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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