

Changes in Muscle Mitochondrial Energetics in Vivo and Physical Fitness in Operable Rectal Cancer Patients Following Neoadjuvant Chemoradiotherapy – An Observational Pilot Study

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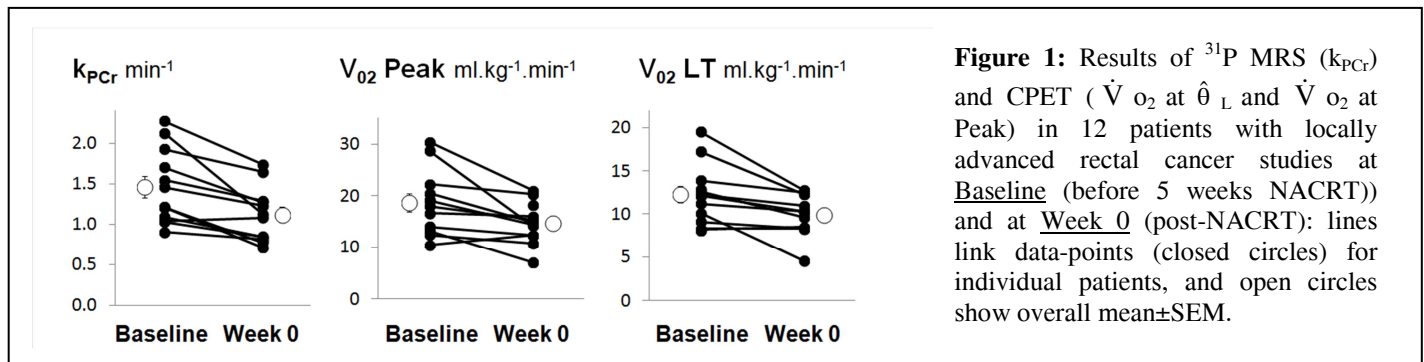
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Target Audience: Clinicians and researchers using magnetic resonance techniques in research and medicine.

Purpose: In the UK, patients with locally advanced rectal cancer routinely receive 5 weeks long-course neoadjuvant chemoradiotherapy (NACRT). However, the effects of this on physical fitness are unclear (1)(2) We aimed to investigate the effect of NACRT on objectively measured muscle mitochondrial function *in vivo* and whole-body physical fitness.

Methods: As part of a larger study (NCT01325909) we prospectively studied 12 patients with rectal cancer who completed standardized NACRT, recruited from a large tertiary cancer centre, between January 2012 and July 2013. This study was approved by the Northwest Research Ethics Committee (11/H1002/12c) and registered with ClinicalTrials.gov (NCT01859442). Written informed consent was obtained from all patients. Patients underwent a cardiopulmonary exercise test (CPET) to assess aerobic fitness (Ergoline Respiratory – GmbH) before ('Baseline') and after ('Week 0') NACRT, and a phosphorus magnetic resonance spectroscopy (³¹P MRS) quadriceps muscle exercise-recovery study at the same time points. ³¹P MRS was conducted in a 3T Trio MR scanner (Siemens, Germany) using an 18 cm dual-tuned surface coil (Rapid Biomedical, Germany) and a purpose-built rig for isometric thigh extension. After resting acquisition (TR=10 s), data were acquired with TR=2 s during 1 min rest, 3 min 60% maximal voluntary contraction force (MVC) exercise (0.25 Hz, 50% duty cycle), 5 min recovery, 2 min 90% MVC exercise and 5 min recovery. Data were quantified by jMRUI-3.0 and analysed by phosphocreatine (PCr) recovery fit (3) CPET and ³¹P MRS analysis were analysed and reported blind. Primary variables of interest were oxygen uptake ($\dot{V}O_2$) at estimated lactate threshold ($\hat{\theta}_L$) and $\dot{V}O_2$ at Peak exercise ($\text{ml.kg}^{-1}.\text{min}^{-1}$), and mean post-exercise PCr recovery rate constant ($k_{\text{PCr}} \text{ min}^{-1}$). Pre- vs. post-NACRT measurements were compared using paired t-test.

Results: Median age was 67 years (IQR 64-75). Differences (95%CI) in $\dot{V}O_2$ at $\hat{\theta}_L$ and at Peak exercise were significantly negative post-NACRT: $\dot{V}O_2$ at $\hat{\theta}_L$ -2.4 (-3.8,-0.9), **p=0.004** and $\dot{V}O_2$ at Peak -4.0 (-6.8, -1.1), **p=0.011**. Differences (in k_{PCr} at the same time-points were also significantly negative -0.34 (-0.51, -0.17); **p<0.001** (Figure 1).



Discussion & Conclusion: We observed a significant decrease in both whole-body aerobic fitness (measured by CPET) and muscle mitochondrial function *in vivo* (measured by ³¹P MRS) following NACRT. The parallel deterioration in the PCr recovery rate constant suggests that muscle mitochondrial mechanisms are important in the loss of physical fitness in this cohort following NACRT. Given the links between fitness and surgical outcome (4), this study suggests a potential role for a targeted intervention to improve physical fitness prior to surgical invention.

References - (1) Marijen C et al. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: Report of a multicenter randomized trial. J. Clin. Oncol. 2002;20(3):817–25. (2) Swellengrebel H M et al. Toxicity and complications of preoperative chemoradiotherapy for locally advanced rectal cancer. Br. J. Surg. 2011 Mar;98(3):418–26. (3) Paganini A et al. Linear dependence of muscle phosphocreatine on oxidative capacity kinetics. Am J Physiol. 1997;272:501–10. (4) West M et al. Perioperative cardiopulmonary exercise testing in the elderly. Best Pract. Res. Clin. Anaesthesiol. 2011 Sep;25(3):427–37.