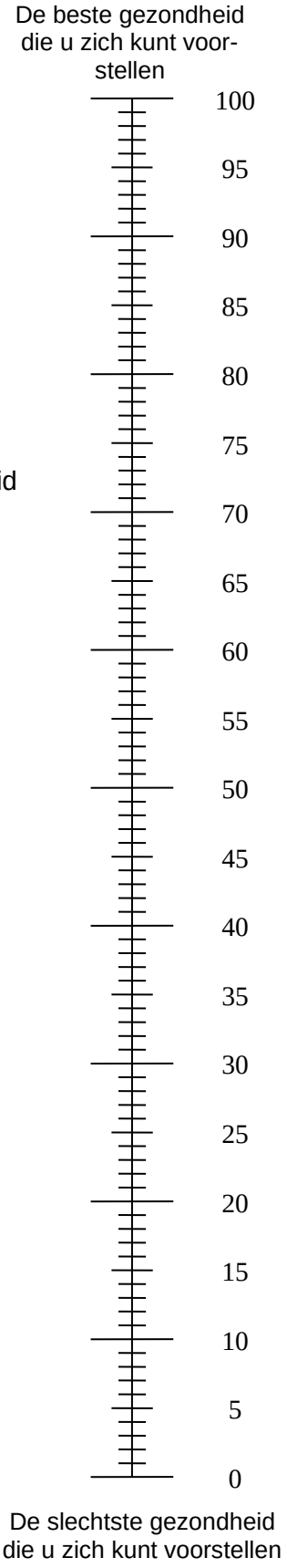
Ik heb geen pijn of ongemak ❑
Ik heb een beetje pijn of ongemak ❑
Ik heb matige pijn of ongemak ❑
Ik heb ernstige pijn of ongemak ❑
Ik heb extreme pijn of ongemak ❑

ANGST / SOMBERHEID

Ik ben niet angstig of somber ❑
Ik ben een beetje angstig of somber ❑
Ik ben matig angstig of somber ❑
Ik ben erg angstig of somber ❑
Ik ben extreem angstig of somber ❑

- We willen weten hoe goed of slecht uw gezondheid VANDAAG is.
- Deze meetschaal loopt van 0 tot 100.
- 100 staat voor de <u>beste</u> gezondheid die u zich kunt voorstellen.
  0 staat voor de <u>slechtste</u> gezondheid die u zich kunt voorstellen.
- Markeer een X op de meetschaal om aan te geven hoe uw gezondheid VANDAAG is.
- Noteer het getal waarbij u de X heeft geplaatst in onderstaand vakje.

UW GEZONDHEID VANDAAG = ☐



12.3 Structured MRI report template

Minimal requirements for baseline MR image acquisition

MRI acquisition should adhere to the following minimal requirements:

Technical requirements

- 1.5T or 3T MR equipment
- Phased-array receiver coil for pelvic-/body imaging

Sequences and sequence angulation requirements

- T2-weighted high-resolution sequences in 3 standard planes (true sagittal, coronal, transverse). Minimal slice thickness of ≤ 3 mm. No fat suppression.
- Diffusion-weighted imaging (DWI): axial plane, b-value ≥ b800, including ADC maps.
- Field of view (FOV) of both T2 and DWI needs to cover the entire pelvic area.

Optional

The following is optional (if part of local protocols), but not required:

- Angulated sequences
- T1-weighted sequences
- Fat suppressed sequences
- (Dynamic) Post-contrast sequences
- Patient preparation (e.g., spasmolytic agents, endorectal filling)

Checklist for imaging assessment: baseline LRRC

When assessing the MRI, the following items must be checked:

- Focality:
  - Number of lesions
- Size:
  - 3 largest lesions: greatest size in mm, measured in any plane
- Type:
  - Mucinous / Solid tumour / Fibrotic / Other (specify)
- Border:
  - Well defined / lobulated or spiculated / irregular
- Venous invasion (mrVI): yes / no; if yes: length in mm
- Lymph nodes: yes / no
  if yes: central / lateral / inguinal / para-aortal, number of nodes ≥8 mm, largest short-axis diameter
- Abscess formation: yes/no
- Previous surgery:

- LAR, APR, Other

- Primary compartment involved:
  - Central / Anterior / Posterior / Lateral
- Compartments
  - Central
    - Involved organs / structures
      - Anastomosis: yes / no / not applicable
      - Levator muscle: left / right / both / no
      - Puborectalis muscle: left / right / both / no
      - Sphincter complex: yes / no
      - Gluteal muscle: left / right / both / no
      - Perineum: yes / no
  - Anterior
    - Involved organs / structures
      - Vagina: anterior wall / posterior wall / introitus / portio / no / not applicable
      - Cervix: yes / no / not applicable
      - Uterus: yes / no / not applicable
      - Ovaries: left / right / both / no / not applicable
      - Prostate: yes / no / not applicable
      - Seminal vesicles: left / right / both / no / not applicable
      - Penis: yes / no / not applicable
      - Urinary bladder: dome / trigonum / no / not applicable
      - Peritoneum: yes / no
      - Small bowel: yes / no
      - Colon: yes / no
      - Omentoplasty: yes / no / not applicable
  - Posterior
    - Most cranial extension:
      - L5 / S1 / S2 / S3 / S4 / S5 / Coccyx
    - Involved organs/structures
      - Presacral fascia: yes / no
      - Periost/cortex: yes / no
      - Marrow: yes / no
      - Neuroforamen S1-S2: yes / no
      - Neuroforamen S3-S5: yes / no
  - Lateral

        - Height: above piriform muscle / at the piriform muscle / below the piriform muscle
        - Location: mainly inside Lateral Pelvic Fascia (LPF) / at LPF / mainly outside LPF
        - Involved organs/structures
            - Ureter: left / right / both
            - Sciatic nerve: yes / no
            - Lumbosacral plexus: yes / no
            - S1-S2 nerve roots: yes / no
            - S3-S5 nerve roots: yes / no
            - Sacrospinous ligament: left / right / both / no
            - Piriformis muscle: left / right / both / no
            - Obturator compartment: left / right / both / no
    - Vasculature
        - Common iliac vein: left / right / both / no
        - Common iliac artery: left / right / both / no
        - Internal iliac vein: left / right / both / no
        - Internal iliac artery: left / right / both / no
        - External iliac vein: left / right / both / no
        - External iliac artery: left / right / both / no

Minimal requirements for MR baseline imaging reporting
The report must include <u>at least</u> the following:

- Number of lesions
- Size of the lesions in mm
- Type of tumour: mucinous/ Solid tumour / Fibrotic / Other
- Abscess formation: yes/no
- Name all involved compartments (i.e., anterior/central/posterior/lateral)
- Name all involved organs or other structures

Follow-up imaging for tumour response after radiotherapeutic treatment
Patients are followed up according to local practice. A high-dose thoracoabdominal CT-scan should be performed three months after completion of radiotherapy, every six months for the first two years, and annually thereafter. An MRI or FDG-PET/CT-scan should be performed to assess local and distant control, in line with local protocols.

Checklist for imaging assessment (thoracoabdominal CT-scan)
When assessing the thoracoabdominal CT, the following items must be checked according to RECIST 1.1:

- Target lesions
    - Length diameter tumour >10mm
    - Max. 5, max. 2 per organ
    - Short-axis lymph node >15mm
    - Determine the sum of the longest diameters (SLD)
- Non-target lesions
    - Lesions <10mm
    - Non-measurable like pleural fluid, ascites, lymphangitis
- New lesions
- Other:
- Conclusion:
    - Complete response: disappearance of all lesions and pathological lymph nodes
    - Partial response: ≥30% decrease SLD, no new lesions, no progression of non-target lesions
    - Stable disease: no partial response, no progressive disease
    - Progressive disease: ≥20% increase SLD compared to smallest SLD in study or progression of non-target lesions, or new lesions