

# Feasibility and Preliminary Efficacy of a 10-Week Resistance and Aerobic Exercise Intervention During Neoadjuvant Chemoradiation Treatment in Rectal Cancer Patients

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## Abstract

**Background:** Neoadjuvant chemoradiation treatment (CRT) in rectal cancer patients is associated with a reduction in physical capacity, lean mass and increased fatigue. As a countermeasure to these treatment-related adverse effects, we examined the feasibility and preliminary efficacy of a 10-week exercise program during CRT. **Methods:** Ten rectal cancer patients (7 men, aged 27-70 years, body mass index =  $26.4 \pm 3.8$  kg/m<sup>2</sup>) receiving CRT undertook supervised resistance and aerobic exercise twice weekly. Assessments were undertaken pre- and post-intervention for upper and lower body muscle strength by 1-RM, muscle endurance, physical performance tests, body composition by dual X-ray absorptiometry, quality of life, and fatigue. **Results:** There was a significant loss in appendicular skeletal muscle ( $-1.1$  kg,  $P = .012$ ), and fat mass ( $-0.8$  kg,  $P = .029$ ) following CRT. Despite the loss in skeletal muscle, leg press ( $P = .030$ ) and leg extension ( $P = .046$ ) strength improved by 27.2% and 22.7%, respectively, and leg press endurance by 76.7% ( $P = .007$ ). Changes in strength were accompanied by improved performance ( $P < .05$ ) in 6-m fast walking speed (6.9%) and dynamic balance as determined by the 6-m backwards walk (15.5%). There was minimal change in quality of life and fatigue, and no adverse events related to training. **Conclusions:** Exercise during neoadjuvant CRT appears to be feasible and well tolerated in rectal cancer patients and may enhance physical function while minimizing adverse changes in body composition and cancer-related fatigue. These initial findings need to be confirmed in randomized controlled trials.

## Keywords

rectal cancer, exercise, chemoradiation, prehabilitation, preoperative, colorectal cancer

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## Introduction

Rectal carcinoma is an invasive cancer with high incidence rates.<sup>1</sup> While surgical resection is standard treatment, local recurrence often occurs.<sup>2</sup> As a result, the implementation of presurgical chemoradiation treatment (CRT) is the gold standard in the treatment of rectal cancer. This strategy enhances local disease control, reduces metastases, and increases survival.<sup>3</sup> However, CRT has been associated with significant adverse effects. It is well acknowledged that patients undergoing chemotherapy and radiation therapy experience an array of treatment-related side effects, with declines in cardiovascular and muscular function, functional capacity, and increased fatigue.<sup>4-7</sup>

Physical exercise is an important treatment modality in the management of physical health and symptoms in cancer patients and survivors.<sup>8</sup> Exercise interventions during either

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chemotherapy<sup>4</sup> or radiation therapy<sup>5</sup> have resulted in numerous positive physiological and psychological benefits in cancer survivors. Although these results provide support for the role of exercise in the reduction of several treatment-related adverse effects of each therapy individually, it is yet to be determined how a comprehensive exercise program would affect patients undergoing combined therapy, such as intensive neoadjuvant CRT.

Current exercise recommendations include the undertaking of aerobic and resistance exercise to enhance the cardiovascular and musculoskeletal function of cancer survivors.<sup>9,10</sup> However, the potential role of exercise in improving physical performance together with body composition and quality of life (QOL) during intensive neoadjuvant CRT for rectal cancer has not been investigated. Cancer patients, despite the challenges of cancer diagnosis, can be highly motivated to make behavioral improvements. This “teachable moment” may be an ideal time to introduce an exercise program and encourage positive behavior change.<sup>11</sup>

In this study, we examined if a supervised aerobic and resistance exercise program implemented during neoadjuvant CRT was feasible and produced any beneficial effects in rectal cancer patients. Specifically, we aimed to determine the feasibility and preliminary efficacy of a 10-week exercise intervention program on muscle strength and endurance, physical performance, body composition, cancer-specific QOL, and fatigue.

## Methods

### Patient Recruitment

Fifteen localized rectal cancer patients scheduled for neoadjuvant chemoradiation prior to rectal resection were referred by their radiation oncologist. Eligibility criteria included patients scheduled for surgery for localized rectal cancer; absence of any acute illness or any musculoskeletal, cardiovascular, or neurological disorder that could inhibit the ability to walk 400-m unassisted and undertake upper and lower body exercise; and obtained medical clearance from their general practitioner. All patients provided written informed consent. The study was approved by the university ethics committee.

### Exercise Intervention

The exercise program was conducted at 2 university-affiliated exercise clinics located in metropolitan Perth and consisted of twice weekly 1-hour supervised sessions by an accredited exercise physiologist for a period of 10 weeks during CRT. Radiation treatment was undertaken prior to the exercise session, while chemotherapy was administered via a portable chemo pump during radiation treatment and exercise. Patients were also required to complete additional aerobic exercise (at least 2 × 15 minutes or more sessions per week), in order to

meet the exercise guideline of 150 minutes per week,<sup>10</sup> and this was monitored weekly throughout the exercise intervention. Each session commenced with a 5-minute warmup followed by progressive resistance training targeting the major upper and lower body muscle groups.<sup>12</sup> Exercises performed were the chest press, seated row, lat pull down, leg press, leg extension, and leg curl. Patients performed 2 to 4 sets per exercise at a 6 to 12 repetition maximum (RM) intensity in a periodized fashion where the number of sets and repetitions were altered.<sup>13</sup> The exercises were performed using standard resistance training machine equipment. Aerobic exercise was undertaken for 20 minutes at an intensity of 60% to 80% of estimated maximum heart rate and included activities such as walking or jogging on a treadmill and cycling or rowing on a stationary ergometer. The session concluded with a 5-minute cooldown period.

### Feasibility

Feasibility was assessed by determining recruitment and completion rates, overall program adherence, which consisted of a number of completed and missed sessions, and program compliance determined by the prescribed versus actual exercise completed.

### Muscle Strength and Endurance

Dynamic muscle strength for the chest press, seated row, leg press, and leg extension was assessed using the 1-RM method, which is the maximal weight that can be lifted one time.<sup>14</sup> To evaluate upper and lower body muscle endurance, the maximal number of repetitions performed at 70% of the pre-exercise 1-RM for the chest press and the leg press were used.<sup>15,16</sup>

### Physical Performance

A battery of tests that included the usual and fast 6-m walk, 6-m backwards walk (as a measure of dynamic balance), repeated chair rise (lower body muscle function incorporating muscle power, strength, and endurance), stair climb, and the 400-m walk (as a measure of cardiorespiratory endurance and walking endurance) were used to assess physical performance.<sup>17</sup> All tests were performed in triplicate, except for the 400-m walk. For the 400-m walk, heart rate recovery was recorded immediately after exercise, at 1 minute, and at 2 minutes via a heart rate monitor (Model S610i; Polar Electro Oy, Kempele, Finland).

### Body Composition

Total body lean mass (LM), fat mass, and percentage fat were assessed by dual-energy X-ray absorptiometry (DXA, Hologic Discovery A, Waltham, MA). In addition, regional

composition was determined by manipulation of the segmental lines according to specific anatomical landmarks.<sup>18</sup> Appendicular skeletal muscle (ASM) was derived using the sum of both the upper and lower limb LM.<sup>19</sup>

### Quality of Life and Fatigue

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) version 3.0 was used to assess changes in levels of health-related QOL, with higher scores indicating better global health and functioning while lower scores for the symptom subcategories, such as pain and fatigue, indicate a reduction in symptoms.<sup>20</sup> Fatigue was measured with the validated 30-item short form of the Multidimensional Fatigue Symptom Inventory (MFSI-SF), with a higher subcategory score and total score representing greater fatigue except for vigor where a higher score represents enhanced vigor.<sup>21</sup>

### Other Measures

Height and body weight were measured using a stadiometer and electronic scales, respectively, with body mass index ( $\text{kg}/\text{m}^2$ ) calculated. Self-reported physical activity was assessed with the Leisure Score Index of the Godin Leisure-Time Exercise Questionnaire.<sup>22</sup>

### Statistical Analysis

All statistical analyses were performed using a statistical software program (PASW v 19 for Windows, SPSS, Inc, Chicago, IL). Normality of the data was assessed using the Shapiro-Wilk test. Analyses included standard descriptive statistics and paired *t* tests or the Wilcoxon signed -rank test, as appropriate, to compare changes in the variables at pre-exercise and post-exercise time points. For consistency, all results are reported as the change in mean values and the 95% confidence intervals (95% CIs). Intention-to-treat was utilized for all analyses using maximum likelihood imputation of missing values (expectation maximization). Effect sizes (ES) were calculated as  $ES = (\text{Mean}_{\text{Post}} - \text{Mean}_{\text{Pre}}) / \text{SD}_{\text{Pre}}$  and defined as small ( $d = .2$ ), medium ( $d = .5$ ), and large effect ( $d \geq .8$ ).<sup>23</sup> All tests were 2-tailed with an  $\alpha$  level of  $P \leq .05$  set as the criterion for statistical significance.

## Results

### Patient Characteristics and Study Feasibility Outcomes

Of the 15 patients, 5 patients declined to participate, citing long travelling distance, no available transport to the testing site, and wanting to focus on medical treatment only, resulting in 10 patients enrolling in the study and a recruitment

**Table 1.** Baseline Physical Characteristics of Rectal Cancer Patients Undergoing Chemoradiation Therapy (n = 10).

Variables	Mean $\pm$ SD	n	%
Age (years)	54.6 $\pm$ 14.1		
Males		7	70
Height (cm)	171.3 $\pm$ 6.6		
Weight (kg)	77.8 $\pm$ 14.1		
BMI ( $\text{kg}/\text{m}^2$ )	26.4 $\pm$ 3.8		
Married		6	60
Number of medications	1.3 $\pm$ 2.5		
Number of comorbidities <sup>a</sup>	0.7 $\pm$ 1.1		
Godin LSI <sup>b</sup>	16.7 $\pm$ 12.8		
Mini Nutritional Assessment	25.3 $\pm$ 2.7		
Smoking			
Past		3	30
Never		6	60
Alcohol intake			
Yes		10	100

Abbreviations: BMI, body mass index; LSI, Leisure Score Index.

<sup>a</sup>Cardiovascular, hypertension, and hyperlipidemia.

<sup>b</sup>LSI with a moderate-to-strenuous LSI  $\geq 24$  classed as active and  $\leq 23$  classed as insufficiently active.

rate of 67%. Two patients completed the training sessions but did not complete the post-intervention assessments, reporting feeling unwell, and 1 patient withdrew after week 4, although this was unrelated to the exercise intervention. The remaining patients completed training and both assessment time points for a completion rate of 70%. Patient pre-exercise characteristics are presented in Table 1. Baseline data for 6 patients have also been reported elsewhere as part of a report focusing on presurgical exercise and follow-up after surgery.<sup>24</sup> The mean age of patients was  $54.6 \pm 14.1$  years with a body mass index of  $26.4 \pm 3.8 \text{ kg}/\text{m}^2$ . Five patients completed 17 sessions or more out of the possible 20 sessions (85% of scheduled sessions), and overall attendance for the 10 participants was 77%. Patients reported feeling unwell as the main reason for not attending the exercise training sessions. Sessions were individualized by the exercise physiologist based on clinical requirements and/or short-term treatment-related adverse effects, such as irritation secondary to radiotherapy, with the resulting program compliance being 100%. Physical activity as determined by the Godin Leisure Score Index increased from 16.7 to 25.6, which approached significance ( $P = .088$ ) and was due to an increase in the frequency of strenuous activity resulting from the intervention. There were no adverse events as a result of the exercise program.

### Muscle Strength and Endurance

Muscle strength significantly improved for the lower limb exercises, the leg press ( $P = .030$ ) and leg extension

**Table 2.** Effect on Physical Performance, Muscular Strength, and Endurance Measures in Rectal Cancer Patients Undergoing CRT (Mean  $\pm$  SD; n = 10).

Variables	Pre-exercise	Post-exercise	Mean Difference [95%CI]		
			Pre to Post	P	ES
<b>Muscular strength (kg)</b>					
Chest press	36.0 $\pm$ 16.8	38.4 $\pm$ 19.6	2.4 [-1.6 to 6.4]	.214	0.14
Seated row	67.0 $\pm$ 23.2	67.8 $\pm$ 25.1	0.8 [-3.1 to 4.8]	.656	0.04
Leg press	121.0 $\pm$ 48.4	153.9 $\pm$ 65.8	32.9 [3.9 to 61.9]	.030*	0.68
Leg extension	56.0 $\pm$ 22.5	68.7 $\pm$ 31.4	12.7 [0.3 to 25.1]	.046 <sup>#,*</sup>	0.56
<b>Muscular endurance (rep)</b>					
Chest press	10.9 $\pm$ 3.4	12.8 $\pm$ 5.5	1.9 [-3.1 to 7.0]	.358 <sup>#</sup>	0.56
Leg press	12.0 $\pm$ 7.1	21.2 $\pm$ 11.2	9.2 [3.2 to 15.3]	.007*	1.30
<b>Physical performance (s)</b>					
6-m usual walk	4.2 $\pm$ 0.4	3.9 $\pm$ 0.5	-0.3 [-0.7 to 0.1]	.167	0.75
6-m fast walk	2.9 $\pm$ 0.3	2.7 $\pm$ 0.4	-0.2 [-0.3 to 0.0]	.047 <sup>#,*</sup>	0.67
6-m backwards walk	14.2 $\pm$ 3.5	12.0 $\pm$ 2.8	-2.2 [-3.8 to 0.6]	.012*	0.63
400-m walk	237.2 $\pm$ 22.5	229.7 $\pm$ 28.2	-7.6 [-24.8 to 9.7]	.347	0.34
Chair rise	10.4 $\pm$ 1.1	9.3 $\pm$ 1.5	-1.2 [-2.3 to 0.0]	.053	1.09
Stair climb	4.6 $\pm$ 0.9	4.4 $\pm$ 1.0	-0.2 [-0.6 to 0.2]	.283	0.22

Abbreviations: CRT, chemoradiation treatment; CI, confidence interval; ES, effect size; rep, repetitions performed at 70% of 1-repetition maximum (1-RM).

\*Significant ( $P \leq .05$ ).

<sup>#</sup>Wilcoxon signed ranked test.

( $P = .046$ ) by 27.2% and 22.7%, respectively (Table 2). There was no significant change in chest press muscle endurance, however, leg press endurance improved by 76.7% ( $P = .007$ ).

### Physical Performance

Following the 10-week training period, there was a significant improvement ( $P < .05$ ) in the 6-m fast walk (6.9%) and 6-m backwards walk (15.5%; Table 2), with moderate to large effect sizes ( $ES > .6$ ). In addition, improved performance in the repeated chair rise test of 10.6% approached significance ( $P = .053$ ). Although there was no significant change in the 400-m walk time, there was a significant reduction ( $P = .006$ ) in heart rate of 10 beats per minute immediately after the completion of the test indicating potential improvement in heart rate recovery.

### Body Composition

There was a significant loss in ASM (-1.1 kg, 95% CI = -1.9 to -0.3,  $P = .012$ ), which was predominantly a result of a decline in lower limb LM (-0.9 kg, 95% CI = -1.5 to -0.3,  $P = .007$ ; Table 3). Total body fat mass was also significantly reduced ( $P = .029$ ) following CRT by -0.8 kg (95% CI = -1.6 to -0.1) and was largely due to a reduction in trunk fat (-0.7 kg, 95% CI = -1.3 to 0.0,  $P = .046$ ).

### Quality of Life and Fatigue

There were significant changes ( $P < .05$ ) in 3 of the measures of QOL (Table 4)—emotional function, diarrhea, and financial difficulties, with patients also reporting a trend for less constipation ( $P = .078$ ) with a moderate effect size ( $ES = .65$ ). In addition, based on the MFSI-SF, patients overall tended to report higher levels of fatigue at post-exercise (Table 4), with a significant change ( $P = .048$ ) in the Mental Scale subcategory.

### Discussion

We examined the feasibility and preliminary efficacy of a combined resistance and aerobic exercise program in rectal cancer patients undergoing neoadjuvant chemoradiation, a period of time inherently stressful to the patient with an array of treatment-related adverse effects. There were 3 important findings: (1) exercise was feasible during this time period and appeared to be well-tolerated with no adverse events; (2) improvements were observed for lower body muscle strength and endurance, and also physical function; and (3) despite undergoing CRT, there were no substantial adverse changes in fatigue or quality of life.

Two to 3 weeks following a diagnosis of rectal cancer, patients scheduled for rectal resection with curative intent undergo at least 6 to 8 weeks of CRT and are then observed for approximately 7 to 8 weeks before surgery. Typically, exercise would not be prescribed or undertaken during this period; however, an expanding role for exercise medicine in

**Table 3.** Total and Regional Body Composition in Rectal Cancer Patients Undergoing CRT (Mean  $\pm$  SD; n = 10).

Variables	Pre-exercise	Post-exercise	Mean Difference [95%CI]		
			Pre to Post	P	ES
<b>Lean mass (kg)</b>					
Total body	55.7 $\pm$ 10.6	54.7 $\pm$ 10.5	-1.0 [-2.6 to 0.6]	.190	0.09
Upper limb	6.3 $\pm$ 1.7	6.1 $\pm$ 1.8	-0.2 [-0.5 to 0.1]	.142	0.12
Lower limb	17.4 $\pm$ 3.3	16.4 $\pm$ 3.9	-0.9 [-1.5 to -0.3]	.007*	0.27
ASM	23.7 $\pm$ 4.9	22.6 $\pm$ 5.6	-1.1 [-1.9 to -0.3]	.012*	0.23
<b>Fat mass (kg)</b>					
Total body	20.0 $\pm$ 7.5	19.2 $\pm$ 6.9	-0.8 [-1.6 to -0.1]	.029*	0.11
Upper limb	2.3 $\pm$ 0.8	2.3 $\pm$ 0.9	0.0 [-0.1 to 0.2]	.710	0.00
Lower limb	6.8 $\pm$ 2.4	6.6 $\pm$ 2.4	-0.2 [-0.6 to 0.2]	.318	0.08
Trunk	9.9 $\pm$ 5.0	9.2 $\pm$ 4.2	-0.7 [-1.3 to 0.0]	.046*	0.14
Body fat (%)	25.3 $\pm$ 7.7	25.0 $\pm$ 7.7	-0.3 [-0.8 to 0.2]	.214	0.04

Abbreviations: CRT, chemoradiation treatment; CI, confidence interval; ES, effect size; ASM, appendicular skeletal muscle.

\*Significant ( $P \leq .05$ ).

**Table 4.** Quality of Life and Fatigue in Rectal Cancer Patients Undergoing CRT (Mean  $\pm$  SD; n = 10).

Measures	Pre-exercise	Post-exercise	Mean Difference [95%CI]		
			Pre to Post	P	ES
<b>EORTC QLQ-C30 subcategories</b>					
Global Health	61.7 $\pm$ 15.3	65.0 $\pm$ 11.9	3.3 [-4.1 to 10.7]	.335	0.22
Physical Functioning	95.3 $\pm$ 7.1	93.1 $\pm$ 8.3	-2.3 [-11.2 to 6.7]	.528 <sup>#</sup>	0.32
Role Functioning	78.3 $\pm$ 27.3	75.8 $\pm$ 21.5	-2.6 [-22.5 to 17.4]	.799 <sup>#</sup>	0.10
Emotional Functioning	75.0 $\pm$ 14.2	84.9 $\pm$ 26.4	9.9 [0.1 to 19.7]	.048*	0.70
Cognitive Functioning	78.3 $\pm$ 17.7	75.7 $\pm$ 20.5	-2.6 [-9.3 to 4.1]	.405	0.15
Social Functioning	73.3 $\pm$ 23.8	73.7 $\pm$ 19.7	0.4 [-16.9 to 17.6]	.964	0.02
Fatigue	25.6 $\pm$ 18.2	21.6 $\pm$ 15.4	-4.0 [-19.0 to 11.0]	.563	0.22
Nausea and Vomiting	5.0 $\pm$ 15.8	4.8 $\pm$ 6.6	-0.2 [-12.5 to 12.0]	.496 <sup>#</sup>	0.01
Pain	13.3 $\pm$ 13.2	10.0 $\pm$ 20.8	-3.3 [-19.1 to 12.5]	.310 <sup>#</sup>	0.25
Dyspnea	6.7 $\pm$ 14.1	0.0	-6.7 [-16.7 to 3.4]	.157 <sup>#</sup>	0.48
Insomnia	23.3 $\pm$ 16.1	28.0 $\pm$ 21.7	4.7 [-2.8 to 12.1]	.141 <sup>#</sup>	0.29
Appetite Loss	20.0 $\pm$ 28.1	26.2 $\pm$ 24.7	6.2 [-12.1 to 24.4]	.684 <sup>#</sup>	0.22
Constipation	20.0 $\pm$ 23.3	4.9 $\pm$ 10.3	-15.1 [-31.5 to 1.3]	.078 <sup>#</sup>	0.65
Diarrhea	36.7 $\pm$ 29.2	21.6 $\pm$ 25.7	-15.1 [-26.1 to -4.2]	.027 <sup>#*</sup>	0.52
Financial Difficulties	33.3 $\pm$ 27.2	23.8 $\pm$ 30.2	-9.5 [-19.0 to 0.0]	.038 <sup>#**</sup>	0.35
<b>MFSI-SF subcategories</b>					
General Scale	6.8 $\pm$ 5.0	8.1 $\pm$ 6.0	1.3 [-3.9 to 6.5]	.587	0.26
Physical Scale	2.0 $\pm$ 1.9	3.1 $\pm$ 4.1	1.1 [-1.6 to 3.7]	.511 <sup>#</sup>	0.58
Emotional Scale	5.0 $\pm$ 4.3	6.3 $\pm$ 6.9	1.3 [-1.9 to 4.4]	.721 <sup>#</sup>	0.30
Mental Scale	3.9 $\pm$ 4.0	4.6 $\pm$ 4.9	0.8 [0.0 to 1.5]	.048*	0.20
Vigor Scale	10.7 $\pm$ 5.4	11.4 $\pm$ 5.2	0.7 [-1.8 to 3.1]	.550	0.13
Total Scale	7.0 $\pm$ 13.8	12.7 $\pm$ 24.3	5.7 [-5.5 to 16.8]	.280	0.41

Abbreviations: CRT, chemoradiation treatment; CI, confidence interval; ES, effect size; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality Of Life Questionnaire-Core 30; MFSI-SF, Multidimensional Fatigue Symptom Inventory-Short Form.

\*Significant ( $P \leq .05$ ).

<sup>#</sup>Wilcoxon signed ranked test.

cancer management prior to surgery has rapidly developed over the past 3 years.<sup>12,24-26</sup> In our study, exercise appeared to be feasible, based on recruitment (67%) and completion

rates (70%), and an overall exercise session attendance of 77%. It is noteworthy that only 2 patients missed an exercise training session due to treatment-related illness and

that we had a 70% completion rate despite patients undergoing CRT. It is also noteworthy that the exercise sessions were undertaken at training facilities located away from the oncology treatment suite, and co-locating exercise facilities with the radiation and chemotherapy suites at the hospital or clinic may be a preferred model to enhance exercise participation.

In addition, we found the exercise intervention to be well tolerated with no adverse events related to the program. However, one important observation was that some patients were possibly less tolerant of the exercise session in terms of pain management and bowel activation. During some exercise sessions, particularly after a radiation therapy session, patients had to reduce the intensity of aerobic exercise because of irritation and activation of the bowel. Bowel irritation is a known effect of radiation therapy for both prostate<sup>27,28</sup> and rectal cancer patients,<sup>29</sup> although no patients were adversely affected such that they had to withdraw from the entire exercise program. Nevertheless, it is important to note for future studies that prescribing exercise prior to radiation therapy sessions may be more beneficial in terms of exercise adherence and reducing bowel irritation. If training needs to be performed after the radiation therapy session, it is essential to consider adjusting the exercise selection and intensity of the session accordingly.

Chemotherapy or radiation therapy and in particular when both treatments are combined as in the setting of CRT results in a range of adverse effects.<sup>26,30-32</sup> For instance, in rectal cancer patients undergoing CRT, West et al<sup>26</sup> reported a significant reduction in fitness levels as indicated by a decline in maximal oxygen consumption of almost 1.9 mL/kg/min, while Herman et al<sup>31</sup> reported a decline in QOL following CRT. Similarly, for head and neck cancer patients undergoing CRT, Jackson et al<sup>30</sup> reported a reduction in LM of ~10%, while Samuel et al<sup>32</sup> reported declines in functional capacity and QOL in another cohort of head and neck cancer patients undergoing CRT.

However, as a result of the training program, lower body muscle strength substantially increased as did muscle endurance. These results are consistent with the magnitude of effect of exercise for cancer patients undergoing chemotherapy, radiation, or hormonal therapies<sup>4,5,16,33</sup> and were likely induced by neural adaptations<sup>34-36</sup> and possibly muscle architecture alterations<sup>37,38</sup> given that whole body or regional LM did not increase. It is important to note that although muscle function at post-intervention for the upper body did not increase, it was at least preserved following the 10-week period. These results indicate that exercise may serve as a buffer to the adverse effects of neoadjuvant CRT on muscle performance and help not only preserve but also increase a patient's muscle function prior to surgery.

Accompanying the improvements in muscle strength were improvements in physical performance. These changes are comparable with those in a previous research trial

undertaken in cancer patients undergoing endocrinal therapies.<sup>16</sup> Patients were physically stronger from the 10-week exercise program, and this likely contributed to the improved physical performance. Importantly, these increments in physical performance can be empowering for individuals who are close to their functional thresholds in performing daily living activities.<sup>30,39</sup> For example, slow walking speed has been associated with reduced muscle strength, mobility disability, and increased mortality<sup>40</sup>; however, participants in our study preserved or improved their walking speed. This highlights the potential beneficial role of exercising during neoadjuvant CRT in maintaining functional levels during treatment and prior to surgery.<sup>41</sup>

Treatment with chemoradiation has a catabolic effect on skeletal muscle such that a substantial loss in LM of 6.1 kg was observed in head and neck cancer patients following 7 weeks of CRT.<sup>30</sup> A reduction in LM may result in complications especially for rectal cancer patients about to undergo rectal resection, with low LM associated with a longer hospital stay<sup>42</sup> and adverse clinical outcomes.<sup>43</sup> In contrast, we observed that LM was largely preserved with only a reduction in ASM of 1.1 kg following training. It is highly likely that if patients did not undertake the exercise program while undergoing CRT, a substantial loss in LM would have occurred. Nevertheless, this loss in ASM does highlight the significant toxicity associated with CRT and the potential beneficial effects of exercise to ameliorate these declines.

The general trend for the QLQ-C30 scores shows that exercise did not have a significant effect on the majority of the various subcategories. Importantly, the majority of the results did not decline significantly suggesting a preservation in QOL, which perhaps could not have been expected during intensive CRT. This was highlighted in the work by Herman et al<sup>31</sup> who reported a decline in QOL during CRT. Measuring QOL at 3 time points using the EORTC QLQ-C30—before, during, and after treatment—it was shown that global QOL was reduced by 9.5 points during treatment. A substantial decline in QOL following adjuvant chemoradiation has also been observed in gastric cancer patients.<sup>44</sup> In contrast, in our exercise trial, patients reported a 3.3-point increase, although this was not statistically significant. Nevertheless, it needs to be highlighted that our patients did have increased insomnia and had a higher loss of appetite post-exercise. These results are consistent with the adverse effects of chemotherapy<sup>6</sup> and radiation therapy treatment.<sup>45</sup>

Our study has several limitations that are worthy of comment. First, this study was not a randomized controlled trial but a preliminary study to determine the feasibility and preliminary efficacy of a structured program being undertaken during CRT. Second, our patients were volunteers for this study trial, and as such, they are not representative of all rectal cancer patients undergoing neoadjuvant treatment prior to rectal resection. Third, our exercise intervention did

not significantly improve all physical assessment variables, possibly attributed to the variability of the adverse effects caused by intensive CRT, as well as small subject numbers. Future studies of exercise interventions for rectal cancer survivors undergoing CRT should consider predominantly resistance exercise training modalities after a radiation therapy session given that we observed aerobic exercise training causes bowel irritation. Consequently, aerobic exercise could be scheduled for times well separated from the radiation therapy session with considerations for easy access to a lavatory facility. Given that both exercise and diet contribute to the maintenance and accretion of LM,<sup>46</sup> future studies should also examine the combined effect of nutritional counselling/supplementation with exercise in this patient population.

In conclusion, our preliminary results show initial feasibility and preliminary efficacy of exercise in this new exercise oncology setting of neoadjuvant CRT and highlight the need for future studies to confirm and expand our initial findings. Importantly, this trial indicates that in rectal cancer patients, exercise helps preserve LM, muscle strength and physical performance, and QOL, despite undergoing CRT.

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### Author Contributions

FS, RUN, MKB, NAS, DAG, and DRT participated in the conception and design of the study. NAS participated in the coordination of recruitment. FS collected the study data, performed all data analysis, and drafted the first draft with inputs from all authors. All authors read and approved the final manuscript.


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