

The effects of neoadjuvant chemoradiotherapy and an in-hospital exercise training programme on physical fitness and quality of life in locally advanced rectal cancer patients: A randomised controlled trial (The EMPOWER Trial)

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Abstract

Background

The EMPOWER trial aimed to assess the effects of a 9-week exercise prehabilitation programme on physical fitness compared with a usual care control group. Secondary aims were to investigate the effect of 1) the exercise prehabilitation programme on psychological health; and 2) neoadjuvant chemoradiotherapy (NCRT) on physical fitness and psychological health.

Methods

Between October 2013 and December 2016, adults with locally advanced rectal cancer undergoing standardised NCRT and surgery were recruited to a multi-centre trial. Patients underwent cardiopulmonary exercise testing (CPET) and HRQoL questionnaires (EORTC-QLQ-C30 and EQ-5D-5L) pre-NCRT and post-NCRT (week 0/baseline). At week 0, patients were randomised to exercise prehabilitation or usual care (no intervention). CPET and HRQoL questionnaires were assessed at week 0, 3, 6 and 9, whilst semi structured interviews were assessed at week 0 and week 9. Changes in oxygen uptake at anaerobic threshold (VO_2 at AT ($\text{ml.kg}^{-1}.\text{min}^{-1}$)) between groups was compared using linear mixed modelling.

Results

Thirty-eight patients were recruited, mean age 64 (10.4) years. Of the 38 patients, 33 were randomised: 16 to usual care and 17 to exercise prehabilitation (26 male and seven female). Exercise prehabilitation significantly improved VO_2 at AT compared to the usual care. The change from baseline to week 9, when adjusted for baseline, between the randomised groups was $+2.9 \text{ ml.kg}^{-1}.\text{min}^{-1}$; 95% CI (0.8 to 5.1); $p = 0.011$.

Conclusion

A 9-week exercise prehabilitation programme significantly rescued fitness following NCRT. These findings have informed the WesFit trial (NCT03509428) which is investigating the effects of community-based multimodal prehabilitation before cancer surgery.

Trial registration

ClinicalTrials.gov NCT01914068. Registered 1 August 2013, <https://clinicaltrials.gov/ct2/show/NCT01914068>.

Background

The standard multi-modal treatment pathway for magnetic resonance imaging (MRI)-defined resection margin threatened locally advanced rectal cancer is long course neoadjuvant chemoradiotherapy (NCRT) followed by a waiting period before surgery with curative intent¹. However, some centres in the United

Kingdom prefer a multi-modal treatment pathway of systemic neoadjuvant chemotherapy prior to NCRT followed by a waiting period before surgery or even short course NCRT with a much shorter wait period before surgery. Although such multimodal treatment pathways have improved cancer outcomes mainly by reducing local recurrence rates²⁻³, they are associated with a risk of toxicity and a significant risk of morbidity and mortality⁴.

There is strong evidence that cardiopulmonary exercise testing (CPET) predicts post-operative morbidity and mortality in several surgical groups⁵⁻¹⁰. In people with newly diagnosed rectal cancer, NCRT prior to surgery has been shown to significantly reduce physical fitness, as measured by CPET, and this reduction has been linked to adverse post-operative outcome¹¹. The standard waiting period between completion of NCRT and surgery is generally at least 8 weeks¹² (or in some NHS hospitals up to 14 weeks) and therefore represents a unique opportunity to intervene with exercise prehabilitation. In this area of research, early evidence demonstrates the feasibility and preliminary effectiveness of exercise training (unimodal prehabilitation delivered in varied formats) for people with rectal cancer scheduled for NCRT and surgery¹³⁻¹⁹. To date, however, no exercise RCTs have been reported on both physical and psychological health measures in people with rectal cancer (although the EXERT trial is currently recruiting)²⁰ or indeed any patient group scheduled for a multimodal treatment pathway²¹.

The primary aim of the EMPOWER trial was to assess the effects of a 9-week exercise prehabilitation programme on physical fitness, compared with a usual care control group. Secondary aims were to investigate the effects of 1) the exercise prehabilitation on psychological health and 2) NCRT on physical fitness and psychological health. Other exploratory outcomes included such as changes in physical activity (PA) and post-operative morbidity, cancer staging and safety were also assessed.

Methods

Setting and participants

The methodology for the EMPOWER trial has been published elsewhere²², registered with ClinicalTrials.gov NCT01914068 (registered 1 August 2013, <https://clinicaltrials.gov/ct2/show/NCT01914068>). EMPOWER is a multi-centre trial which was conducted in five UK National Health Service (NHS) hospitals. Briefly, this was a parallel group (exercise vs. usual care control), observer blinded (blind to CPET data, group allocation and outcomes), randomised controlled clinical trial. Patients with MRI-defined, circumferential margin-threatened, potentially curable, locally advanced rectal cancer undergoing both NCRT and elective surgery were recruited. All potentially eligible patients were identified at multi-disciplinary meetings and approached at an outpatient appointment. Patients were contacted by telephone to provide additional information about the trial. Written informed consent was provided at the pre-NCRT visit. Recruitment took place between 2013 and 2016.

Neoadjuvant cancer treatment

Neoadjuvant cancer treatments varied depending on the hospital. The 'standard' chemoradiotherapy programme was 45 Gy in 25 fractions on weekdays using a 3D conformal technique with CT guidance and oral capecitabine 900 mg.m⁻² twice daily on radiotherapy days. Although the role of neoadjuvant systemic chemotherapy is still under investigation²³⁻²⁵, during recruitment to the EMPOWER trial, University Hospital Southampton NHS Foundation Trust adopted systemic neoadjuvant chemotherapy prior to chemoradiotherapy as a standard treatment. This consisted of oxaliplatin 130 mg.m⁻² intravenously on day 1, oral capecitabine 1000 mg.m⁻² (days 1-14) given in a 3 weekly cycle x 4 cycles over 12 weeks, followed the 'standard' chemoradiotherapy programme as described above.

Randomisation

Following neoadjuvant CRT (week 0), patients were allocated to the in-hospital exercise training group or usual care control group. Patients are randomised (1:1) to either an in-hospital exercise training programme or usual care control group using the Trans European Network for patient randomisation in clinical trials system (TENAELA System) and concealed by the research team.

Interventions

Usual care control group

The usual care control group received routine care throughout their cancer pathway from diagnosis to surgical resection (no exercise intervention).

Exercise prehabilitation intervention group

Participants started their exercise training on the first week after NCRT (Week 0) in their treating hospital and were scheduled to attend 3 sessions/week for 9 weeks. The delivery of the exercise programme is described elsewhere²² and in Supplementary Appendix 1 using the Consensus on Exercise Reporting Template guidelines²⁶

Exercise training adherence

Exercise adherence was assessed by number of sessions attended compared to number of planned sessions (i.e. 3 sessions/week x 9 weeks)

Outcome measurements

All patients were assessed pre-NCRT, after completion of NCRT (week 0/baseline) and at weeks 3, 6 and 9.

Primary Outcome

Physical fitness

The CPET-derived variable, oxygen uptake at anaerobic threshold (VO_2 at AT ($\text{ml.kg}^{-1}.\text{min}^{-1}$), was used to assess physical fitness at all time points. CPET data was reported according to the Perioperative Exercise Testing and Training Society (POETTS) guidelines (which were co-developed by authors SJ and MPG)²⁷. The CPET protocol was identical at each hospital (described elsewhere²²) using the same software and the same metabolic cart (Geratherm Respiratory BmbH, Love Medical Ltd). Final CPET analysis was conducted using the modified V-Slope method by two independent physiological assessors blinded to group allocation, each other and clinical outcomes. Any discrepancies (variance by more than 5% in VO_2 at AT between the first two assessors) were resolved by a third assessor.

Secondary outcome

Health-Related Quality of Life (HRQoL)

HRQoL was assessed by:

(1) Semi-structured interviews: at week 0 (following NCRT) and at week 9 (prior to surgery) to explore patients' perspectives of their HRQoL using methods previously piloted by our group (Fit-4-Surgery)²⁸.

(2) Questionnaires: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; 30 items)²⁹ and EQ-5D-5L³⁰ were administered at the same time-points as CPET.

Exploratory Outcome Measures

Physical activity (PA)

Daily PA measured using a multi-sensory accelerometer (SenseWear Pro® armband (Model MF-SW, display model DD100); BodyMedia, Inc., Pittsburgh, PA, USA) at the same time-points as CPET, measured over 3 consecutive days and nights (72 hours of continuous data). Outcome measures of interest for PA were daily step count and sleep efficiency.

Post-Operative Morbidity Survey (POMS)

Post-operative outcome was objectively recorded using POMS³¹ at days 3, 5, 8 and 15.

Cancer staging

Rectal cancer tumour regression was quantified by MRI assessment using the MRI-based T-staging tumour regression grade (ymrTRG) utilizing the MERCURY group protocol³²⁻³³ and the histopathological tumour regression grading (ypTRG)³⁴.

Safety

All adverse events to CPET or the exercise prehabilitation programme were recorded in the relevant case report forms.

Data analysis

Sample size calculation

A sample of 46 patients was required to detect a difference between groups of $2.0 \text{ ml.kg}^{-1}.\text{min}^{-1} \text{ VO}_2$ at AT using a two-sample t-test at the 5% significance level with 90% power. This was based on a standard deviation of the change in VO_2 at AT of $1.8 \text{ ml.kg}^{-1}.\text{min}^{-1}$ and was inflated to allow for 20% patient drop-out³⁵.

Statistical analyses

Descriptive analyses were carried out to summarise patients' characteristics. Continuous variables are reported as mean (SD) or median and inter-quartile range (IQR), depending on distribution, and categorical variables as frequency (%). The

Shapiro-Wilk test for normality of distributions was applied. The effect of NCRT on physical fitness was assessed using a paired t-test. The primary analysis was intention to treat. For the primary outcome of VO_2 AT (and VO_2 peak), all randomised participants with baseline (week 0) were included. Multiple imputation was used to handle any missing outcome data.

A linear regression model (using age and gender) was used to investigate the effect of the exercise prehabilitation intervention on physical fitness and a 95% confidence interval on the mean difference between the two groups for both unadjusted and baseline-adjusted models. In order to assess the sensitivity of results to covariates a further 'adjusted' effect was calculated using linear regression with age and gender as covariates³⁶. Linear mixed modelling was employed to compare fitness over all time points.

Linear regression models were used to compare overall HRQoL scores between groups and EORTC QLQ-30 sub-scales, and multilevel mixed effects ordinal regression was used to assess EQ-5D-5L sub-scales. Interview data were analyzed using a thematic framework approach²⁸.

The effect of exercise prehabilitation on PA was analysed in the same way as physical fitness. Cancer staging was reported as tumour, node metastasis version 5 (TNM) staging with T3 sub-staging, Response Evaluation Criteria in Solid Tumours (RECIST) and ymrTRG³⁷. Pathological outcomes were graded according to the pathological tumour regression grading (ypTRG) and ypTNM. In our protocol paper²² we stated that we would conduct univariate logistic regression analysis to analyse the association between demographic variables (patient age and sex), MR parameters and pathologic tumour response, to enable the calculation of odds ratios for the probability of an unfavourable pathological outcome, and to analyse the sensitivity, specificity, positive and negative likelihood ratios. However, because of low number of participants in each group who completed NCRT and surgery, this analysis was not performed.

Results

Between October 2013 and December 2016, seventy-eight patients met the inclusion criteria and 38 agreed to participate (Fig. 1). Of the 38 patients recruited, 33 were randomised (16 to the usual care control group and 17 to the exercise prehabilitation group), 25 completed the follow-up assessment at week 9 and 21 underwent surgery. Patient characteristics are presented in Table 1. Sixteen participants received neoadjuvant chemotherapy prior to the standard NCRT regimen whilst the remainder received the standard NCRT regimen. Adherence to the 9-week exercise programme was 91%.

Table 1
Patient Characteristics

	Exercise (n = 17)	Control (n = 16)	Non-randomised (n = 5)
Age (years)	64 (14) ^a	57 (10) ^a	68 (7) ^a
Gender (% Male)	14 (82)	12 (75)	4 (80)
Smoking (%) current	4 (24)	2 (13)	1 (20)
Body mass index (BMI) (kg/m²)	26 (4) ^a	26 (3) ^a	24 (4) ^a
Past medical history			
Heart failure	0 (0)	0 (0)	0 (0)
Diabetes	2 (12)	1 (6)	0 (0)
Ischemic heart disease	0 (0)	0 (0)	0 (0)
Cerebrovascular disease	0 (0)	0 (0)	0 (0)
Cancer staging			
<i>Tumor</i>			
T2	1 (6)	2 (13)	0 (0)
T3/T3a	9 (53)	8 (50)	1 (20)
T3b	2 (12)	2 (13)	0 (0)
T3c	2 (12)	1 (6)	0 (0)
T3d	0 (0)	1 (6)	0 (0)
T4	3 (18)	2 (13)	3 (60)
Missing	0 (0)	0 (0)	1 (20)
<i>Node</i>			
N0	4 (24)	4 (25)	0 (0)
N1	7 (41)	7 (44)	3 (60)
N2	6 (35)	5 (31)	1 (20)
Missing	0 (0)	0 (0)	1 (20)

All data are presented as n (%) mean except for age and BMI which are mean (SD)^a.

Cancer staging is reported using TNM classification (V.5, 1997) with sub-classifications. Central pelvic exenteration included excision of rectum and pelvic side wall +/- lymphadenectomy

	Exercise (n = 17)	Control (n = 16)	Non-randomised (n = 5)
<i>Metastases</i>			
M0	16 (94)	16 (100)	4 (80)
M1	1 (6)	0 (0)	0 (0)
Missing	0 (0)	0 (0)	1 (20)
Operation			
Abdomino-perineal excision	4 (24)	3 (19)	0 (0)
Anterior resection	8 (47)	3 (19)	0 (0)
Central pelvic exenteration	0 (0)	2 (13)	0 (0)
Hartmann's and liver resection	1 (6)	0 (0)	0 (0)
No surgery (Complete responder)	1 (6)	3 (19)	0 (0)
No surgery (Disease progression)	1 (6)	1 (6)	3 (60)
No surgery (Drop-out/withdrawn)	2 (12)	4 (25)	2 (40)
All data are presented as n (%) mean except for age and BMI which are mean (SD) ^a .			
Cancer staging is reported using TNM classification (V.5, 1997) with sub-classifications. Central pelvic exenteration included excision of rectum and pelvic side wall +/- lymphadenectomy			

Primary outcome

Physical fitness

From pre- to post-NCRT, VO_2 at AT significantly decreased in all participants: $-1.3 \text{ ml.kg}^{-1}.\text{min}^{-1}$; 95% CI (0.4, 2.3); $p = 0.008$ (Table 2). Changes in all CPET variables between pre- and post-NCRT are presented in Supplementary Appendix 2, Table 1.

Table 2

Physical fitness, health related quality of life (questionnaires) and physical activity pre- and post-neoadjuvant cancer treatment

	Pre-NCRT, n	Post-NCRT, n	Mean Difference (95% CI)	P-Value
Primary outcome: VO ₂ at AT (ml.kg ⁻¹ .min ⁻¹)	11.7 (3.4),38	11.2 (3),28	1.3 (0.4, 2.3)	0.008 ^a *
VO ₂ at Peak (ml.kg ⁻¹ .min ⁻¹)	21.0 (7.6),38	20.5 (6.2),28	1.7 (-0.1, 3.5)	0.065 ^a
Secondary outcome: EORTC C30 questionnaire (scale scores between 0 and 100 (best))				
<i>Global health status</i>	69.8 (18.3),37	63.7 (16.2),28	7.1 (0.8, 13.5)	0.030 ^a *
<i>Physical functioning</i>	93.3 (80, 100),37	86.7 (73.3, 100),28		0.119 ^b
<i>Emotional functioning</i>	83.3 (66.7, 91.7),37	75.0 (66.7, 91.7),28	1.2 (-4.9, 7.3)	0.740 ^a
<i>Fatigue</i>	22.2 (11.1, 33.3),37	33.3 (22.2, 55.6),28	-16.5 (-26.5, -6.4)	0.002 ^a *
<i>Pain</i>	16.7 (0, 33.3),37	16.7 (0, 33.3),28	-9.3 (-20.1, 1.6)	0.092 ^a
<i>Insomnia</i>	33.3 (0, 33.3),37	33.3 (0, 66.6),28	-11.1 (-20.8, -1.4)	0.026 ^a *
EQ5D questionnaire: Usual Activities	Pre-NCRT, n	Post-NCRT, n	Odds ratio (95% CI)	P-Value
<i>No problems doing usual activity</i>	24 (64.9%),37	14 (50%),28	8.6 (1.4, 52.8)	0.020 ^a *
<i>Slight problems doing my usual activity</i>	11 (29.7%),37	8 (28.6%),28		
<i>Moderate problems doing usual activity</i>	2 (5.4%),37	5 (17.9%),28		
<i>Severe problems doing usual activity</i>	0 (0%),37	1 (3.6%),28		
Self-care				

Data are presented as mean (SD), median (IQR) or n (%). * P < 0.05 was taken as statistically significant. ^a P value following paired sample t-tests; ^b P value following Wilcoxon signed-rank tests.

Abbreviations: VO₂ at AT (oxygen uptake at anaerobic threshold); VO₂ at Peak (oxygen uptake at peak exercise); PA (physical activity); METS (metabolic equivalent threshold); n (sample of patients assessed). Note: physical activity data is mean over 3 days.

	Pre-NCRT, n	Post-NCRT, n	Mean Difference (95% CI)	P-Value
<i>No problems washing or dressing</i>	36 (97.3%),37	26 (92.9%),28	2.4 (0.2, 28.4)	0.476 ^a
<i>Slight problems washing or dressing</i>	1 (2.7%),37	1 (3.6%),28		
<i>Moderate problems washing or dressing</i>	0 (0%),37	1 (3.6%),28		
Pain / Discomfort				
<i>No pain or discomfort</i>	10 (27.0%),37	8 (28.6%),28	0.8 (0.3, 2.4)	0.721 ^a
<i>Slight pain or discomfort</i>	17 (46.0%),37	15 (53.6%),28		
<i>Moderate pain or discomfort</i>	9 (24.3%),37	5 (18.9%),28		
<i>Severe pain or discomfort</i>	1 (2.7%),37	0 (0%),28		
Anxiety / Depression				
<i>Not anxious or depressed</i>	20 (54.1%),37	15 (53.6%),28	0.6 (0.2, 2.2)	0.478 ^a
<i>Slightly anxious or depressed</i>	11 (29.7%),37	11 (39.3%),28		
<i>Moderately anxious or depressed</i>	5 (13.5%),37	1 (3.6%),28		
<i>Severely anxious or depressed</i>	1 (2.7%),37	1 (3.6%),28		
Health scale (between 0 and 100 (best))	73.0 (17.5),37	70.9 (14.4),28	4.2 (-1.4, 9.9)	0.121 ^a
Exploratory outcome: Physical activity				
Step count	5102 (3301, 8275),35	5641 (3602, 8929),25	84.3 (-1340.5, 1509.1)	0.904 ^a
Sleep efficiency (%)	80.2 (71.3, 85.3),33	79.1 (67.5, 82.9),33		0.354 ^b
PA duration (min/day)	43.5 (27, 112.0),35	70.3 (28, 121),25	-0.2 (-20.0, 19.5)	0.982 ^a
Energy expenditure (kcal/day)	2186.6 (655.8),35	2419.8 (593.5),25	-37.5 (-199.8, 124.8)	0.636 ^a

Data are presented as mean (SD), median (IQR) or n (%). * P < 0.05 was taken as statistically significant. ^a P value following paired sample t-tests; ^b P value following Wilcoxon signed-rank tests.

Abbreviations: VO₂ at AT (oxygen uptake at anaerobic threshold); VO₂ at Peak (oxygen uptake at peak exercise); PA (physical activity); METS (metabolic equivalent threshold); n (sample of patients assessed). Note: physical activity data is mean over 3 days.

	Pre-NCRT, n	Post-NCRT, n	Mean Difference (95% CI)	P-Value
Sleep duration (min/day)	417.6 (117.5),35	377.3 (79.6),25	9.6 (-40.9, 60.1)	0.697 ^a
Average METS	1.3 (0.2),34	1.3 (0.2),34	0.02 (-0.07, 0.1)	0.593 ^a
Data are presented as mean (SD), median (IQR) or n (%). * P < 0.05 was taken as statistically significant. ^a P value following paired sample t-tests; ^b P value following Wilcoxon signed-rank tests.				
Abbreviations: VO ₂ at AT (oxygen uptake at anaerobic threshold); VO ₂ at Peak (oxygen uptake at peak exercise); PA (physical activity); METS (metabolic equivalent threshold); n (sample of patients assessed). Note: physical activity data is mean over 3 days.				

The change in VO₂ at AT from baseline to week 9, adjusted for baseline, between treatment groups was + 2.9 ml.kg⁻¹.min⁻¹; (0.8, 5.1); p = 0.011 (Table 3a) (when unadjusted for baseline was + 2.8 (0.6, 5.0); p = 0.014). Sensitivity analysis between treatment groups for a further 'adjusted' effect using linear regression for age and gender was + 3.4 ml.kg⁻¹.min⁻¹; (1.1, 5.7); p = 0.005.

Table 3
a Physical fitness at week 0 and week 9 between exercise and usual care control groups

Physical fitness	Week 0, n	Week 9, n	Difference in endpoint week 9 (95% CI), P-value
Primary outcome:			
VO ₂ at AT (ml.kg ⁻¹ .min ⁻¹)			
<i>Exercise</i>	11.6 (3.4), 15	15.0 (4.2), 13	2.9 (0.8, 5.1), 0.011
<i>Usual care control</i>	10.8 (2.5), 13	11.5 (2.5), 12	
VO ₂ at Peak (ml.kg ⁻¹ .min ⁻¹)			
<i>Exercise</i>	21.4 (7.7), 15	27.1 (8.7), 13	2.7 (-0.4, 5.7) 0.085
<i>Usual care control</i>	19.5 (4.1), 13	22.9 (3.8), 12	
Data are presented as median (IQR). * P < 0.05 was taken as statistically significant. P Value adjusted for baseline following linear regression with the difference between week 9 and week 0.			
Abbreviations: VO ₂ at AT (oxygen uptake at anaerobic threshold); VO ₂ at Peak (oxygen uptake at peak exercise); n (sample of patients assessed).			

Table 3

b Physical fitness, health related quality of life (questionnaires) and physical activity at week 0 and week 9 between exercise and usual care control groups

	Exercise		Control		P-Value
	Week 0, n	Week 9, n	Week 0, n	Week 9, n	
Secondary outcome: EORTC C30 questionnaire (scale scores between 0 and 100 (best))					
<i>Global health status</i>	63.9 (16.6),15	77.8 (13.0),12	63.5 (16.5),13	72 (19.5),11	0.668 ^a
<i>Physical functioning</i>	86.7 (73.3, 100.0),15	100 (86.7, 100.0), 2	86.7 (66.7, 93.3),13	86.7 (86.7, 100),11	0.782 ^b
<i>Emotional functioning</i>	75.0 (66.7, 100.0),15	95.8 (66.7, 100.0),12	75.0 (66.7, 83.3),13	75.0 (50, 83.3),11	0.132 ^a
<i>Fatigue</i>	33.3 (11.1, 55.6),15	11.1 (0.0, 33.3),12	33.3 (22.2, 55.6),13	11.1 (0, 33.3),11	0.603 ^a
<i>Pain</i>	16.7 (0.0, 33.3),15	0 (0.0, 8.3),12	16.7 (16.7, 33.3),13	16.7 (0, 33.3),11	0.708 ^b
<i>Insomnia</i>	33.3 (0.0, 66.7),15	16.7 (0.0, 33.3),12	33.3 (0.0, 66.7),13	33.3 (0, 33.3),11	0.248 ^a
EQ5D questionnaire: Usual Activities					
<i>No problems doing usual activity</i>	8 (53%),15	6 (46%),12	9 (75%),13	7 (64%),11	0.630 ^a
<i>Slight problems doing usual activity</i>	4 (27%),15	4 (31%),12	3 (25%),13	4 (36%),11	
<i>Moderate problems doing usual activity</i>	2 (13%),15	3 (23%),12	0 (0%),13	0 (%),11	
<i>Severe problems doing usual activity</i>	1 (7%),15	0 (0%),12	0 (0%),13	0 (0%),11	
Self-care					
<i>No problems washing/dressing</i>	15 (100%),15	11 (85%),12	12 (100%),13	10 (91%),11	0.491
<i>Slight problems washing/dressing</i>	0 (0%),15	1 (8%),12	0 (0%),13	1 (9%),11	

Data are presented as mean (SD) or median (IQR) except EQ5D data which is presented as n (%). * P < 0.05 was taken as statistically significant. ^aP value following linear regression with the difference between

week 9 and 0 adjusted for baseline; ^b P value following Wilcoxin Mann-Whitney test. Abbreviations: PA (physical activity); METS (metabolic equivalent threshold); n (sample of patients assessed). Note: physical activity data is mean data over 3 days.

	Exercise	Control			P-Value
<i>Moderate problems washing/dressing</i>	0 (0%),15	1 (8%),12	0 (%),13	0 (0%),11	
Pain / Discomfort					
<i>No pain or discomfort</i>	4 (27%),15	4 (31%),12	9 (75%),13	5 (45%),11	0.512 ^a
<i>Slight pain or discomfort</i>	9 (60%),15	6 (46%),12	2 (17%),13	4 (36%),11	
<i>Moderate pain or discomfort</i>	2 (13%),15	3 (23%),12	1 (8%),13	2 (18%),11	
Anxiety / Depression					
<i>Not anxious or depressed</i>	10 (67%),15	5 (38%),12	9 (75%),13	5 (45%),11	0.111 ^a
<i>Slightly anxious or depressed</i>	4 (27%),15	7 (54%),12	3 (25%),13	4 (36%),11	
Moderately anxious or depressed	1 (7%),15	0 (0%),12	0 (0%),13	1 (9%),11	
Severely anxious or depressed	0 (0%),15	1 (8%),12	0 (0%),13	0 (0%),11	
Extremely anxious or depressed	0 (0%),15	0 (%),12	0 (0%),13	1 (9%),11	
Health scale (between 0 and 100 (best))	69.6 (14),15	72.4 (15.2),12	78.8 (14),13	75.1 (20.3),11	0.040 ^a *
Exploratory outcome: Physical activity					
Step count	7058 (4981),12	7023 (5562),11	6321 (3456),13	6749 (2959),12	0.877 ^a
Sleep efficiency (%)	74.5 (8.3),12	72.1 (13.2),11	75.7 (10.5),13	74.4 (12.8),12	0.919 ^a
Energy expenditure (kcal/day)	2467 (676),12	2326 (639),11	2376 (530),13	2424 (559),12	0.145 ^a
PA duration (min/day)	96.9 (79.5),12	89.5 (81.8),11	70.8 (51.2),13	81.2 (43.8),12	0.313 ^a

Data are presented as mean (SD) or median (IQR) except EQ5D data which is presented as n (%). * P < 0.05 was taken as statistically significant. ^aP value following linear regression with the difference between

week 9 and 0 adjusted for baseline; ^b P value following Wilcoxin Mann-Whitney test. Abbreviations: PA (physical activity); METS (metabolic equivalent threshold); n (sample of patients assessed). Note: physical activity data is mean data over 3 days.

	Exercise		Control		P-Value
Sleep duration (min/day)	380.4 (75.7),12	373.9 (82.8),11	374.5 (86.1),13	361.6 (98.5),12	0.803 ^a
Average METS	1.4 (0.2),12	1.4 (0.2),11	1.3 (0.2),13	1.3 (0.2),12	0.525 ^a
Data are presented as mean (SD) or median (IQR) except EQ5D data which is presented as n (%). * P < 0.05 was taken as statistically significant. ^a P value following linear regression with the difference between					
week 9 and 0 adjusted for baseline; ^b P value following Wilcoxin Mann-Whitney test. Abbreviations: PA (physical activity); METS (metabolic equivalent threshold); n (sample of patients assessed). Note: physical activity data is mean data over 3 days.					

Changes in VO₂ at AT throughout the entire cancer journey: pre-NCRT, post NCRT (week 0), week 3, 6 and 9 between the treatment groups is graphically presented in Fig. 2. Changes in all CPET variables between the groups over the 9-week study period are presented in Supplementary Appendix 3, Table 2

Secondary outcomes

HRQoL

(1) HRQoL questionnaires

From pre- to post-NCRT, there was a significant reduction in EORTC Global Health Status – 7.1 (-0.8,-13.5); p = 0.030 and EQ5D usual activities – 8.6 (1.4, 52.8), p = 0.020 (Table 2). There were no other significant changes in HRQoL quantitative measurements between the treatment groups over the 9-week study period (Table 3b).

(2) Semi-structured interviews

From pre- to post-NCRT, the semi-structured interviews revealed that cancer treatment adversely impacted participants HRQoL. Four main themes (each involving subthemes) were identified: physical ill-being, social problems, behavioural/lifestyle disruptions and psychological ill-being. However, participation in the 9-week exercise prehabilitation programme resulted in positive changes in perceptions in HRQoL. Two main themes (each involving subthemes) were identified: physical well-being and psychological well-being i.e (Supplementary 4, Table 3).

Exploratory outcomes

Physical activity

From pre- to post- NCRT, there were no significant differences in daily step count, 95% CI, 84.3 (-1340.5, 1509.1); p = 0.904, or for sleep efficiency median (interquartile range) 80.2 (71.3, 85.3) and week 9: 79.1 (67.5, 82.9), p = 0.354 (Table 2). Direct comparison between treatment groups found no significant

difference between week 9 and week 0 using a linear model adjusted for baseline in daily step count: -46.3 (-2045, 1952); $p = 0.877$, or sleep efficiency: -3.0 (-15.2, 9.3); $p = 0.919$. There were no significant differences between week 9 and week 0 for any other PA outcomes (Table 3b).

POMS and Cancer staging

POMS data for both treatment groups are reported descriptively in Supplementary Appendix 5, Table 4 (no formal analyses were conducted).

The response of NCRT for both treatment groups are reported descriptively in Supplementary Appendix 6 Table 5. Four participants had a complete clinical response and did not undergo any surgery.

Safety

There were no serious adverse events. There was one adverse event attributable to exercise training where a participant sustained a pre-syncope episode following one of the exercise sessions. The participant was reviewed by the hospital medical team and by the patient's own general practitioner, with no pause in exercise training.

Discussion

The EMPOWER trial demonstrates physical fitness levels and HRQoL were significantly reduced following NCRT in people with locally advanced rectal cancer. However, a 9-week exercise prehabilitation programme offered in local treating hospitals initiated following completion of NCRT significantly rescued these outcomes compared to the usual care control group.

Effect on the primary outcome: physical fitness

This trial confirms findings from our previous single-centre study that NCRT significantly reduces physical fitness in this patient population¹¹. Participation in the 9-week exercise programme, following completion of NCRT, had a clinically significant improvement on physical fitness levels. These improvements were evident at week 3 and 6 on repeat CPET's (Fig. 2). Findings may be generalizable to other surgical cancer patients with a shorter time frame between diagnosis and surgery. The increase in physical fitness may have clinical importance as the VO_2 at AT reported at week 9 (pre-surgery) is higher than the previously established cut-off point ($11.1 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) for in-hospital post-operative morbidity³⁸. Of interest, even before initiating NCRT, the physical fitness levels of participants' in the EMPOWER trial was lower than aged-matched healthy counterparts³⁹. Similarly, lower baseline fitness levels have also been reported in a breast cancer study⁴⁰. Future programmes should intervene with an exercise programme during the cancer staging process, as it would allow patients the opportunity to improve physical fitness levels prior to starting NCRT and maintain fitness during NCRT. Although POMS data were recorded, the exploratory nature of the outcome and small sample size preclude quantitative inference. However, currently the WesFit trial (Identifier: NCT03509428) and the PREPARE ABC trial (Identifier: ISRCTN8223315) are currently investigating whether pre-operative exercise training improves post-operative morbidity.

Effects on secondary outcome: health-related quality of life

The EMPOWER trial shows that NCRT adversely impacts HRQoL domains related to physical, psychosocial, and behavioural functioning. Participants reported experiences of physical ill-being, social problems, behavioural/lifestyle disruptions and psychological concerns. The exercise prehabilitation programme however resulted in positive changes in perceptions of physical well-being and psychological well-being. To our knowledge, no other study has explored this apart from our preliminary work in the same population²⁸, where we showed that a 6-week pre-operative exercise training programme promoted positive changes in HRQoL overtime whereby participants experienced improved vitality, a positive attitude, enhanced social connections, and a sense of purpose in life²⁸. Additionally, the EMPOWER trial also shows that the 9-week exercise prehabilitation programme had a significant improvement on participants' health status and usual activities. These positive HRQoL findings at week 9 may be of importance as psychological variables are associated with early surgical recovery⁴¹. To our knowledge, no studies have investigated the effects of exercise prehabilitation on HRQoL and surgical outcome. However, this area is emerging with the development of prehabilitation programmes which aim to optimise physical fitness, nutrition and psychological outcomes pre-operatively.

Effect on the exploratory outcome: physical activity

The EMPOWER trial shows no significant changes in PA following NCRT or the exercise prehabilitation programme. At present, little is known about objective PA levels in this regard. To our knowledge, our pilot study was the first to report this in a non-randomised controlled trial. We showed that NCRT significantly reduced daily step count however participating in a 6-week exercise programme immediately following NCRT significantly increased PA outcome measures sleep efficiency and duration. Contributing factors to the difference in these findings from our pilot study and the EMPOWER trial may be due to the difference in pre-NCRT daily step count (higher in the EMPOWER trial), study design (RCT vs. a non-randomised contemporaneous controlled study) and co-morbidity (50% of participants in the previous pilot study had co-morbid disease compared to 8% in the EMPOWER trial). The PA data in EMPOWER does suggest however that the positive findings presented for physical fitness are attributable to the structured exercise training programme and not due to any significant changes in PA over the 9-week period. Interestingly, in both our initial pilot work and EMPOWER, we reported a low metabolic equivalent threshold (MET) scores across the cancer care pathway (from diagnosis to surgery), suggestive of light intensity activity. This may be clinically important: a MET score of 27 MET-hours per week in men with colorectal cancer is associated with a 50% reduced risk of colorectal cancer-specific mortality and overall mortality, compared with engaging in < 3 MET-hours/week⁴². The MET score at week 0 and week 9 in both groups equates to between 9.1–9.8 MET-hours per week which is almost 60% less than that reported for disease-free survival benefits. Perhaps there's a role for issuing PA monitors at outpatient clinic at the point of cancer diagnosis and educate patients on the importance of moderate intensity PA.

Strengths and weaknesses of this study

Strengths of this multi-centre RCT include a homogeneous group including MRI defined circumferential margin threatened (locally advanced) rectal cancer patients, the novel in-hospital programme with a clearly defined exercise intervention, prescribed individually, with training intensities derived and reported by two assessors. CPET used a constant protocol and software; analysis was by two independent physiological assessors blind to group allocation, all outcome data and independent of the intervention; and the multi-disciplinary team caring for the patients were not provided with any information regarding predictive measures (CPET variables). Additionally, the inclusion of the HRQoL which was collected at the same time points as CPET. PA was measured in an objective manner using validated SenseWear activity monitors; participants in the exercise group did not wear the PA monitors during exercise sessions, allowing for accurate comparisons between the groups. Randomization was computerized. Data were handled using a double-entry data system. The statisticians conducting the analyses were blind to the group allocation until after the analysis was complete.

Weaknesses are that the target sample size was not achieved. This is mainly due to a change in treatment pathways at recruiting sites during the trial conduct: a lower number of patients undergoing long-course NCRT and surgery than originally forecasted became apparent (note: some NHS trusts have a variation of NCRT options for MRI threatened rectal cancer i.e. short course NCRT with a short waiting time to surgery or neoadjuvant systemic chemotherapy prior to NCRT with a variable wait time between the end of NCRT and surgery). To overcome this challenge, the recruitment period was extended for an additional year (from Dec 2015 to Dec 2016) and three additional sites were invited to participate from 2014 to 2015 (recruitment initially started in UHS and UHA in 2013/2014). Therefore, the nature of this underpowered trial increases the false negative rate. Potential weaknesses also lie in the high dropout rate, the heterogeneity of the neoadjuvant CRT regimen (due to a change in clinical treatment pathway during the study period in UHS). Additionally, the recruitment uptake rate was 48%. Although there is limited literature published in the neoadjuvant setting to make comparisons against, one previous study in the same study setting reported a recruitment uptake rate of 56%¹⁶. Additionally, the high risk of performance and detection bias as both participants and personnel were not blinded, and the sample population largely consisted of males.

Conclusions

NCRT significantly reduced physical fitness levels and HRQoL. A 9-week exercise prehabilitation programme initiated following NCRT resulted in a clinical and significant increase in VO_2 at AT and had a positive effect on HRQoL compared to a usual care control group. The findings from the EMPOWER trial informed the WesFit trial that is investigating whether fitness, behaviour change support and emotional support programmes delivered in the community can boost recovery rates after major cancer surgery (in collaboration with Wessex Cancer Alliance). This is the first ever RCT funded trial through the Sustainability and Transformation Partnership Programme.

Abbreviations

AT - anaerobic threshold

CPET – Cardiopulmonary exercise testing

EORTC QLQ-C30 - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

EQ-5D-5L – 5-level EQ-5D questionnaire

HRQoL – Health related quality of life

MET - Metabolic equivalent threshold

MRI – Magnetic resonance imaging

NCRT – Neoadjuvant chemoradiotherapy

NHS – National health service

PA – Physical activity

PEOETTS – Perioperative exercise testing and training society

POMS – Post-operative morbidity survey

RECIST - Response evaluation criteria in solid tumours

TNM - tumour, node metastasis

VO₂ - oxygen uptake

y_{mr}TRG - MRI-based T-staging tumour regression grade

y_pTRG - histopathological tumour regression grading

Declarations

Ethical approval and consent to participate

The trial was approved by North West Centre for Research Ethics Committees (13/NW/0259) and registered with clinicaltrials.gov (NCT01914068).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MPWG, SJ, MAW and GJK conceived the study. LL, MAW, HM, GJK, SMB, TC, PC, CB, PC, TC, DP, MM, MPWG and SJ contributed to the study design. LL, MAW, AB, LH, JV-S and SJ undertook data collection. LL and MAW drafted the manuscript, which underwent revision by all other authors. All authors read and approved the final manuscript.

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Figures

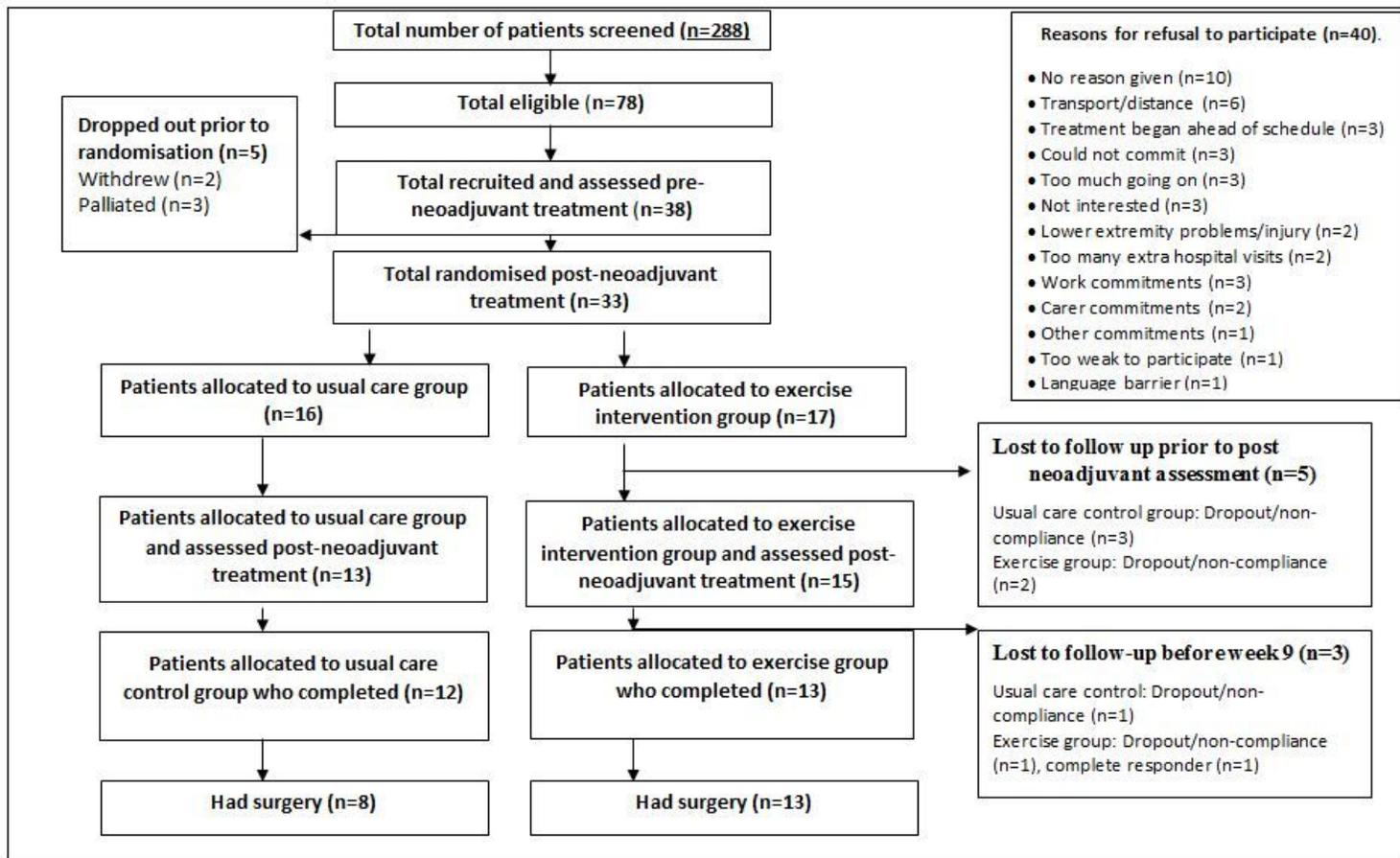


Figure 1

Screening and recruitment algorithm

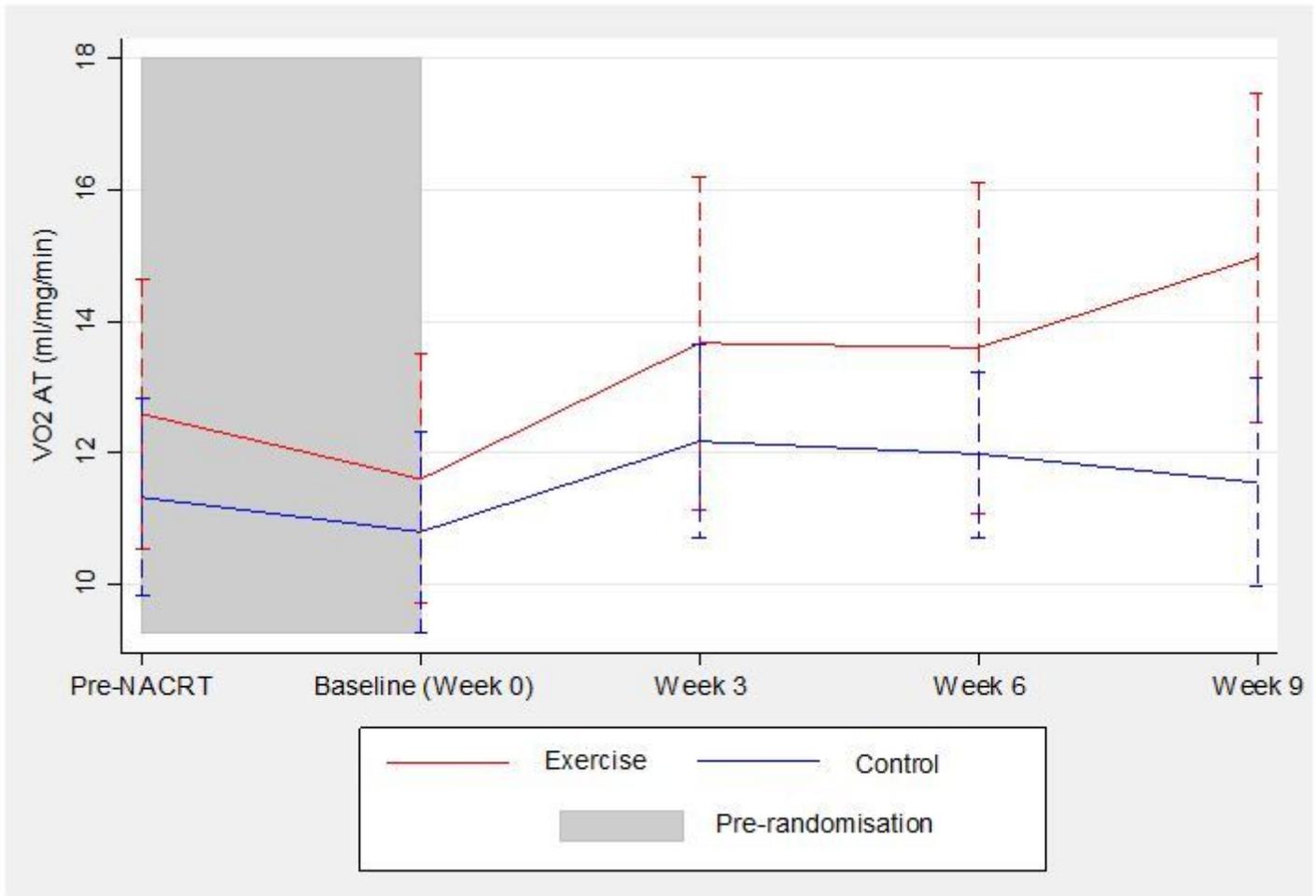


Figure 2

Changes in oxygen uptake at lactate threshold ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) throughout the entire cancer journey: pre-NCRT, post NCRT (baseline/week 0), week 3, 6 and 9 between the exercise group and the usual care control group.

Supplementary Files

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- [SupplementaryAppendix.docx](#)