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

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**Short title** – **Augmented tumour regression with exercise following chemoradiotherapy in rectal cancer.**

**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) was measured 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 fitnessand augmented pathological tumour regression.

**Keywords**

Magnetic resonance imaging, surgery, rectal cancer, tumour regression grade, exercise, neoadjuvant chemoradiotherapy, prehabilitation

**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)). Whilst 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 (45Gy in 25 fractions) concomitant with a radiosensitiser (Capecitabine), NACRT aims to promote tumour 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 tumour 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) programme 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 tumour growth involves neo-angiogenesis, tissue proliferation, and alterations in cellular redox state, whilst NACRT-mediated tumour effects involve the mitigation of such processes, we considered it important to ensure that our exercise intervention did not decrease the efficacy of NACRT or promote tumour growth. We therefore undertook a *post hoc* exploratory analysis of two previously published trials, to interrogate the impact of an exercise intervention on tumour regression in a cohort of locally advanced rectal cancer patients following NACRT.

# PATIENTS 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 ≥18 years, with locally advanced (circumferential resection margin threatened – defined as tumour within 1 mm of the mesorectal fascia or if any T3/4 tumour was arising at <5 cm from the anal verge) resectable rectal cancer, scheduled for standardized NACRT on the basis of Tumour, 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 non-standard NACRT.

Consenting patients underwent tumour staging (methodology reported elsewhere (12,13)) and completed 5 weeks of NACRT with periodic 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 (VO2) at anaerobic threshold (AT) ≥2.0 ml.kg-1.min-1 between post-NACRT and week 6).

*MRI Technique and Image Analyses*

MRI acquisition technique was performed as described by Patel and colleagues (21,22). MR images were reviewed both centrally and locally. MR image analysis was carried out, using the terms ymrT (T stage on MRI images obtained after NACRT), ymrTRG (tumour regression grade on MRI images obtained after NACRT), ypT (T stage on post-treatment histopathological examination of the resection specimen), and ypTRG (tumour 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 5 blocks of tumour taken. If no tumour was found on the first set of haematoxylin and eosin sections the rest of the tumour area was embedded, and if no tumour was seen then a final three levels were taken through each block to look for tumour to confirm a complete response. Each specimen was graded by degree of tumour 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 favourable and unfavourable pathology was also undertaken. Favourable pathology was defined as ypT stages 0, 1, 2, and 3a or ypTRG stages 3 and 4. Unfavourable pathology was defined as ypT stages 3b, c, d, and 4 or ypTRG stages 0, 1, and 2. ypT3a was included in the favourable group as these tumours have been shown to have a similar prognostic outcome as ypT2 tumours (26,27).

*Statistical Analysis*

Central reviewer (Royal Marsden; GB) data was used for the primary analysis based on validated methodology also used by Patel and colleagues (21,24). Data were described as frequency (percentage) and mean (SD), with 95% confidence intervals (95%CIs), as appropriate. To analyse the association between demographic variables (age and sex), CPET parameters (VO2 at AT and VO2 at peak exercise), MRI parameters (ymrT, ymrTRG, volume change) and pathologic tumour 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 5 patients who deviated from the MRI reporting protocol due to technical MR sequence acquisition standards and 1 patient in the control group whose VO2 at AT improved by more than 2.0 ml.kg-1.min-1 between post-NACRT and week 6. Two-tailed p<0.05 was considered statistically significant unless specified otherwise. Calculations were performed using Statistical Package for Social Sciences program, version 22.0 (SPSS, IBM, USA) and Stata, version 11.2 (StataCorp. College Station, TX). 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 3 patients (control group) from West et al (12) and 6 (exercise group) and 6 (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. Tumour characteristics; MRI parameters (ymrT, ymrTRG, volume change) and their changes at week 9 and 14, together with histopathological tumour responses and outcomes (ypT and ypTRG) and tumour outcomes are reported elsewhere (24), with a limited summary provided in table 2.

*T stage, tumour 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 (VO2 at AT and VO2 at peak exercise) over time between the exercise and control groups. Figure 1 depicts changes in VO2 at AT over the whole study period. NACRT was associated with a mean decrease in VO2 at AT of -2.0 ml.kg-1.min-1 (p<0.0001 95%CI -1.3 to -2.6) and VO2 at peak of -3.4 ml.kg-1.min-1 (p<0.0001 95%CI -4.7 to -1.9) across the cohort. Exercise was associated with a significant rescue in these parameters (VO2 change) (VO2 at AT +2.3 ml.kg-1.min-1 (p<0.0001; 95%CI 1.52 to 2.95) and VO2 at peak +3.0 ml.kg-1.min-1 (p=0.0004 95%CI 1.48 to 4.46). Sixteen patients of 26 in the exercise group were classified as exercise responders (2.3 ml.kg-1.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.

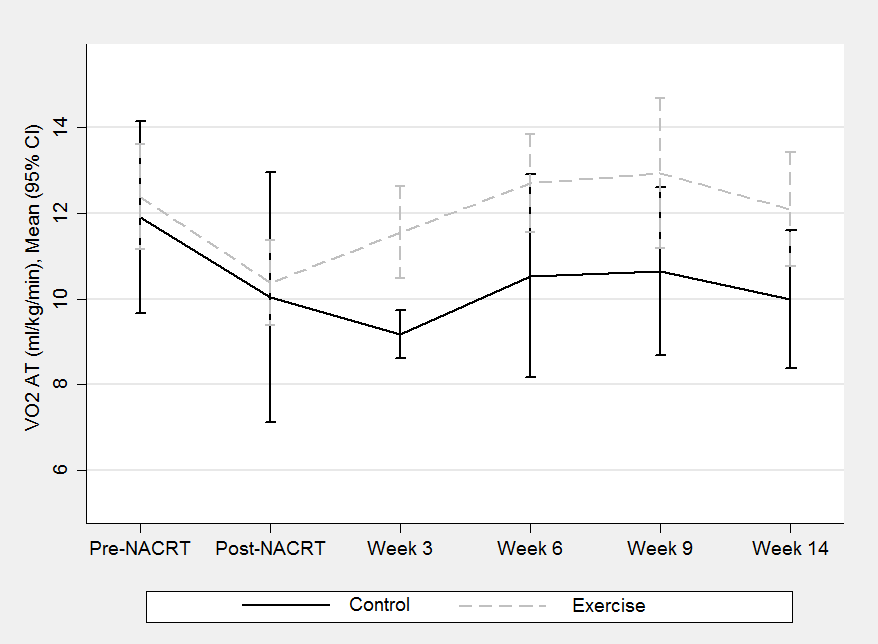


Figure 1 – Line diagram showing fitted means and 95%CI for VO2 at LT (ml.kg-1.min-1) for the exercise and control groups.

*Tumour outcomes and exercise response*

Table 3 and 4 shows MRI (ymrTRG and ymrT stage at week 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=0.7, categorical data; OR 2.2 95%CI 0.4 to 10.5, p=0.3) or week 14 (continuous data; OR -0.9 95%CI -1.9 to 0.1, p=0.1, categorical data; OR 4.4 95%CI 0.8 to 23.9, p=0.09). A linear mixed model comparing ymrTRG in both groups over time showed a significant time effect (Coefficient 0.8 95%CI -1.4 to -0.1, p=0.02) (figure 2). At the time of surgery there was significantly greater histological tumour regression in the exercise group (continuous data OR 1.2 95%CI 0.2 to 2.2, p=0.02, categorical data; OR 8.5 95%CI 1.4 to 51.5, p=0.02). This tumour regression did not result in a significant difference in ypT-stage (continuous data; OR -1.3 95%CI -3.9 to 1.3, p=0.3, categorical data; OR 1.1 95% CI 0.2 to 6.9, p=0.9).

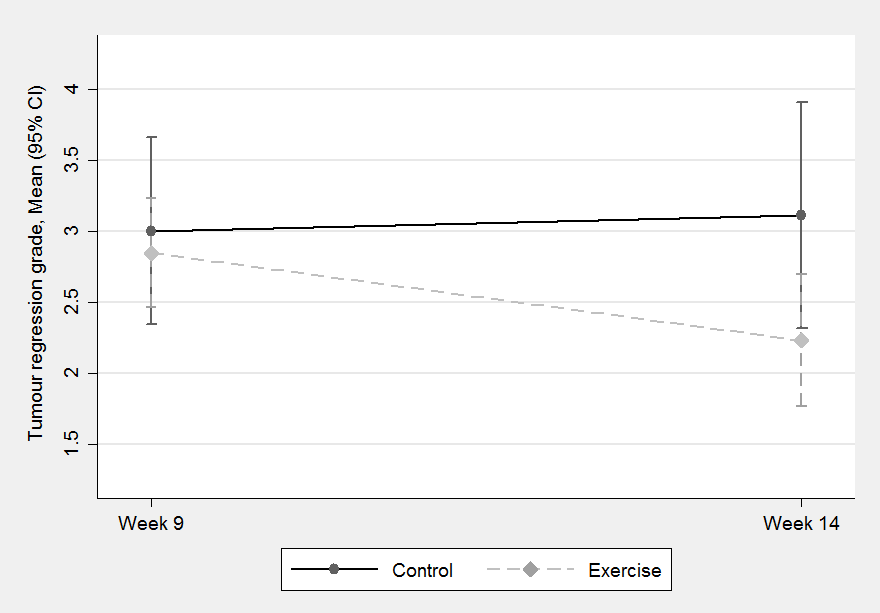


Figure 2 – A line diagram showing fitted means and 95%CI for ymrTRG for exercise and control groups

# DISCUSSION

This post hoc analysis of two prospective clinical trials provides exploratory evidence that undergoing a structured exercise programme following NACRT may be associated with greater tumour regression at the time of surgery. To our knowledge, this is the first clinical study that has observed a significant increase in tumour 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.

Whilst we cannot prove causation, there is biological plausibility in suggesting an effect of exercise in augmenting tumour 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 tumour hypoxia, angiogenesis, blood flow and the tumour 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 of adenocarcinoma possibly through activation of p53 tumour suppressor function and increased apoptosis (39). Meanwhile, immunotherapy is increasingly sought as a means of chemotherapy, with new understanding that tumours 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 tumour 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 tumour regression. The tumour 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 radiosensitised cells could also be related to improved vascular supply (48), insulin sensitivity (49) or cytokine profile (50).

The increased tumour regression observed in the overall patient cohort as previously described (24), was not apparent when analysed 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 week 9 and 14 (Figure 2) that doesn’t reach significance when between 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 towards a decrease in tumour 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= 0.07, categorical data; OR 4.4 95%CI 0.9 to 38.1, p=0.06).

*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 analyses from a larger published clinical patient cohort which was not powered to detect a significant change in tumour size in association with exercise, exposing analyses to possible type 2 and type 1 errors. Moreover, these findings were discovered with these post-hoc intention 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 tumour 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 optimisation. Understanding the mechanism by which exercise works to augment NACRT would allow training programmes to be tailored to individuals to achieve the appropriate response and possibly provide new pharmaco-therapeutic targets for patients undergoing exercise programmes.

# Acknowledgments

# This work was undertaken whilst MW and MPWG were funded by the National Institute of Health Research and the Royal College of Anaesthetists British Oxygen Company Fellowship awarded by the National Institute of Academic Anaesthesia for the Fit-4-Surgery programme of research. Aintree University Hospitals NHS Foundation Trust, Liverpool, Colorectal Multi-Disciplinary Team. Special thanks go to Dr Monica Terlizzo, Consultant Histopathologist, for histopathological analysis. MW, HM, DZHL, JC, MPWG and SJ are partly supported by the Southampton NIHR Biomedical Research Centre at University Hospital Southampton NHS Foundation Trust. RA is partly supported by the NIHR Biomedical Research Centre at University College London Hospitals.

# Role of the Funding Source

This work was undertaken whilst MW and MPWG were funded by the National Institute of Health Research and the Royal College of Anaesthetists British Oxygen Company Fellowship awarded by the National Institute of Academic Anaesthesia for the Fit-4-Surgery programme of research. Funders and study sponsors had no role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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