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Feasibility and preliminary effectiveness of a physical exercise training program during neoadjuvant chemoradiotherapy in individual patients with rectal cancer prior to major elective surgery

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Abstract

Background: Diverse fractions of patients with locally advanced resectable rectal cancer receive neoadjuvant chemoradiotherapy (NACRT). NACRT is known to decrease physical fitness, an undesirable side effect. This pilot aimed to determine the feasibility and preliminary effectiveness of a supervised outpatient physical exercise training program *during* NACRT in these patients.

Methods: We included 13 out of 20 eligible patients (11 males, mean ± SD age: 59.1 ± 19.7 years) with rectal cancer who participated in the exercise training program during NACRT. Feasibility was determined by adherence and number of adverse events. Physical fitness was compared at baseline (B), after five (T1) and ten weeks (T2) of training, and eight weeks postoperatively (T3) using repeated-measures analysis of variance.

Results: Nine patients (69.2%) completed the program without adverse events. Four patients dropped out. The program was feasible and safe, with a total attendance rate of 95.7%. Leg muscle strength (mean ± SD: 104.0 ± 32.3 versus 144.8 ± 45.6 kg; $P < 0.001$) and arm muscle strength (mean ± SD: 48.7 ± 13.8 kg versus 36.1 ± 11.0 kg, $P = 0.002$) increased significantly between B and T2, respectively. A slight, non-significant, increase in functional exercise capacity was found.

Conclusion: This pilot demonstrated that a supervised outpatient physical exercise training program for individual patients with locally advanced resectable rectal cancer during NACRT is feasible for a large part of the patients, safe and seems able to prevent an often seen decline in physical fitness during NACRT. A larger study into the cost-effectiveness of this approach is warranted.

Keywords: Neoadjuvant therapy; Prehabilitation; Exercise; Physical fitness; Surgery; Rectal cancer

Introduction

Nowadays, colorectal cancer is the second most common diagnosis of cancer in the Netherlands.[1] In 2014, 15,003 new cases of colorectal cancer (69.2% colon, 30.8% rectal) were registered.[1] In 2014, 2846 patients diagnosed with rectal cancer underwent rectal resection surgery (29% aged >75 years), in which the 30-day complication

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rate and the 30-day mortality rate were 37% and 1.1%, respectively.[2]

Patients with locally advanced rectal cancer (Tumour, Node, Metastasis (TNM) stage cT3 or cT4N with involvement of the mesorectal fascia and/or extramesorectal lymph node metastases) are considered for an extensive treatment protocol of neoadjuvant chemoradiotherapy (NACRT)[3−6] to improve long-term outcome. NACRT aims to control local disease and improve resectability by downsizing the tumour and hereby increasing negative resection margins.[6,7] In the Netherlands, 34% of the patients scheduled for rectal resection received NACRT in 2014.[2] However, chemoradiotherapy is a regimen with a high toxicity profile, which can lead to extensive diarrhoea, hand-foot syndrome, cardiotoxicity and haematological toxicity.[8] Additionally, chemoradiotherapy has negative physical side effects, of which fatigue[9] and a decrease in cardiorespiratory fitness[3−5,10] are the most common. Recently published studies explored the impact of neoadjuvant therapy on cardiorespiratory fitness prior to rectal resection.[3−5] Following NACRT, oxygen uptake (VO_2) at the ventilatory threshold and VO_2 at peak exercise (VO_{2peak}) was reduced, as objectively measured during cardiopulmonary exercise testing.[3−5]

Preoperative cardiorespiratory fitness has a consistent positive relation with postoperative outcome in major abdominal surgery.[11−15] Major abdominal surgery is associated with an increase of oxygen demand of 40% or more, which must be met by an increase in cardiac output or an increase in oxygen extraction.[16,17] Patients with a higher preoperative level of cardiorespiratory fitness may have a greater physiological reserve to tolerate this metabolic stress.[14] Patients who receive NACRT may have and/or gradually develop a lower physiological reserve to tolerate the metabolic stress of surgery, because of the decrease in cardiorespiratory fitness caused by NACRT[3−5] and a decrease in physical activity.[3] These findings suggest that preservation or even improvement of cardiorespiratory fitness may be important for rectal cancer patients exposed to the dual challenges of NACRT and major surgery. A poor cardiorespiratory fitness in these patients is associated with postoperative outcomes.[4] A recent study from West et al.[3] showed that a preoperative physical exercise training program following NACRT was feasible and may be beneficial for patients undergoing rectal resection surgery, as cardiorespiratory fitness returned to baseline values within six weeks after the completion of NACRT.

There is currently no literature available on physical exercise programs *during* NACRT in patients with rectal cancer aiming to slow-down or prevent a decline in cardiorespiratory fitness. Therefore the primary aim of this pilot study was to determine the feasibility of a supervised outpatient physical exercise training program *during* NACRT in patients with rectal cancer. Secondly, the preliminary effectiveness of the physical exercise training program during NACRT on physical capacity, fatigue and quality of life of individual patients was studied.

Patients and methods

Participants

This study was performed between April 2014 and April 2015 as a single group prospective pilot study, in which the medical oncologist and colorectal nurse referred patients receiving NACRT to the physical therapy department for participation in a physical exercise training program. Patients were included when they were >18 years of age, diagnosed with locally advanced resectable rectal cancer, and undergoing NACRT based on cTNM stage. Patients were excluded when their medical status contraindicated exercise or when they were not capable to cooperate with the training and/or testing procedures. After evaluation, the Medical Ethical Committee of the Maastricht University Medical Center (MUMC+) decided that this study met the ethical policies of the MUMC+ and the regulations of the Dutch government. Oral informed consent was obtained from all patients.

Neoadjuvant chemoradiotherapy

All consecutive patients received standardized NACRT during a period of 5.5 weeks. Radiotherapy consisted of 45 Gy in 25 fractions of 1.8 Gy over a period of 5 weeks. In addition, in week six, a boost of three fractions of 1.8 Gy was performed. Capecitabine, an oral fluoropyrimidine chemotherapy, 625 mg/m^2 bid was given continuously during 5.5 weeks. Chemotherapy consisted of oxaliplatin 130 mg/m^2 intravenously on day one in combination with capecitabine 1000 mg/m^2 bid orally on day one to 14, in a three weekly cycle. During the standard waiting period after NACRT, which is necessary to induce optimal effect of the radiotherapy, another two cycles of chemotherapy were performed when possible.[18]

Physical exercise training program

Throughout their complete NACRT treatment, patients attended an individual supervised outpatient physical exercise training program (two sessions a week) designed to slow-down or prevent a decline in cardiorespiratory fitness and muscular endurance capacity. The physical exercise training program started in the first week of NACRT and the duration was dependent on the planning for surgery for each individual patient.

The program was executed at the physical therapy department of the MUMC+ and was guided alternatingly by two trained physical therapists. Additionally, patients were encouraged to be physically active at home (e.g. walking, cycling, gardening, sports club). Training sessions were individual and consisted of 45−60 min of endurance and resistance exercises, at moderate exercise intensity, as described in previous studies.[19] In the first week, endurance exercises (treadmill and cycle ergometer) were performed at 50−60% of the estimated maximal heart rate (220 −