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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.
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*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 −

age (in years)), with a duration of 15 min each. Moreover, three resistance exercises were performed (leg press, chest press, and lateral pull down, TECA innovative fitness technology, Otana, Italy) at 40% of the one-repetition maximum, with three series of 15 repetitions for each muscle group, to train muscular endurance capacity. This way, patients became familiar with the exercise equipment and their own abilities. As of week two of the physical exercise training program, the Borg rating of perceived exertion scale (6–20) was used. All patients indicated their Borg score after completing each training component. Overall, a patient's Borg score of 13–14 was used to achieve a moderate exercise intensity and to provide an individualized, patient-tailored program. To maintain an adequate (moderate-intensity) training stimulus (Borg score >13), Borg rating of perceived exertion titration-tactics were used (as advocated by Glasziou and colleagues[20]) to individually adjust exercise intensity and training duration for every next training session when patients did score <13. When patients (n = 2; 22.2%) used a beta blocker, the Borg scale was used (score 13 or 14 for moderate-intensity) as of week 1. Patients were instructed to stop exercising if any unusual symptoms were experienced (e.g. dizziness or chest pain).

### *Measurements*

#### *Feasibility*

Feasibility of the physical exercise training program during NACRT was determined by the registration of the number and severity of adverse events, as well as by adherence to the program. These data were recorded by the physical therapist, including the reasons for missing a training session. Moreover, patient motivation and satisfaction were measured after the physical exercise training program by asking patients to rate their appreciation of the content of the program, as well as the guidance during the program and the sport facilities with help of a scale from 0 to 10. All measurements were performed by the two physical therapists that guided the program (not blinded).

#### *Preliminary effectiveness*

Changes in physical functioning parameters during the physical exercise program and NACRT were evaluated per patient by visually and statistically comparing physical fitness (functional exercise capacity and muscle strength) and perceptions of fatigue and quality of life at baseline (B), after five weeks of training (T1), after ten weeks of training (T2) and eight weeks postoperatively (T3).

#### *Functional exercise capacity*

To measure functional exercise capacity of the patients, the 6-min walk test (6 MWT) was used, with maximum walking distance as primary outcome measure. The 6 MWT was performed according to the American Thoracic Society guidelines[21]; however, the test was performed on a 44 m square surface instead of a 30-meter course.

#### *Muscle strength*

Muscle strength was measured with the submaximal multiple-repetition (X-RM) test procedure for two resistance exercises. The leg extension machine (Horizontal Leg Press, TECA innovative fitness technology, Otana, Italy) and the chest press machine (Chest Press, TECA innovative fitness technology, Otana, Italy) were used to estimate maximal muscle strength of the legs and arms, respectively. For practical purposes, the lateral pull down was not used as an evaluative measurement. The patient was asked to perform as many repetitions as possible with a weight chosen by the physical therapist. Based on the number of completed repetitions, the maximal muscle strength of the patient was determined, using the Oddvar Holten diagram.[22]

#### *Perception of fatigue and quality of life*

To determine patient's perception of fatigue, patients filled out the multidimensional fatigue index (MFI).[23] The MFI is a self-reporting questionnaire with 20 propositions about the different dimensions and consequences of fatigue. A higher score means a higher level of perceived fatigue. The short-form 36 health survey (SF-36) was used to gain insight in the patient's perceived health-related quality of life. The SF-36 contains 36 questions concerning the patient's own health status perceptions in the following domains: physical, mental and social health.[24] A higher score (percentage) corresponds with a better perceived health status.

#### *Statistical analysis*

The Statistical Package for the Social Sciences for Windows (version 20.0; IBM, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Data are presented for each individual patient for visual analysis and as mean values ± standard deviation (SD) for statistical analysis. Shapiro–Wilk tests for normality were performed in order to evaluate the data distribution of each measurement. Because all data were distributed normally, differences in test scores were examined using repeated-measures analysis of variance (ANOVA). Additional post-hoc analyses with manual Bonferroni adjustment for multiple testing were performed on the outcomes of the repeated-measures ANOVA tests to locate the exact significant differences. A P-value <0.05 was considered statistically significant.

## Results

### *Feasibility*

Fig. 1 depicts the patient flow in this study, including reasons for not participating and dropouts. Twenty patients were eligible for participating in the training program, of which five patients (25.0%) refused participation. After baseline examination, two patients were excluded. Hence, 13 of 20 participants (65.0%) started the physical exercise

training program in the first week of their NACRT. Of these 13 patients, four (30.8%) dropped out during the program. Eventually, nine of 13 patients (69.2%) completed the program without any adverse events. Six patients (66.7%) underwent elective surgery at the end of the physical exercise training program. Three patients (33.3%), did not undergo surgery as a result of a clinical complete response after NACRT *wait and see policy*; omission of surgery with follow up.[25] Of the six patients who underwent surgery, one patient (16.7%) refused participation in the follow up after surgery. Consequently, there are postoperative data available for five of six patients (83.3%). Patient characteristics of the total population (n = 9) and the population that underwent surgery (n = 6) are summarized in Table 1.

The minimum duration of the physical exercise training program was nine weeks and the maximum duration was 17 weeks, with mean ± SD duration of 11.8 ± 3.0 weeks, dependent on the planning for surgery. Out of the 13 patients, nine (69.2%) were able to follow the entire program without any adverse problems and with a progressive build up (intensity and duration of the exercises). Throughout the program, mean ± SD duration of the training session increased with 23.3 ± 7.2%. Training intensity at the ergometer and treadmill increased with 72.6 ± 38.9% and with 24.7 ± 18.0%, respectively, whereas mean ± SD training intensity at the leg press and chest press increased with 50.8 ± 31.5% and 55.4 ± 21.9%, respectively.

Total attendance at the training sessions was 198 out of 207 sessions, meaning an attendance rate of 95.7%. Two patients (22.2%) missed two of 30 training sessions (6.7%), because of feeling ill. One patient (11.1%) missed one of 18 training sessions (5.6%) because of a busy schedule that day and one patient (11.1%) missed four of 34 training sessions (11.1%), because he had to undergo a percutaneous coronary intervention in the same period as the NACRT. Five patients (55.6%) did not miss any training sessions. Hence, the mean ± SD percentage of missed training sessions was 3.4 ± 4.4%. Patients were satisfied and during the training sessions Borg scores of 12, 13 or 14 were achieved in all individuals. Leg muscle strength could not be measured eight weeks postoperatively, because of the abdominal wound. Moreover, one of nine patients (11.1%) did not have T2 measurements, because surgery was brought forward. For two of nine

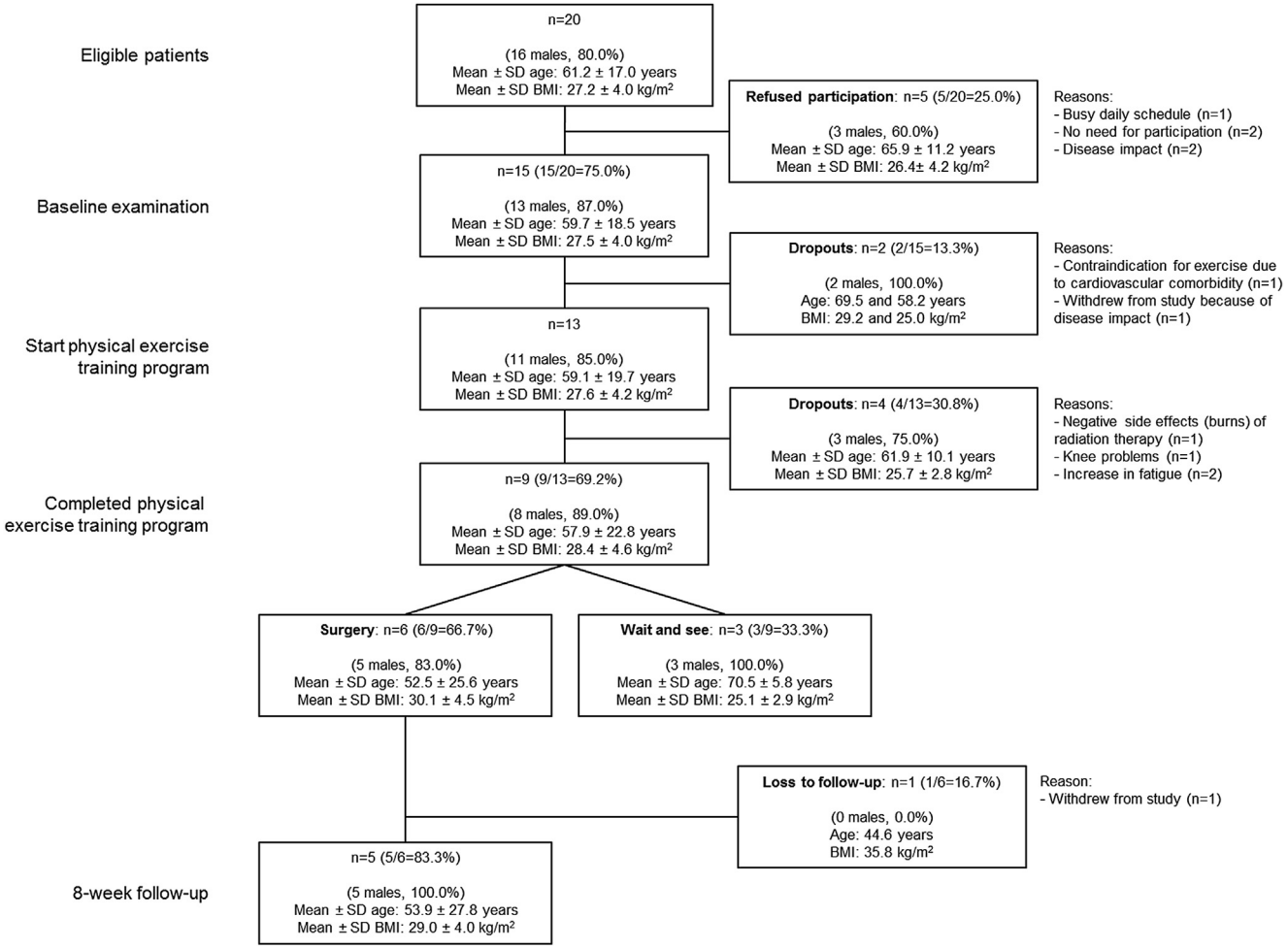


Figure 1. Flow chart visualizing patient flow in this study. Abbreviations: BMI = body mass index; SD = standard deviation.

Table 1
Patient demographics and clinical characteristics.

| | Total (n = 9) | | Surgery (n = 6) | |
|---|---|---|---|---|
| | Mean ± SD | | Mean ± SD | |
| Age (years) | 64.4 ± 10.9 | | 61.3 ± 11.9 | |
| BMI (kg/m$^2$) | 28.4 ± 4.6 | | 30.1 ± 4.5 | |
| | **n** | **%** | **N** | **%** |
| Sex (males) | 8 | 89 | 5 | 83 |
| Smoking (yes) | 2 | 22 | 2 | 33 |
| Alcohol (yes) | 4 | 44 | 4 | 67 |
| Comorbidities | | | | |
| Heart disease | 4 | 44 | 2 | 33 |
| Diabetes | 1 | 11 | 1 | 17 |
| COPD | 1 | 11 | 1 | 17 |
| Orthopaedic | 1 | 11 | 1 | 17 |
| None | 3 | 33 | 2 | 33 |
| Physical activity (MET values) | | | | |
| MET 7 | 1 | 11 | 0 | 0 |
| MET 8 | 1 | 11 | 1 | 17 |
| MET 9 | 2 | 22 | 2 | 33 |
| MET 10 | 3 | 33 | 2 | 33 |
| MET 11 | 2 | 22 | 1 | 17 |
| Tumour distance from anal verge (cm) | | | | |
| <5.0 | 5 | 56 | 3 | 50 |
| 5.1–10.0 | 3 | 33 | 2 | 33 |
| >10.1 | 1 | 11 | 1 | 17 |
| TNM stage | | | | |
| cT3 | 7 | 78 | 4 | 67 |
| T4 | 2 | 22 | 2 | 33 |
| cN0 | 3 | 33 | 1 | 17 |
| cN1 | 1 | 11 | 1 | 17 |
| cN2 | 5 | 56 | 4 | 67 |
| cM0 | 9 | 100 | 6 | 100 |
| ASA score | | | | |
| I | 5 | 56 | 3 | 50 |
| II | 3 | 33 | 2 | 33 |
| III | 1 | 11 | 1 | 17 |
| Surgical method | | | | |
| LAP LAR | | | 4 | 67 |
| OPEN LAR | | | 2 | 33 |

Abbreviations: ASA = American Society of Anaesthesiologists score; BMI = Body mass index (kg/m$^2$); COPD = Chronic obstructive pulmonary disease; IQR = Interquartile range; LAP = Laparoscopic; LAR = Low anterior resection; MET = Metabolic equivalent (1 MET equals 3.5 ml/min/kg); SD = Standard deviation; TNM = Tumour, Node, Metastasis.

patients (22.2%), it was not possible to train on heart rate during the first week of the program, because they were on a beta blocker. In these patients, the Borg scale was used from the start of the training program. All patients rated the content of the training sessions, the guidance during the training sessions and the sport facilities with high mean scores (1–10) of 9, 9 and 8, respectively.

### *Preliminary effectiveness*

#### *Functional exercise capacity*

Preoperatively, six of nine patients (67.0%) improved their walking distance at the 6 MWT between baseline and T1 (mean ± SD distance of 509.6 ± 124.5 m versus 528.7 ± 99.7 m, respectively; not statistically significant; P = 0.526). Between T1 and T2, six of eight (75.0%) improved their walking distance (mean ± SD distance of 528.7 ± 99.7 m versus 555.6 ± 101.7 m, respectively; not statistically significant; P = 0.202). At T2, seven of eight (87.5%) patients walked a longer distance compared to baseline (mean ± SD distance of 555.6 ± 101.7 m versus 509.6 ± 124.5 m, respectively; not statistically significant; P = 0.075). This equals a mean increase of 9.0%. Postoperatively (T3, eight weeks after surgery), five of five patients (100.0%) had a decreased walking distance (mean ± SD distance of 540.8 ± 147.9 m), of which three of five patients (60.0%) scored below baseline level.

#### *Muscle strength*

Preoperatively, seven of nine patients (77.8%) improved their leg muscle strength between baseline and T1 (mean ± SD strength of 104.0 ± 32.3 kg versus 120.7 ± 34.0 kg, respectively; not statistically significant; P = 0.035). Between T1 and T2, six of eight (75.0%) patients improved their leg muscle strength (mean ± SD strength of 120.7 ± 34.0 kg versus 144.8 ± 45.6 kg, respectively; not statistically significant; P = 0.019). At T2, eight of eight patients (100.0%) improved their leg muscle strength statistically significant compared to baseline (mean ± SD strength of 144.8 ± 45.6 kg versus 104.0 ± 32.3 kg, respectively; P < 0.001). This equals a mean improvement of 39.2%.

Preoperatively, seven of nine patients (77.8%) improved their arm muscle strength between baseline and T1 (mean ± SD strength of 36.1 ± 11.0 kg versus 42.1 ± 13.7 kg, respectively; not statistically significant; P = 0.158). Between T1 and T2, six of eight patients (75.0%) improved their arm muscle strength (mean ± SD strength of 42.1 ± 13.7 kg versus 48.7 ± 13.8 kg, respectively; not statistically significant; P = 0.098). At T2, eight of eight patients (100.0%) improved their arm muscle strength compared to baseline (mean ± SD strength of 48.7 ± 13.8 kg versus 36.1 ± 11.0 kg, respectively; statistically significant; P = 0.002). This is a mean increase of 34.9%. Postoperatively (T3), arm muscle strength decreased in five of five patients (100%) (mean ± SD strength of 40.4 ± 11.3 kg), of which no one showed a decrease below baseline values. Figs. 2 and 3.

## Discussion

This is the first pilot study that investigated the feasibility and preliminary effectiveness of a supervised outpatient physical exercise training program for patients with locally advanced resectable rectal cancer *during* NACRT. Although the physical exercise program was safe, feasible and able to prevent an often seen decline in physical fitness during NACRT in the patient who completed the program, it appeared to be difficult to include all eligible patients in the program.

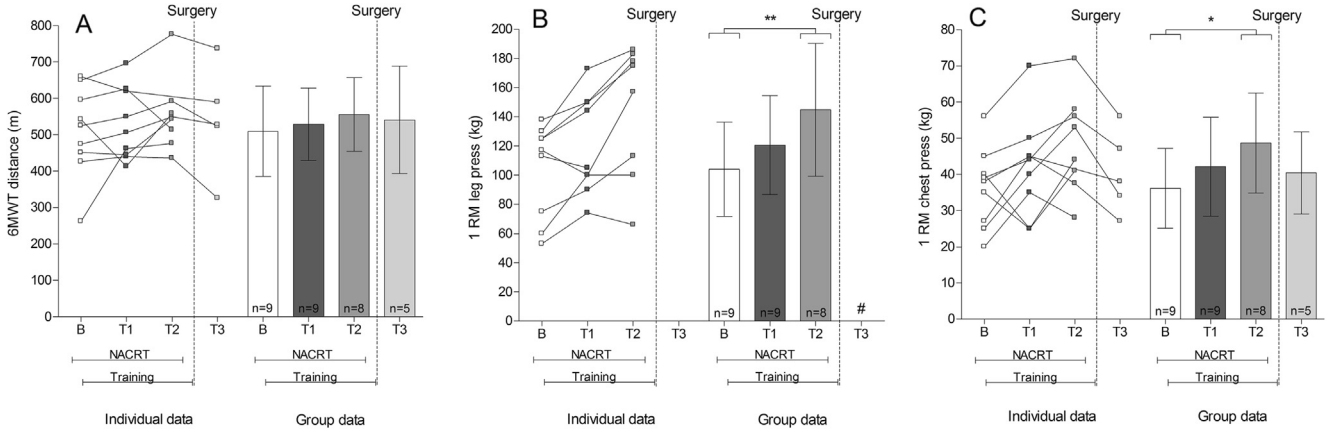


Figure 2. Preliminary effectiveness of the physical exercise training program during NACRT on physical fitness, both on the individual (lines) and group (bars) level, at baseline (B), after 5 weeks of training (T1), after 10 weeks of training (T2), and 8 weeks after surgery (T3). Group data are expressed as mean ± SD. Graph A: functional exercise capacity (6 MWT distance); graph B: muscle strength of the legs (1 RM at the leg press); graph C: muscle strength of the arms (1 RM at the chest press). Abbreviations: 1 RM = one-repetition maximum; 6 MWT = 6-min walk test; NACRT = neoadjuvant chemoradiotherapy; SD = standard deviation. *P < 0.01; **P < 0.001. # Leg muscle strength could not be measured eight weeks postoperatively due to the abdominal wound.

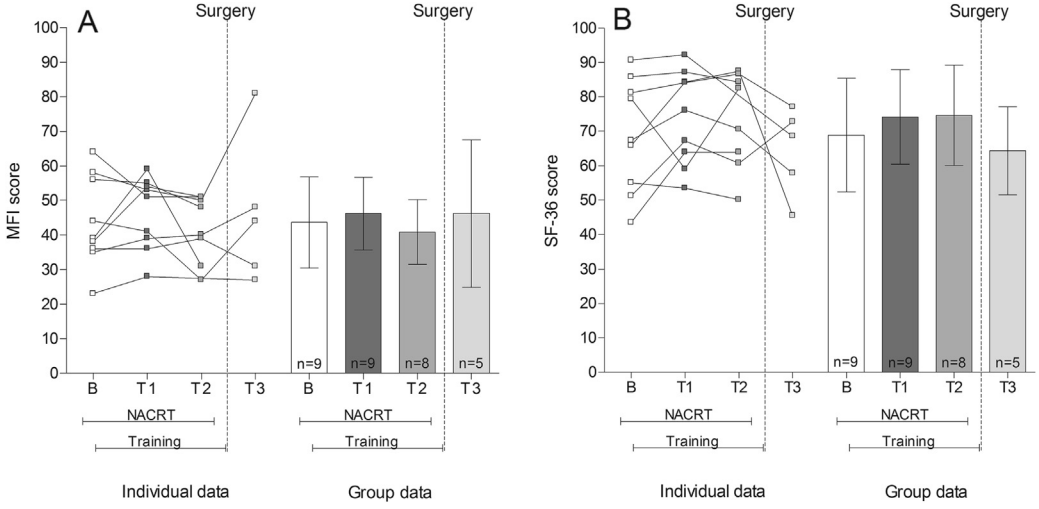


Figure 3. Preliminary effectiveness of the physical exercise training program during NACRT on fatigue and perceived quality of life, both on the individual (lines) and group (bars) level, at baseline (B), after 5 weeks of training (T1), after 10 weeks of training (T2), and 8 weeks after surgery (T3). Group data are expressed as mean ± SD. Graph A: fatigue (MFI score); graph B: perceived quality of life (SF-36 score). Abbreviations: MFI = multidimensional fatigue index; NACRT = neoadjuvant chemoradiotherapy; SD = standard deviation; SF-36 = short-form 36 health survey.

The current study demonstrated that only a significant part of patients with rectal cancer was willing and able to participate in the physical exercise training program during NACRT. Their attendance rate was 95.7%, without any adverse events. Of the 20 eligible patients, seven (35.0%) were not able or not willing to participate and during the program four of 13 patients (30.8%) dropped out. Six of 20 eligible patients preferred NACRT without participating in the physical exercise training program. Reasons mentioned for this were a busy day schedule (n = 1), disease impact (n = 3) and no need for participation (n = 2). For one patient, participation was contraindicated due to cardiovascular comorbidity. Four of 13 patients that started with the physical exercise training program dropped out due to side effects (radiation burns) of the NACRT (n = 1), already existing knee problems (n = 1), and an increase in perceived fatigue (n = 2). It is unknown whether the increase in perceived fatigue can be explained by the physical exercise training program alone, as other studies demonstrate a positive effect of training on fatigue in these patients.[26] The remaining nine patients completed the program and evaluations. For these patients, the supervised physical exercise training program during NACRT was safe and feasible. Patients adhered to the program with progressive overload and did not report discomfort or adverse effects. This is in line with revenues from a recent other type of study from West et al.[3] In the latter study, 22 patients with locally advanced rectal cancer participated in a six-week preoperative physical exercise

training program *after* completing NACRT. This program was also found to be safe and feasible (96% adherence, with no adverse events). Likewise in breast cancer patients, a physical exercise training program during neoadjuvant chemotherapy (NACT) has been reported to be safe and feasible. Rao et al.[27] performed a randomized pilot trial to investigate the effects of physical exercise training (boot camp) in patients with breast cancer throughout their NACT treatment (n = 10). All patients in the exercise group (n = 5) completed the program and all attended >80% of the advised exercise sessions. The combined study of Jones et al.[28] and Hornsby et al.[29] completed a randomized pilot trial in breast cancer patients receiving NACT (n = 20), in which the exercise group (n = 10) performed a moderate-to-high intensity aerobic exercise training program during NACT. One patient in the exercise group did not complete the physical exercise training program, because of deep vein thrombosis and pulmonary embolism. The patients appreciated the training sessions and were satisfied about the program.

Participating in the moderate-intensity physical exercise training program during NACRT in the current study did not only prevent the expected decline in physical fitness due to NACRT. It led to a significant increase in leg muscle strength (+39.2%) and arm muscle strength (+34.9%) after ten weeks of training with a slight, non-significant, increase in functional exercise capacity throughout NACRT (+9.0%). Fatigue and quality of life remained relatively stable throughout the program. Three studies of West et al.[3–5] demonstrated that NACRT acutely reduces objectively measured cardiorespiratory fitness significantly in patients awaiting rectal cancer surgery (a reduction in $VO_2$ at the ventilatory threshold of 12.4%,[4] 19.5%,[5] and 14.2%,[3] and a reduction in $VO_{2peak}$ of 7.7%,[4] 21.4%,[5] and 15.3%[3]). A study of Jack et al.[10] in patients undergoing oesophagogastric cancer surgery also showed that NACT before surgery significantly reduces objectively measured cardiorespiratory fitness (a reduction in $VO_2$ at the ventilatory threshold of 15.2% and in $VO_{2peak}$ of 12.0%). The structured preoperative physical exercise training program immediately post-NACRT in rectal cancer patients as described by West et al.[3] was able to return cardiorespiratory fitness to baseline levels in six weeks (an increase in $VO_2$ at the ventilatory threshold of 20.4% and in $VO_{2peak}$ of 16.9%). The current pilot study is the first study that demonstrates that a moderate-intensity physical exercise training program *during* NACRT in rectal cancer patients may prevent a decline in physical fitness caused by NACRT. Also in breast cancer patients, objectively measured cardiorespiratory fitness increased in the group that performed moderate-to-high intensity aerobic exercise training during NACT (an increase in $VO_{2peak}$ of 13.3%).[28,29] On the other hand, patients in the control group showed a reduction in cardiorespiratory fitness after NACT (a reduction in $VO_{2peak}$ of 8.6%), in which the between-group difference was significant.[28,29]

Based on the current study results, it seems possible for patients with rectal cancer to maintain their physiological reserve by training during NACRT. A higher level of physical fitness is associated with better postoperative outcomes[11–15] and also may facilitate a faster functional recovery after surgery.[30] Our results are in line with a recently published systematic review that evaluated the evidence in support of preoperative exercise training in cancer patients undergoing the dual challenges of neoadjuvant therapy and surgery.[31] The authors concluded that supervised moderate-to-severe intensity exercise training significantly improved cardiorespiratory fitness in these patients. Nowadays, it is clear that a poor cardiorespiratory fitness is associated with a complicated postoperative period. Exercise training during NACRT in rectal cancer patients can prevent the expected decline in physical fitness caused by NACRT to improve surgical outcome. Postoperative data in the current study show a decline in physical fitness compared to the preoperative data in all patients; however, mean values for functional exercise capacity and arm muscle strength were still above baseline values, which may facilitate a faster functional recovery. The latter are interesting facts that need to be confirmed by hard evidence from a full blown trial.

### *Lessons learned*

Only 13 of 20 eligible patients started with the training program, which might be attributable to the location of the training sessions, as well as to the lack of adequate patient education by physicians about the effects and importance of physical exercise training during NACRT. During the first 5.5 weeks, training sessions were combined with the radiotherapy sessions in our hospital which was well-appreciated by the patients. For the remaining preoperative period, patients had to visit the hospital for the training sessions alone, which might have been an extra burden to participate. The participation rate might have been higher if the exercise program was delivered at the patient's own living situation, as there is evidence that (frail) elderly are less likely to participate in a clinic-based exercise program than they are in a home-based exercise program. Moreover, patients should be stimulated and adequately informed by their physician regarding the importance of physical fitness throughout the course of their treatment.

### *Study limitations*

We performed this pragmatic pilot study in a routine care setting; however, not blinding the physical therapists that performed the outcome measures is a limitation of the current study. Moreover, we did not measure objective cardiorespiratory fitness using respiratory gas analysis measurements. We used the 6 MWT to assess functional exercise capacity. After the first week of the physical exercise training program, training intensity was based on Borg

scores instead of heart rate. It would be best to use CPET to objectively measure cardiorespiratory fitness, to set-up an individually tailored training program and to evaluate whether there are any contraindications to physical exercise training. Finally, training intensity in the current study was moderate. To the authors' knowledge, this is the first study in which patients performed physical exercise training during NACRT. During NACRT alone, patients often complain about tiredness and a lack of energy. We believe however that at least the majority of our patients could have been trained at a higher exercise intensity during NACRT. Training intensity is an important factor in the success of an exercise training program and higher intensities might have led to even better results. Literature about high-intensity training prior to major surgery is increasing,[32,33] seems promising and should therefore be investigated properly in future pilot and non-pilot studies, even during NACRT.

## Conclusion

The current study revealed that a supervised outpatient physical exercise training program for patients with locally advanced resectable rectal cancer during NACRT is feasible for a large part of the patients, safe and seems effective in the prevention of an often seen decline in physical fitness during NACRT. Fatigue and quality of life remained relatively stable during the program. Because of its potential effects, we should look for means to have more patients to profit from such an approach, hand in hand with an approach to proof its cost-effectiveness in a larger study.

## Conflict of interest statement

The authors declare no conflicts of interest.

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