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ORIGINAL ARTICLE

Exercise prehabilitation may lead to augmented tumor regression following neoadjuvant chemoradiotherapy in locally advanced rectal cancer

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ABSTRACT

Purpose: We evaluate the effect of an exercised prehabilitation programme on tumour response in rectal cancer patients following neoadjuvant chemoradiotherapy (NACRT).
Patients and Methods: Rectal cancer patients with (MRI-defined) threatened resection margins who completed standardized NACRT were prospectively studied in a post hoc, explorative analysis of two previously reported clinical trials. MRI was performed at Weeks 9 and 14 post-NACRT, with surgery at Week 15. Patients undertook a 6-week preoperative exercise-training programme. Oxygen uptake (VO2) at anaerobic threshold (AT) wasmeasured at baseline (pre-NACRT), after completion of NACRT and at week 6 (post-NACRT). Tumour related outcome variables: MRI tumour regression grading (ymrTRG) at Week 9 and 14; histopathological T-stage (ypT); and tumour regression grading (ypTRG)) were compared.
Results: 35 patients (26 males) were recruited. 26 patients undertook tailored exercise-training with 9 unmatched controls. NACRT resulted in a fall in VO2 at AT −2.0 ml/kg^{-1}/min^{-1}(−1.3,−2.6), $p < 0.001$. Exercise was shown to reverse this effect. VO2 at AT increased between groups, (post-NACRT vs. week 6) by +1.9 ml/kg^{-1}/min^{-1}(0.6, 3.2), $p = 0.007$. A significantly greater ypTRG in the exercise group at the time of surgery was found ($p = 0.02$).
Conclusion: Following completion of NACRT, exercise resulted in significant improvements in fitness and augmented pathological tumour regression.

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Introduction

In the United Kingdom, 25% of patients with rectal cancer present with locally advanced disease (cancer threat to the circumferential resection margin on magnetic resonance imaging (MRI)). While surgery is the mainstay of curative treatment for these patients, neoadjuvant chemoradiotherapy (NACRT) has been shown to improve long-term outcomes [1–6]. Typically delivered over 5 weeks (45 Gy in 25 fractions) concomitant with a radiosensitizer (Capecitabine), NACRT aims to promote tumor down-sizing (with a view to potential down-staging), volume reduction and circumferential resection margin clearance [7]. However, there is no clear consensus on the optimal time interval between NACRT and surgery, since the effect of NACRT on tumor size continues for some time following completion of NACRT course, with patients operated up to 15 weeks from the end of their neoadjuvant treatment [8–10].

Though effective in controlling pelvic disease, NACRT causes reduction in objectively measured physical fitness [11] that is in turn associated with increased postoperative surgical morbidity [11]. Previous work from our group has shown that in patients who have undergone NACRT, a 6-week structured responsive tailored exercise training (SRETP) program significantly rescues fitness and *in vivo* mitochondrial function to baseline levels [12,13].

The physiological mechanisms through which exercise improves fitness are complex and incompletely understood, but it is widely accepted that there are local muscle, cardiovascular and whole body effects following an acute bout of exercise, with alterations in circulating antioxidant levels, increased muscle angiogenesis and myogenesis, release of myokines and redox balance shifts [14–16]. Since tumor growth involves neo-angiogenesis, tissue proliferation, and alterations in cellular redox state, while NACRT-mediated tumor effects involve the

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mitigation of such processes, we considered it important to ensure that our exercise intervention did not decrease the efficacy of NACRT or promote tumor growth. We therefore undertook a *post hoc* exploratory analysis of two previously published trials [12,13], to interrogate the impact of an exercise intervention on tumor regression in a cohort of locally advanced rectal cancer patients following NACRT.

Material and methods

Patients and study design

This is a *post hoc* explorative analysis of data from two prospective interventional trials [12,13] approved by the North West – Liverpool East Research and Ethics Committee (11/H1002/12) and registered with ClinicalTrials.gov (NCT01325909 and NCT01859442). Written informed consent was obtained from all patients. Additional consent was sought for a pre-operative MRI and inclusion in these analyses. We recruited patients between August 2012 and August 2014 referred to the Colorectal Multi-Disciplinary Team (MDT), age $\geq$18 years, with locally advanced (circumferential resection margin threatened – defined as tumor within 1 mm of the mesorectal fascia or if any T3/4 tumor was arising at $<$5 cm from the anal verge) resectable rectal cancer, scheduled for standardized NACRT on the basis of Tumor, Node, Metastasis (TNM) classification $>$ T2/N + with no distant metastasis [17] and WHO Performance Status $<$ 2 [18]. Exclusion criteria were: inability to give informed consent, non-resectable disease, and patients who declined surgery or NACRT, or who received nonstandard NACRT.

Consenting patients underwent tumor staging (methodology reported elsewhere [12,13]) and completed 5 weeks of NACRT with periodic cardiopulmonary exercise testing (CPET) to evaluate physiological responses and to tailor the responsive exercise intervention (methodology of the standardized chemoradiotherapy regime is reported elsewhere [12]). No patients received brachytherapy. Immediately after NACRT, patients were allocated to the exercise-training group by default. Patients unable to commit to the exercise schedule (residing $>$15miles from the hospital) were asked to act as contemporaneously recruited controls (no exercise intervention) with the same CPET follow-up. At 9 weeks post-NACRT, patients were restaged using chest, abdomen and pelvic CT and pelvic MRI as per local standard of care rectal cancer pathway. At 14 weeks, post-NACRT patients were restaged using pelvic MRI (additional research scan), prior to surgery at week 15.

Cardiopulmonary exercise testing protocol and exercise intervention

The CPET protocol followed the consensus clinical guidelines on conduct and physiological interpretation defined by the Perioperative Exercise testing and Training Society [19]. The exercise intervention is described in Appendix 1 according to Consensus on Exercise Reporting Template (CERT) [20]. The same method was used for participants during both trials. Exercise adherence is calculated as a percentage of prescribed exercise sessions that were completed by trial participants.

Patients in the exercise group were classified as responders or non-responders to the exercise intervention (responder definition was an increase in oxygen uptake (VO_2) at anaerobic threshold (AT) $\geq$2.0 ml·kg^{-1}·min^{-1} between post-NACRT and week 6). Pre-operative CPETs were analyzed by two CPET accredited clinicians, blinded to patient intervention group allocation and any outcome measure. If interpretation of AT varied by $>$0.5 ml·kg^{-1}·min^{-1}, the CPET was analyzed by a third adjudicator.

MRI technique and image analyses

MRI acquisition technique was performed as described by Patel et al. [21,22]. MR images were reviewed independently both centrally and locally, blinded to each other, the patient intervention group allocation and any other outcome measure. MR image analysis was carried out, using the terms ymrT (T stage on MRI images obtained after NACRT), ymrTRG (tumor regression grade on MRI images obtained after NACRT), ypT (T stage on post-treatment histopathological examination of the resection specimen) and ypTRG (tumor regression grade on post-treatment histopathological examination of the resection specimen) to describe the data [21,23]. The MRI protocol and image analyses are reported elsewhere [24].

Surgical resection

All patients underwent total mesorectal excision (TME) [25] with or without abdominoperineal excision, performed 15 weeks (±4 days) after the completion of NACRT.

Histopathology assessment

After surgical resection, the specimen was fixed in formalin for 48 h, cross-sectioned into 3–5 mm slices, and histologically sampled. A predefined protocol assessed pathological complete response, with a minimum of five blocks of tumor taken. If no tumor was found on the first set of hematoxylin and eosin sections, the rest of the tumor area was embedded, and if no tumor was seen then a final three levels were taken through each block to look for tumor to confirm a complete response. Each specimen was graded by degree of tumor regression, according to the Dworak system and also by ypT stage. As well as grading and staging by the five-point ypTRG and TNM version 7 systems, a simplified pathological grading of favorable and unfavorable pathology was also undertaken. Favorable pathology was defined as ypT stages 0, 1, 2 and 3a or ypTRG stages 3 and 4. Unfavorable pathology was defined as ypT stages 3b, c, d, and 4 or ypTRG stages 0, 1 and 2. ypT3a was included in the favorable group as these

Table 1. Patient demographics.

	Exercise $N = 26$	Control $N = 9$	p Value
Age	64.8 (10.5)	70.2 (8.2)	.23
Sex (male)	17 (65.4)	9 (100.0)	**.04**
WHO performance status			
0	21 (80.8)	7 (77.8)	.74
1	5 (19.2)	1 (11.1)	
2	0 (0.0)	1 (11.1)	
Past medical history			
Alcohol	6 (23.1)	4 (44.4)	.22
Currently smoking	10 (38.5)	3 (33.3)	.84
Diabetes	2 (7.7)	1 (11.1)	.83
Ischemic heart disease	5 (19.2)	2 (22.2)	.84
Heart failure and cerebrovascular disease	3 (11.5)	0 (0.0)	.35
ASA status			
Healthy	14 (53.8)	2 (22.2)	.15
Mild systemic disease	10 (38.5)	6 (66.7)	
Severe systemic disease	2 (7.7)	1 (11.1)	
POSSUM score[a]	3.3 (1.1)	9.1 (5.9)	**<.001**
POSSUM – physiology score[a]	8.0 (1.7)	9.3 (2.2)	.12
POSSUM – operative severity score[a]	11 (8, 12)	11.5 (11, 12)	.06

ASA: American Society of Anaesthesiologists score.
Values are *n* (%), mean [a](SD) or median (IQR).
Bold values significance *p* value.

tumors have been shown to have a similar prognostic outcome as ypT2 tumors [26,27].

Statistical analysis

Central reviewer (Royal Marsden; GB) data were used for the primary analysis based on validated methodology also used by Patel et al. [21,24]. Data were described as frequency (percentage) and mean (SD), with 95% confidence intervals (95%CIs), as appropriate. To analyze the association between demographic variables (age and sex), CPET parameters (VO_2 at AT and VO_2 at peak exercise), MRI parameters (ymrT, ymrTRG, volume change) and pathologic tumor response (ypT and ypTRG), univariate logistic regression analysis or Fischer's exact test was used. Univariate logistical regression models with ypT, ypTRG, ymrT and ymrTRG as outcomes, and explanatory variables exercise/control were undertaken. Linear regression models using ymrTRG, ypTRG and ypT as continuous variables were undertaken. Logistic regression enabled calculation of odds ratio (OR) along with 95%CIs where possible. In addition to an intention to treat analyses a per protocol analysis was carried out excluding five patients who deviated from the MRI reporting protocol due to technical MR sequence acquisition standards and one patient in the control group whose VO_2 at AT improved by more than $2.0\,ml{\cdot}kg^{-1}{\cdot}min^{-1}$ between post-NACRT and week 6. Two-tailed $p<.05$ was considered statistically significant unless specified otherwise. Calculations were performed using Statistical Package for Social Sciences program, version 22.0 (SPSS, IBM, Armonk, NY, USA) and Stata, version 11.2 (StataCorp, College Station, TX, USA). A sample size calculation based on changes in fitness variables was undertaken for the main trial [12]. As these interesting observations arise from *post hoc* analyses they should be treated as feasibility data to power future work.

Results

Twenty (exercise group) and three patients (control group) from West et al. [12] and six (exercise group) and six (control group) patients from West et al. [13] consented for a pre-operative research MRI scan and were included in these analyses. Baseline patient characteristics are reported in Table 1. Tumor characteristics; MRI parameters (ymrT, ymrTRG, volume change) and their changes at weeks 9 and 14, together with histopathological tumor responses and outcomes (ypT and ypTRG) and tumor outcomes are reported elsewhere [24], with a limited summary provided in Table 2.

T stage, tumor regression grading and volume change at week 9 and week 14 on MRI images obtained after NACRT

Univariate logistical regression models of age, gender, ymrT, ymrTRG and volume change at week 9 and week 14 compared to ypT and ypTRG histopathology grading are reported elsewhere [24].

Changes in objectively measured fitness over time in both exercise and control groups

Table 2 reports changes in selected CPET variables (VO_2 at AT and VO_2 at peak exercise) over time between the exercise and control groups. Figure 1 depicts changes in VO_2 at AT over the whole study period. NACRT was associated with a mean decrease in VO_2 at AT of $-2.0\,ml{\cdot}kg^{-1}{\cdot}min^{-1}$ ($p<.0001$ 95%CI −1.3 to −2.6) and VO_2 at peak of $-3.4\,ml{\cdot}kg^{-1}{\cdot}min^{-1}$ ($p<.0001$ 95%CI −4.7 to −1.9) across the cohort. Exercise was associated with a significant rescue in these parameters (VO_2 change) (VO_2 at AT $+2.3\,ml{\cdot}kg^{-1}{\cdot}min^{-1}$ ($p<.0001$; 95%CI 1.52–2.95) and VO_2 at peak $+3.0\,ml{\cdot}kg^{-1}{\cdot}min^{-1}$ ($p=.0004$ 95%CI 1.48–4.46). Sixteen patients of 26 in the exercise group were classified as exercise responders ($2.3\,ml{\cdot}kg^{-1}{\cdot}min^{-1}$ (SD 1.0)).

A total of 98% of the sessions were completed by participants, according to the prescription. There were no missed neoadjuvant chemo- or radiotherapy sessions due to the exercise and no attributable adverse events.

Tumor outcomes and exercise response

Tables 3 and 4 show MRI (ymrTRG and ymrT stage at weeks 9 and 14) and histopathological outcomes (ypT and ypTRG) in the exercise and control groups, with data treated as either categorical (Table 3) or continuous (Table 4).

There was no significant difference in ymrTRG between exercise and control groups at week 9 (continuous data; OR −0.2 95%CI −1.0 to 0.7, $p=.7$, categorical data; OR 2.2 95%CI 0.4–10.5, $p=.3$) or week 14 (continuous data; OR −0.9 95%CI −1.9 to 0.1, $p=.1$, categorical data; OR 4.4 95%CI 0.8–23.9, $p=.09$). A linear mixed model comparing ymrTRG in both groups over time showed a significant time effect (coefficient

Table 2. Tumor staging and exercise variable characteristics.

	Exercise N = 26	Control N = 9
Height of primary tumor (from anal verge)		
Low (0–5 cm)	11 (42.3)	7 (77.8)
Medium/high (>5 cm)	15 (57.7)	2 (22.2)
mrT-stage		
T2	5 (19.2)	3 (33.3)
T3a	6 (23.1)	1 (11.1)
T3b	3 (11.5)	1 (11.1)
T3c	6 (23.1)	0 (0.0)
T3d	2 (7.7)	1 (11.1)
T4a	3 (11.5)	3 (33.3)
T4b	1 (3.9)	0 (0.0)
ymrT-stage		
Week 9		
T0	2 (7.7)	2 (22.2)
T1	1 (3.9)	0 (0.0)
T2	8 (30.8)	2 (22.2)
T3a	7 (27.0)	0 (0.0)
T3b	3 (11.5)	1 (11.1)
T3c	3 (11.5)	0 (0.0)
T3d	0 (0.0)	1 (11.1)
T4a	2 (7.7)	3 (33.3)
Week 14		
T0	5 (19.2)	2 (22.2)
T1	5 (19.2)	0 (0.0)
T2	5 (19.2)	1 (11.1)
T3a	5 (19.2)	2 (22.2)
T3b	3 (11.5)	1 (11.1)
T3c	0 (0.0)	1 (11.1)
T3d	1 (3.9)	0 (0.0)
T4a	2 (7.7)	2 (22.2)
ymrTRG		
Week 9		
1	1 (3.9)	2 (22.2)
2	9 (34.6)	1 (11.1)
3	9 (34.6)	2 (22.2)
4	7 (26.9)	3 (33.3)
5	0 (0.0)	1 (11.1)
Week 14		
1	8 (30.8)	2 (22.2)
2	9 (34.6)	1 (11.1)
3	5 (19.2)	2 (22.2)
4	3 (11.5)	2 (22.2)
5	1 (3.9)	2 (22.2)
Volume change		
Week 9		
<60%	6 (23.1)	3 (33.3)
60–80%	8 (30.8)	3 (33.3)
>80%	7 (26.9)	3 (33.3)
Missing	5 (19.2)	0 (0.0)
Week 14		
<60%	2 (7.7)	2 (22.2)
60–80%	4 (15.4)	2 (22.2)
>80%	15 (57.7)	5 (55.6)
Missing	5 (19.2)	0 (0.0)
ypT-stage		
T0	7 (26.9)	1 (11.1)
T1	1 (3.9)	1 (11.1)
T2	6 (23.1)	1 (11.1)
T3	3 (11.5)	0 (0.0)
T3a	2 (7.7)	4 (44.4)
T3b	2 (7.7)	0 (0.0)
T4a	0 (0.0)	1 (11.1)
T4b	3 (11.5)	1 (11.1)
Missing	2 (7.7)	0 (0.0)
ypTRG		
0	1 (3.9)	2 (22.2)
1	5 (19.2)	3 (33.3)
2	4 (15.4)	2 (22.2)
3	7 (26.9)	1 (11.1)
4	7 (26.9)	1 (11.1)
Missing	2 (7.7)	0 (0.0)
Exercise variables		
VO_2 at AT ($ml \cdot kg^{-1} \cdot min^{-1}$)[a]		
Pre-NACRT	12.4 (3.0)	11.9 (2.9)
Week 0 (post-NACRT)	10.4 (2.5)	10.0 (3.8)
Week 6	12.7 (2.9)	10.5 (3.1)
Week 9	12.9 (3.7)	10.6 (2.5)
Week 14	12.09 (2.9)	10.0 (1.7)
VO_2 at peak ($ml \cdot kg^{-1} \cdot min^{-1}$)[a]		
Pre-NACRT	19.4 (5.8)	18.5 (3.9)
Week 0 (post-NACRT)	16.1 (4.2)	14.9 (5.4)
Week 6	19.1 (4.7)	16.4 (4.6)
Week 9	19.3 (5.5)	16.2 (4.2)
Week 14	18.7 (4.5)	15.8 (4.2)

Values are *n* (%), mean [a](SD) or median (IQR).
ASA: American Society of Anaesthesiologists score; MR: magnetic resonance scan; AT: anaerobic threshold; VO_2: oxygen uptake; NACRT: neoadjuvant chemoradiotherapy; ITT: intention to treat; OR: odds ratio; 95%CI: 95% confidence interval.
Tumor stage at baseline on MR (mrT-stage). Tumor regression grade on MR (ymrTRG). Tumor stage at post-NACRT MR (ymrT-stage). Postoperative tumor stage pathology (ypT-stage). Postoperative pathological tumor regression stage (ypTRG).

0.8 95%CI −1.4 to −0.1, p=.02) (Figure 2). At the time of surgery, there was significantly greater histological tumor regression in the exercise group (continuous data OR 1.2 95%CI 0.2–2.2, p=.02, categorical data; OR 8.5 95%CI 1.4–51.5, p=.02). This tumor regression did not result in a significant difference in ypT-stage (continuous data; OR −1.3 95%CI −3.9 to 1.3, p=.3, categorical data; OR 1.1 95%CI 0.2–6.9, p=.9).

Discussion

This post hoc analysis of two prospective clinical trials provides exploratory evidence that undergoing a structured exercise program following NACRT may be associated with greater tumor regression at the time of surgery. To our knowledge, this is the first clinical study that has observed a significant increase in tumor regression following an exercise intervention in a patient group that has undergone NACRT. These findings could inform sample size calculations for an adequately powered, prospective study to investigate the validity of these results.

While we cannot prove causation, there is biological plausibility in suggesting an effect of exercise in augmenting tumor regression, and possibly improved chemoradiotherapy efficacy. It is now well established that physical activity decreases the risk of developing multiple cancers [28,29] and has also been associated with lower rates of recurrence and cancer-specific deaths [30–32]. However, a potential benefit of exercise in established cancer has been suggested. Preclinical studies in breast and prostate cancer clearly document the modulation of tumor hypoxia, angiogenesis, blood flow and the tumor microenvironment [16,33–38]; however, evidence in a clinical population remains elusive. In a murine model of lung cancer, daily cardiovascular exercise appeared to mitigate the growth

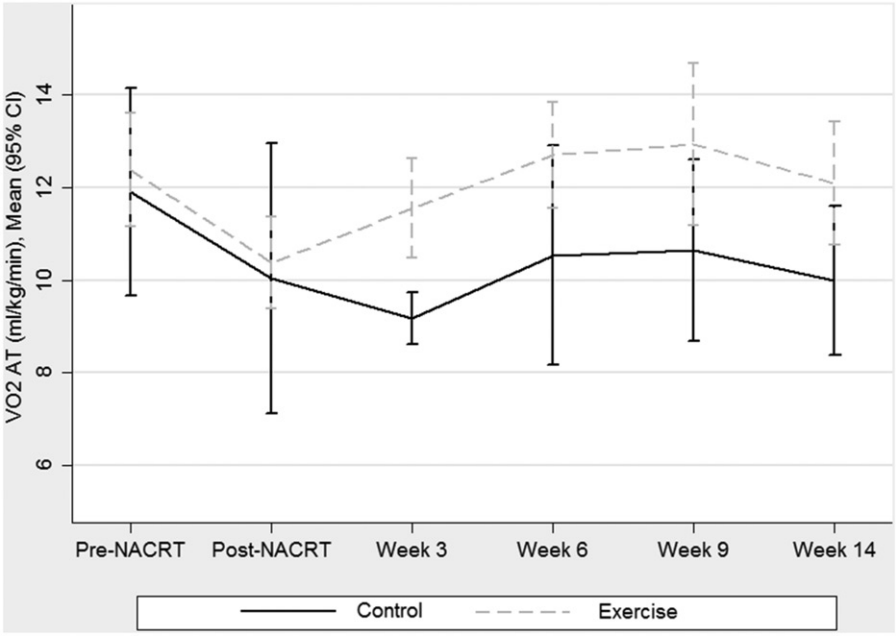

Figure 1. Line diagram showing fitted means and 95%CI for VO_2 at LT ($ml \cdot kg^{-1} \cdot min^{-1}$) for the exercise and control groups.

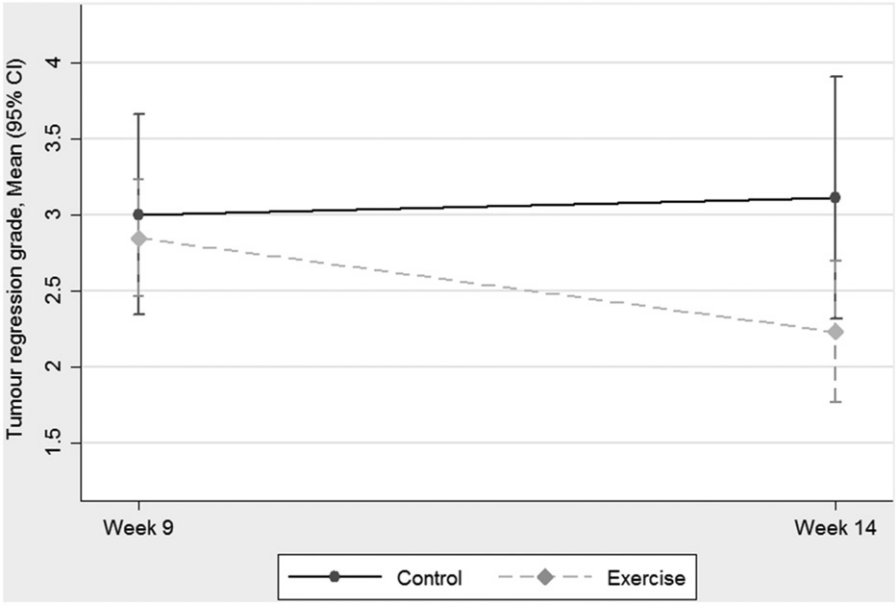

Figure 2. A line diagram showing fitted means and 95%CI for ymrTRG for exercise and control groups.

of adenocarcinoma possibly through activation of p53 tumor suppressor function and increased apoptosis [39]. Meanwhile, immunotherapy is increasingly sought as a means of chemotherapy, with new understanding that tumors evolve to evade immune recognition, such that immune escape is now considered a 'hallmark of cancer'. Exercise is immune-modulatory [40,41] and conceivably may induce immune cell recruitment to tumor microenvironments. Further, radiotherapy acts to prime the immune system against cancer cells via immunogenic cell death [42]; exercise may potentiate this effect leading to greater tumor regression. The tumor and surrounding microenvironment is exposed to oxidative stress following radiotherapy; exercise is known both to increase oxidative and reductive stress after acute bouts of strenuous activity [43–46] but can act as an overall antioxidant in increasing average levels of circulating antioxidants including superoxide dismutase, glutathione and catalase [47]. An effect of exercise on radiosensitized cells could also be related to improved vascular supply [48], insulin sensitivity [49] or cytokine profile [50].

The increased tumor regression observed in the overall patient cohort as previously described [24], was not apparent when analyzed in their assigned exercise and control groups. This may be due to the fact that ymrTRG is changing over time, such that the exercise group shows a progressive decrease in ymrTRG between weeks 9 and 14 (Figure 2) that does not reach significance when between

Table 3. MRI (ymrTRG and ymrT stage at weeks 9 and 14) and histopathological outcomes (ypT and ypTRG) in the exercise and control groups, with data treated as categorical variables.

Outcome variable	Explanatory variable	OR (95%CI)	*p* Value
ymrTRG outcomes			
Week 9	*Exercise/control*		
	ITT	2.2 (0.4, 10.5)	.3
	Per protocol	2.5 (0.5, 13.4)	.3
	Responder/control		
	ITT	2.4 (0.4, 13.6)	.3
	Per protocol	3.0 (0.4, 20.2)	.3
Week 14	*Exercise/control*		
	ITT	4.4 (0.8, 23.9)	.09
	Per protocol	6.0 (0.9, 38.1)	.06
	Responder/control		
	ITT	5.6 (0.8, 40.6)	.09
	Per protocol	11.0 (0.9, 130.3)	.06
ymrT-stage			
Week 9	*Exercise/control*		
	ITT	2.8 (0.6, 13.3)	.2
	Per protocol	1.6 (0.3, 8.4)	.6
	Responder/control		
	ITT	3.8 (0.7, 21.3)	.1
	Per protocol	2.0 (0.3, 12.5)	.5
Week 14	*Exercise/control*		
	ITT	2.7 (0.5, 13.2)	.2
	Per protocol	1.9 (0.3, 11.0)	.5
	Responder/control		
	ITT	2.4 (0.4, 13.6)	.3
	Per protocol	1.8 (0.3, 12.5)	.6
Pathology outcomes			
ypTRG	*Exercise/control*		
	ITT	8.5 (1.4, 51.5)	**.02**
	Per protocol	6.5 (1.0, 42.2)	**.05**
	Responder/control		
	ITT	12.8 (1.7, 97.2)	**.01**
	Per protocol	12.0 (1.3, 111.3)	**.03**
ypT-stage	*Exercise/control*		
	ITT	1.1 (0.2, 6.9)	.9
	Per protocol	1.3 (0.2, 8.7)	.8
	Responder/control		
	ITT	1.7 (0.2, 15.0)	.6
	Per protocol	3.0 (0.2, 40.9)	.4

Tumor stage at baseline on MR (mrT-stage). Tumor regression grade on MR (ymrTRG). Tumor stage at post-NACRT MR (ymrT-stage). Postoperative tumor stage pathology (ypT-stage). Postoperative pathological tumor regression stage (ypTRG).
ITT: intention to treat; OR: odds ratio; 95%CI: 95% confidence interval.
Bold values significance *p* value.

Table 4. MRI (ymrTRG and ymrT stage at weeks 9 and 14) and histopathological outcomes (ypT and ypTRG) in the exercise and control groups, with data treated as continuous variables.

Variable	Regression coefficient (95%CI)	*p* Value	*R*-squared
ymrTRG outcomes			
Week 9			
Exercise/control			
ITT	−0.2 (−1.0, 0.7)	.7	0.005
Per protocol	−0.2 (−1.2, 0.7)	.6	0.01
Responder/control			
ITT	−0.2 (−1.1, 0.8)	.7	0.01
Per protocol	−0.3 (−1.5, 0.8)	.6	0.02
Week 14			
Exercise/control			
ITT	−0.9 (−1.9, 0.1)	.1	0.09
Per protocol	−1.0 (−2.2, 0.1)	.07	0.1
Responder/control			
ITT	−0.8 (−1.9, 0.3)	.1	0.1
Per protocol	−1.0 (−2.3, 0.2)	.09	0.1
ymrT-stage			
Week 9			
Exercise/control			
ITT	−1.1 (−3.3, 1.1)	.3	0.03
Per protocol	−1.1 (−3.7, 1.5)	.4	0.03
Responder/control			
ITT	−1.5 (−3.9, 0.8)	.2	0.07
Per protocol	−1.8 (−4.7, 1.2)	.2	0.08
Week 14			
Exercise/control			
ITT	−1.4 (−3.7, 0.8)	.2	0.05
Per protocol	−1.7 (−4.1, 0.8)	.2	0.07
Responder/control			
ITT	−1.3 (−3.8, 1.1)	.3	0.05
Per protocol	−1.8 (−4.6, 0.9)	.2	0.1
Pathology outcomes			
ypTRG			
Exercise/control			
ITT	1.2 (0.2, 2.2)	**.02**	0.2
Per protocol	1.3 (0.1, 2.4)	**.03**	0.2
Responder/control			
ITT	1.4 (0.4, 2.4)	**.01**	0.3
Per protocol	1.6 (0.4, 2.8)	**.01**	0.3
ypT-stage			
Exercise/control			
ITT	−1.3 (−3.9, 1.3)	.3	0.03
Per protocol	−1.9 (−4.7, 0.9)	.2	0.07
Responder/control			
ITT	−1.8 (−4.4, 0.8)	.2	0.09
Per protocol	−2.9 (−5.6, −0.2)	**.04**	0.2

ITT: intention to treat; OR: odds ratio; 95%CI: 95% confidence interval.
Per protocol: excludes five patients who did not follow MRI acquisition protocol and one patient in the control group whose VO_2 at LT improved by more than 2.0 $ml \cdot kg^{-1} \cdot min^{-1}$ between post-NACRT and week 6.
Tumor stage at baseline on MR (mrT-stage). Tumor regression grade on MR (ymrTRG). Tumor stage at post-NACRT MR (ymrT-stage). Postoperative tumor stage pathology (ypT-stage). Postoperative pathological tumor regression stage (ypTRG).
Bold values significance *p* value.

group testing is performed. Extending the MRI imaging to beyond week 15 may have revealed a significant difference between groups. An alternative explanation might be that the significant deviations from MRI acquisition protocol incurred a type 2 error. Five subjects in the exercise group had an MRI acquisition protocol deviation. Excluding these from analysis, a *per protocol* analysis (also excluding the responder in the control group) revealed a trend toward a decrease in tumor size in the exercise group compared to the control group, though the difference remained non-significant at week 14 (continuous data; OR −1.0 95%CI −2.2 to 1.1, p=.07, categorical data; OR 4.4 95%CI 0.9–38.1, p=.06).

Limitations to this study

The main limitations in this study are the small cohort size, intervention participation was on a voluntary basis and the lack of matched controls with similar sample size. This analysis was performed as an explorative *post hoc* sub-group analysis from a larger published clinical patient cohort which was not powered to detect a significant change in tumor size in association with exercise, exposing analyses to possible type 2 and type 1 errors. Moreover, these findings were discovered with these post hoc intentions to treat and per protocol analyses presented in this study, after publication of findings in West et al. [24]. The findings need to be replicated in an appropriately powered study to confirm our preliminary observations which our group have recently undertaken [51].

No mechanistic investigations were included in the design of this study and so we can offer no insight on possible

causation or mechanism of any relationship between exercise and tumor response to NACRT. Further work is required in establishing whether causation exists in the relationship, and its scientific basis.

Confirmation of an effect of exercise in augmenting chemoradiotherapy would have significant impact on treatment pathways in rectal cancer patients, establishing structured exercise as a legitimate anti-cancer therapy in addition to its role in pre-surgical optimization. Understanding the mechanism by which exercise works to augment NACRT would allow training programs to be tailored to individuals to achieve the appropriate response and possibly provide new pharmacotherapeutic targets for patients undergoing exercise programs.

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