Exercise during Neoadjuvant chemoradiation Treatment to improve rectal and esophageal cancer Outcome - pilot trial.

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To 1) evaluate feasibility and fidelity of a three-arm RCT containing a twice-weekly exercise intervention supervised by a first-line (oncology) physiotherapist and a 5-day weekly in-hospital exercise intervention versus usual care in patients with...

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

Summary

ID

NL-OMON53636

Source
ToetsingOnline

Brief title
EXENTRO

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
rectal and oesophageal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Fysiologie

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Exercise intervention, Feasibility, Immune function, Vascularisation

Outcome measures

Primary outcome

The main study parameters will be the feasibility in terms of trial participation rate and attendance, and intervention fidelity (e.g. extend of and reasons for adaptations to the exercise intervention).

Secondary outcome

The secondary study parameters are the average effect sizes and measures of variability on immune function, infiltration, vascularisation, and composition and function of the microbiome. Measurements will take place at baseline, directly after finishing NCRT, and within a week before surgery.

Study description

Background summary

Patients with primary rectal or esophageal carcinoma are often treated with neoadjuvant chemoradiation therapy (NCRT) for 5 weeks, followed by a waiting period (8 - 10 weeks for rectal cancer and 6 - 12 weeks for esophageal cancer). This treatment aims to reduce the tumour size and stage prior to surgical resection. However, Pathological complete response rate after NCRT is relatively low for these patient populations: 15-20% for rectal cancer and 30% for esophageal cancer. Additionally, many patients face severe side effects during NCRT, reducing their physical function and health-related quality of life (HRQoL).
Strong evidence from randomized controlled trials (RCT) showed that physical exercise during chemotherapy or radiotherapy benefits physical fitness, muscle mass, muscle strength, fatigue, and HRQoL. Moreover, exercise may counteract treatment-related side effects and help prevent treatment modifications, which might benefit survival. To date, the majority of RCTs

examining the effects of exercise during cancer-treatment have been conducted in patients with breast cancer or prostate cancer who were treated with curative intent. Due to differences in treatment trajectories and side effects, generalisability of these findings to patients with rectal and esophageal carcinoma receiving NCRT is limited. Additionally, exercise type, timing, intensity, and duration may impact the effects of the intervention. For example, aerobic exercise at higher intensities may provide larger cardiovascular benefits, but may result in more gastrointestinal side effects. Therefore, it is important to study whether exercise is feasible during neoadjuvant chemoradiation, and whether different exercise frequency, intensity, and timing can induce different effects on underlying physiological mechanisms.

Observational studies in patients with breast, colorectal or prostate cancer showed that physical activity and fitness were positively associated with cancer-specific survival, however, the causality and underlying mechanisms linking exercise to clinical outcome are largely unknown. These mechanisms are essential to understand the potential and limitations of exercise as integral part of cancer care, and to further optimize exercise prescriptions.

Pre-clinical studies showed that both a chronic exercise intervention as well as an acute exercise bout can impact the tumour microenvironment via several underlying mechanisms. Studies focusing on these mechanisms have shown that exercise can directly impact tumour growth via normalising tumour vasculature, increasing perfusion, reducing hypoxia, and thereby increasing sensitivity for anticancer treatment. Furthermore, exercise can induce a mobilisation, activation and redistribution of natural killer (NK) cells which leads to a better infiltration of activated NK cells in the tumour. Moreover, studies in healthy participants showed that one bout of exercise can already largely mobilise immune cells including NK cells and T cells. Nevertheless, it is unclear whether these results can be translated to patients with cancer. A recent study in patients with esophageal cancer showed that patients with more circulating T cells prior NCRT are more likely to have a pathological complete response. Hence, exercise prior to each radiotherapy session may mobilise immune cells including T cells and thereby enhance radiotherapy response. A study in patients receiving NCRT would provide an opportunity to directly assess the effects of exercise on the tumour in situ.

A phase II randomised controlled exercise trial in patients with rectal cancer showed that exercise is feasible during NCRT and may enhance tumour regression. Similarly, feasibility of an exercise trail in patients with esophageal cancer was shown, including a non-randomised exercise trial which suggests an improved tumour regression in the exercise group. Additionally, a RCT in patients with non-small cell lung cancer showed that aerobic exercise prior to each radiotherapy session was feasible. None of these studies included evaluations of underlying mechanisms of action, nor did they compare different exercise programs.

Knowledge on the feasibility of different exercise programs and variability in immune activation, immune cell infiltration and vascularisation is essential to design a future well-powered RCT examining exercise

intervention efficacy. Increasing the efficacy of neoadjuvant treatment in these patient populations would benefit organ-conserving surgery and survival.

Study objective

To 1) evaluate feasibility and fidelity of a three-arm RCT containing a twice-weekly exercise intervention supervised by a first-line (oncology) physiotherapist and a 5-day weekly in-hospital exercise intervention versus usual care in patients with rectal cancer or esophageal cancer receiving NCRT, and 2) generate preliminary data on the variability in exercise responses on immune function, immune infiltration, and vascularisation of the tumour, and the composition and function of the microbiome.

Study design

pilot randomized controlled trial

Intervention

Participants will be randomized in one of three study arms: 1) AE + RE - group; combined moderate-to-high intensity aerobic exercise (AE) and resistance exercise (RE) twice a week supervised by a specially trained first-line physiotherapist, and a home-based moderate intensity aerobic exercise session once a week; 2) ExPR - group; in-hospital exercise intervention consisting of 30 min moderate intensity aerobic exercise within one hour prior to every radiotherapy session (five times a week); and 3) UC - group; a control group that receives usual care.

Study burden and risks

Patients will visit the hospital three times for study measurements. These visits will be combined with regular preoperative hospital visits as much as possible. Prior to the start of the treatment and randomisation, blood samples will be taken and a fitness test will be performed (T0). These measurements will be repeated directly after completion of the NCRT (T1) and within a week before surgery (T2). The risks of the blood drawing and fitness tests are negligible. Both a biopsy at diagnosis and the removal of the tumour will be performed as part of usual care. The ExPR exercise intervention will be combined with regular radiotherapy appointments. The safety of the exercise intervention during radiotherapy or chemotherapy has been well documented.

Contacts

Public

Selecteer

Philips van Leydenlaan 15
Nijmegen 6500 HB
NL
Scientific
Selecteer

Philips van Leydenlaan 15
Nijmegen 6500 HB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Diagnosed with rectal or esophageal carcinoma
- Patients with rectal or esophageal carcinoma need to be scheduled for treatment with neoadjuvant chemoradiation therapy
• Oral capecitabine combined with concurrent radiotherapy (50 Gy in 25 fractions) for rectal cancer
• CROSS regimen (carboplatin, paclitaxel with concurrent 41.4 Gy in 23 fractions radiation) for esophageal cancer
- Aged > 18 years

Exclusion criteria

A participant who meets any of the following criteria will be excluded from participation in this study:
- Unable to perform basic activities of daily living such as walking or biking
- Presence of other disabling co-morbidity that might hamper or endanger

physical exercise e.g. heart failure, chronic obstructive pulmonary disease, orthopaedic conditions and neurological disorders
- Presence of cognitive disorders or severe emotional instability (e.g., Schizophrenia, Alzheimer, alcohol addiction)
- Immunodeficiency (primary or secondary)
- Insufficient mastery of the Dutch language
- Participation in another exercise and/or dietary intervention study at the same time. Participation in Fit4Surgery is allowed as this starts after NCRT and we have alighted the logistics.
- Already participating in structured vigorous aerobic and/or resistance exercise >= 2 times per week comparable to our intervention and planning to continue this throughout the period of neoadjuvant chemoradiation.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	06-09-2022
Enrollment:	39
Type:	Actual

Ethics review

Approved WMO

Date:	13-07-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	07-03-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL81016.091.22