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CLINICAL PRACTICE

Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study†

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Editor's key points

- Preoperative interventions might improve post-surgical outcomes in high-risk patients.
- A prehabilitation exercise programme was evaluated using cardiopulmonary exercise testing in preoperative rectal cancer patients.
- A structured exercise training programme improved preoperative physical fitness to baseline, an effect that is being validated in a larger randomized trial.

Background. Patients requiring surgery for locally advanced rectal cancer often additionally undergo neoadjuvant chemoradiotherapy (NACRT), of which the effects 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 ($\dot{V}O_2$) at lactate threshold ($\hat{\theta}_L$) in such patients.

Methods. We prospectively studied 39 consecutive subjects (27 males) with T3–4/N+ resection margin threatened rectal cancer who completed standardized NACRT. Subjects underwent cardiopulmonary exercise testing at baseline (pre-NACRT), at week 0 (post-NACRT), and week 6 (post-SRETP). Twenty-two subjects undertook a 6 week SRETP on a training bike (three sessions per week) between week 0 and week 6 (exercise group). These were compared with 17 contemporaneous non-randomized subjects (control group). Changes in $\dot{V}O_2$ at $\hat{\theta}_L$ over time and between the groups were compared using a compound symmetry covariance linear mixed model.

Results. Of 39 recruited subjects, 22 out of 22 (exercise) and 13 out of 17 (control) completed the study. There were differences between the exercise and control groups at baseline [age, ASA score physical status, World Health Organisation performance status, and Colorectal Physiologic and Operative Severity Score for the Enumeration of Mortality and Morbidity (CR-POSSUM) predicted mortality]. In all subjects, $\dot{V}O_2$ at $\hat{\theta}_L$ significantly reduced between baseline and week 0 [-1.9 ml kg^{-1} min^{-1}; 95% confidence interval (CI) -1.3, -2.6; $P<0.0001$]. In the exercise group, $\dot{V}O_2$ at $\hat{\theta}_L$ 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 the control group values were unchanged (-0.7 ml kg^{-1} min^{-1}; 95% CI -1.66, $+0.37$; $P=0.204$).

Conclusions. NACRT before rectal cancer surgery reduces physical fitness. A structured exercise intervention is feasible post-NACRT and returns fitness to baseline levels within 6 weeks.

Clinical trial registration. NCT: 01325909.

Keywords: anaerobic threshold; cardiopulmonary exercise test; exercise; prehabilitation; rectal cancer; surgery

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In the UK, colorectal cancer is the third most common cause of cancer death.[1 2] In 2012, ~9000 patients were diagnosed with rectal cancer (35% aged >75 yr), of whom 75% underwent major resection with 90 day postoperative mortality of 3.2%.[3] Twenty-five per cent 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 i.v. fluoropyrimidines cause dose-limiting toxicity, reaching grade 3–5 in 20%. The UK National Bowel Cancer Audit found the ASA-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 [World Health Organisation (WHO) score >1] have worse postoperative outcome after combined chemotherapy or chemoradiation and surgery.[9 10]

Interventions to improve post-surgical recovery have usually been intra- 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, that is, 'prehabilitation'.[13 14] Presurgical 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 optimize preoperative fitness is therefore a priority.[22]

The primary aim of this pilot study was to evaluate, in patients undergoing rectal cancer surgery after 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 (PA) 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-randomized, 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 yr, with locally advanced (circumferential resection margin threatened) resectable rectal cancer, undergoing standardized NACRT on the basis of 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 subjects 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 (Fig. 1). CPET data were reported blind by two experienced assessors. All subjects underwent a continuous 72 h period of 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.

Subjects in the exercise group attended a 6 week supervised in-hospital exercise training programme (three 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 $\dot{V}O_2$ at $\hat{\theta}_L$ and $\dot{V}O_2$ at peak exercise). Exercise training consisted of 40 min (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 at $\dot{V}O_2$ at $\hat{\theta}_L$ – 4 by 3 min intervals) to severe (50% of the difference in work rates between $\dot{V}O_2$ at peak and $\dot{V}O_2$ at $\hat{\theta}_L$ – 4 by 2 min intervals) intensities (total 20 min) for the first two sessions. This is then increased to 40 min (6×3 min intervals at moderate intensity and 6×2 min intervals at severe intensity) (Supplementary Appendix S1). The training programme was modified for each individual's ramped CPET protocol results ensuring consistent and individualized intensities for all subjects.[25] All subjects 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 T pelvic magnetic resonance imaging (MRI). All subjects 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 three fractions) to the primary tumour only. Oral capecitabine (825 mg m^{-2}) was given twice daily on radiotherapy days. No subjects received brachytherapy. At 9 weeks post-NACRT, subjects were restaged using chest, abdomen, and pelvic CT and pelvic MRI. The colorectal MDT was blind to CPET results and patient allocation. All subjects underwent total mesorectal excision,[26] and a defunctioning stoma was constructed at the discretion of the surgeon.

Measurements

CPET (Geratherm Respiratory GmbH; Love Medical Ltd, Manchester, UK) followed a standard protocol described elsewhere.[27] Subjects characteristics were recorded included as shown in

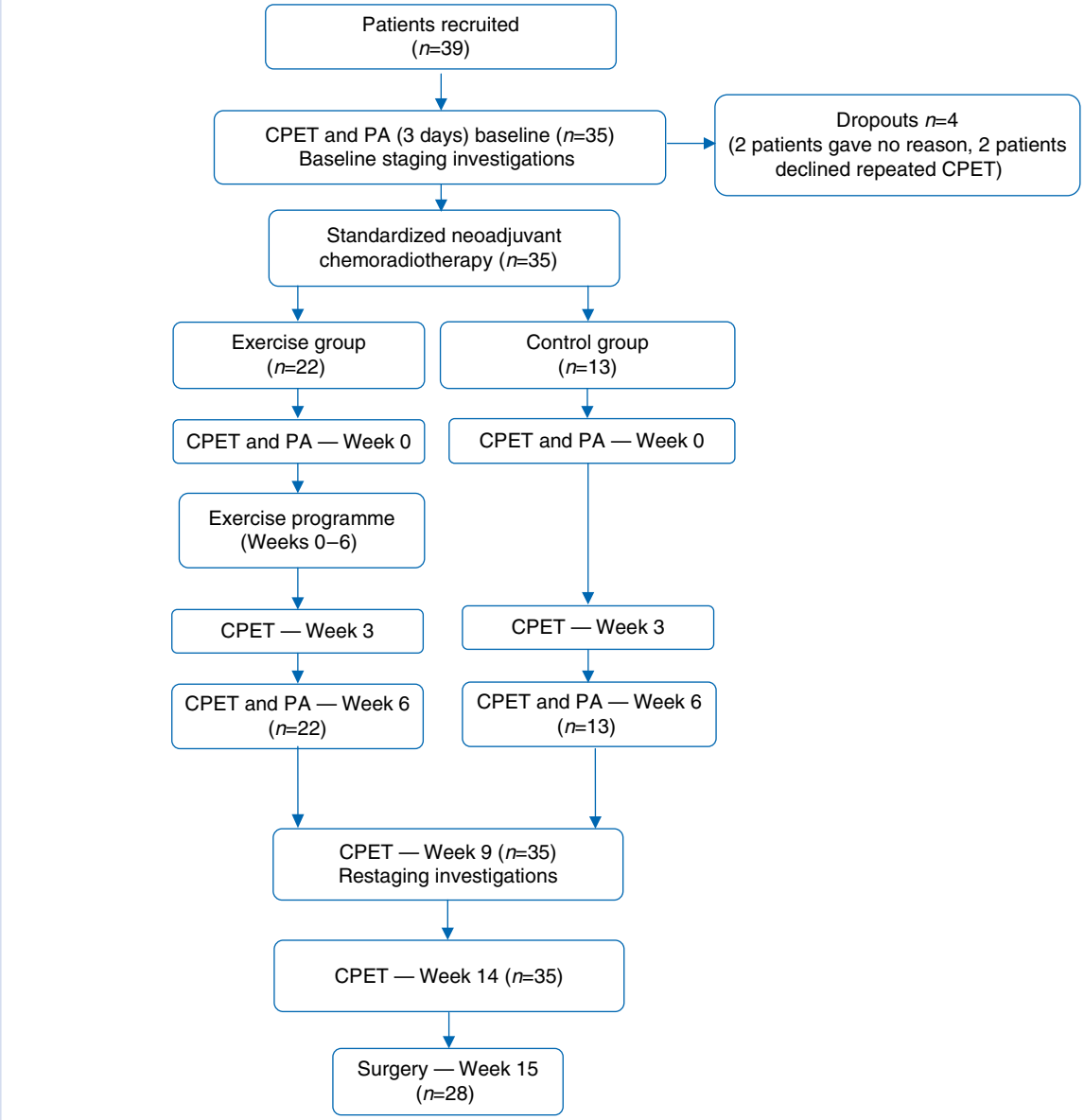

Fig 1 Consort diagram. CPET, cardiopulmonary exercise test; PA, physical activity monitoring.

Table 1. Resting flow–volume loops were used to derive forced expiratory volume over 1 s (FEV1) and forced vital capacity (FVC). Ventilation and gas exchange variables included oxygen uptake ($\dot{V}O_2$), ventilatory equivalents for oxygen and carbon dioxide ($\dot{V}_E/\dot{V}O_2$; $\dot{V}_E/\dot{V}CO_2$), and oxygen pulse ($\dot{V}O_2$/heart rate), all measured both at estimated lactate threshold ($\hat{\theta}_L$) 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 before operation; the operative details of CR-POSSUM were completed after operation.

We aimed to evaluate changes in $\dot{V}O_2$ at $\hat{\theta}_L$ 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 the exercise and control groups (between week 0 and week 6); changes in $\dot{V}O_2$ at $\hat{\theta}_L$ 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).

Table 1 Subject characteristics. *Values presented as mean (range); †frequencies with percentages in parentheses, smoking status assessed as currently smoking: yes (1) *vs* no (0); ‡number of patients (%) WHO performance status and ASA physical status; §values are mean (SD) for CR-POSSUM components—exercise ($n=17$) and control ($n=11$). Four patient dropouts immediately before first CPET (dropouts not included in patient characteristics). $P<0.05$ was taken as statistically significant (bold values).

	Exercise ($n=22$)	Control ($n=13$)	*P*-value
Age (yr)*	64 (45–82)	72 (62–84)	**0.015**
Gender M:F (%)	14 (64):8 (36)	9 (69):4 (31)	1
Smoking (%)	10 (45)	4 (31)	0.617
Past medical history†			
Heart failure	3 (14)	1 (8)	1
Diabetes	2 (9)	1 (8)	1
Ischaemic heart disease	5 (23)	5 (38)	0.444
Cerebrovascular disease	0	0	1
ASA‡			
I	11 (50)	0	**0.003**
II	9 (41)	11 (85)	
III	2 (9)	2 (15)	
WHO performance status‡			
0	18 (82)	8 (62)	**0.035**
1	4 (18)	3 (23)	
2	0	2 (15)	
CR-POSSUM—physiological score§	8.0 (1.8)	9.3 (2.3)	0.162
CR-POSSUM—predicted mortality (%)§	3.2 (1.1)	9.4 (8.9)	**0.003**
CR-POSSUM—operative severity score§	9.8 (2.0)	11.4 (0.5)	0.236

Statistical methods

Our aim was to recruit 30 subjects (15 each in the exercise and control group) who would undergo standardized 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 $\dot{V}O_2$ at $\hat{\theta}_L$ of 1.5 ml kg^{-1} min^{-1} and an SD of 1.1 ml kg^{-1} min^{-1} and allowed for 20% subjects drop-out (based on a previous study).[29]

Continuous variables are reported as mean (range), mean (SD) or median and inter-quartile range (IQR), depending on distribution, and categorical variables as frequency (%). Univariate statistical comparisons of patient characteristics between the 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, χ^2 tests or, when cell counts were insufficient, Fisher's 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 $\dot{V}O_2$ at $\hat{\theta}_L$ and $\dot{V}O_2$ at peak exercise over the three 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 three relevant formal comparisons for each of these two endpoints: (i) all subjects, 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 the groups corrected for between-group differences at week 0). These six comparisons were considered to be statistically significant at a Bonferroni-corrected level of $P<0.008$. Residuals and model fit were assessed using Q–Q 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 CIs 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, USA).

Results

A total of 39 subjects were recruited, of whom 22 out of 22 and 13 out of 17 completed the study in the exercise and control groups, respectively (four subjects having dropped out before baseline CPET). PA data were complete in 22 out of 22 and 10 out of 17 subjects. Subject 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.

Supplementary Table S1 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.

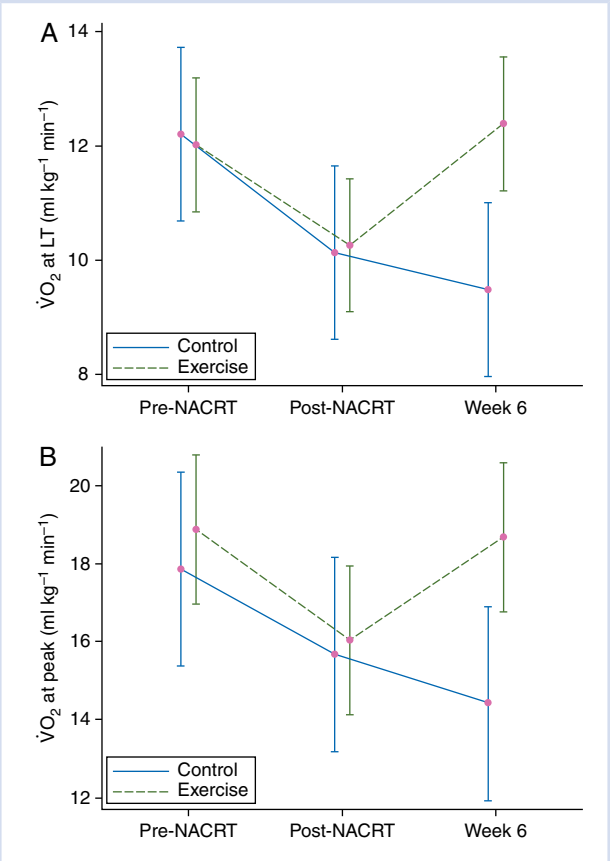

Fig 2 Line diagram showing fitted means and 95% CI for $\dot{V}O_2$ at $\hat{\theta}_L$ (ml kg^{-1} min^{-1}) (A) and $\dot{V}O_2$ at peak (ml kg^{-1} min^{-1}) (B) at baseline (pre-NACRT), week 0 (post-NACRT), and week 6 for the exercise (dashed line) and control groups (solid line).

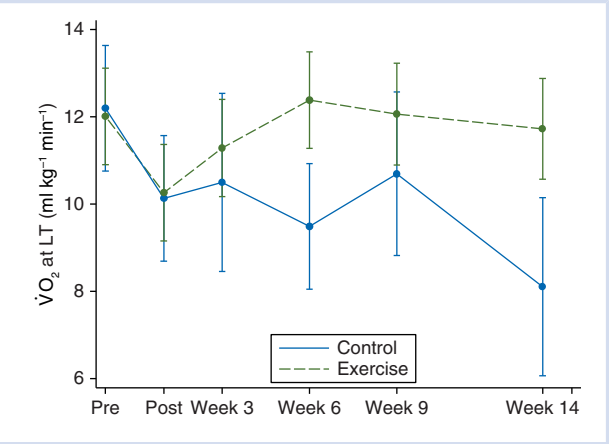

Fig 3 Line diagram showing fitted means and 95% CI for $\dot{V}O_2$ at $\hat{\theta}_L$ (ml kg^{-1} min^{-1}) for the exercise group and the control group over the whole study period (baseline pre-NACRT to week 14 pre-surgery—secondary analysis).

Supplementary Table S2 shows tumour and treatment characteristics. A significant difference was found between the groups in TNM down-staging in response to NACRT. All subjects completed NACRT. One subject needed capecitabine dose reduction, while four subjects (three in the exercise group and one 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).

Supplementary Table S3 shows changes in CPET and PA variables. The median time to starting exercise after completion of NACRT was two working days (IQR 1–7 days). The mean (SD) %adherence to the exercise programme (percentage of the 18 sessions completed) was 96 (5)%. The mean (SD) %adherence to CPETs (percentage 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 $\dot{V}O_2$ at $\hat{\theta}_L$ (-1.91 ml kg^{-1} min^{-1}; 95% CI -1.27 to -2.55; $P<0.0001$) and $\dot{V}O_2$ 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 (weeks 0–6), in contrast to the worsening fitness in the control group (Fig. 2A and B). The exercise group improved $\dot{V}O_2$ at $\hat{\theta}_L$ by $+2.12$ ml kg^{-1} min^{-1} (95% CI $+1.34$–2.90; $P<0.0001$), while the control group did not (-0.65 ml kg^{-1} min^{-1}, 95% CI -1.66 to $+0.37$; $P=0.204$). A direct comparison of $\dot{V}O_2$ at $\hat{\theta}_L$ between the groups at week 6, correcting for differences in $\dot{V}O_2$ at $\hat{\theta}_L$ between the groups at week 0, shows a difference of $+2.77$ ml kg^{-1} min^{-1} (95% CI $+1.49$–4.05; $P<0.0001$).

$\dot{V}O_2$ at peak shows similar changes in the exercise group: $+2.65$ ml kg^{-1} min^{-1} (95% CI $+1.19$–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 $\dot{V}O_2$ at peak between the groups at week 6, correcting for differences in $\dot{V}O_2$ at peak at week 0, shows a change of $+3.90$ ml kg^{-1} min^{-1} (95% CI $+1.52$–6.28; $P=0.0017$). Adjusting for potential confounders had negligible effect on these analyses (not shown). Results of a secondary analysis of $\dot{V}O_2$ at $\hat{\theta}_L$, 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 subjects ($P=0.0004$) and for the exercise and control groups between week 0 and week 6 ($P<0.0001$ and $P=0.003$) (Supplementary Table S3), but the improvement seen between week 0 and week 6 did not differ between the 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 undergoing rectal cancer surgery after standardized NACRT, 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 the 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 to become part of routine clinical practice. Patients' initial fitness and willingness to participate in a prehabilitation programme, travel time, and distance from the prehabilitation centre, and also 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 PA after standardized NACRT, and a clinically meaningful improvement in physical fitness with SRETP after NACRT before elective rectal cancer surgery. Poor preoperative physical fitness, reflecting poor physiological reserves, is associated with postoperative morbidity,[20 30 31] and rehabilitation after 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) before 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 compared with 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] Randomized 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) in $\dot{V}O_2$ at $\hat{\theta}_L$ of 2.0 ml kg^{-1} min^{-1}; although they found that a moderate continuous exercise programme significantly improved objectively measured physical fitness ($\dot{V}O_2$ at $\hat{\theta}_L$) 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 $\dot{V}O_2$ at $\hat{\theta}_L$ 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 $\dot{V}O_2$ at $\hat{\theta}_L$ at week 6 of +2.77 ml kg^{-1} min^{-1} (95% CI +1.49–4.05; $P<0.0001$), a substantial clinically important difference.

Our subjects achieved far less than the recommended daily step count of 10 000 steps per day[39] (49% and 55% in the exercise and control group, respectively). PA declines with NACRT in both groups (Fig. 4), mirroring the acute loss of physical fitness,

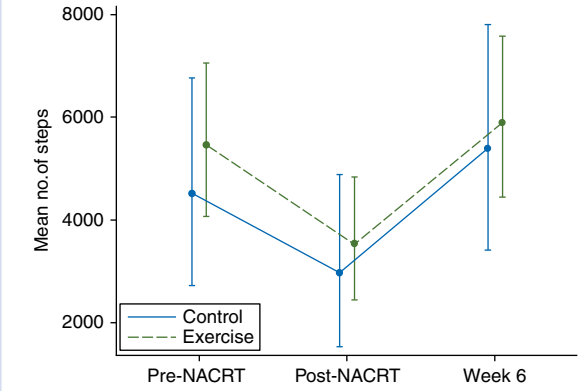

Fig 4 Line diagram showing fitted means and 95% CI for averaged number of steps for the exercise group and the control group [pre-NACRT (baseline), post-NACRT (week 0), and week 6].

but then improves in both groups, probably because of the natural resumption of activities of daily living post-NACRT. Of note, the exercise group re-attained their baseline activity levels with a significant change in fitness after the intervention period; however, the control group sustained a decline in fitness while their activity overshot 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 (Fig. 3), while the control group, unable to recover from NACRT, showed a sustained decline from week 3 to week 14. The exercise group overshot baseline (pre-NACRT) at week 6, but fitness thereafter declined. By week 6, subjects in the exercise group recovered from the effects of NACRT on fitness and PA, while the control group, recovering only PA, were at high risk of adverse surgical outcome on the basis of conventional risk stratification cut-off points for $\dot{V}O_2$ at $\hat{\theta}_L$ 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 before 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 patient characteristics, group allocation, and timeline), the rigorous exercise intervention, the standardized NACRT regime, and the statistical modelling undertaken to show difference in effect sizes with CIs.

Potential weaknesses of this study include the non-randomized design which may have resulted in unobserved

differences between the groups and also the observed differences between the groups that we reported (notably performance status, CR-POSSUM predicted mortality, response to NACRT, peak work rates, and 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 randomized 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 reduced objectively measured physical fitness, while SRETP immediately post-NACRT before surgery (proving safe and feasible) improved fitness. 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 that needs to be validated by a randomized 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 after 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.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

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

M.P.W.G. received honoraria for speaking, for travel expenses, or both from Edwards Lifescience, Fresenius-Kabi, BOC Medical (Linde Group), Ely-Lilly Critical Care, and Cortex GmBH. He has also received research grants from National Institute of Health Research, Association of Anaesthetists of Great Britain and Ireland, Sir Halley Stuart Trust, and Francis and Augustus Newman Foundation. He leads the Xtreme-Everest hypoxia research consortium, who have received unrestricted research grant funding from BOC Medical (alinde Group) Ely-Lilly Critical Care, Smiths Medical, Deltex Medical, London Clinic, and Rolex.

References

1 Statistical Bulletin Cancer registrations in England, 2010
2 Statistical Bulletin Cancer Incidence and Mortality in the United Kingdom, 2008–10
3 Finan P, Greenaway K. National Bowel Cancer Audit, 2012
4 Habr-Gama A, Perez RO, Nadalin W, *et al.* Operative versus nonoperative treatment for Stage 0 distal rectal cancer following chemoradiation therapy. *Ann Surg* 2004; **240**: 711–8
5 Chau I, Brown G, Cunningham D, *et al.* Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. *J Clin Oncol* 2006; **24**: 668–74
6 Mohiuddin M, Winter K, Mitchell E, *et al.* Randomized phase II study of neoadjuvant combined-modality chemoradiation for distal rectal cancer: Radiation Therapy Oncology Group Trial 0012. *J Clin Oncol* 2006; **24**: 650–5
7 Bosset JF, Collette L, Calais G, *et al.* Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**: 1114–23
8 Gérard JP, Conroy T, Bonnetain F, *et al.* Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3–4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006; **24**: 4620–5
9 Swellengrebel HAM, Marijnen CAM, Verwaal VJ, *et al.* Toxicity and complications of preoperative chemoradiotherapy for locally advanced rectal cancer. *Br J Surg* 2011; **98**: 418–26
10 Marijen C, Kapiteijn E, vab de Velde C, *et al.* Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a mulitcenter randomized trial. *J Clin Oncol* 2002; **20**: 817–25
11 Kehlet H. Manipulation of the metabolic response in clinical practice. *World J Surg* 2000; **24**: 690–5
12 Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg* 2002; **183**: 630–41
13 Ditmyer N, Topp R, Pifer M. Prehabilitation in preparation for orthopaedic surgery. *Orthop Nurs* 2002; **21**: 43–51
14 Carli F, Charlebois P, Stein B, *et al.* Randomized clinical trial of prehabilitation in colorectal surgery. *Br J Surg* 2010; **97**: 1187–97
15 Singh F, Newton R, Galvao D, Spry N, Baker M. A systematic review of pre-surgical exercise intervention studies with cancer patients. *Surg Oncol* 2013; **22**: 92–104
16 Doherty AFO, West M, Jack S, Grocott MPW. Preoperative aerobic exercise training in elective intra-cavity surgery: a systematic review. *Br J Anaesth* 2013; **110**: 679–89
17 Lai CW, Minto G, Challand CP, *et al.* Patients' inability to perform a preoperative cardiopulmonary exercise test or demonstrate an anaerobic threshold is associated with inferior outcomes after major colorectal surgery. *Br J Anaesth* 2013; **111**: 607–11

18 Wilson RJT, Davies S, Yates D, Redman J, Stone M. Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. *Br J Anaesth* 2010; **105**: 297–303

19 Snowden CP, Prentis J, Jacques B, *et al.* Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people. *Ann Surg* 2013; **257**: 999–1004

20 West M, Jack S, Grocott MPW. Perioperative cardiopulmonary exercise testing in the elderly. *Best Pract Res Clin Anaesthesiol* 2011; **25**: 427–37

21 Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *Br J Surg* 2007; **94**: 966–9

22 Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. *Am J Phys Med Rehabil* 2013; **92**: 715–27

23 Sobin LH, Fleming ID. TNM classification of malignant tumors. *Cancer* 1997; **80**: 1803–4

24 Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–55

25 Roston W, Whipp B, Davis J, Cunningham D, Effros R, Wasserman K. Oxygen uptake kinetics and lactate concentration during exercise in humans. *Am Rev Respir Dis* 1987; **135**: 1080–4

26 MacFarlane JK, Ryall RDH, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; **341**: 457–60

27 West MA, Lythgoe D, Barben C, *et al.* Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. *Br J Anaesth* 2014; **112**: 665–71

28 Bromage SJ, Cunliffe WJ. Validation of the CR-POSSUM risk-adjusted scoring system for major colorectal cancer surgery in a single center. *Dis Colon Rectum* 2007; **50**: 192–6

29 West MA, Jack S, Kemp G, Barben C, Grocott M. The effect of neoadjuvant chemoradiotherapy on fitness in patients undergoing rectal cancer surgery—fit for surgery? *Am J Respir Crit Care Med* 2012; **185**: A6395

30 Hennis PJ, Meale PM, Grocott MPW. Cardiopulmonary exercise testing for the evaluation of perioperative risk in non-cardiopulmonary surgery. *Postgrad Med J* 2011; **87**: 550–7

31 Smith TB, Stonell C, Purkayastha S, Paraskevas P. Cardiopulmonary exercise testing as a risk assessment method in non cardiopulmonary surgery: a systematic review. *Anaesthesia* 2009; **64**: 883–93

32 Piepoli MF, Davos C, Francis DP, Coats AJS. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *Br Med J* 2004; **328**: 189

33 Riario-Sforza GG, Incorvaia C, Paterniti F, *et al.* Effects of pulmonary rehabilitation on exercise capacity in patients with COPD: a number needed to treat study. *Int J Chron Obstruct Pulmon Dis* 2009; **4**: 315–9

34 Sandercock G, Hurtado V, Cardoso F. Changes in cardiorespiratory fitness in cardiac rehabilitation patients: a meta-analysis. *Int J Cardiol* 2013; **167**: 894–902

35 Li C, Carli F, Lee L, *et al.* Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surg Endosc* 2013; **27**: 1072–82

36 Kim DJ, Mayo NE, Carli F, Montgomery DL, Zavorsky GS. Responsive measures to prehabilitation in patients undergoing bowel resection surgery. *Tohoku J Exp Med* 2009; **217**: 109–15

37 Dronkers JJ, Lamberts H, Reutelingsperger IMMD, *et al.* Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. *Clin Rehabil* 2010; **24**: 614–22

38 Kothmann E, Batterham AM, Owen SJ, *et al.* Effect of short-term exercise training on aerobic fitness in patients with abdominal aortic aneurysms: a pilot study. *Br J Anaesth* 2009; **103**: 505–10

39 Choi BCK, Pak AWP, Choi JCL, Choi ECL. Daily step goal of 10,000 steps: a literature review. *Clin Invest Med* 2007; **30**: 146–51

40 Snowden CP, Prentis JM, Anderson HL, *et al.* Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major elective surgery. *Ann Surg* 2010; **251**: 535–41

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