ORGAN PRESERVATION IN PATIENTS WITH A GOOD CLINICAL RESPONSE AFTER NEOADJUVANT (CHEMO)RADIATION FOR RECTAL CANCER:

OPTIMIZATION OF TREATMENT STRATEGIES AND DEFINING THE ROLE OF ADDITIONAL CONTACT X-RAY BRACHYTHERAPY VERSUS EXTENDING THE WAITING INTERVAL AND LOCAL EXCISION

OPAXX STUDY

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Protocol ID	**NL75896.031.20**
Short title	**OPAXX study**
Version	**4.0 17AUG2022**
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Sponsor	**Antoni van Leeuwenhoek / Netherlands Cancer Institute, Amsterdam in collaboration with Catharina Hospital, Eindhoven**
Subsidising party	**ZonMW Topspecialistische Zorg en Onderzoek (TZO) 10070012010003 –** **“De multidisciplinaire behandeling van het complexe rectumcarcinoom (Catharina Ziekenhuis)”**
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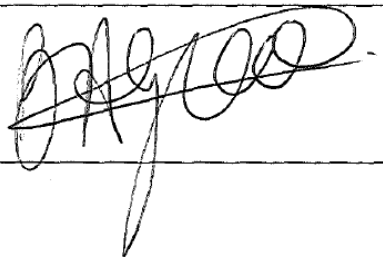
Coordinating Investigator: ***B.A. Grotenhuis MD PhD*** ***Antoni van Leeuwenhoek***		24/11/2020

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CRT	**Chemoradiation therapy**
CTC	**Common toxicity criteria**
CTCAE	**Common terminology criteria of adverse events**
CXB	**Contact x-ray brachytherapy**
DRE	**Digital Rectal Examination**
DSMB	**Data Safety Monitoring Board**
EORTC	**The European Organization for Research and Treatment of Cancer**
ICMJE	**The International Committee of Medical Journal Editors**
IRC	**Intermediate rectal cancer**
IWWD	**International Watch & Wait Database**
LARC	**Locally advanced rectal cancer**
LARS	**Low anterior resection syndrome**
LE	**Local excision**
NKI	**Nederlands Kanker Instituut**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MRF	**Mesorectal fascia**
MRI	**Magnetic resonance imaging**
SAE	**Serious Adverse Event**
TAMIS	**Transanal minimally invasive surgery**
TME	**Total mesorectal excision**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: The organ preservation approach for rectal cancer has been explored increasingly, aiming at improving quality of life by prevention of total mesorectal excision (TME-surgery). In patients with intermediate rectal cancer (IRC) and locally advanced rectal cancer (LARC) who receive neoadjuvant (chemo)radiotherapy (in general a short-course radiotherapy or a long-course chemoradiation, respectively) subsequent TME-surgery is still standard of care.

In patients with a good clinical response after neoadjuvant (chemo)radiation, organ preservation may be considered, depending on the extent of the response monitored by radiological and endoscopic assessment. Some patients show a clinical complete response and can be monitored closely in a watch-and-wait approach. In case of a good, but not complete response, it remains unclear which patients may benefit from extension of the observation period after (chemo)radiation in order to achieve a complete clinical response over time, or in whom additional local treatment options (such as contact x-ray brachytherapy or local excision) are beneficial in obtaining organ preservation eventually.

Objective: The aim of this study is to investigate which rate of organ preservation can be achieved in patients with rectal cancer treated with neoadjuvant (chemo)radiotherapy with a good clinical response, and to optimize the different treatment strategies (Figure 1). In patients with a near-complete response or with a small residual tumour mass, participation is offered in a phase II feasibility trial, in which two potential organ preservation treatment strategies are evaluated: contact x-ray brachytherapy or extension of the waiting interval with or without additional local excision in case of residual disease.

Study design: This is a prospective study with a mixed design. It concerns a phase II feasibility study for patients in whom a good, but not complete response has been achieved after (chemo)radiation (OPAXX study): two parallel single study-arms evaluate the efficacy of experimental organ preservation approaches. To allow for a better comparison of secondary parameters (toxicity and morbidity of both additional local treatments) eligible patients will be randomized between two experimental arms. Furthermore, an observational cohort study is established to register rectal cancer patients with a good but not complete clinical response after (chemo)radiation who are not eligible for randomisation in the OPAXX study (OPAXX registration study).

Study population: In general, patients with IRC receiving short-course radiotherapy with delayed surgery (patients with initially a cT1-3, cN1-2 lymph nodal status, no involved MRF or cT3c-d, N0-1 lymph nodal status) or patients with LARC receiving neoadjuvant long-course chemoradiation (patients with initially cT4 tumour, cN2 lymph node status, lateral lymph node involvement and/or an involved mesorectal fascia (MRF+)) according to the

Dutch national guideline are eligible for this study when at the first response assessment 6-8 weeks after finishing the (chemo)radiation a good clinical response is seen. A good clinical response has been defined as a clinical complete response, a near-complete response or a small residual tumour mass <3 cm on endoscopy, but also no evidence of residual nodal disease on magnetic resonance imaging (MRI) (ycN0). In case of a clinical complete response the current strategy of watchful waiting is offered. Eligible patients in whom a good, but not complete response is detected will be randomized to one of the two experimental OPAXX study arms, provided that both additional local treatment options are technically feasible.

Intervention arms OPAXX study:

Arm 1: Contact x-ray brachytherapy will be given applied after randomisation with a maximum interval of 14 weeks after finishing the neoadjuvant (chemo)radiation. Contact x-ray brachytherapy consists of three fractions of 30Gy per fraction applied to the tumour, with a 2 week interval between each boost. Response evaluation takes place every 3 months thereafter. Patients in whom a clinical complete response is detected during follow-up are offered a watch-and-wait approach; patients in whom an incomplete response or disease progression is noted, completion or salvage TME-surgery is advised.

Arm 2: The waiting interval will be extended with 6-8 more weeks after the first response evaluation, followed by a second (or third in case of ongoing response) re-assessment. Patients with a clinical complete response at the time of the second (or third) response evaluation will be offered a watch-and-wait approach without any surgical treatment. Patients with a remaining small lesion will be offered transanal local excision. Depending on the final pathological staging after local excision, patients are categorized as low-risk or high-risk, and will be offered a watch-and-wait strategy or completion TME-surgery, respectively.

Main study parameters/endpoints: The primary endpoint of the OPAXX study reflects the efficacy of both additional treatment options: the rate of successful organ preservation (defined as an in-situ rectum, no defunctioning stoma and absence of active locoregional cancer failure) at one year following randomisation in rectal cancer patients with a good, but not complete clinical response after (chemo)radiation. Secondary endpoints are related to toxicity and morbidity of the two additional treatment options in the randomisation study, as well as to oncological and functional outcomes at one, two and five years of follow-up.

For patients with a good but not complete clinical response after (chemo)radiation who are not eligible for randomisation in the OPAXX study an observational cohort study is conducted (OPAXX registration study).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Standard treatment of IRC and LAR consists of neoadjuvant short-course or long-course (chemo)radiotherapy followed by TME-surgery. If a clinical complete

response is seen at response evaluation, a watch-and-wait approach is currently considered a valid strategy in selected patients according to the Dutch national guidelines. In the ongoing Dutch national prospective registry patients with a near-complete response are currently offered an extension of the observation period rather than TME-surgery, and, subsequently, a watch-and-wait policy when a clinical complete response is noted over time. On the other hand, all patients with a persistent residual lesion will proceed to TME-surgery. In the current study, two experimental approaches are introduced that could increase organ preservation rates in patients with a good, but not-complete response at the first response evaluation: additional endoluminal contact x-ray brachytherapy and local excision of the tumour remnant.

Prior to randomisation, eligible patients are well informed about the risks of the two experimental treatment strategies (i.e. unclear long-term oncological outcome), and are offered standard-of-care TME-surgery. Moreover, patients will be informed that additional treatment with contact x-ray brachytherapy or local excision might increase the morbidity rates in case completion or salvage TME-surgery is required.

Finally, in both arms of this phase II study an intensive surveillance program has been established, in order 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.

Figure 1. OPAXX FLOW CHART

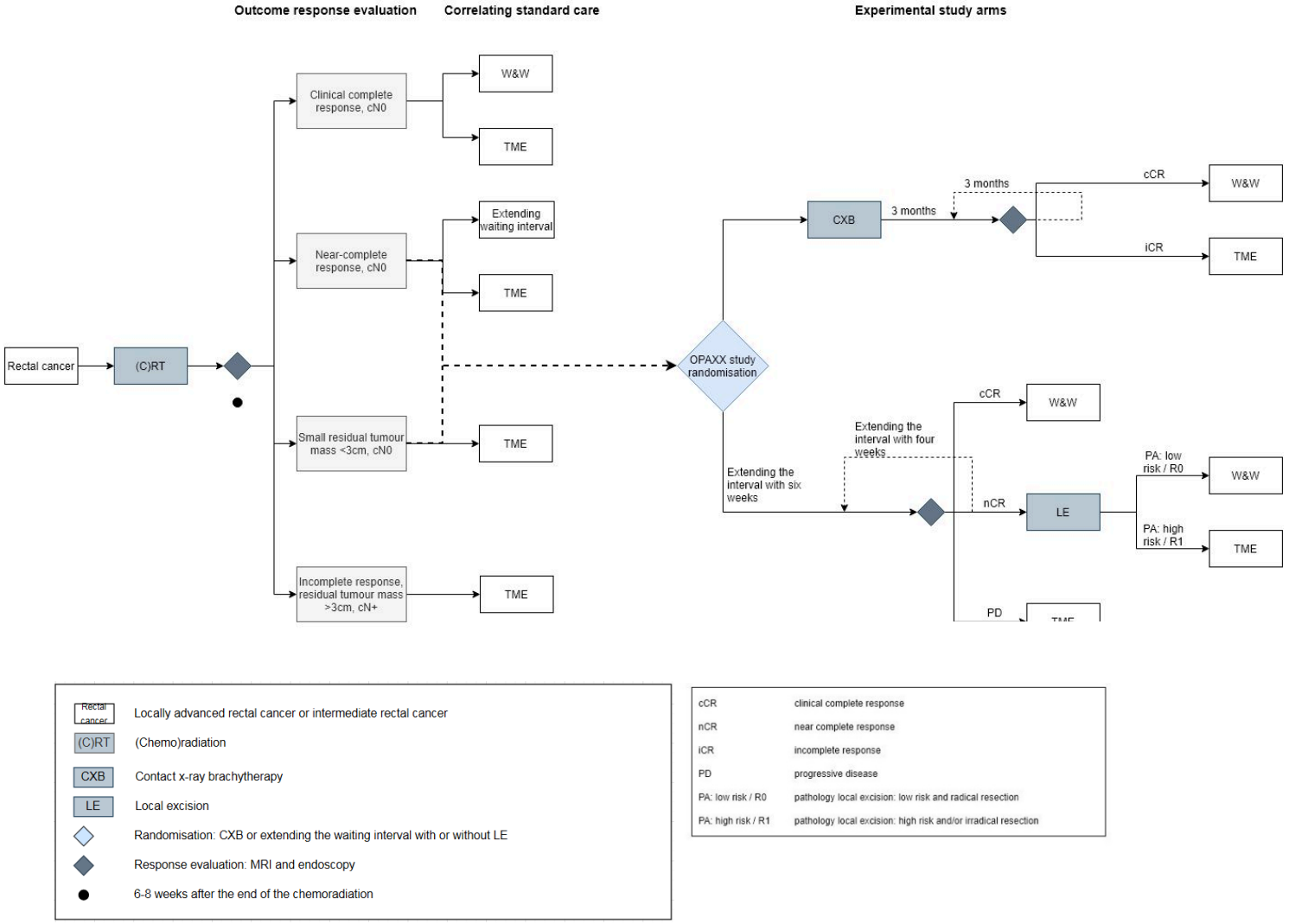


Figure 1: Patients with a clinical good response after neoadjuvant (chemo)radiation for rectal cancer

1. INTRODUCTION AND RATIONALE

Patients with IRC or LARC are in general treated with a neoadjuvant short-course or long-course (chemo)radiotherapy followed by TME-surgery, usually 8-12 weeks after completion of the (chemo)radiation. In 15-20% a pathologically complete response is noted, i.e. no residual tumour is found in the resection specimen(1). In recent years, the organ preservation approach for rectal cancer has been explored increasingly, aiming at improving quality of life by prevention of TME-surgery. The watch-and-wait approach for patients with a clinical complete response after neoadjuvant (chemo)radiation was first reported by Habr-Gama in 2004(2). Studies about this watch-and-wait approach reported good oncological outcomes with five-year disease-specific survival and overall survival of respectively 93,8 and 84,7 percent(3). Therefore, interest in this approach is increasing, also due to an improved quality of life in patients treated with the watch-and-wait approach(4, 5).

Over recent years a shift is noted from very strict selection criteria (including patients in whom all diagnostic examinations show an unequivocal complete response) towards a slightly less strict approach in which organ preservation is also considered in patients with a clinical near-complete response. In these patients significant downsizing of the primary tumour has been established after neoadjuvant (chemo)radiation; however, on endoscopy and MRI still some abnormalities in the rectal wall are noted suspicious for the presence of residual tumour. Although TME-surgery may be the most prudent approach for near-complete responders (standard treatment remains TME-surgery in terms of solid evidence on long-term oncological outcome), it is of note that resection specimens of these patients sometimes show no residual tumour (i.e. pathological complete response), indicating that response evaluation can be difficult and inaccurate(6).
Moreover, an increasing group of patients is highly interested in achieving organ preservation and a better quality of life. Outside the national guidelines or in studies aiming at primary organ preservation, patients with early rectal cancer or IRC and a strong wish for organ preservation occasionally receive neoadjuvant chemoradiation to increase the chance of a clinical complete response. Several factors may be of influence in this decision making, which includes a trade-off between risks and gains of both clinical and functional outcomes(7). For patients (in contrast to their physicians), avoiding surgery with a permanent stoma appears sometimes more important than a prolonged disease-free survival(7, 8).

With the knowledge of patients' preferences, several organ preservation strategies are now carefully explored in patients with a good clinical response after (chemo)radiation: not only the watch-and-wait approach in case of a clear clinical complete response, but also

extension of the waiting interval after (chemo)radiation to obtain eventually a clinical complete response, or additional local treatment options such as contact x-ray brachytherapy or local excision for a good but not complete response.

Watch-and-wait approach

Surgeons in The Netherlands have been very active in prospective research in this area, and have provided a significant part of the current evidence and knowledge. This resulted in a leading role in the International Watch and Wait Database (IWWD), that reported on the long-term outcome of clinical complete responders after neoadjuvant treatment for rectal cancer. In 880 highly-selected patients with a clinical complete response the 2-year incidence of local regrowth was 25%, which equals a sustained clinical complete response of 75%; 97% of local regrowth was located in the bowel wall (i.e. not in locoregional lymph nodes). Distant metastases were diagnosed in 8% of patients, resulting in a 5-year overall survival rate of 85% and 5-year disease-specific survival of 94%. More importantly, local unsalvageable disease after watch-and-wait was rare (1%); therefore it was concluded that patients with a sustained clinical complete response clearly have no oncological disadvantage from a watch-and-wait policy.

At present there is a national ongoing multicentre implementation and registration trial, sponsored by the Dutch Cancer Society “Wait-and-see policy in complete responders after chemoradiotherapy for rectal cancer” (NCT03426397). The study is coordinated by the Netherlands Cancer Institute in Amsterdam, and is believed to capture the far majority of Dutch patients treated by a wait-and-see policy aiming at organ preservation in rectal cancer patients.

Extension of the observation period

It seems reasonable to monitor a potentially optimal tumour response after neoadjuvant neoadjuvant (chemo)radiation before considering and offering any kind of additional treatment. The standard interval between finishing the (chemo)radiation course and first response assessment is 6-8 weeks; by extending this interval higher rates of a complete response can be achieved(9, 10). With a second (or third) assessment after another 6-12 weeks interval in patients with a near-complete response, even more patients can be diagnosed with a clinical complete response: waiting intervals of 18-20 weeks, predominantly after CRT have been described. Success rates of achieving a clinical complete responses have been reported in up to 90% of these highly-selected patients, without evidence that oncological outcome is compromised(11, 12). Also, it has been shown that it is safe to extend the waiting interval after (chemo)radiation before proceeding to surgical treatment(13). However, thus far there is limited evidence about the proportion and selection

of patients who will benefit from this extended interval; more importantly, a clear and uniform applicable definition of a near-complete response is lacking.

Contact x-ray brachytherapy (CXB)
With contact x-ray brachytherapy an intraluminal radiation boost up to 90 Gy is applied to the primary rectal tumour, with minimal collateral damage to the surrounding normal tissues due to minimal penetration of the 50 kVolt therapy(14). Contact x-ray brachytherapy has been introduced in elderly rectal cancer patients and in patients with comorbidities unfit for surgery. The additional role of contact x-ray brachytherapy in relation to (chemo)radiation has been explored in order to avoid major surgery; these studies report good oncological outcomes, with clinical complete response rates of 64 to 72 percent(15, 16). However, the majority of these study patients had been diagnosed with early rectal cancer rather than locally advanced tumours: 55 up to 74 percent were initially cT1 or cT2 (15, 17, 18). These studies were not randomized, so selection bias can be a factor attributing to the outcome.

For radiobiological reasons the contact x-ray brachytherapy seems best given as close to the external beam therapy as possible, to avoid long radiotherapy treatment interruptions that can stimulate tumour regeneration(19). A number of studies have reported intervals of 2-8 weeks between the two radiation modalities, sometimes applying the contact x-ray brachytherapy regardless of the initial response to the neoadjuvant (chemo)radiation course (15-17). However, in a recently published guidelines with recommendations for contact x-ray brachytherapy no consensus has been reached on the optimal interval between the end of (chemo)radiation and the first application of contact x-ray brachytherapy(20).
Most commonly reported toxicity after contact x-ray brachytherapy 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 hemostasis(15-18). Rectal ulceration after contact x-ray brachytherapy may occur in up to 30% of patients, which is usually healed after 3-6 months(16). With regard to functional outcome after contact x-ray brachytherapy it is described that most patients are satisfied with the resulting bowel function, although more systematically evaluated data on this subject is scarce (17, 18).

Although more outcome data is available on additional contact x-ray brachytherapy after a short-course radiotherapy rather than after a long-course chemoradiation, there are small reliable cohorts in which short-course radiotherapy was given in combination with contact x-ray brachytherapy. One cohort showed grade 1 or 2 toxicity in 33 percent of the cases, grade 3 toxicity wass only observed in one patient (2 percent)(18). Further subgroup analyses show

that there was no significant difference in acute or long-term toxicity between short-course or long-course radiotherapy.

Local excision (LE)

Local excision is another treatment option for rectal cancer patients that can avoid major surgery. Transanal local excision is the standard of care in early low-risk T1 rectal cancers. Some studies including patients with early to intermediate (but not locally advanced) rectal cancers have explored the role of local excision after neoadjuvant (chemo)radiation, aiming at organ preservation(21-24). When histological examination of the local excision specimen revealed sufficient pathological downstaging (definition varied between ypT0-1 and ypT0-2), patients were considered to be successfully treated with (chemo)radiation and local excision alone and were offered a watch-and-wait approach. In general, the majority of these selected patient groups were treated successfully in terms of organ preservation, with completion TME-surgery rates for insufficient pathological downstaging in only 5-35% percent of patients (21-23).

These studies have shown that additional local excision is a feasible organ preservation approach, and it provides accurate information about the presence and extent of the residual tumour. There is however some postoperative morbidity, including pain, wound dehiscence and infection (25), as well as a potentially compromised functional outcome, with one study reporting up to 50% of major symptoms of the low anterior resection syndrome (LARS) (21, 26). However, one should realize that in case of a clinical complete response after (chemo)radiation, subsequent local excision can also be omitted.

The current data on local excision for rectal cancer after (chemo)radiation are mainly focused on early to intermediate rectal cancers; surgeons are more reluctant to perform local excision in downsized locally advanced rectal tumours because of the higher risk of lymph node involvement and the unknown long-term oncological outcome for this treatment strategy.

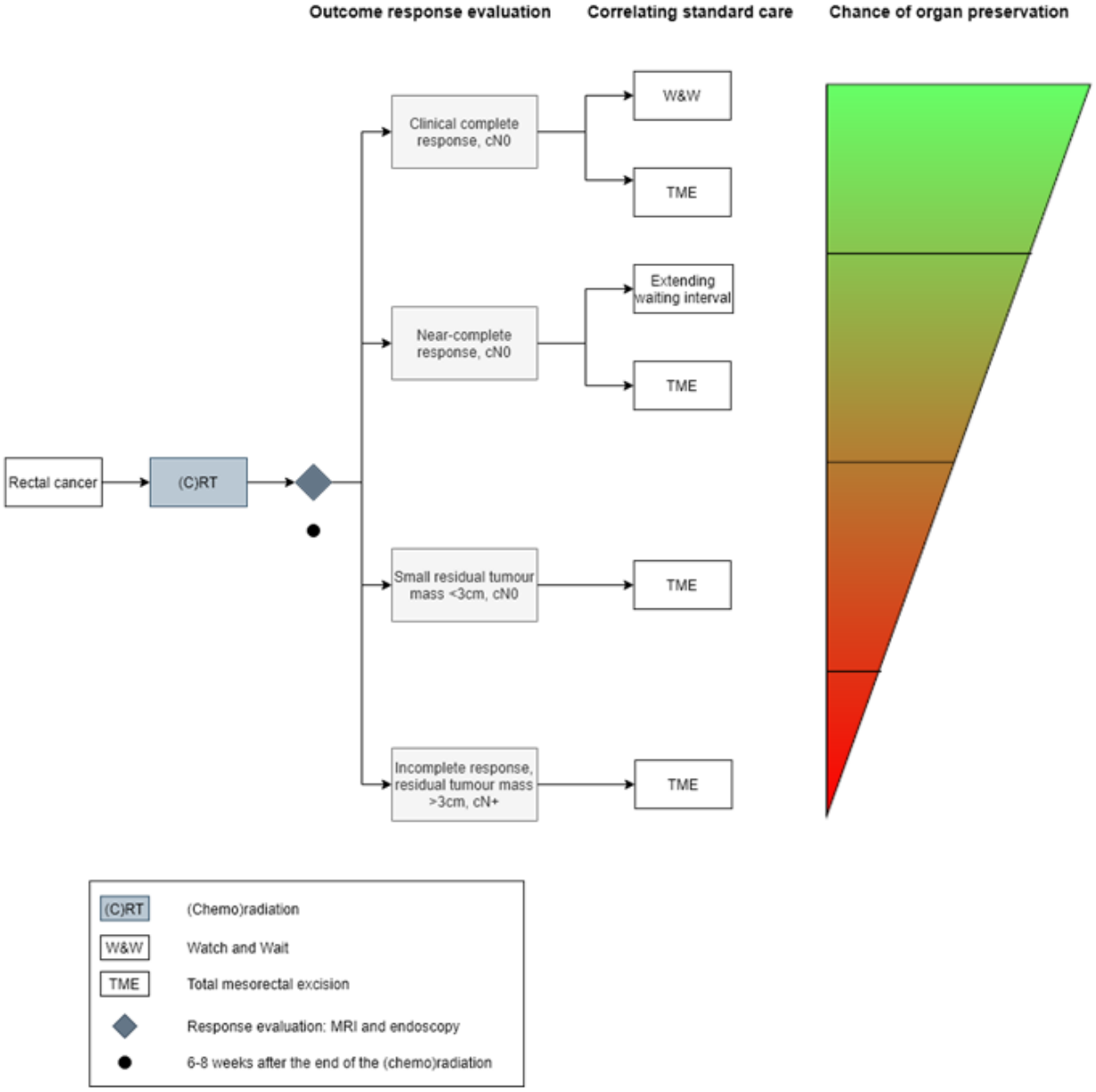
Rationale current study

The question remains what the best treatment strategy is to increase the chances for organ preservation in patients with a good response after neoadjuvant (chemo)radiation; both after a short-course radiotherapy or a long-course chemoradiation. No randomized controlled trials have been conducted to compare additional treatment strategies in patients with a good, but not complete response after neoadjuvant (chemo)radiation. Results of the previously mentioned available studies exploring the role of additional treatment strategies may not be applicable to patients with locally advanced tumours. Furthermore, it is likely that chances of organ preservation will gradually decrease with a less pronounced tumour response, as

shown in Figure 2. It has been shown that in patients with LARC (cT3b-d/cT4) a longer waiting interval (>16 weeks after chemoradiation) is needed to obtain a clinical complete response than in smaller tumours (cT2-cT3a)(12). In current practice, patients may be offered a second, or even third re-assessment in case of an ongoing response. Still we are not well informed about the additional value of local treatment options such as contact x-ray brachytherapy and local excision in this specific group of patients compared to only extending the waiting interval. While local excision can be offered after an extended waiting interval without compromising the treatment effect, contact x-ray brachytherapy should be offered shortly after neoadjuvant (chemo)radiation for optimal radiobiological effect (preferably <14 weeks after having finished the long course CRT).

Obviously, further research on this clinically relevant topic is needed to clarify the optimal treatment strategy for rectal cancer patients with a good response after neoadjuvant (chemo)radiation aiming at organ preservation, and to define the role of additional contact x-ray brachytherapy versus extending the waiting interval with or without local excision. We propose a phase II feasibility study for patients in whom a good, but not complete response has been achieved after (chemo)radiation (OPAXX study): two parallel single study-arms evaluate the efficacy of experimental organ preservation approaches in contrast to the current strategy of simply extending the observation period after the first response assessment. For patients with a good but not complete clinical response after (chemo)radiation who are not eligible for randomisation in the OPAXX study an observational cohort study is conducted (OPAXX registration study).

Figure 2. Chances of organ preservation depend on the degree of tumour response to (chemo)radiation



2. OBJECTIVES

The aim of this study is to investigate which rate of organ preservation can be achieved in rectal cancer patients with a good clinical response after neoadjuvant (chemo)radiation, and to optimize different treatment strategies in patients with a good, but not complete clinical response (Figure 1). In patients with a clinical complete response a watch-and-wait strategy is provided. In patients with a near-complete response or with a small residual tumour mass, participation is offered in the OPAXX study, a phase II feasibility trial in which randomisation takes place between two potential organ preservation treatment strategies: contact x-ray brachytherapy or extension of the waiting interval with or without additional local excision.

Primary objectives:

- OPAXX: Aim of the phase II feasibility OPAXX study is to determine the rate of organ preservation that can be achieved in patients with a good, but not complete response after neoadjuvant (chemo)radiaton by implementing an additional local treatment option: contact x-ray brachytherapy after the first response assessment or extending the waiting interval followed by local excision in case of suspected residual tumour. This part of the study will evaluate the feasibility of both study arms as a potentially new treatment strategy aiming at organ preservation in patients with rectal cancer.
- OPAXX registration study: To investigate which rate of organ preservation can be achieved in patients with rectal cancer with a good but not complete clinical response after neoadjuvant (chemo)radiation. In this observational cohort all patients with a good but not complete clinical response after (chemo)radiation who are not eligible for randomisation in the OPAXX are registered (OPAXX registration study). This will give insight in the proportion of patients in whom an organ preservation strategy can be considered, dependent on the degree of tumour response to neoadjuvant (chemo)radiation.

3. STUDY DESIGN

This is a prospective study with a mixed design. The OPAXX study is a phase II feasibility study to explore two potentially new treatment strategies particular in two patient groups: 1) patients treated with short-course radiotherapy for IRC according the Dutch national guidelines or for LARC in case of comorbidities or frailty 2) patients treated with long-course chemoradiation for LARC according the Dutch national guidelines or for early rectal cancer or IRC due to a strong wish for organ preservation. All patients with a good, but not complete response after neoadjuvant treatment are considered study patiets for two additional treatments to evaluate the efficacy of alternative experimental approaches (Figure 1). To be able to compare results of both treatment strategies, patients are randomized between contact x-ray brachytherapy given immediately after the randomisation moment, and extension of the waiting interval with or without additional local excision.

Patients included in the OPAXX study will be randomized (1:1 ratio) between the two single-arm phase II studies for two reasons:

- to prevent discussion about the comparability of those two single-arm studies if just one of the two studies turned out to be effective.
- to reduce the bias in a comparison of secondary parameters (aimed at toxicity and morbidity of these additional treatment modalities, as well as oncological and functional outcome);

Finally, the data obtained in this study can be used for a larger phase III trial with the most successful approach.

4. STUDY POPULATION

4.1 Population (base)

Rectal cancer patients who have received neoadjuvant short-course radiotherapy or long-course chemoradiation are eligible when a good clinical response is seen at the first response assessment after (chemo)radiation. The indication for either a short-course or long-course radiotherapy has been described below:

1. Short-course radiotherapy (radiation dose of 25 Gy in 5 fractions in one week on the primary tumour and regional lymph node areas):
- Patients treated with neoadjuvant short-course radiotherapy for IRC with delayed surgery according to the Dutch national guidelines (patients with initially cT1-3, cN1-2 lymph nodal status, no involved MRF or cT3c-d, N0-1 lymph nodal status without presence of significant distant metastases)
- Patients treated with neoadjuvant short-course radiotherapy for locally advanced rectal cancer in whom chemoradiation can not be given due to comorbidities or frailty.

2. Long-course (chemo)radiation (radiation dose of 45 – 50.4 Gy on the primary tumour and regional lymph node areas:
- Patients treated with chemoradiation for LARC according to the Dutch national guidelines (patients with initially a cT4 tumour, cN2 lymph node status, lateral lymph nodes and/or involved MRF, without the presence of significant distant metastases
- Patients treated with chemoradiation for early rectal cancer or IRC with a strong wish for organ preservation.

In general no boost dose on the primary tumor or a more hypofractionated radiation schedule is allowed. Patients treated with neoadjuvant or induction chemotherapy prior to chemoradiation cannot be included, or patients in whom chemotherapy is given after short-course radiotherapy (RAPIDO or M1-scheme).

The first response evaluation consists of MRI pelvis and CT chest/abdomen, and is completed with endoscopy and digital rectal examination in case of a good clinical response. A good clinical response (its characteristics are summarized in Table 1) has been defined as:
- a clinical complete response;
- a near-complete response; or
- a small residual tumour mass <3 cm on endoscopy.

Patients are eligible for the OPAXX study in case of a good, but not complete response (near-complete response or small residual tumour mass <3 cm), and in whom it is technically

feasible to perform both additional local treatment options (contact x-ray brachytherapy or local excision). In addition, there should be no evidence of residual nodal disease on MRI (i.e. clinically node-negative status, ycN0). In case a good clinical response of the primary tumour is noted, but distant metastases are detected at this first response assessment (e.g. non-specific long nodules are now suspicious for metastases), patients are still eligible for the OPAXX study.

Patients are eligible for the OPAXX registration study in case a good but not complete clinical response is noted at the first response assessment but randomisation is not possible (e.g. strong patient preference for specific additional local treatment, contact x-ray brachytherapy is technically not feasible or the time-interval for first application of contact x-ray brachytherapy is exceeded).

Setting

The current study will be rolled out over the Dutch wait-and-see consortium network of 12 hospitals that are currently participating in the ongoing wait-and-see registration study. Therefore, the setting will be a national multicenter study, in a pre-existent network of cooperating hospitals, including the two coordinating centres.

Table 1: Characteristics of a good clinical response after (chemo)radiation(27, 28).

Clinical complete response after (chemo)radiation			
DRE[1]	Endoscopy	MRI-T2W[2]	MRI-DWI[3]
Normal, no palpable tumour (if initially palpable with DRE).	Flat, white scare with telangiectasia. No residual tumour or ulcer.	Substantial downsizing with no residual tumour, or with residual fibrosis, or with residual wall thickening because of oedema. No suspicious lymph nodes.	Low signal on high b-value MRI. No suspicious lymph nodes.
Clinical near-complete response after (chemo)radiation			
DRE	Endoscopy	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)radiation			
DRE	Endoscopy	MRI-T2W	MRI-DWI
Small (palpable) tumour mass < 3cm.	Visible tumour or an ulcer with irregular borders <3cm.	Obvious downsizing, though with a heterogeneous and irregular aspect of the residual fibrosis <3cm.	Focal area of high signal on high b-value MRI.

NB. 1: DRE = digital rectal examination 2: MRI-T2W = magnetic resonance imaging - T2 weighted 3: MRI-DWI = magnetic resonance imaging - diffusion weighted imaging.

4.2 Inclusion criteria OPAXX study

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

- histologically verified adenocarcinoma above the dentate line and within 10cm of the anal verge;
- neoadjuvant short-course radiotherapy for patients with 1) IRC and delayed response evalation according to the Dutch national guidelines (cT1-3, cN1-2 lymph nodal status, no involved MRF or cT3c-d, N0-1 lymph nodal status without presence of significant distant metastases) without full dose chemotherapy in the interval (e.g. Rapido-scheme) or 2) LARC due to comorbidity or frailty; OR
- neoadjuvant long-course radiotherapy (chemoradiation) for patients with 1) LARC according to the Dutch national guidelines (cT4 tumour, cN2 lymph nodal status, lateral lymph node involvement, and/or involved MRF, without the presence of significant distant metastases) or 2) early rectal cancer or IRC and a strong wish for organ preservation;
- clinically near-complete response or a small residual tumour mass <3 cm;
- technically feasible to perform both treatment options (contact x-ray brachytherapy or local excision);
- age >18 years;
- written informed consent.

4.3 Exclusion criteria OPAXX study

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

- neoadjuvant or induction chemotherapy prior or adjacent to (chemo)radiation, e.g. patients with a Rapido or M1-scheme are not eligible;
- radiation dose >50.4 Gy or boost dose on the primary tumour;
- presence of suspicious lymph nodes (yN1/N2) at first response evaluation;
- residual tumour ≥ 3cm or over half of the circumference of the rectal lumen;
- patients who are unable to undergo contact x-ray brachytherapy or local excision;
- patients who cannot tolerate a completion- or salvage-TME because of comorbidity or frailty;

4.4 Sample size calculation

The sample size for the OPAXX study will be 168 patients : 80 patients per study arm plus an expected dropout rate of 5%. For the detailed sample size calculation see paragraph 8.1 OPAXX study: statistical design, interim analysis and sample size calculation.

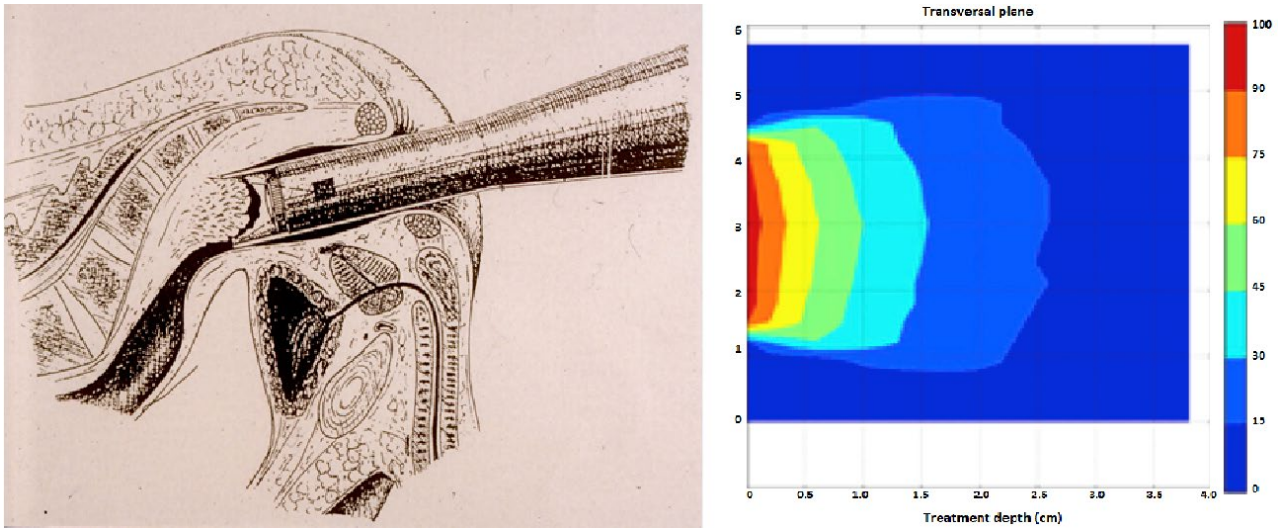
5. TREATMENT OF OPAXX STUDY PATIENTS

In this phase II feasibility trial, patients with a good, but not complete response at the first reassessment 6-8 weeks after finishing neoadjuvant (chemo)radiation, and who are enrolled in the OPAXX study, will be allocated to additional contact x-ray brachytherapy or to an extended waiting interval followed by local excision in case of a remaining near-complete response (see OPAXX flow-chart, Figure 1).

Arm 1 contact x-ray brachytherapy

In case patient is allocated to the contact x-ray radiotherapy arm, an additional endoscopic evaluation will be organized in one of the two contact x-ray brachytherapy centres to evaluate technical ability to perform contact x-ray brachytherapy. Contact x-ray brachytherapy consists of three fractions of 30Gy per fraction applied to the tumour intraluminally, with a 2 week interval after each fraction. An applicator with size 20, 25 or 30mm is used dependent on the size of the residual tumour. Contact x-ray brachytherapy will be given in one of the two expert study centres of this study by dedicated radiation oncologists in an outpatients clinical setting. The first application of contact x-ray brachytherapy will be given at the latest of 14 weeks after the end of (chemo)radiation. Three months after the contact x-ray brachytherapy course, the response will be evaluated with MRI, endoscopy and digital rectal examination. When a complete clinical response 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 contact x-ray brachytherapy. TME-surgery will be advised when residual disease becomes obvious.
More detailed technical information is given in Appendix 1 of the current manuscript.

Figure 3. Contact x-ray brachytherapy*



**Minimal invasive technique with application of a local dose of 30 Gy aimed directly at the rectal mucosa with a dose at 5 mm depth of 60% (18 Gy), and at 10 mm depth of 38% (11Gy).(29)*

Arm 2 extended waiting interval followed by watchful waiting or local excision

The waiting interval will be extended with 6-8 more weeks after the first re-assessment, followed by a second response evaluation (MRI pelvis, endoscopy and digital rectal examination). When a clinical complete response is noted at this second assessment, patient is offered a watch-and-wait approach. When there is no clinical complete response but the response is still improving, the waiting interval can be extended with another 4 weeks, or it can be decided to perform local excision. When the waiting interval is again extended, there will be a third response evaluation (by endoscopy only) to evaluate if a clinical complete response (patient can proceed to a watch-and-wait approach) or a near-complete response (patient can proceed to local excision) 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. The reassessments, decisions and treatment are performed at the initially treating hospital. Transanal excision will preferably be performed within a 20 week timeframe after the end of the chemoradiation course.

Local excision will basically be performed by the TAMIS-procedure (transanal minimally invasive surgery) using a single port transanal platform (see Figure 4a/b), or an equivalent technique under general anesthesia in the operating theatre. The tumour site is removed by sharp dissection, aiming for a 1cm margin of normal mucosal tissue. Taking into account the possibility of microscopic intramural spread after neoadjuvant chemoradiation (residual tumour extension beneath normal appearing mucosa), an absolutely minimal margin of 5mm

should be aimed for, up to 1 cm preferably. A full thickness graft will be harvested (consisting of tumour, underlying muscular wall and a thin layer of perirectal fat, without dissecting the mesorectum extensively); only at tumours located anteriorly a more superficial dissection is allowed, provided that no concessions are made in terms of macroscopic radicality of the resection. The specimen is then pinned out on corkboard in the operating theatre according to histopathology guidelines.

After histological evaluation of the local excision surgical specimen, the tumour will be graded as low-risk (radical resection of ypT0-1 residual tumour) or high-risk. In case of a high-risk tumour, patient is advised to undergo completion TME-surgery.
The following definition of a high-risk tumour is applicable:

- Margin involved by tumour (≤ 1mm tumour clearance)
- Tumour stage ≥ ypT2
- N+ (in very rare cases a lymph node will be retrieved by full thickness local excision)

The following histopathological criteria will also be assessed by the pathologist, an can play a role in the decision whether completion TME-surgery is advised:

- Lymphatic invasion
- Vascular invasion: intramural (submucosa/muscularis propria) or extramural (mesorectal/adventitial fat)
- Perineural growth
- High-grade tumour budding
- Poorly differentiated tumour

The histopathological assessment of the surgical specimen after transanal excision or after TME-surgery will be additionally evaluated for:

- Tumour regression (minimal/no regression, moderate regression, complete pathological response)
- Tumour regression, graded according to the Mandard approach(30):
    - 1. Complete regression, fibrosis without detectable tissue of tumour
    - 2. Fibrosis with scattered tumour cells
    - 3. Fibrosis and tumour cells with preponderance of fibrosis
    - 4. Fibrosis and tumour cells with preponderance of tumour cells
    - 5. Tissue of tumour without changes of regression
- Classification of residual tumour as solid or fragmented
- Presence of microscopic intraluminal spread (i.e. lateral spread)

Figure 4a/b. Local excision small residual tumour mass by TAMIS technique

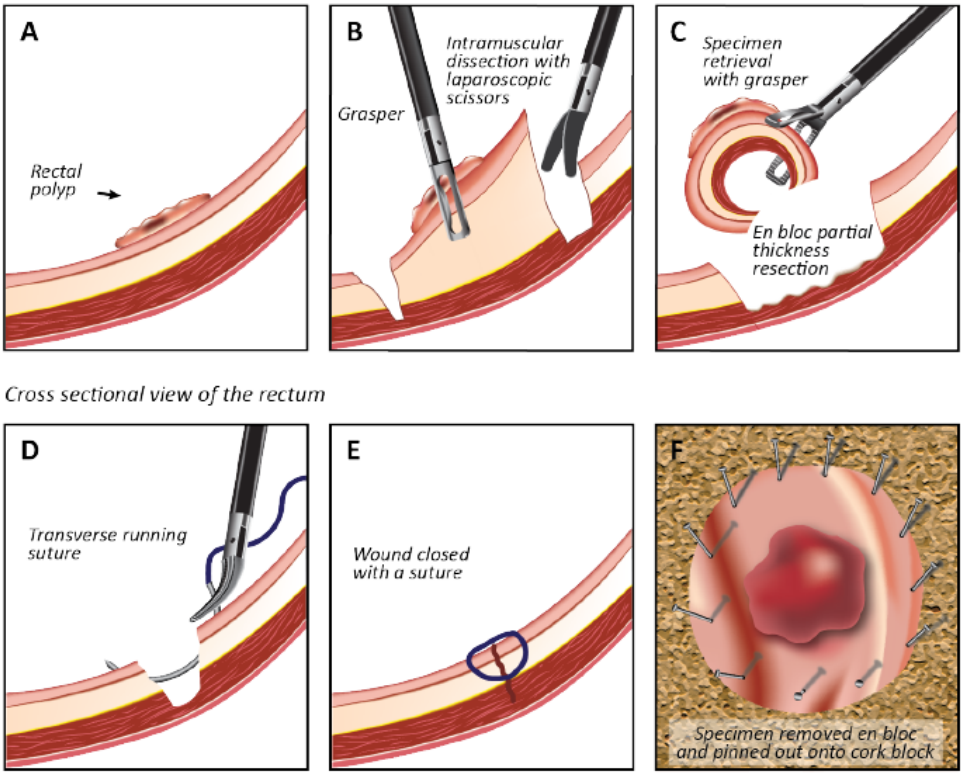


Figure 4a

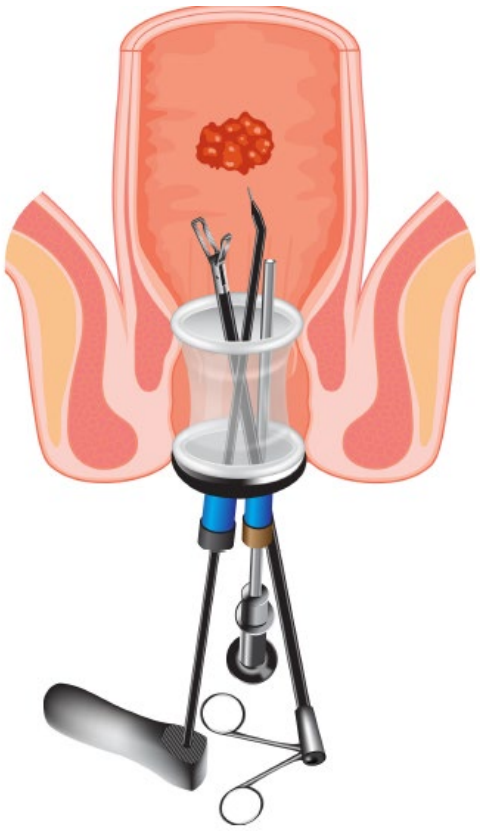


Figure 4b

6. METHODS

6.1 Study parameters/endpoints OPAXX study

6.1.1 Main study parameter/endpoint

The primary OPAXX study endpoint reflects the efficacy of both additional treatment options for rectal cancer patients with a good clinical response after neoadjuvant (chemo)radiation, and has been defined as the rate of organ preservation at one year following randomisation, including an in-situ rectum (including patients subjected to local excision), no defunctioning stoma and absence of active loco-regional cancer failure (indicated as either local intraluminal tumour regrowth or regional recurrence in lymph nodes requiring TME-surgery). The rate of organ preservation achieved in both study arms will be defined separately for IRC and LARC, as well as the related organ preservation failure rate (derivative of the success rate).

6.1.2 Secondary study parameters/endpoints

Secondary analyses will focus on toxicity of both additional treatment options, and on functional and oncological outcomes. These secondary parameters can be compared mutually between the two experimental study arms, but also to the current standard organ preservation approach in patients with a clinical complete response registered in the wait-and-see study (which can serve as baseline outcome after (chemo)radiation as no additional treatment is performed).

The following secondary endpoint have been defined:
(1) treatment toxicity or morbidity: short-term (< 3 months) and long-term (< 12 months)*
(2) functional outcome after one and two years (bowel/bladder/sexual dysfunction)**
(3) one- and two-year regrowth rate
(4) one- and two-year disease free survival
(5) one- and two-year overall survival
(6) organ preservation rate after two years
(7) complications within the first 30 days after completion or salvage TME-surgery, in terms of postoperatieve morbidity and mortality rates defined by Clavien-Dindo(31)
(8) overall quality of life and well-being***

**Treatment toxicity and morbidity are defined as:*
- acute treatment related toxicity grade 3 and 4 radiotherapy toxicity occurring within 3 months after end of radiotherapy, defined by the common terminology criteria of adverse events (CTCAE) version 5.0 (see Appendix 2.1 of the current manuscript);

- late treatment related toxicity grade 3 and 4 radiotherapy toxicity occurring after 3 months until one year after end of treatment, defined by the common terminology criteria of adverse events (CTCAE) version 5.0 (Appendix 2.1);
- postoperative morbidity occurring within 3 months after local excision, defined as post-operative complication grade 3-4 according to Clavien-Dindo (Appendix 2.2), and postoperative complications after one year.

*** Functional outcomes*
Functional outcomes regarding bowel function, bladder function and sexual function, will be assessed at baseline (within two weeks of the randomisation moment), at 3 months, 12 months, 24 months, and 60 months after the randomisation moment. The questionnaires/questions used in this study can be found in Appendix F1:

- the Low Anterior Resection Syndrome (LARS) score;
- selected items from the European Organization for Research and Treatment of Cancer (EORTC) QLQ-PR25, QLQ-CX29, and QLQ-ANL27.

**** Overall quality of life and well-being*
Quality of life of patients will be evaluated with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-CR29 (Appendix F1). The quality of life will be assessed at baseline (within two weeks of the randomisation moment), at 3 months, 12 months, 24 months, and 60 months after the randomisation moment.

6.2 Study procedures

Trial entry
The first response evaluation with MRI and endoscopy is performed 6-8 weeks after finishing (chemo)radiation. This first assessment consists of MRI pelvis and CT chest/abdomen, followed by endoscopy combined with a digital rectal examination in case of a clinical good response on imaging. Treating physicians are asked to classify the good clinical response in the following subgroups: patients with a clinical complete response, patients with a near-complete response and patients with a small residual tumour mass (Figure 1).
In case of a clinical complete response, patients are offered a watch-and-wait strategy as an alternative to TME-surgery. When a near-complete response is noted, patients will receive information on the two current standard treatment options (TME-surgery or extending the observation period and proceed with a watch-and-wait strategy only when a clinical complete response is achieved over time) versus participation in the OPAXX study. Patients with a

clear small residual tumour lesion will be informed about the current standard (TME-surgery) versus participation in the OPAXX study.

6.2.1 OPAXX study

Trial entry

Patients in whom a near-complete response or a small residual tumour mass < 3cm is detected at the first response evaluation after (chemo)radiation (a good, but not complete response), will be informed about the OPAXX study. Again, of note is that in all eligible patients TME-surgery will be offered as standard of care; when a patient is interested in organ preservation, the treating physician will explore the possibilities of participation in the current randomisation study.

Screening of the eligibility criteria and review of the endoscopy and MR images will be performed by the initial treating centre. Structured endoscopy and MRI report templates are used during assessment (Appendix 3). To ensure quality of data and to promote uniform decision making, central review of all imaging of randomized patients will be performed in a multidisciplinary team meeting between the 2 coordinating centres on a scheduled time base.

Randomisation process

If eligible, patient is asked to sign the informed consent form of the OPAXX study. Randomisation will be performed by means of the ALEA database. When allocated to the study arm of additional contact x-ray brachytherapy boost, patient will be referred to one of the two centres that provide contact x-ray brachytherapy (Amsterdam or Eindhoven). When allocated to the extended observation arm with optional local excision, patient will stay in the initial treating centre.

Follow-up

Patients who have received additional treatment according to the allocated treatment arm following randomisation, will be subjected to a follow-up schedule, dependent on treatment outcome (see Figure 1).

Patients with a clinical complete response 3-9 months after contact x-ray brachytherapy, with a clinical complete response after an extended waiting interval, or with a pathological low-risk residual tumour (ypT0-1) in case of a radical local excision, are offered a watch-and-wait follow-up scheme. The watchful waiting consists of an intensified follow-up schedule including digital rectal examination, flexible sigmoidoscopy (with periodic colonoscopy), MRI-T2W and MRI-DWI, CEA tumour marker and CT chest/abdomen for five years (Table 2). Structured endoscopy and MRI templates are used in response evaluation and during follow-

up (Appendix 3). In the first two years of follow-up patients are seen in outpatient practices every three months; thereafter follow-up will be organized twice yearly. At 3, 12, 24 and 60 months patients are asked to fill in the questionnaires with regard to quality of life and functional outcome.

Treatment failure

Patients with an incomplete response at 6-9 months after contact x-ray brachytherapy, with progressive disease during the extended waiting interval after the second or third round of response evaluation, or with a pathologically staged high-risk residual tumour after local excision (ypT2-3 or an irradical resection) are strongly advised to undergo completion surgery according to the principles of total mesorectal excision (cTME). Patients with a regrowth or a local recurrence are evaluated for salvage TME (sTME).

6.2.2 OPAXX registration study

The OPAXX registration study observational cohort will consist of patients with a good but not complete clinical response who are not eligible for randomization in the OPAXX study that have consented for data collection in the national registration wait-and-see study (M16WAS local study code).

Database management

The following data are registered for all patients in the OPAXX registration study cohort:

- Baseline clinical staging pre- and post-(chemo)radiation (cTNM and involvement of MRF), as well as location of the primary tumour (proximal, mid or distal rectum)
- Time between end of (chemo)radiation and response evaluation
- Degree of good response: clinical complete response, near-complete response or small residual tumour mass (according to the classification as shown in Table 1)
- Final treatment plan (watch-and-wait approach, extension of observational period followed by watch-and-wait, extension of observational period followed by TME-surgery, additional local treatment)
- Final pathology report in case of TME-surgery (ypTN classification, radicality of resection, and size of residual tumour)

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

Procedure		Distant metastasis #	CEA ¥	Digital Rectal Exam	Endoscopy/ biopsy	MRI
Year 1	3 months		X	X	X	X
	6 months		X	X	X	X
	9 months		X	X	colonoscopy‡	
	12 months	X	X	X	X	X
Year 2	3 months		X	X	X	
	6 months		X	X	X	X
	9 months		X	X	X	
	12 months	X	X	X	X	X
Year 3	3 months					
	6 months		X	X	X	
	9 months					
	12 months	X	X	X	X	X
Year 4	3 months					
	6 months		X			
	9 months					
	12 months		X	X	colonoscopy‡	X
Year 5	3 months					
	6 months		X			
	9 months					
	12 months		X	X	X	X

6.3 Withdrawal of individual patients

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a patient from the study for urgent medical reasons. In the specific case patients have already been referred to one of the coordinating centres for the allocated contact x-ray brachytherapy after randomisation, and contact x-ray brachytherapy appears not feasible due to location or size of the residual lesion, patient will be excluded from the OPAXX study and labelled as “screening failure”. These patients do not count as failures of treatment in the OPAXX study, but will be sent back to the referring hospital to consider alternative treatment options.

6.4 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 patient 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 patient health or safety. The sponsor will notify the accredited METC 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 accredited METC. The investigator will take care that all patients are kept informed.

7.2 AEs and SAEs

7.2.1 Recording Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a patient during the study, when related to the experimental intervention arms of the OPAXX study. All adverse events reported spontaneously by the patient or observed by the investigator will be recorded. At each contact with the patient, the study personnel must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded promptly in the patient's medical records. This information must be as complete as possible and preferably include start and stop date of the event, common toxicity criteria (CTC) grading according to CTCAE version 5.0 (Appendix 2.1 of the current manuscript) and the relation to the experimental intervention arms of the current study. At a later moment this information will be transferred from the medical records to the Case Report Forms.

7.2.2 Recording 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; 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.

Any serious adverse event which occurs within 90 days after last date contract x-ray brachytherapy (Arm 1) or study inclusion date (Arm 2) and is considered to be possibly related to study intervention or study participation should be recorded as well.

Not related:	The clinical adverse event is definitely unrelated to the study intervention (contact x-ray brachytherapy or extended wait and see procedure) (e.g., does not follow a reasonable temporal sequence from start of the study intervention, present prior to receiving study intervention). The study intervention is not likely to have had reasonable association with the observed experience; however, relationship cannot be definitely excluded.
Related:	The connection with the study intervention appears unlikely, but cannot be excluded with certainty (e.g., follows a reasonable temporal sequence from start of study intervention, may be related to known characteristics of the patients' clinical state or other modes of therapy administered to the patient, etc.). The clinical adverse event appears related to the study intervention with a high degree of certainty (e.g., follows a reasonable temporal sequence from start of study intervention and abates upon discontinuation of the study intervention, cannot be reasonably explained by known characteristics of the patient's clinical state or other modes of therapy administered to the patient, etc.). The event follows a reasonable temporal sequence from the start of the study intervention, and follows a known response pattern to the study intervention, cannot be reasonably explained by other factors such as the patient’s condition, other therapeutic interventions or concomitant drugs; AND occurs immediately following start study intervention, improves on stopping the study intervention, or reappears on re-exposure.

The intensity of an adverse event will be graded according to CTCAE version 5.0 (Appendix 2.1).

7.3 Reporting of SAE’s

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events. All serious adverse events starting during and after study intervention and within 90 days after the last study visit of the patient, whether considered by the principle investigator to be related to study related events or not, must be medically well documented and reported to the NKI Data Center within 24 hours or, at the latest, on the following working day. Reporting must be done using the Serious Adverse Event Form of the study. The forms will be filed at the NKI Data Center.

The report must be sent by **email (drugsafety@nki.nl)** to the **Antoni van Leeuwenhoek Data Centre.** The Data Centre can also be contacted by **telephone** (+31 20 512 9047) between **09.00 and 17.00 hours (GMT+1)** Monday to Friday**.**

Serious adverse events occurring more than 90 days after the last contact x-ray brachytherapy (Arm 1) or study inclusion date (Arm 2) will NOT be reported unless the investigator feels that the event may have been caused by the study intervention or a protocol procedure. Study-specific clinical outcomes of death because of disease progression are exempt from serious adverse event reporting, unless the investigator deems them related to the study intervention.

SAE's for this multicenter oncological study will not be reported through the web portal *ToetsingOnline* to the accredited METC.

7.4 Follow-up of adverse events

All AEs will be followed until they have declined, or until a stable situation has been reached. All SAEs must be followed up until resolution or stabilization, and this information must be reported to the NKI Data Center as soon as it becomes available, using a follow-up Serious Adverse Event Form. This form will be signed by the responsible study coordinator and filed together with the initial report.

7.5 Data Safety Monitoring Board (DSMB) / Safety Committee

An independent DSMB consisting of a surgical oncologist, a statistician and a radiation oncologist will be installed to monitor quality and patient safety in this multicenter trial. The DSMB will review the safety data, report their findings to the principal investigator and advise on study continuation at the interim analysis. During the study, the committee may decide to change the frequency of discussion. The members of the DSMB do not have conflict of interest with the sponsor of the study.

7.6 Annual safety report

In addition to the expedited reporting of (S)AE's, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC and competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all serious adverse events, along with an aggregated summary table, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the treatment under investigation.

8. STATISTICAL ANALYSIS

8.1 OPAXX study: statistical design, interim analysis and sample size

Patients with IRC or LARC in whom a good, but not complete response is established after neoadjuvant (chemo)radiation, will be invited to participate in the OPAXX study. In this study, two parallel single-arm phase II studies will evaluate the efficacy of two experimental organ-preserving approaches, rather than the current strategy of simply extending the observation period after the first response assessment. The primary endpoint in this study is the rate of successful organ preservation at one year in both phase II study arms.

Organ preserving rates described in literature vary from 62 up to 97 percent after treatment with contact X-ray brachytherapy and from 64 up to 91 percent after local excision (15, 17, 21, 23). These studies predominantly included patients with early to intermediate rectal cancer, instead of LARC. Therefore, it is expected that the organ preservation rate (i.e. the success rate) in this study will be lower in case the additional treatment options are technically feasible: approximately 50% in both experimental organ preserving approaches.

Without any additional local treatment but extension of the waiting interval only, the success rate for an organ-preserving approach is estimated 25%: this is based on the response rate observed in the Dutch national watch-and-wait registration cohort in patients with a near-complete response. An additional success rate of 10% is considered the minimum clinically relevant increase in order to justify the additional local treatment (both contact X-ray brachytherapy and local excision): an organ-preservation rate or success rate of 35% or less (which equals a failure rate of 65% or more) at 1 year after randomization is deemed unacceptable in both treatment arms. This will be applicable for both groups of rectal cancer patients receiving a short-course or long-course radiotherapy.

The study will not have enough statistical power to determine which of the two experimental organ preserving approaches is superior; therefore, the organ preservation failure rate will be analysed. The failure rate is a derivative of the rate of successful organ preservation, and has been defined as the proportion of patients that has to undergo (or is strongly advised to undergo) completion or salvage surgery by means of TME-surgery, but also the patients who received a defunctioning stoma during follow-up contribute to this failure rate (as described in the primary endpoint of the study).
In the OPAXX study a single-arm design will be used. In order to make maximum use of all information (e.g. including patients that have not been followed for one year yet at time of the interim analysis), the failure rate will be analyzed as a time-to-event endpoint. The failure

rates in each arm will be analyzed separately using a one-sided log-rank test. Taking into account the considerations in the preceding paragraph, the null hypothesis will be that the failure rate equals $\lambda 0 = 1.050$, which corresponds to an organ preservation/failure-free percentage of 35% at one year (the unacceptable scenario). Thus, the failure rate of the concerning treatment can be defined as acceptable or unacceptable, and, subsequently, the feasibility of both study arms is evaluated as a potential new treatment strategy.

An interim analysis is planned, which will take place when 20 events are observed. The interim analysis can be at different moments for two study arms, depending on the success/failure rate of the study arm (see Table 3). At the interim analysis, the z statistic of the one-sample log-rank test will be calculated, and the study arm will be stopped for futility if the z-statistic $z < -0.299$, the (non-binding) futility bound. The final analysis of a study arm takes places when 40 events are observed. The conclusion at the final analysis be based on the one-sample log-rank test, with a one-sided alpha of 0.05 (so the treatment will be considered successful if $z > 1.645$). Subanalyses will be conducted for the different patient groups.

The operating characteristics of this design were investigated by means of simulation. It was assumed that the sample size per group will be 80 patients, and that the inclusion of patients into a group follows a Poisson process with an accrual rate of 30 patients per year.
An exponential distribution was assumed for the occurrence of failures, and the event rate varied in the simulations to investigate the operating characteristics in three scenarios:

1. An optimistic scenario in which the event-free percentage at 1 year is 50% (this is the expected scenario);
2. A pessimistic scenario in which the event-free percentage at 1 year is 35% (this is the unacceptable scenario);
3. An extremely pessimistic scenario in which the event-free percentage at 1 year is 25% (this scenario is to investigate if the chance to stop at the interim analysis is high enough in case the safety is at risk).

The number of simulations was 5000 per scenario; these results are presented in Table 3:

Finally, to take into account a drop-out rate of 5%, the total sample size of the OPAXX study will be N=168 patients (80+80+8 patients).

Table 3: Operating characteristics in the three simulation scenarios

	optimistic scenario 50% failure free	pessimistic scenario 35% failure free	extreme scenario 25% failure-free
probability treatment is declared successful	82.1% (power)	3.9% (alpha)	<0.01%
probability to stop at the interim analysis	2.5%	41.1%	85.3%
expected time of the interim analysis	1.6 years	1.4 years	1.3 years
expected no. of patients at interim analysis	49	42	38
expected time of the final analysis	2.5 years	2.2 years	2.0 years

8.2 Primary study parameter

The main OPAXX study parameter reflects the efficacy of both additional treatment options, with the primary endpoint defined as the rate of successful organ preservation at one year following randomisation. This has been defined as an in-situ rectum (including patients subjected to local excision), no defunctioning stoma and absence of active loco-regional cancer failure (indicated as either local intraluminal tumour regrowth or regional recurrence in lymph nodes requiring TME-surgery). The rate of successful organ preservation achieved in both study arms will be defined, as well as the related organ preservation failure rate (derivative of the success rate).

The failure rate will be analyzed in both study arms using a one-side log-rank test; thus, both study arms can be defined as “acceptable” or “unacceptable”. Before one of the concerning treatment arms will be stopped when labelled as “unacceptable”, first the assumptions made for this analysis (success rate of 25% without additional treatment) will be re-evaluated with data from this current study (patients who will be offered a watch-and-wait strategy as they have developed a clinical complete response after extension of the waiting interval only).

8.3 Secondary study parameters

Secondary analyses will focus on toxicity of both additional treatment options, and on functional and oncological outcomes. These secondary parameters can be compared mutually between the two experimental study arms after randomisation, but also to the current standard organ preservation approach in patients with a clinical complete response

registered in the wait-and-see study (which can serve as baseline outcome after chemoradiation as no additional treatment has been performed).

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 6.2. In case of good clinical response, the potential organ preservation strategies are explored in case patient is interested. When a clinical good, but not complete response is noted, patient will be informed by the supervising doctor about the OPAXX study as an alternative to the standard of TME-surgery. Each patient has at least 48 hours to consider participation. The patient will be included after consent by their supervising doctor or researchers who have contact with the patient at the outpatient clinic or by telephone. Important is that screening for inclusion will take place after extensive informing (about risks and benefits) of the patient and obtaining written informed consent.

9.3 Benefits and risks assessment, group relatedness

Standard treatment of LARC consists of neoadjuvant CRT followed by TME-surgery. When a clinical complete response is seen at response evaluation, a watch-and-wait approach is currently considered a valid strategy in selected patients according to the Dutch national guidelines. In the ongoing Dutch national prospective registry patients with a near-complete response are currently offered an extension of the observation period rather than TME-surgery, and, subsequently, a watch-and-wait policy when a clinical complete response is noted over time. On the other hand, all patients with a persistent residual lesion will proceed to TME-surgery.

In the current study two experimental approaches are introduced that could increase organ preservation rates in patients with a good, but not-complete response at the first response evaluation: additional endoluminal contact x-ray brachytherapy and local excision of the tumour remnant. Contact x-ray brachytherapy for rectal cancer is a relatively new technique that is performed in two centres in The Netherlands. Patients who are randomized to this arm of the study will be referred to one of these centres. Local excision is performed in several dedicated surgical units, and is considered a good option for remaining small lesions after neoadjuvant (chemo)radiation for early to intermediate tumours. However, local excision is not yet standard of care for residual lesions from a locally advanced tumour, mainly due to a lack of data on long-term oncological outcome.

To all patients eligible for this study, TME-surgery will be offered as standard of care, to provide the safest option from oncological point of view; when patients are interested in exploring the possibilities of an organ preserving strategy, the treating physician will evaluate the feasibility of participation in the current study. Prior to randomisation, eligible patients are well informed about risks of the two experimental treatment strategies (i.e. unclear long-term oncological outcome), and are offered standard-of-care TME-surgery. Moreover, patients will be informed that additional treatment with contact x-ray brachytherapy or local excision might increase the morbidity rates in case completion or salvage TME-surgery needs to be performed. A recently published study showed that in a small cohort of patients completion TME-surgery after TAMIS was not associated with increased peri- or postoperative morbidity or mortality(32).

Finally, in both arms of this phase II study an intensive surveillance program has been established, in order 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.

9.4 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 subjects 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.

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 patients identification code to the participants details will be safe-guarded by a password, known only by the responsible local study coordinators of the coordinating centres. Hereby, outsiders cannot relate any results or data back to the participant. All clinical imaging and (questionnaire) data will be encoded to ensure an anonymous data collection.
ALEA 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 Registration of patients in the International Watch & Wait Database (IWWD)

More evidence supporting organ preserving strategies is needed to implement these strategies as a safe treatment option for selected cases. For this reason, an international watch-and-wait database was established in February, 2014. This database was initiated in the Netherlands by a collaboration of high-profile clinical experts, including one of the coordinating investigators of the current study professor G.L. Beets. The aim of this database is to collect all available data worldwide to expand knowledge on the benefits, risks, and oncological safety of organ-preserving strategies in rectal cancer. Data is entered online at the centre under supervision of the investigator and stored in a highly secured NEN7510 certified and encrypted research data server (ProMISe), located in the Netherlands. The database contains pseudo-anonymized information on patient and tumour characteristics at the time of diagnosis, the reason for organ-preserving treatment, type of neoadjuvant therapy, results of imaging modalities at diagnosis, reassessment after neoadjuvant therapy and follow-up, details of the treatment for disease recurrence, and survival status, and the written informed consent.
All patients in the OPAXX study will be invited to participate in the IWWD; patients are asked for their written informed consent in the patient information letter. Withdrawal to consent to the collection of data in the IWWD will not affect participation in the OPAXX study. The patient information letter and informed consent form can be found in Appendix E1 and E2.

10.3 Monitoring and Quality Assurance

This study is classified as a low risk study. For this reason, no monitoring will take place.

10.4 Amendments

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

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

10.5 Annual progress report

The principle investigators will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.6 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of a study arm is defined when more than 40 events have occurred in the respective study arm. The other study arm will proceed until 40 events have occurred in this study arm as well.

The sponsor will notify the METC 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 accredited METC 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 accredited METC.

10.7 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 enrollment as a condition of consideration for publication.

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12. APPENDICES

1. Radiotherapy Treatment Planning and Quality Assurance

2. Treatment toxicity and morbidity

- **2.1 Common toxicity criteria of adverse events (CTCAE) version 5.0**
- **2.2 The Clavien-Dindo Classification, surgical complications**

3. Structured endoscopy and MRI report templates

- **3.1 Structured endoscopy report template – restaging after neoadjuvant treatment**
- **3.2 Structured endoscopy report template – response evaluation after CXB**
- **3.3 Structured MRI report template – response evaluation after CXB**

1. Radiotherapy Treatment Planning and Quality Assurance

This document describes the process for radiotherapy treatment for patients in the OPAXX trial. The aim is to facilitate the delivery of a protocol defined radiotherapy technique and to allow quality assurance (QA) procedures by the Trial Management Group (TMG) to evaluate the incorporation of all predefined treatment specifications. The target volume for the contact x-ray brachytherapy in the OPAXX trial incorporates the residual tumour as seen during the endoscopy.

It is recognised that during the conduct of OPAXX, it may be necessary to modify the defined protocol either because of the publication of new data regarding or new perspectives on treatment delivery of contact x-ray brachytherapy. It is likely that any changes will be minor and can be introduced through modification of this radiotherapy document as they will not interfere with the key primary and secondary end points of the study. In the event of the need for a major change requiring alteration of the main protocol, a formal protocol amendment will be initiated.

Contact x-ray brachytherapy will be given within two weeks after the randomization moment, at the latest of 14 weeks after having finished the (chemo)radiation (see figure 1: OPAXX trial scheme). The treatment will be delivered with the low energy (50 KV) x-ray tube with a dose rate of >20 Gy/min.

Dose and fractionation
Contact x-ray brachytherapy consists of three fractions of 30Gy per fraction applied to the surface of the tumour intraluminal, with a 2 week interval after each fraction.

Applicator placement
Before placing the applicator, digital rectal examination is performed, followed by rigid endoscopy. Thereafter, the radiation applicator is positioned around the tumour so that the whole tumour area is encompassed by the applicator. The position is checked by a camera on the applicator, a photograph is taken just before and after the radiation.

Target volume
The clinical target volume (CTV) is defined as the macroscopic residual tumour (with normal tissue on all sides), based on the endoscopy and DRE (digital rectal examination).

Treatment delivery

To perform contact x-ray brachytherapy an applicator with size 20, 25 or 30mm is used dependent on the size of the residual tumour based on DRE and rigid endoscopy.

Quality Control

Contact x-ray brachytherapy will be given in expert study centers of this study by dedicated radiation oncologists in an outpatients clinical setting. A team of dedicated gastroenterologists and surgeons are involved with the decision making for appropriate application of the radiation treatment.

For the first 5-10 patients an evaluation is done after the first fraction by the multidisciplinary teams of all centers involved. The photographs taken during the application will be evaluated combined with the original endoscopy images. Based on these results a grading is done of the accuracy of the application and technical issues can be discussed.

To become a dedicated radiation oncologist for contact x-ray brachytherapy a training procedure has to be followed with at least 3 times (different patients) watchful attendance during a complete procedure of the contact x-ray brachytherapy, followed by 3 times (different patients) successful application of the contact x-ray brachytherapy under supervision.

Follow-up

After having finished the contact x-ray brachytherapy course, response evaluation (MRI pelvis, endoscopy, digital rectal examination) will be done at 3 months as stated in the OPAXX protocol.

2. Treatment toxicity and morbidity

2.1 Common terminology criteria of adverse events (CTCAE) version 5.0

In the present study, adverse events and/or adverse drug reactions will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (November 27, 2017).

Grades	Definition
Grade I	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive 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 selfcare 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.*

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

At the time this protocol was issued, the full CTC document was available on the NCI website, at the following address:

https://www.eortc.be/services/doc/ctc/CTCAE_v5_Quick_Reference_5x7.pdf

2.2 The Clavien-Dindo Classification, surgical complications

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusionsand total parenteral nutritionare also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	single organ dysfunction (including dialysis)
- IVb	Multiorgandysfunction
Grade V	Death of a patient

**brain hemorrhage, ischemic stroke, subarrachnoidalbleeding, but excluding transient ischemic attacks (TIA); CNS: central nerve system; IC: Intermediate care; ICU: Intensive care unit.*

3. Structured endoscopy and MRI report templates

3.1 Structured endoscopy report template – restaging after neoadjuvant treatment

Structured endoscopy report template
restaging after neoadjuvant treatment

Digital rectal examination

palpable lesion?	Yes / No
If yes:	Soft minor abnormalities / stiff wall / flat ulcer / ulcer with elevated edges / clear residual tumour

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Endoscopy

Distance lesion to anal verge	…….. cm
Location	Anterior / Posterior
Is there residual elevated tumour?	Yes / No
If yes:	Small (<1cm)/ Large
Is there residual adenomatous tissue?	Yes / No
If yes:	
Size:	…… cm
Is there residual ulcer?:	Yes / No
If yes:	Small flat (<1cm) / large flat / elevated edges
Is there a flat scar?	Yes / No
If yes:	White / White with some redness / predominantly red
Are there telangiectasia:	Yes / No
Is there proctitis/bleeding:	Yes / No
If yes:	Light / moderate / severe
Is there stenosis?	Yes / No

Are local excision and contact brachytherapy feasible?	Yes / No

Confidence level tumour response

1. Definitely complete response
2. Probably complete response
3. Maybe (no) complete response
4. Probably no complete response
5. Definitely no complete response

Response on endoscopy

- Clinical complete response
- Clinical near-complete response
- Clinical good response but small residual tumour mass
- Clinical incomplete response

3.2 Structured endoscopy report template – response evaluation after CXB

Structured endoscopy report template
Response evaluation after contact x-ray brachytherapy

Digital rectal examination

palpable lesion?	Yes / No
If yes:	Soft minor abnormalities / stiff wall / flat ulcer / ulcer with elevated edges / clear residual tumour
If yes: distance lesion to anal verge	…….. cm

Endoscopy

Is there residual elevated tumour?	Yes / No
Is there residual adenomatous tissue?	Yes / No
Is there residual ulcer?:	Yes / No
If yes:	Small (<1cm) / large (≥1cm)
If yes:	Regular edges / irregular edges
Is there a flat scar?	Yes / No
Are there telangiectasia:	Yes / No
Is there proctitis/bleeding:	Yes / No
Is there stenosis?	Yes / No
Is there a healing trend?	Yes / No / Not applicable
Distance lesion to anal verge	…….. cm
Size	…….. cm

Most dominant feature:

- Residual tumour mass Yes / No
- Residual adenomatous tissue Yes / No
- Small ulcer with regular edges Yes / No
- Large ulcer with irregular edges Yes / No
- Flat scar Yes / No

Confidence level tumour response

1. Definitely complete response
2. Probably complete response
3. Maybe (no) complete response
4. Probably no complete response
5. Definitely no complete response

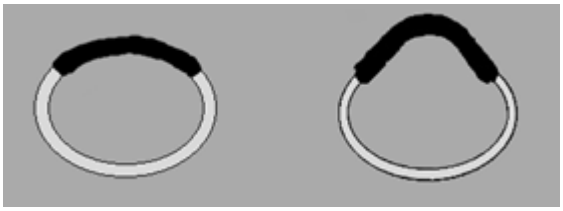
3.3 Structured MRI report template – response evaluation after CXB

Structured MRI report template
Response evaluation after contact x-ray brachytherapy

T2W-MRI

1. Ulcer

☐ No ☐ Yes



If yes:
- Width …….mm
- Depth …….mm

2. Morphology of the fibrosis

☐ Regular ☐ Layered ☐ Irregular

3. Maximal thickness of the fibrosis …….mm

Circumference ……

4. Tumour signal

☐ No
☐ Spots/irregular
☐ Focal/Tumour

If tumour: ……..mm

5. Confidence level tumour response based on T2W-MRI

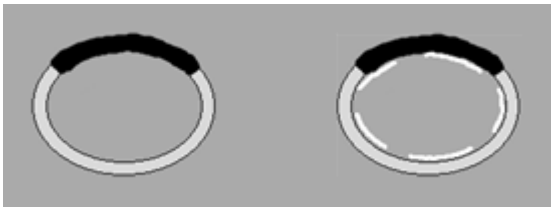
Response

☐ 1. Definitely complete response
☐ 2. Probably complete response
☐ 3. Maybe (no) complete response
☐ 4. Probably no complete response
☐ 5. Definitely no complete response

DWI - MRI

1. Reactive mucosal signal

☐ No ☐ Yes



2. Morphology DWI signal

☐ Nog signal ☐ Spots/Linear ☐ Mass-like

3. Confidence level tumour response based on DWI

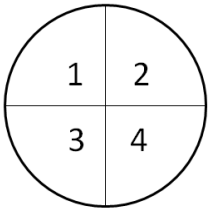
Response

☐ 1. Definitely complete response
☐ 2. Probably complete response
☐ 3. Maybe (no) complete response
☐ 4. Probably no complete response
☐ 5. Definitely no complete response

Lymph nodes

☐ No/ <5mm
☐ ≥ 5mm unsuspected
☐ ≥ 5mm suspected

Location of the lymph nodes



Size of the largest lymph node……mm

The lymp node is under / at / above the level of the fibrosis

T2W-MRI and DWI

Confidence level tumour response based on both T2W-MRI and DWI

Response	☐ 1. Definitely complete response ☐ 2. Probably complete response ☐ 3. Maybe (no) complete response ☐ 4. Probably no complete response ☐ 5. Definitely no complete response