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.

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52264

Source
ToetsingOnline

Brief title
OPAXX study

Condition

- Gastrointestinal neoplasms malignant and unspecified
- Gastrointestinal therapeutic procedures

Synonym

rectal adenocarcinoma, rectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: ZonMw subsidie

Intervention

Keyword: contact x-ray brachytherapy, Organ preservation, rectal cancer, TEM/TAMIS/local excision

Outcome measures

Primary outcome

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. 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).

Secondary outcome

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.

Study description

Background summary

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.

Study 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).

Intervention

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.

Study burden and risks

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.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion 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 re-sponse 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 pres-ence of significant distant metastases) without full dose chemotherapy in the inter-val (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 brachythera-py or local excision);
• age >18 years;
• written informed consent.

Exclusion criteria

• 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 comorbidi-ty or frailty;

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-04-2021
Enrollment:	168
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	12-02-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-01-2025
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL75896.031.20