**The effect of prehabilitation on objectively measured physical fitness following neoadjuvant treatment in preoperative rectal cancer patients – a blinded interventional pilot study**

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**Short title** – Prehabilitation in rectal cancer patients

**Summary**

**Background**: Patients requiring surgery for locally advanced rectal cancer often additionally undergo neoadjuvant chemoradiotherapy (NACRT), the effects of which on physical fitness are unknown. The aim of this feasibility and pilot study was to investigate the effects of NACRT and a 6-week Structured Responsive Exercise Training Programme (SRETP) on oxygen uptake (o2) at lactate threshold (L) in such patients.

**Methods:** We prospectively studied 39 consecutive patients (27 male) with T3-4/N+ resection margin threatened rectal cancer who completed standardized NACRT. Patients underwent cardiopulmonary exercise testing (CPET) at baseline (pre-NACRT), at week 0 (post-NACRT) and week 6 (post-SRETP). Twenty-two patients undertook a 6-week SRETP on a training bike (3 sessions per week) between week 0 and week 6 (exercise group). These were compared with 17 contemporaneous non-randomised patients (control group). Changes in o2 at L over time and between groups were compared using a compound symmetry covariance linear mixed model.

**Results:** Of 39 recruited patients, 22/22 (exercise) and 13/17 (control) completed the study. There were differences between the exercise and control groups at baseline (age, American Society of Anaesthesiologists Score (ASA), World Health Organisation (WHO) performance status and Colorectal Physiologic and Operative Severity Score for the Enumeration of Mortality and Morbidity (CR-POSSUM) predicted mortality). In all patients o2 at L significantly reduced between baseline and week 0 (-1.9ml.kg-1.min-1; 95%CI -1.3,-2.6; p<0.0001). In the exercise group o2 at L significantly improved between week 0 and week 6 (+2.1 ml.kg-1.min-1; 95%CI +1.3,+2.9; p<0.0001) whereas control group values were unchanged (-0.7 ml.kg-1.min-1; 95%CI -1.66,+0.37; p=0.204).

**Conclusions:** NACRT prior to rectal cancer surgery reduces physical fitness. A structured exercise intervention is feasible post-NACRT and returns fitness to baseline levels within 6 weeks in contrast to unchanged fitness in a contemporaneous (non-randomised) control group.

**Keywords**

Cardiopulmonary exercise test, surgery, rectal cancer, anaerobic threshold, prehabilitation, exercise

**Trial Registration Number**

**NCT**: 01325909

# INTRODUCTION

In the UK colorectal cancer is the third commonest cause of cancer death (1,2). In 2012, ~9000 patients were diagnosed with rectal cancer (35% aged > 75 years), of whom 75% underwent major resection with 90-day postoperative mortality of 3.2% (3). Twenty-five percent are locally advanced (Tumour, Node, Metastasis (TNM) stage - T3/T4N+) cancers considered for neoadjuvant chemoradiotherapy (NACRT) to control local disease, achieve tumour downsizing and negative resection margins (4–8); however, external beam radiation and oral or intravenous fluoropyrimidines cause dose-limiting toxicity, reaching Grade 3–5 in 20%. The UK National Bowel Cancer Audit found the American Society of Anaesthesiologists – Physical Status (ASA-PS) score (a categorical descriptor of fitness for surgery) as the strongest predictor of death within 30 days of surgery (3). Only two trials have suggested that rectal cancer patients with a lower subjective performance status (WHO Score >1) have worse post-operative outcome after combined chemotherapy or chemo-radiation and surgery (9,10).

Interventions to improve post-surgical recovery have usually been intra-operative and postoperative (11,12), which for high risk populations might be too late. The preoperative period might be a better time to engage patients in enhancing physical fitness, i.e. ‘prehabilitation’ (13,14). Pre-surgical exercise interventions are feasible, safe, improve function and quality of life (15,16), but little is known of their effects on physical fitness measured by cardiopulmonary exercise testing (CPET); yet poor fitness is linked to poor postoperative outcomes (17–21). Identifying prehabilitation programmes to optimise preoperative fitness is therefore a priority (22).

The primary aim of this pilot study was to evaluate, in patients scheduled for rectal cancer surgery following neoadjuvant chemoradiotherapy (NACRT), how objectively-measured physical fitness changes with NACRT and a preoperative 6-week structured responsive exercise training programme (SRETP). Other exploratory aims were to observe changes in physical activity and physical fitness, and to explore safety and feasibility of the exercise programme in this high risk patient cohort.

# METHODS

## Patients and Study Design

This prospective pilot, non-randomised, parallel group, interventional controlled trial was approved by the North West – Liverpool East Research and Ethics Committee (11/H1002/12) and registered with clinicaltrials.gov (NCT01325909). Written informed consent was obtained from all patients. We recruited consecutive patients between March 2011 and February 2013 referred to the Colorectal Multi-Disciplinary Team (MDT), age ≥18 years, with locally advanced (circumferential resection margin threatened) resectable rectal cancer, scheduled for standardized NACRT on the basis of Tumour, Node, Metastasis (TNM) classification >T2/N+ with no distant metastasis (23) and WHO Performance Status < 2 (24). Exclusion criteria were: inability to give informed consent, non-resectable disease, inability to perform CPET or bicycle exercise, and patients who declined surgery or NACRT, or who received non-standard NACRT. After completing NACRT, patients were allocated to the exercise training group by default. If unable to commit to the exercise schedule (or living > 15 miles from the hospital), they were asked to act as contemporaneously recruited controls (no exercise intervention) with the same CPET follow-up.

All patients underwent CPET 2 weeks before NACRT (baseline) and immediately post-NACRT (week 0), then at weeks 3, 6, 9 and 14 before surgery at week 15. Patients in the exercise group undertook the intervention continuously between week 0 and week 6 (Figure 1). CPET data were reported blind by two experienced assessors. All patients underwent a continuous 72 hour period of physical activity (PA) monitoring (Sensewear biaxial accelerometer, worn over the right triceps) during weekdays at baseline (2 weeks before NACRT), immediately post-NACRT (week 0) and week 6.

Patients in the exercise group attended a 6 week supervised in-hospital exercise training programme (3 sessions/week). The exercise training intensities were responsive to each individual CPET at week 0 and week 3 (informed and altered according to measured work rates at o2 at L and o2 at peak at peak exercise). Exercise training consisted of 40 minutes (including 5 min warm-up and 5 min cool-down) of interval training on an electromagnetically braked cycle ergometer (Optibike Ergoline GmbH, Germany). The training programme was preloaded on a chip-and-pin card which executed the interval intensities automatically. The interval-training programme consisted of alternating moderate (80% of work rate ato2 at L – 4 by 3 minute intervals) to severe (50% of the difference in work rates between o2 at peak and o2 at L – 4 by 2 minute intervals) intensities (total 20 minutes) for the first 2 sessions. This is then increased to 40 minutes (6 by 3 minute intervals at moderate intensity and 6 by 2 minute intervals at severe intensity) (Appendix 1 - online). The training programme was modified for each individual’s ramped CPET protocol results ensuring consistent and individualised intensities for all subjects (25). All patients exercised in pairs for camaraderie.

TNM staging involved flexible sigmoidoscopy for histological diagnosis, colonoscopy, chest, abdomen and pelvis computer-aided tomography (CT) and 1.5 tesla pelvic magnetic resonance imaging (MRI). All patients underwent 5 weeks NACRT. Standardized radiotherapy consisted of 45 Gy in 25 fractions on weekdays using a 3D conformal technique with CT guidance. A boost dose was given (5.4 Gy in 3 fractions) to the primary tumour only. Oral capecitabine (825 mg.m-2) was given twice daily on radiotherapy days. No patients received brachytherapy. At 9 weeks post-NACRT patients were restaged using chest, abdomen and pelvic CT and pelvic MRI. The colorectal MDT was blind to CPET results and patient allocation. All patients underwent total mesorectal excision (TME) (26) and a defunctioning stoma was constructed at the discretion of the surgeon.

## Measurements

CPET (Geratherm Respiratory GmbH; Love Medical Ltd.) followed a standard protocol described elsewhere (27). Patient characteristics recorded included age, gender, height, weight, diagnosis, staging, surgical procedure planned, WHO classification, ASA-PS, and diagnoses of diabetes, ischaemic heart disease, cerebrovascular disease, or heart failure. Resting flow-volume loops were used to derive Forced Expiratory Volume over 1 second (FEV1) and Forced Vital Capacity (FVC). Ventilation and gas exchange variables included oxygen uptake (o2), ventilatory equivalents for oxygen and carbon dioxide (E/o2; E/co2) and oxygen pulse (o2/heart rate), all measured both at estimated lactate threshold (L) and at peak exercise. Averaged step count while active was measured over 72 h using the PA monitor.

NACRT associated toxicity and CPET-related adverse events were discussed at the weekly MDT meeting. Toxicity events were graded on the National Cancer Institute Common Terminology Criteria (version 3.0), and acute radiation-induced skin toxicity using the Radiation Therapy Oncology Group scoring system. The physiological variables of the Colorectal Physiologic and Operative Severity Score for the Enumeration of Mortality and Morbidity (CR-POSSUM) (28) were completed immediately pre-operatively; the operative details of CR-POSSUM were completed post-operatively.

We aimed to evaluate changes in o2 at L between baseline, week 0 and week 6 in the exercise and control groups as a measure of the impact of NACRT and SRETP on physical fitness. Exploratory aims include observing: changes in number of steps (PA) with NACRT (between baseline and week 0) and in both exercise and control groups (between Week 0 and week 6); changes in o2 at L and at Peak until week 15; and the safety and feasibility of the exercise intervention (number of adverse events and adherence recorded to CPET or exercise training sessions).

## Statistical Methods

Our aim was to recruit 30 patients (15 each in exercise and control group) who would undergo standardised NACRT and the intervention period as an intention to treat for rectal cancer. This was based on an unpaired t-test with 90% power to detect a minimum difference in o2 at L of 1.5 ml.kg-1.min-1 and an SD of 1.1 ml.kg-1.min-1 and allowed for 20% patient drop-out (based on a previous study (29)).

Continuous variables are reported as mean (SD) or median and inter-quartile range (IQR), depending on distribution, and categorical variables as frequency (%). Univariate statistical comparisons of patient demographics between groups were undertaken: for continuous variables a two-sample t-test when relevant distributional assumptions were met and the Mann-Whitney U test otherwise; for categorical variables Chi-Square tests or, when cell counts were insufficient, Fishers Exact test. *p* <0.05 was taken as statistically significant.

For the primary analysis, compound symmetry covariance pattern linear mixed models were used to model o2 at L and o2 at peak exercise over the 3 time-points: baseline (pre-NACRT), week 0, and week 6 post-NACRT. Group (exercise/control) and visit (baseline, week 0 and week 6) were included as main effects in addition to the interaction between them. We identified 3 relevant formal comparisons for each of these two endpoints: (i) all patients, pre vs. week 0, (ii) exercise group only, week 0 vs. week 6, and (iii) between-group comparison of the change between week 0 and week 6 (effectively a week 6 comparison between groups corrected for between-group differences at week 0). These 6 comparisons were considered to be statistically significant at a Bonferroni-corrected level of p<0.008. Residuals and model fit were assessed using QQ plots and residual vs. predicted mean plots. The impact of potential confounders on between-group comparisons was assessed by incorporating variables listed in Table 1 into the final models as sensitivity analyses. For PA these comparisons were considered as exploratory and tested against the uncorrected 5% significance level; the need to square-root transform PA makes it impossible to recover the differences and confidence intervals on a meaningful scale, so only p-values and predicted means are presented. All mixed model statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary NC).

# RESULTS

39 patients were recruited, of whom 22/22 and 13/17 completed the study in the exercise and control groups respectively (4 patients having dropped out before baseline CPET). PA data was complete in 22/22 and 10/17 patients. Patient characteristics are shown in Table 1. There were significant baseline differences between the groups in age, ASA, WHO performance status and CR-POSSUM predicted morbidity scores, the control group being older and having poorer subjective performance.

Table 2 (online only) shows BMI, spirometry variables (FEV1, FVC, FEV1/FVC) and haemoglobin over the whole study period, along with MRI tumour staging and re-staging post-NACRT (week 9) clinical data. There were no significant baseline differences in these variables.

Table 3 (online only) shows tumour and treatment characteristics. A significant difference was found between the groups in TNM downstaging in response to NACRT. All patients completed NACRT. One patient needed capecitabine dose reduction, while 4 patients (3 in the exercise group and 1 control) sustained perineal radiation skin changes (maximum score 2 out of 4). The control group responded significantly less to NACRT on restaging MRI (as classified by MRI tumour regression scores).

Table 4 (online only) shows changes in CPET and PA variables. The median time to starting exercise after completion of NACRT was 2 working days (IQR 1-7 days). The mean (SD) % adherence to the exercise programme (% of the 18 sessions completed) was 96 (5) %. The mean (SD) % adherence to CPETs (% of 6 CPETs attended) was 92 (14) % in the exercise group vs. 60 (5) % in controls. There were no adverse events associated with CPET or SRETP. The control group had a lower peak work rate and lower ventilatory efficiency at baseline.

There was a significant reduction in o2 at L (-1.91 ml.kg-1.min-1; 95%CI -1.27 to -2.55; p<0.0001) and o2 at Peak (-2.52 ml.kg-1.min-1; 95%CI -1.33 to -3.71; p<0.0001) post-NACRT. The exercise group showed a significant improvement in both primary endpoints during the intervention period (week 0 to week 6), in contrast to the worsening fitness in the control group (Figure 2 A and B). The exercise group improved o2 at L by +2.12 ml.kg-1.min-1 (95%CI +1.34 to +2.90; p<0.0001), while the control group showed a non-significant decline in o2 at L by -0.65 ml.kg-1.min-1 (95% CI: -1.66 to +0.37; p=0.204). A direct comparison of o2 at L between groups at week 6, correcting for differences in o2 at L between the groups at week 0, shows a difference of +2.77 ml.kg-1.min-1 (95%CI +1.49 to +4.05; p<0.0001).

o2 at Peak shows similar changes in the exercise group: +2.65 ml.kg-1.min-1 (95%CI +1.19 to +4.10; p=0.0005), while the control group worsened by -1.25 ml.kg-1.min-1 (95% CI: -3.14 to + 0.64; p=0.19). A direct comparison of o2 at Peak between groups at week 6, correcting for differences in o2 at Peak at week 0, shows a change of +3.90 ml.kg-1.min-1 (95%CI +1.52 to +6.28; p=0.0017). Adjusting for potential confounders had negligible effect on these analyses (not shown). Results of a secondary analysis of o2 at L,including all time-points, are shown in Figure 3.

There was a significant difference in the averaged number of steps between baseline and week 0 for all patients (p=0.0004) and for the exercise and control groups between week 0 and week 6 (p<0.0001 and p=0.003) (table 4), but the improvement seen between week 0 and week 6 did not differ between exercise and control groups (p=0.84).

# DISCUSSION

## Main findings and comparison with other studies

This blinded interventional pilot study shows that a 6-week SRETP improves objectively measured physical fitness in patients scheduled for rectal cancer surgery following standardised NACRT; there was a significant mean benefit in o2 at L of +2.12 ml.kg-1.min-1 (95%CI +1.34 to +2.90; p<0.0001) in the exercise group at the end of the intervention period. Furthermore, we observed a detrimental effect of NACRT on physical fitness, with a decline in o2 at L between baseline and week 0 of -1.91 ml.kg-1.min-1 (95%CI -1.27 to -2.55; p<0.0001) consistent with our previous work (a small pilot study studying the changes in fitness with NACRT) (29). We also found a significant decline in PA with NACRT, and a subsequent improvement over 6 weeks post-NACRT which did not differ between groups. The training programme was safe and feasible (96% adherence to the intervention), with no adverse events, however the practical day-to-day running of the prehabilitation programme needs careful execution and management if this is to become part of routine clinical practice. Patients’ initial fitness and willingness to participate in a prehabilitation programme, patients’ travel time and distance from the prehabilitation centre, as well as flexibility in accessing the intervention, all need to be given careful consideration from the outset.

Our study is the first to show a meaningful decline in objectively measured physical fitness and physical activity after standardised NACRT, and a clinically meaningful improvement in physical fitness with SRETP following NACRT prior to elective rectal cancer surgery. We know that poor preoperative physical fitness, reflecting poor physiological reserves, is associated with postoperative morbidity (20,30,31), and rehabilitation following acute or chronic stressors (32–34) can improve fitness and quality of life. It therefore seems reasonable to aim an exercise intervention (prehabilitation) at restoring physical fitness back to baseline (pre-NACRT) prior to another acute stressor (major cancer surgery). Recent systematic reviews (15,16) conclude that preoperative aerobic exercise training is feasible, safe and tolerable in several surgical patient groups, and improves at least one measure of physical fitness. However, because of the small number of studies, limitations in study design and heterogeneous reporting of interventions and outcomes, evidence is lacking on its effects on physical fitness and surgical outcome.

A randomized controlled trial in colorectal cancer (14) found no differences between a structured bike and strengthening regime vs. simple walking and breathing exercises. A subsequent observational study of a trimodal prehabilitation programme showed better postoperative 6 min walking distance in the intervention group (35). Randomised studies on aerobic prehabilitation in colonic resection showed improvement in subjectively measured oxygen uptake, peak power output and heart rate (36,37). Kothmann and colleagues (38) define a minimum clinically important difference (MCID) ino2 at L of 2.0 ml.kg-1.min-1; although they found that a moderate continuous exercise programme significantly improved objectively measured physical fitness (o2 at L) in a high-risk cohort of patients with aortic abdominal aneurysms, MCID was not obtained, possibly because of too low an exercise duration and intensity (38). Our sample size estimate was based on the changes in o2 at L between baseline and week 0 of +1.5 ml.kg-1.min-1 in our pilot work (29) with an aim of returning patients fitness back to pre-NACRT levels. Using a higher intensity, interval training regime of longer duration, as suggested by Kothmann and colleagues (38) we attained a between group difference in o2 at L at week 6 of +2.77 ml.kg-1.min-1 (95%CI +1.49 to +4.05; p<0.0001), a substantial clinically important difference.

Our patients achieved far less than the recommended daily step count of 10,000 steps/day (39) (49% vs. 55% in the exercise vs. control group). PA declines with NACRT in both groups (Figure 4), mirroring by the acute loss of physical fitness, but then improves in both groups, probably due to the natural resumption of activities of daily living post-NACRT. Of note the exercise group re-attain their baseline activity levels with a significant change in fitness after the intervention period; however the control group sustain a decline in fitness while their activity overshoots their baseline levels. The dramatic changes in physical fitness between the groups are therefore mediated by the structured exercise intervention; improving PA is not enough.

These findings have important clinical implications. Fitness improves rapidly in the first 3 weeks of the intervention (Figure 3), while the control group, unable to recover from NACRT, show a sustained decline from week 3 to week 14. The exercise group overshoot baseline (pre-NACRT) at week 6, but fitness thereafter declines. By week 6 patients in the exercise group have recovered from the effects of NACRT on fitness and PA, while the control group, recovering only PA, are now at high risk of adverse surgical outcome on the basis of conventional risk stratification cut-off points for o2 at L of 10.1-10.9 ml.kg-1.min-1 (18,27,40). In units where CPET is part of the routine perioperative cancer pathway, rectal cancer patients usually undergo testing prior to NACRT, not upon restaging. Such fitness for surgery assessments might be less predictive of outcome than post-NACRT measurements, as they do not account for variability in changes in fitness with NACRT.

## Strengths and weaknesses

Strengths of this study include its prospective nature, the homogenous study population (only operable locally advanced rectal cancer patients), the blinded reporting of objectively measured CPET outcome variables (blind to demographics, group allocation and timeline), the rigorous exercise intervention, the standardized NACRT regime and the statistical modelling undertaken to show difference in effect sizes with confidence intervals.

## Potential weaknesses of this study include the non-randomised design which may have resulted in unobserved differences between groups as well as the observed differences between groups that we have reported (notably performance status, CR-POSSUM predicted mortality, response to NACRT, lower peak work rates and less efficient ventilatory equivalents). Although some sensitivity analyses were undertaken to assess the importance of these potential confounders, they might be sufficient to account for a proportion of the observed differences between the control and the exercise group, and there is clearly no substitute for a randomised design with a larger sample size. Other weaknesses include the single-centre design which may limit the generalizability of the results.

## Conclusion and further research

NACRT acutely reduces objectively measured physical fitness (o2 at L -1.91 ml.kg-1.min-1; 95%CI -1.27 to -2.55; p<0.0001), while SRETP immediately post-NACRT prior to surgery (proving safe and feasible) improves fitness, with a clinically significant difference in o2 at L in the exercise group at week 6 of +2.12 ml.kg-1.min-1 (95%CI +1.34 to +2.90; p<0.0001). The exercise programme aimed to return patients to a pre-NACRT level of fitness, and actually showed an improvement above baseline fitness at week 6. The control group sustained the same decline in NACRT, which remained uncorrected despite their regaining baseline PA. This is a novel finding in this high risk surgical cohort, which needs however to be validated by a randomised controlled trial. Our group is conducting such a trial which is currently recruiting (NIHR-funded PB-PG-0711-25093). This assesses changes in physical fitness and quality of life following a 9-week intervention in this patient group. A larger trial is also needed to investigate the effects of prehabilitation on postoperative surgical and tumour outcomes.

**Author contribution**

M.A.W: Conception, study design, data acquisition, analysis, drafting article, revision and final approval

L.L: data acquisition, drafting article, revision and final approval

D.L: Analysis and interpretation of data, drafting article, revising for intellectual content and final approval

C.P.B: Study design, data acquisition, analysis, drafting article, revision and final approval

R.S: Study design, data acquisition, analysis, drafting article, revision and final approval

S.J: Conception, study design, critical revision of manuscript and final approval

G.J.K: analysis and interpretation of data; critical revision of manuscript and final approval

M.P.W.G: Conception, study design, critical revision of manuscript and final approval

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**Declaration of interest**

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