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Optimisation of Organ Preservation treatment strategies in patients with rectal cancer with a good clinical response after neoadjuvant (chemo) radiotherapy: Additional contact X-ray brachytherapy versus eXtending the observation period and local excision (OPAXX) — protocol for two multicentre, parallel, single-arm, phase II studies

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ABSTRACT

Introduction Standard treatment for patients with intermediate or locally advanced rectal cancer is (chemo) radiotherapy followed by total mesorectal excision (TME) surgery. In recent years, organ preservation aiming at improving quality of life has been explored. Patients with a complete clinical response to (chemo)radiotherapy can be managed safely with a watch-and-wait approach. However, the optimal organ-preserving treatment strategy for patients with a good, but not complete clinical response remains unclear. The aim of the OPAXX study is to determine the rate of organ preservation that can be achieved in patients with rectal cancer with a good clinical response after neoadjuvant (chemo) radiotherapy by additional local treatment options.

Methods and analysis The OPAXX study is a Dutch multicentre study that investigates the efficacy of two additional local treatments aiming at organ preservation in patients with a good, but not complete response to neoadjuvant treatment (ie near-complete response or a small residual tumour mass <3 cm). The sample size will be 168 patients in total. Patients will be randomised (1:1) between two parallel single-arm phase II studies: study arm 1 involves additional contact X-ray brachytherapy (an intraluminal radiation boost), while in study arm 2 the observation period is extended followed by a second response evaluation and optional transanal local excision. The primary endpoint of the study is the rate of successful organ preservation at 1 year following randomisation. Secondary endpoints include toxicity, morbidity, oncological and functional outcomes at 1 and 2 years of follow-up. Finally, an observational cohort study for patients who are not eligible for randomisation is conducted.

Ethics and dissemination The trial protocol has been approved by the medical ethics committee of the Netherlands Cancer Institute (METC20.1276/M20PAX). Informed consent will be obtained from all participants. The trial results will be published in an international peer-reviewed journal.

Trial registration number NCT05772923.

INTRODUCTION

Background and rationale

The standard treatment for patients with intermediate or locally advanced rectal cancer involves neoadjuvant (chemo)radiotherapy followed by total mesorectal excision (TME-surgery), which is associated with impaired functional outcomes and the risk of a permanent colostomy. In recent years, organ-preserving strategies have emerged as an alternative treatment approach for patients with rectal cancer, aiming to improve quality of life by omitting TME-surgery, without compromising oncological outcome. Patients with a complete clinical response (cCR) to neoadjuvant (chemo)radiotherapy can be safely managed with a watch-and-wait

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This multicentre phase II study will provide valuable insights in the role of additional local treatment options (contact X-ray brachytherapy or local excision) and the potential rate of successful organ preservation that can be achieved in patients with rectal cancer with a good, but not complete response after neoadjuvant (chemo) radiotherapy.
- ⇒ Patients participating in the OPAXX study will be randomised between two single-arm studies, ensuring comparability of treatment strategies and minimising bias in secondary parameter analysis.
- ⇒ The OPAXX study will be conducted within a collaborative and experienced watch-and-wait network in the Netherlands: an intensive surveillance programme has been established to detect treatment failure, tumour regrowth or disease recurrence at an early stage, in order to proceed to completion or salvage TME-surgery when needed and when possible.
- ⇒ The optimal timing for contact X-ray brachytherapy remains a topic of ongoing debate; consequently, the OPAXX study allows the first fraction to be applied up to 14 weeks after the last radiotherapy.
- ⇒ The specific time interval for contact X-ray brachytherapy entails the risk of overtreatment for a subset of patients with a near-complete response in whom a clinical complete response would have been obtained overtime.

approach: studies on watch-and-wait reported good oncological outcomes with 5-year disease-specific survival of 94% and overall survival of 85%, and an improved quality of life.[1–5] However, the optimal treatment strategy for patients with a good, but not complete response, remains unclear.

Several organ-preserving strategies are explored in patients with a good, but not complete response after (chemo)radiotherapy: extension of the observation period is commonly used after (chemo)radiotherapy to eventually obtain a cCR. Alternative approaches that can be considered are additional local treatment options such as contact X-ray brachytherapy (CXB) or a surgical local excision (LE).

Extending the standard 6–8 weeks interval between completing (chemo)radiotherapy and the first response assessment can result in increased cCR rates.[6 7] Therefore, patients with a near-complete response could benefit from a second (or third) assessment: time intervals of 18–20 weeks have been described before a cCR has been established.[8] Success rates of achieving cCR have been reported in up to 90% in these highly selected patients with an extended observation period, without evidence that the oncological outcome is compromised.[8 9]

The role of additional CXB in relation to (chemo) radiotherapy has been explored in elderly patients with rectal cancer and in patients with comorbidities to avoid major surgery.[10–14] CXB provides an intraluminal radiation boost up to 90 Gy to the primary rectal tumour, while sparing surrounding normal tissues.[15] Related studies report good oncological outcomes and cCR rates of 64%–81%.[14 16–19] Moreover, organ preservation rates of 97% are described for small rectal cancers <3 cm with CXB prior to chemoradiation.[14] However, these findings mainly apply to patients with early rectal cancer rather than locally advanced tumours.

LE may be an alternative treatment for selected patients with rectal cancer with a good, but not complete, response to neoadjuvant (chemo)radiotherapy in order to avoid TME-surgery. The current data on LE for rectal cancer after (chemo)radiotherapy are mainly focused on early to intermediate rectal cancers aiming at primary organ preservation: the majority of these selected patients were treated successfully with additional LE, with low completion TME rates (5%–35%) for insufficient pathological downstaging.[20–23] However, less data are available on the role of LE for more advanced tumours after (chemo)radiotherapy, as these good responders may carry a higher risk of lymph node involvement; moreover, long-term oncological outcome is unknown.

Although TME-surgery is still the standard of care in most patients with rectal cancer, more patients are even willing to make oncological compromises for treatment strategies that preserve their rectum and maintain their quality of life.[24 25] Organ preservation strategies such as extending the observation period followed by CXB or LE are promising interventions. It is, however, unclear which patients will benefit from an extended interval after (chemo)radiotherapy in order to achieve a cCR over time, or in whom additional local treatment options, such as CXB or LE, contribute to eventually organ preservation possibilities.

We therefore initiated the OPAXX study: two different treatment strategies are evaluated for patients with rectal cancer with a good, but not complete, response after neoadjuvant (chemo)radiotherapy aiming at organ preservation; the role of additional CXB and LE will be explored.

METHODS AND ANALYSES

Study design

The OPAXX is a multicentre, phase II trial that investigates the efficacy of two potential organ preservation treatment strategies in patients with rectal cancer with a good, but not complete, response after neoadjuvant (chemo)radiotherapy. Patients are randomised (1:1) between two parallel single study-arms: additional CXB versus extending the observation period with or without LE (figure 1).

The OPAXX study is conducted within the Dutch Wait-and-See consortium, with 16 hospitals in the Netherlands that are currently participating in the ongoing wait-and-see registry (ClinicalTrials.gov NCT03426397). The total required number of patients is 168. Patient accrual has started in February 2021 and is expected to finish in February 2026. Patients who are not eligible for randomisation will be registered in an observational cohort (OPAXX registration study).

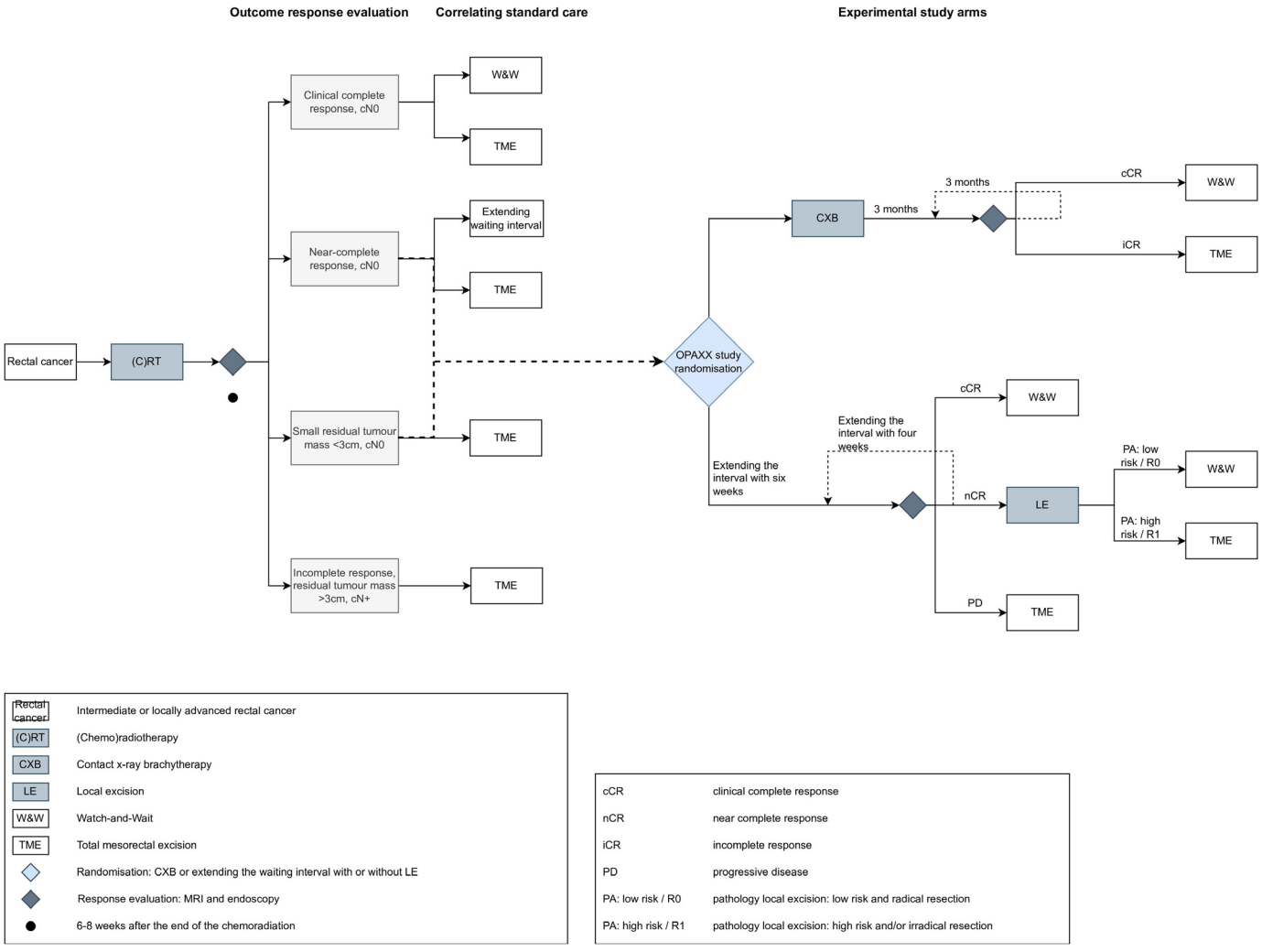

Figure 1 Flowchart for the OPAXX study for patients with a clinical good response after neoadjuvant (chemo)radiotherapy for rectal cancer.

Objectives

The primary objective of the OPAXX study is to determine the rate of organ preservation that can be achieved in patients with rectal cancer with a good clinical response after neoadjuvant (chemo)radiotherapy by additional local treatment options: CXB or extending the observation period with or without LE.

The secondary objectives are to assess safety in terms of toxicity and complication rates of both additional treatment options, and functional and oncological outcomes.

Study population

Patients with rectal cancer who have received neoadjuvant short-course radiotherapy or long-course chemoradiation are eligible when a good, but not complete response is seen at the first response assessment, usually 6–8 weeks after the last (chemo)radiotherapy. A good, but not complete clinical response is defined as a near-complete response or a small residual tumour mass <3 cm; the characteristics are described in table 1.

The first response evaluation consists of MRI of the rectum and CT of the thorax and abdomen, sigmoidoscopy and digital rectal examination. Patients will be discussed in multidisciplinary tumour board meetings and will be informed about the OPAXX study by their treating physician. TME-surgery will be offered to all patients as standard of care. Patients have at least 48 hours to consider their participation in the OPAXX study and to sign the informed consent form (see online supplemental materials for the participant informed consent form).

Trial participation includes consent to randomisation for allocation to one of the study arms and participation in the assigned treatment strategy. Additionally, patients are asked to share their medical data within the Dutch Wait-and-See registration (ClinicalTrials.gov NCT03426397) and the International Watch and Wait Database.

Inclusion criteria

- Clinically near-complete response or a small residual tumour mass <3 cm at first response evaluation after neoadjuvant short-course radiotherapy (5×5 Gy) or long-course chemoradiotherapy (25×2 Gy or 28×1.8 Gy and capecitabine).

Table 1 Characteristics of a good clinical response after (chemo)radiotherapy[32 33]

Clinical near-complete response after (chemo)radiotherapy			
DRE	**Sigmoidoscopy**	**MRI-T2W**	**MRI-DWI**
Small superficial soft irregularity.	Small residual erythematous ulcer or irregular wall thickening.	Obvious downsizing with residual fibrosis but heterogeneous or irregular aspect and signal.	Small focal area of high signal on high b-value MRI.
Clinical good response, but small residual tumour mass after (chemo)radiotherapy			
DRE	**Sigmoidoscopy**	**MRI-T2W**	**MRI-DWI**
Small (palpable) tumour mass <3 cm.	Visible tumour or an ulcer with irregular borders <3 cm.	Obvious downsizing, though with a heterogeneous and irregular aspect of the residual fibrosis <3 cm.	Focal area of high signal on high b-value MRI.

DRE, digital rectal examination 2; MRI-DWI, magnetic resonance imaging with diffusion weighted imaging; MRI-T2W, magnetic resonance imaging of the rectum T2 weighted.

- Technically feasible to perform both treatment options (CXB or LE).
- Histologically verified adenocarcinoma above the dentate line and within 10 cm of the anal verge.
- Age ≥18 years.
- Written informed consent.

Exclusion criteria

- Neoadjuvant or induction chemotherapy prior to (chemo)radiotherapy, or chemotherapy given as consolidation therapy after (chemo)radiotherapy (eg, patients with total neoadjuvant therapy).
- Radiation dose >50.4 Gy or boost dose on the primary tumour.
- Presence of (remaining) suspicious (mesorectal or lateral) lymph nodes (ycN1/N2) at the first response assessment.
- Residual tumour mass ≥3 cm or >50% of the circumference of the rectal lumen.
- Patients who cannot tolerate a completion or salvage TME because of comorbidity or frailty.

Interventions

Contact X-ray brachytherapy

CXB consists of three fractions of 30 Gy per fraction applied to the tumour intraluminally in an outpatient setting, with a 2-week interval after each fraction. An applicator with size 20, 25 or 30 mm is used depending on the size of the residual tumour. CXB is best given as soon as possible after the external beam therapy for radiobiological reasons.[26] Therefore, the first application of CXB will be given at the latest of 14 weeks after the end of (chemo)radiotherapy. Three months after completion of the CXB course, the response will be evaluated with MRI, sigmoidoscopy and digital rectal examination. When a cCR is noted, patients will be offered a watch-and-wait approach. In case of an ongoing but incomplete clinical response, patients can be offered another response evaluation at 6, and if necessary at 9 months after CXB. TME-surgery will be advised when a cCR is not achieved at 9 months or when residual disease or progression or regrowth is evident (figure 1).

Extended observation period followed by watch-and-wait or local excision

The observation period will be extended with 6–8 more weeks after the first response assessment, followed by a second response evaluation with MRI, sigmoidoscopy and digital rectal examination. When a cCR is noted at this second assessment, the patient is offered a watch-and-wait approach. When there is no cCR but the response is still improving, the observation period can be extended with another 4 weeks, or it can be decided to perform a LE. A third response evaluation (by sigmoidoscopy only) will evaluate if a cCR (patient can proceed to a watch-and-wait approach) or a near-complete response (patient can proceed to LE) has been established. Patient with progressive disease at the second or third response evaluation, or with suspected nodal disease, are advised to undergo TME-surgery. LE will basically be performed by transanal minimally invasive surgery using a single port transanal platform, or an equivalent technique under general anaesthesia in the operating theatre. After histological evaluation of the LE surgical specimen, the tumour will be graded as low-risk (based on radical resection of ypT0-1 residual tumour with low-risk features) or high-risk (based on resection margin involvement by tumour, tumour stage ypT1 with high-risk features or ≥ypT2), also including histopathological criteria such as lymphovascular invasion or perineural growth. In case of a high-risk tumour, the patient is advised to undergo completion TME-surgery (figure 1).

Follow-up

All patients will be subjected to a follow-up schedule dependent on the allocated treatment strategy following randomisation (figure 1). All patients will be evaluated during follow-up in multidisciplinary tumour board meetings. Patients with a cCR 3–9 months after CXB, patients with cCR after an extended observation period,

Table 2 Follow-up schedule and procedures wait-and-see approach

	3 months	6 months	9 months	12 months
Year 1	CEA; sigmoidoscopy*; MRI	CEA; sigmoidoscopy; MRI	CEA; full colonoscopy*	CEA; sigmoidoscopy; MRI; CT-th/abd
Year 2	CEA; sigmoidoscopy; MRI	CEA; sigmoidoscopy; MRI	CEA; sigmoidoscopy	CEA; sigmoidoscopy; MRI
Year 3		CEA; sigmoidoscopy		CEA; sigmoidoscopy; MRI
Year 4		CEA		CEA; full colonoscopy; MRI
Year 5		CEA		CEA; sigmoidoscopy; MRI

*All sigmoidoscopies and full colonoscopies include digital rectal examination.
CEA, carcinoembryonic antigen tumour marker; CT-th/abd, CT of the thorax/abdomen; MRI, MRI of the rectum with T2 and diffusion weighted imaging.

or patients with a pathological low-risk residual tumour (ypT0-1) after a radical LE, are offered a watch-and-wait follow-up scheme. This consists of an intensified follow-up schedule including digital rectal examination, flexible sigmoidoscopy (with periodic full colonoscopy), MRI of the rectum (including T2W and DWI) and CEA tumour marker monitoring for 5 years (see table 2).

In the first 2 years of follow-up, patients are seen in outpatient practices every 3 months; thereafter, follow-up will be organised twice yearly. Patients with a regrowth or a local recurrence are evaluated for salvage TME. In general, CT of thorax and abdomen is made at 1 and 2 years of follow-up, according to the Dutch national guidelines.

Outcomes

Primary endpoint

The primary endpoint reflects the efficacy of both additional treatment options and is defined as the rate of successful organ preservation at 1 year following randomisation, including an in situ rectum, no defunctioning stoma and absence of loco-regional cancer failure (indicated as either local intraluminal tumour regrowth or regional recurrence in lymph nodes requiring TME-surgery).

Secondary endpoints

Secondary endpoints focus on toxicity of both additional treatment options, and on functional and oncological outcomes.

- Short-term (<3 months) and long-term (<12 months) radiation toxicity (defined by grade 3 and 4 according to the common terminology criteria of adverse events (CTCAE) V.5.0).
- 90-day postoperative morbidity after local excision (defined by postoperative complication grade 3–4 according to Clavien-Dindo[27]).
- Functional outcomes regarding bowel function assessed with the Low Anterior Resection Syndrome (LARS) score at baseline, 3 months, 12 months and 24 months.
- Functional outcomes regarding bladder function assessed with selected items from the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-PR25, QLQ-CX24 and QLQ-ANL27 at baseline, 3 months, 12 months and 24 months.
- Functional outcomes regarding sexual function assessed with selected items from the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-PR25, QLQ-CX24, and QLQ-ANL27 at baseline, 3 months, 12 months, and 24 months, 1 and 2-year local regrowth rate.
- Overall quality of life and well-being evaluated with the EEORTC QLQ-C30 and QLQ-CR29 at baseline, 3 months, 12 months and 24 months.
- One-year and 2-year disease-free survival.
- one-year and 2-year overall survival.
- Organ preservation rate after 2 years.
- Complications within the first 30 days after completion or salvage TME-surgery, in terms of postoperative morbidity and mortality rates defined by Clavien-Dindo.[27]

Statistical design and analysis

The current study is conducted as two separate single-arm phase II studies and will not have enough statistical power to determine which of the two experimental organ-preserving approaches is superior. In the OPAXX, randomisation of patients in a 1:1 ratio between two single-arm studies will be conducted to prevent debate over the comparability of treatment strategies in case just one of the two studies turns out to be effective. Additionally, this will help to reduce bias in the analysis of secondary parameters, which evaluate the toxicity and morbidity of the additional treatment modalities, as well as the oncological and functional outcomes. The approach that will be considered most successful in the OPAXX study can be used for a larger phase III trial.

Organ preservation rates described in the literature range from 62% up to 97% after additional local treatment in patients with early to intermediate rectal cancer.[16 18 20 22] Due to inclusion of patients with intermediate and locally advanced rectal cancer in this study, it is expected that the organ preservation rate will be lower. Without any additional local treatment but extension of the observation period only, the success rate for an organ-preserving approach is estimated 25% based on data from the Dutch wait-and-see registry. An additional

success rate of 10% is considered the minimal clinically relevant increase in order to justify the additional local treatment; therefore, an organ-preservation rate of 35% or less (which equals a failure rate of 65% or more) at 1 year after randomisation is considered unacceptable in both treatment arms.

The null hypothesis will thus be an organ preservation/failure-free percentage of 35% at 1 year. An interim analysis will be conducted when 20 events are observed (ie, patients had to undergo, or are strongly advised to undergo, completion or salvage surgery by means of TME-surgery, or patients who received a defunctioning stoma during follow-up). The failure rates in each arm will be analysed separately as a time-to-event endpoint, using a one-sided log-rank test. Both study arms can be defined as 'acceptable' or 'unacceptable' and can be stopped for futility. The final analysis of a study arm takes places when 40 events are observed, based on the one-sample log-rank test, with an one-sided α of 0.05.

The sample size for the OPAXX study will be 168 patients in total (with power (1-β) = 0.82 and α of 0.05): 80 patients per study arm, plus an expected dropout rate of 5%.

Randomisation

Randomisation will be performed through the ALEA database (1:1). When allocated to the study arm of additional CXB boost, patients will be referred to one of the two centres in the Netherlands that provide CXB (Netherlands Cancer Institute, Amsterdam, and Catharina hospital, Eindhoven). When allocated to the extended observation arm with optional LE, patients will stay in the initial treating centre.

Data management

Clinical data are collected from medical files by the study coordinator and will be transferred to the ALEA database using electronic Case Report Forms.

Safety

An independent Data Safety Monitoring Board has been installed, consisting of a surgical oncologist, a radiation oncologist and a statistician in order to monitor quality and patient safety in this multicentre trial and to advise on continuation of the study at the interim analysis.

All serious adverse events during and after study intervention and within 90 days should be reported to the Netherlands Cancer Institute Data Centre within 24 hours, or at the latest, on the following working day.

Ethics and dissemination

This study is 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). The trial protocol has been approved by the medical ethics committee of the Netherlands Cancer Institute in December 2020 (METC20.1276/M20PAX). The trial is registered at ClinicalTrials.gov, NCT05772923 (https://trialsearch.who.int/Trial2.aspx?TrialID=NCT05772923). Patients have at least 48 hours to consider their participation in the OPAXX study and sign the informed consent form. The trial results will be published in an international peer-reviewed journal.

DISCUSSION

The OPAXX study investigates the rate of organ preservation that can be achieved in patients with rectal cancer with a good, but not complete clinical response after neoadjuvant (chemo)radiotherapy by randomisation between two additional local treatment options: additional CXB and extending the observation period followed by optional LE. It is currently unclear which organ-preserving treatment strategy is superior regarding treatment toxicity and functional outcomes when a good, but not complete response is noted after neoadjuvant (chemo)radiotherapy in patients with rectal cancer. Therefore, the OPAXX study may help to differentiate between distinct roles of CXB and LE.

Several factors associated with these approaches aiming at organ preservation must be considered. CXB for rectal cancer is a relatively new technique in the Netherlands that is only performed in two expert centres. Patients who are randomised to this arm of the study will be referred to one of these centres. The optimal timing for the first CXB application remains a topic of debate. For radiobiological reasons, CXB should be offered shortly after neoadjuvant (chemo)radiotherapy to avoid long radiotherapy treatment interruptions that can stimulate tumour regeneration.[26 28] Therefore, in the OPAXX study the first application is given within 14 weeks after completing the (chemo)radiotherapy course. However, this entails the risk of overtreatment for a subset of CXB-allocated patients with a near-complete response (ie, small remaining ulcer) in whom a clinical complete response would have been obtained overtime. In the other study arm, LE can be offered after an extended observation period without compromising this surgical treatment. Patients who received neoadjuvant chemotherapy (eg, total neoadjuvant therapy) are excluded for randomisation as they exceed the specific time interval between the last radiotherapy and the first application of CXB. However, in patients where randomisation is not feasible anymore, an observational study cohort is conducted (the OPAXX registration).

The most commonly reported toxicity in CXB is rectal bleeding due to telangiectasia: grade I-III rectal bleeding is observed in approximately 30% of patients, usually starting 6 months after treatment, sometimes requiring local coagulation therapy for haemostasis.[16–19] Rectal ulceration after CXB may occur in up to 30% of patients, which usually heals in 3–6 months.[17] With regard to functional outcome after CXB it is described that most patients are satisfied with the remaining bowel function, although more systematically evaluated data on this subject are scarce.[18 19] Furthermore, data on CXB after a short-course radiotherapy are limited to a single study which primarily

involved elderly or patients unfit for surgery, highlighting the need for additional research on efficacy and treatment toxicity.[12]

Multiple studies have shown that additional LE in case of a near-complete response or small tumour remnant after neoadjuvant therapy is a feasible approach aiming at organ preservation, and it provides accurate information about the presence and extent of the residual tumour. LE is performed in several dedicated surgical units. However, LE is not yet standard of care for residual lesions from a primary locally advanced tumour, mainly due to a lack of data on long-term oncological outcome. Furthermore, there is some postoperative morbidity, including pain, wound dehiscence and infection,[29] as well as a potentially compromised functional outcome, with one study reporting up to 50% of major symptoms of LARS.[20 30] Therefore, when a patient achieves cCR after extension of the observation period, subsequent LE can be omitted in this study.

In both arms of this phase II study, an intensive surveillance programme is scheduled in order to detect treatment failure, tumour regrowth and/or disease recurrence at an early stage, and to proceed to completion or salvage TME-surgery when needed and when possible. Patients will be informed that additional treatment with CXB or LE might increase the morbidity rate in case completion or salvage TME-surgery needs to be performed. The GRECCAR-2 trial compared LE and TME-surgery in patients with a good response after chemoradiotherapy: the trial failed to show superiority of LE over TME-surgery, because many patients with LE underwent completion TME-surgery that probably increased morbidity and compromised the potential advantages of LE.[21] However, a recently published study showed that in a small cohort of patients, completion TME-surgery after LE was not associated with increased postoperative morbidity or mortality.[31]

In conclusion, the OPAXX study aims to evaluate two additional local treatment options that may potentially increase the organ preservation rate in patients with rectal cancer with a good, but not complete response after neoadjuvant (chemo)radiotherapy: CXB or extension of the observation period with or without additional LE.

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