Adjuvant chemotherapy for prevention of recurrence in patients with detectable ctDNA after surgery in high-risk rectal cancer.

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This study has been transitioned to CTIS with ID 2024-517700-12-00 check the CTIS register for the current data. To improve disease-free survival in patients with high-risk rectal cancer by treating these patients with adjuvant chemotherapy in case...

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

Summary

ID

NL-OMON56933

Source
ToetsingOnline

Brief title
REACT

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
rectal cancer. rectal carcinoma.

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Erasmus MC Foundation

Intervention

Keyword: adjuvant chemotherapy, circulating tumor DNA, liquid biopsy, Rectal cancer

Outcome measures

Primary outcome

Primary endpoint

The primary endpoint of the study will be disease-free survival in the intention-to-treat population, calculated from the date of surgery to the date of recurrence or death from any cause of the patient, whichever occurs first. The main analysis addressing the primary endpoint will be performed after 118 events, and is planned two years after the last included patient.

Secondary outcome

Secondary endpoints

Secondary outcomes will be disease-free survival, carried out as per protocol analysis to analyse pure treatment effect. In addition, overall survival will be calculated measured from the date of surgery to the date of death from any cause. Quality of life will be assessed in both groups by obtaining questionnaires already provided by the PLCRC cohort study to compare the effect of adjuvant chemotherapy on quality of life. The robustness of ctDNA as biomarker will be analysed by comparing the disease-free survival of patients with detectable ctDNA who are not treated adjuvant chemotherapy (control group) with patients with undetectable ctDNA.

Study description

Background summary

Rectal cancer is a worldwide cause of cancer related mortality. The incidence of rectal cancer in the Netherlands is approximately 3500 patients per year. The introduction of combined neoadjuvant (chemo)radiotherapy and total mesorectal excision (TME) has significantly reduced the local recurrence rate, but distant recurrence rates remain around 30%. Recurrences are likely to derive from residual local disease or subclinical metastatic disease (minimal residual disease). These micro metastases are undetectable by the currently used imaging techniques but still present after surgery.
Adjuvant chemotherapy might be beneficial for patients at high risk for recurrence. However, there are only a few randomised controlled trials on adjuvant chemotherapy available. Studies on adjuvant chemotherapy in rectal cancer yielded conflicting results. As a consequence, treatment with adjuvant chemotherapy in patients with rectal cancer is not evidence based and therefore not standard of care in the Netherlands. A recent study suggested that preoperative intensive chemotherapy with radiotherapy, compared to standard chemotherapy and radiotherapy, resulted in a prolonged disease-free survival. However, this was at the cost of increased toxicity, and has yet to translate into an improved overall survival. Consequently, there is an urgent need for biomarkers to identify those patients at high risk to recur after standard treatment, to select the patients that might benefit the most from perioperative chemotherapy. Circulating tumour DNA (ctDNA) in peripheral blood samples is a potential biomarker to identify patients at high risk for recurrence. Studies have already demonstrated the strong prognostic value of detectable ctDNA after surgery in patients with locally advanced rectal cancer, as it is thought that the presence of ctDNA after surgery is indicative of minimal residual disease. The REACT study will investigate whether adjuvant chemotherapy in high-risk rectal cancer patients with postoperative detectable ctDNA (approximately 15% of the population) improves outcomes.

Study objective

This study has been transitioned to CTIS with ID 2024-517700-12-00 check the CTIS register for the current data.

To improve disease-free survival in patients with high-risk rectal cancer by treating these patients with adjuvant chemotherapy in case of detectable ctDNA after surgery.

Our hypothesis is that adjuvant chemotherapy will be beneficial patients with high-risk rectal cancer and detectable ctDNA after surgery. Patients in this subgroup have an extremely poor prognosis, with a chance of recurrence estimated at 70% within two years after surgery. We aim to demonstrate that

adjuvant chemotherapy in these patients will lead to a 25% absolute increase of the two-year disease-free survival rate compared to follow-up in the control group (55% vs 30%).

Study design

The proposed study is conducted within the prospective Dutch ColoRectal Cancer (PLCRC) cohort and follows the trial within cohort (TwiCs) design, i.e. a randomised controlled trial within a prospective cohort.

Blood samples from rectal cancer patients included in the PLCRC study, meeting the inclusion criteria and eligible for adjuvant chemotherapy, will be analysed for the presence of detectable ctDNA. Patients with detectable ctDNA will be randomised 1:1 according to the TwiCs design to an experimental and a control group. Patients with undetectable ctDNA will receive treatment and follow-up according to the current standard of care, and will not receive information regarding the results of the ctDNA analysis.

Experimental group: Patients with detectable ctDNA and randomised to the experimental arm will be informed about the test result with associated worse prognosis and about the study with the possibility to receive adjuvant chemotherapy. The expected benefits and harms of adjuvant chemotherapy will be discussed. After thorough counselling, patients will decide whether they are willing to receive adjuvant chemotherapy consisting of capecitabine and oxaliplatin (CAPOX) or leucovorin, fluorouracil and oxalilplatin (FOLFOX). Those willing to receive chemotherapy are asked for informed consent.

Control group: Patients with detectable ctDNA and randomised to the control arm will not be informed about the test result and will receive routine follow-up. They had already given informed consent for the possibility of randomisation in a certain trial within PLCRC with the possibility to serve as a control patient without being informed as such. Neither the treating physicians will receive information about the allocation to the control arm and the result of the ctDNA analysis. Patients in the control arm will not receive experimental adjuvant chemotherapy (no consequences for this group).

Registration cohort: All patients with undetectable ctDNA will be followed within PLCRC.

Intervention

Patients with detectable ctDNA after surgery and randomised to the experimental group will be offered adjuvant chemotherapy within 8 weeks of surgery and no longer than 12 weeks after surgery. Adjuvant chemotherapy consists of 6 cycles of 5FU/LV and oxaliplatin (FOLFOX) every 2 weeks or 3-weekly cycles with capecitabine and oxaliplatin (CAPOX). Duration of treatment will be 3 months

(12 weeks).

Study burden and risks

In current clinical practice there is no indication for adjuvant chemotherapy for patients after surgery for primary rectal cancer. Therefore all participating patients have no indication for adjuvant chemotherapy. Patients randomised to the experimental group will be offered adjuvant chemotherapy to reduce recurrence. After detailed information and counselling about adjuvant chemotherapy given by their treating physician, patients will decide whether they are willing to receive adjuvant chemotherapy. If decided to receive adjuvant chemotherapy patients will start within 12 weeks after surgery. According to routine clinical care, patients receiving adjuvant chemotherapy will undergo blood withdrawals and visit their treating physician before every cycle of chemotherapy. The combination chemotherapy schedule of CAPOX and FOLFOX is commonly administered in the adjuvant setting in current practice for colorectal cancer, therefore the risks and toxicity of the used adjuvant chemotherapy are well-known. The majority of side-effects are manageable and transient. Most encountered side-effects of adjuvant chemotherapy are fatigue, myelosuppression, hand-foot syndrome, nausea, diarrhea, sensory neuropathy, dysesthesia and rarely cardiac arrhythmias and ischemia. The risk of the withdrawal of extra tubes of blood during regular blood withdrawal in all study participants is negligible.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Age >= 18 years
• WHO performance score 0-1
• Informed consent for PLCRC with specific consent for additional blood withdrawals and offering of future experimental research
• Histological confirmed rectal cancer; either treated with neoadjuvant (chemo)radiotherapy, and/or clinical T4 and/or N+ in case no neoadjuvant therapy was administered.
• Eligible to receive treatment with combination adjuvant chemotherapy (CAPOX/FOLFOX) according to the treating physician

Exclusion criteria

• Another malignancy in previous 5 years, with the exception of treated carcinoma in situ or skin cancer other than melanoma
• Incomplete primary tumour resection (R1 or R2 resection)
• Contra-indication for fluoropyrimidines or oxaliplatin
• Neoadjuvant oxaliplatin based systemic treatment, e.g. treated with the RAPIDO regimen consisting of short course radiotherapy followed by 6 cycles of CAPOX or 9 cycles of FOLFOX prior to surgery
• Patients with a clinical complete response, who will not undergo surgery.
• Pregnant and lactating women

Study design

Design

Study phase: 3

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2024
Enrollment:	206
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	5-Fluorouracil
Generic name:	5-Fluorouracil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Capecitabine Accord
Generic name:	Capecitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Leucovorine Sandoz
Generic name:	Leucovorin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Oxaliplatin Accord
Generic name:	Oxaliplatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	22-11-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-08-2024
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EU-CTR	CTIS2024-517700-12-00
EudraCT	EUCTR2022-002580-30-NL
CCMO	NL82006.078.22