Exercise During and After Neoadjuvant Rectal Cancer Treatment

by

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ABSTRACT

Background: A standard treatment option for locally advanced rectal cancer includes 5-6 weeks of neoadjuvant chemoradiation (NACRT) followed by surgery about 6-8 weeks later. NACRT improves outcomes for rectal cancer patients but also causes acute toxicities which may impede quality of life (QoL), treatment completion, treatment response, and long-term prognosis. Moreover, even if completed, only 15-27% of patients achieve a pathologic complete response (pCR) to NACRT which is associated with better long-term survival. Interventions to manage toxicities and improve treatment outcomes that are safe, tolerable, and low-cost are highly desirable. Evidence from other cancer patient groups has demonstrated that exercise may be an effective intervention for mitigating some treatment-related side effects and improving QoL. Moreover, limited research suggests that exercise may improve cancer treatment outcomes. To date, however, only preliminary research has examined the feasibility of exercise during and after NACRT for rectal cancer and no study has examined the potential benefits of exercise in this clinical setting. **Purpose:** The purpose of this dissertation was to further examine the feasibility and safety of exercise during and after NACRT for rectal cancer and to test its effect on various outcomes in this clinical setting. **Methods:** This dissertation included two studies. Study 1, a phase I single-arm trial, explored the motivational outcomes and predictors of adherence to a supervised moderate-intensity aerobic exercise program during NACRT followed by ≥ 150 minutes of unsupervised moderate-intensity aerobic exercise/week after NACRT. Study 2 was a phase II randomized controlled trial called the Exercise During and After Neoadjuvant Rectal Cancer Treatment (EXERT) Trial which assessed the feasibility, safety, and efficacy of a supervised high-intensity interval training (HIIT) program during NACRT followed by ≥ 150 minutes of unsupervised moderate-to-vigorous intensity continuous exercise/week after NACRT. Assessments were completed at baseline (pre-NACRT), post-NACRT, and pre-surgery. The

primary outcome was cardiorespiratory fitness post-NACRT. Secondary outcomes included symptom management, QoL, and clinical endpoints (i.e. treatment toxicities, treatment completion, and treatment response). **Results:** Analyses from the phase I trial revealed that rectal cancer patients (N=18) found exercise during NACRT to be more enjoyable and less difficult than anticipated despite several treatment-related barriers. Moreover, they identified potential benefits but also potential harms of exercise during NACRT that were tracked in the phase II trial. From June 2017 to August 2019, 36 rectal cancer patients were enrolled in the EXERT Trial (18 exercise; 18 usual care). Median attendance at supervised HIIT sessions during NACRT was 82% and median self-reported exercise minutes/week post-NACRT was 90 minutes. Exercise did not improve fitness, treatment toxicities, or treatment completion rates; however, exercise, compared to usual, significantly improved the rate of pCR/near pCR (56% vs. 18%; p=0.020). Furthermore, during NACRT, exercise significantly worsened stool frequency (p=0.022; d=0.99), role functioning (p=0.039; d=-0.90), emotional functioning (p=0.028; d=-0.80), and cognitive functioning (p=0.004; d=-0.58) compared to usual care. After NACRT, exercise significantly worsened diarrhea (p=0.030; d=0.59) and embarrassment (p=0.003; d=0.68) compared to usual care. **Conclusions:** Exercise during and after NACRT is feasible and may improve treatment response without improving cardiorespiratory fitness, treatment toxicities, or treatment completion rates. Moreover, exercise may worsen some symptoms and QoL during NACRT; however, most of these effects appear to dissipate prior to surgery. Larger trials are warranted to confirm the beneficial effects of exercise on treatment response and the harmful effects of exercise on symptoms and QoL. If the clinical benefit of exercise is confirmed, then the modest symptom exacerbation during NACRT may be tolerable; however, in the absence of any clinical benefit, exercise may be contraindicated in this clinical setting.

PREFACE

This dissertation is an original work by Andria R. Morielli. Study 1entitled "Feasibility and Efficacy of Aerobic Exercise in Rectal Cancer Patients Receiving Neoadjuvant Chemoradiotherapy" received research ethics approval from the Health Research Ethics Board of Alberta-Cancer Committee (No. 26200) on March 22, 2014. Study 2 entitled "Exercise During and After Neoadjuvant Rectal Cancer Treatment (EXERT) Trial" received research ethics approval from the Health Research Ethics Board of Alberta-Cancer Committee (No. HREBA.CC-16-0986) on March 20, 2017.

Chapter 2 of this dissertation has been published as Morielli, A.R., Usmani, N., Boulé, N.G., Severin, D., Tankel, K., Nijjar, T., Joseph, K. & Courneya, K.S. (2016). Exercise motivation in rectal cancer patients during and after neoadjuvant chemoradiotherapy. *Supportive Care in Cancer,* 24 (7), 2919-2926. DOI: 10.1007/s00520-016-3110-9. I conceived and designed the study, collected and managed the data, analyzed and interpreted the data, and wrote the first draft of the manuscript. KS Courneya, N Usmani, and NG Boulé made important contributions to the conception and design of the study and data analyses and interpretation. All authors revised the manuscript critically for important intellectual content and approved the final manuscript.

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important contributions to the conception and design of the study and data analyses and interpretation. All authors revised the manuscript critically for important intellectual content and approved the final manuscript.

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Appendix B of this dissertation has been published as Morielli, A.R. & Courneya, K.S. (2020). Effects of exercise on cancer treatment completion and efficacy. In K.H. Schmitz (Ed), *Exercise Oncology: Prescribing Physical Activity Before and After a Cancer Diagnosis* (pp. 209-227). Cham, Switzerland. Springer. I reviewed the literature, conceived the figure, and wrote the first draft of the chapter with input from KS Courneya at all stages of the process. KS Courneya conceived the table with my input and revised the chapter critically for important intellectual content.

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LIST OF KEY ABBREVIATIONS

- Gy: gray (unit)
- HIIT: high-intensity interval training
- NACRT: neoadjuvant chemoradiation
- pCR: pathologic complete response
- QoL: quality of life
- TME: total mesorectal excision
- VO_2: volume of oxygen consumption
- 5-FU: 5-fluorouracil

CHAPTER 1: INTRODUCTION

1.1 Rectal Cancer

As the third most common cancer worldwide and the second leading cause of cancer death, colorectal cancer is a major public health burden (1). In 2020, 26,900 Canadians are expected to be diagnosed with colorectal cancer and 9,700 are expected to die from the disease accounting for approximately 12% of all cancers diagnosed and 12% of all deaths from cancer (2). There are no Canadian statistics that distinguish between colon and rectal cancer in terms of their incidence; however, according to statistics from the American Cancer Society (3), rectal cancer accounts for approximately one third of colorectal cancers.

Improvements in prevention, screening, and treatments have led to a reduction in the number of deaths from colorectal cancer. According to the American Cancer Society (3), the overall 5-year relative survival rate for rectal cancer is 67%. The American Cancer Society tracks survival rates for colorectal cancer based on whether the cancer is localized (i.e. no sign the cancer has spread outside the rectum), regional (i.e. the cancer has spread outside the rectum to nearby structures or lymph nodes), or distant (i.e. the cancer has spread to distant parts of the body). It is estimated that approximately 38% of rectal cancers are diagnosed at a localized stage (data not available for other stages); therefore, a significant proportion of rectal cancers are still diagnosed at a more advanced stage (3). Compared to localized-stage rectal cancer which has a 5-year relative survival rate of 89%, regional- and distant-stage disease are associated with worse prognosis (5-year relative survival rate 71% and 15%, respectively) (3). Moreover, compared to earlier stages of the disease, more advanced stages of rectal cancer are associated with more complex treatments.

Surgery is the primary treatment for rectal cancer; however, the invasiveness of the surgical procedure and extent of the surgical resection vary greatly based on stage of the disease as

determined by the American Joint Committee on Cancer (AJCC) TNM system (i.e. stages I-IV). Further treatments are not usually required for early stage rectal cancer (i.e. stage I); however, additional radiation and/or chemotherapy are administered before and/or after surgery for locally advanced rectal cancer (i.e. stages II-III). Although the optimal treatment regimen for locally advanced rectal cancer is still being debated, the most common treatment worldwide is trimodal therapy involving long-course (5-6 weeks) neoadjuvant (pre-surgical) combined chemotherapy and radiation (chemoradiation) followed by surgery 6-8 weeks later using a total mesorectal excision technique (TME), and an additional 4-4.5 months of adjuvant (post-surgical) chemotherapy initiated 4-12 weeks after surgery (4) **(Figure 1-1)**. Neoadjuvant chemoradiation (NACRT) consists of 25-30 fractions of radiation delivered over a period of 5-6 weeks with concurrent chemotherapy in the form of oral capecitabine or intravenous 5-fluorouracil (5-FU) (4). For a more detailed overview of the treatments for locally advanced rectal cancer please refer to **Appendix A**. Of note, metastatic rectal cancer may be treated with trimodal therapy if the metastatic tumor(s) are considered resectable and in other cases where the patient has a favorable prognosis.

Figure 1-1. Standard trimodal therapy for rectal cancer.

Compared to other treatment regimens, NACRT improves local disease control and surgical outcomes for rectal cancer patients. Still, only 15-27% of patients achieve a pathologic complete response (pCR) which has been associated with better disease-free survival and overall

survival (5). Moreover, trials are ongoing to determine if patients with a favorable response to NACRT can avoid surgery altogether (6). Unfortunately, NACRT is associated with acute toxicities including fatigue, diarrhea, radiation dermatitis, pain, hand-foot-syndrome, cardiotoxicity, hematologic toxicity, and physical deconditioning (4, 7) which can negatively impact quality of life (QoL) (8) and may impede treatment tolerance. Safe, tolerable, and low-cost interventions to manage toxicities, improve QoL, and treatment outcomes in this clinical setting are highly desirable.

1.2 Exercise and Cancer

Evidence from large meta-analyses has demonstrated that exercise interventions during and after adjuvant cancer treatment are feasible, safe, and effective at mitigating some treatment-related side effects and improving QoL in several cancer patient groups (9-11). Moreover, preliminary evidence from large randomized controlled trials suggests that exercise may improve chemotherapy completion rates in early stage breast cancer patients (12), and possibly even survival outcomes in breast (13, 14) and lymphoma patients (15). Emerging evidence from preclinical studies supports several biologically plausible mechanisms via which exercise may improve the effectiveness of cancer therapies. For a detailed review of the preclinical and clinical evidence of the potential effects of exercise on treatment completion and efficacy please see **Appendix B**. In the pre-surgical setting, evidence has demonstrated the preliminary feasibility, safety, and efficacy of exercise interventions for improving health-related fitness outcomes and surgical outcomes in cancer patients (16). Moreover, evidence from a limited number of pilot exercise intervention studies suggests that exercise is feasible and safe during neaodjuvant cancer treatment (17).

Despite the emerging evidence for the benefits of exercise in several clinical oncology settings, only preliminary research has examined exercise in rectal cancer patients during and after NACRT (18-24). For a detailed review of the exercise intervention trials to date in this clinical setting please refer to **Appendix C**. Briefly, in the first exercise intervention study in this clinical setting, West et al. (23) demonstrated that a supervised moderate-to-vigorous intensity aerobic exercise intervention initiated after NACRT and prior to surgery, was feasibility and improved cardiorespiratory fitness. These promising findings raised the question of whether initiating an exercise intervention during NACRT may have even greater benefits for rectal cancer patients including preventing declines in cardiorespiratory fitness, managing symptoms, improving QoL, and possibly even treatment outcomes. This prompted the study for my master's thesis, a phase I non-randomized trial, designed to test the feasibility and safety of moderate-intensity continuous exercise training both during and after NACRT in rectal cancer patients (22). I reported an excellent recruitment rate of 56% (18 of 32 patients) and a follow-up assessment rate of > 80%. Moreover, the median attendance rate for the supervised exercise during NACRT was 83%. After NACRT, patients completed an average of 222 ± 155 minutes/week of unsupervised exercise. No adverse events were observed, and our evaluation was that even higher intensity aerobic exercise would be feasible in this clinical setting.

1.3 Summary and Rationale

Long-course (5-6 weeks) NACRT consisting of radiation (45-54 Gy) with concurrent chemotherapy (oral capecitabine or intravenous 5-fluorarcil) followed by surgical resection using TME 6-8 weeks later is a standard treatment option for locally advanced (stage II-III) rectal cancer. Compared to other treatment regimens, NACRT improves local disease control and surgical outcomes for rectal cancer patients. Nevertheless, only a small proportion of patients

achieve a pCR which has been associated with better long-term outcomes for rectal cancer patients. Unfortunately, NACRT is associated with acute side effects which negatively affect QoL and may impede treatment tolerance. Exercise may be an effective intervention for managing the side effects of NACRT, maintaining QoL, and possibly even improving treatment outcomes in rectal cancer patients.

1.4 Overview of the Dissertation

The overarching purpose of this dissertation was to (1) further establish the feasibility and safety of exercise in rectal cancer patients during and after NACRT and (2) examine the preliminary effects of exercise on outcomes including health-related fitness, symptoms, QoL, treatment toxicities, treatment completion, and treatment response in this clinical setting. To help inform the design of the trial for this dissertation, I further analyzed data collected during the phase I trial. The results from these analyses are reported in chapters 2 and 3 of this dissertation. **Chapter 2** (paper 1) examines the motivational outcomes, perceived benefits and harms, and perceived barriers to exercise during and after NACRT. **Chapter 3** (paper 2) examines the predictors of adherence to exercise during and after NACRT including demographic, health, psychosocial, and motivational variables. The results from the phase I trial (reported in my master's thesis and in chapters 2 and 3 of this dissertation) informed the design of the phase II trial implemented for the purpose of this dissertation. **Chapter 4** (paper 3) reports the rationale and protocol for the phase II trial called the Exercise During and After Neoadjuvant Rectal Cancer Treatment (EXERT) Trial. **Chapter 5** (paper 4) examines the feasibility, safety, and effects of the EXERT Trial on health-related fitness outcomes and clinical outcomes including treatment toxicities, treatment completion, and treatment response. **Chapter 6** (paper 5) examines the effects of the EXERT Trial on patient-reported outcomes including symptom

burden and QoL. Finally, **Chapter 7** discusses the strengths and limitations of this dissertation, future directions, and practical implications.

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CHAPTER 2: PAPER 1

Exercise motivation in rectal cancer patients during and after neoadjuvant chemoradiotherapy

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2.1 Abstract

Purpose: Aerobic exercise is safe and feasible for rectal cancer patients during and after neoadjuvant chemoradiotherapy (NACRT) but their motivation to perform such exercise is unknown. Here, we explore the motivational outcomes, perceived benefits and harms, and perceived barriers to exercise during and after NACRT. **Methods:** Rectal cancer patients (n=18) participated in supervised aerobic exercise during NACRT followed by unsupervised exercise after NACRT. Using the theory of planned behavior, we assessed perceived benefits, harms, enjoyment, support, difficulty, and barriers for exercise both during and after NACRT. **Results:** Patients reported that exercise during NACRT was more enjoyable (p=0.003) and less difficult (p=0.037) than initially anticipated. The most common perceived benefits of exercise during NACRT were cardiovascular endurance (75%), quality of life (75%), and self-esteem (65%). After NACRT, the most common perceived benefits were physical functioning (93%), cardiovascular endurance (86%), and quality of life (79%). The most common perceived harms of exercise during NACRT were fatigue (31%), diarrhea (31%), and skin irritation (24%). After NACRT, the most common perceived harms were fatigue (21%) and hand-foot-syndrome (15%). Side effects from NACRT was the most common exercise barrier during NACRT (88%) whereas lack of motivation was the most common barrier after NACRT (79%). **Conclusions:** Rectal cancer patients reported aerobic exercise during NACRT to be more enjoyable and less difficult than anticipated despite significant barriers. This positive motivational response may facilitate recruitment and adherence in future interventions. Moreover, rectal cancer patients identified potential benefits and harms that should be closely monitored in future interventions.

2.2 Introduction

Standard treatment for locally advanced rectal cancer involves 5-6 weeks of neoadjuvant chemoradiotherapy (NACRT) followed by definitive surgery 6-8 weeks later [1]. Unfortunately, NACRT is associated with toxicity and side effects that may impact quality of life, treatment response and post-surgical recovery [2,3]. Preliminary research has demonstrated that a supervised aerobic exercise intervention started immediately after NACRT is feasible and improves cardiovascular fitness in rectal cancer patients prior to surgery [4]. More recently, we have demonstrated that a supervised aerobic exercise intervention during NACRT followed by unsupervised but closely monitored aerobic exercise after NACRT is also feasible and safe for rectal cancer patients [5]. In particular, we found that patients were able to attend a median of 83% of their supervised exercise sessions during NACRT and reported an average of 222 ± 155 minutes/week of aerobic exercise after NACRT. Moreover, no serious adverse events were reported or observed.

In this secondary paper, we further explore the safety and feasibility of the exercise program by reporting the motivational outcomes, perceived benefits and harms, and perceived barriers associated with exercise during and after NACRT. Understanding the motivational outcomes and perceived barriers related to the exercise program may improve recruitment and adherence in future intervention trials. Moreover, identifying the perceived benefits and harms of the exercise program may identify potential new outcomes to target or adverse events to track.

The study was guided by the theory of planned behavior (TPB) [6]. The TPB is a social cognitive model of human behavior that proposes that intention (i.e. motivation) is the immediate determinant of behavior. Intention, in turn, is influenced by (1) instrumental attitudes (i.e. perceived benefits and harms of performing the behavior), (2) affective attitudes (i.e. perceived

enjoyment or unenjoyment of performing the behavior), (3) subjective norms (i.e. perceived support for performing the behavior) and, (4) perceived behavioral control (i.e. perceived ease or difficulty of performing the behavior).

2.3 Methods

The methods of our feasibility study have been reported elsewhere [5]. Here, we present a summary of the main methods and additional information on the assessment of motivational outcomes. The study was approved by the Health Research Ethics Board-Cancer Committee. Patients were included in the study if they were scheduled to receive long-course NACRT followed by definitive surgery, were between the ages of 18 and 80, did not have any uncontrolled medical or psychiatric conditions, and were cleared to participate in exercise as determined by the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+).

Design and Procedures

The study was a prospective single group study with assessments at three timepoints: (1) pre-NACRT, (2) post-NACRT, and (3) pre-surgery. Patients were recruited directly from gastrointestinal new patient clinics at the Cross Cancer Institute in Edmonton, Alberta. During these clinics, rectal cancer patients were screened for eligibility by their radiation oncologist and the study coordinator. The study coordinator then followed up by phone with patients who were eligible and expressed interest in the study. Written informed consent was obtained from all patients prior to undergoing the pre-NACRT assessments.

Intervention

Details of the aerobic exercise intervention have been described elsewhere [5]. Briefly, the exercise intervention was divided into two components: (1) during NACRT and (2) post-NACRT. During NACRT, the primary goal of the exercise intervention was to attend 18

supervised aerobic exercise sessions (3 sessions/week for the 6 weeks during which patients were receiving NACRT). A secondary goal was to determine if patients could reach and maintain 150 minutes of moderate-intensity aerobic exercise in 3 sessions/week (i.e. 50 minutes/session). The exercise prescription was individually tailored to each patient based on the results of the pre-NACRT treadmill test (40-60% of estimated VO_2 reserve). The intensity of the exercise sessions was monitored using heart rate monitors and the Borg rating of perceived exertion scale (0-10). Exercise modalities included treadmill, upright bike, elliptical and rower. All exercise sessions were supervised by an exercise specialist at the Behavioral Medicine Fitness Centre at the University of Alberta.

After NACRT, patients were provided with the option of continuing with the supervised exercise program, completing an unsupervised exercise program, or a combination. The option of unsupervised exercise was provided because patients were no longer coming daily to the cancer centre for radiation and many patients were from out of town. During this phase, the goal of the exercise program was to maintain (or achieve) 150 minutes of moderate-intensity aerobic exercise/week in bouts of 10 minutes or more. Again, the exercise prescription was individually tailored to each patient based on the results of the post-NACRT treadmill test (40-60% of estimated VO_2 reserve). Patients were provided with a heart rate monitor and an exercise log in which they recorded exercise frequency, intensity, duration and modality. The study coordinator completed weekly telephone or email follow-ups to support patients in meeting the exercise prescription. Adherence to the unsupervised exercise program was assessed at the end of the intervention by self-report using the Godin Leisure Time Exercise Questionnaire (GLTEQ) [7].

Measures

Demographic, Behavioral and Medical Profile

Demographic and behavioral information was collected at baseline using self-report and included: age, sex, marital status, education level, annual income, employment status, ethnicity, smoking behavior and co-morbidities. Baseline physical activity levels were assessed using the Godin Leisure-Time Exercise Questionnaire (GLTEQ) [7]. Medical data was extracted from medical records and included: disease stage, treatments administered and treatment dates.

Motivational Outcomes

The TPB constructs (instrumental and affective attitudes, subjective norms, intention and perceived behavioral control) were assessed using standard items as recommended by Ajzen [8]. Items used were taken from previous research and modified to fit the context of the current study [9]. Evaluations for all questions were on a 5 point scale (1=not at all, 2=a little bit, 3=somewhat, 4=quite a bit, 5=very much). Motivational outcomes were assessed at all three time points. At pre-NACRT, patients completed a prospective motivational evaluation of the supervised exercise program in which they were asked to anticipate how beneficial, how enjoyable, how supported, how motivated, and how difficult it would be for them to exercise during their chemoradiotherapy. After the completion of NACRT, patients completed a retrospective motivational evaluation of the supervised exercise program in which they were asked to look back and report how beneficial, enjoyable, supported, motivated and difficult it actually was to complete the aerobic exercise intervention during their chemoradiotherapy.

At the post-NACRT timepoint, patients also completed a prospective motivational evaluation of the exercise program after NACRT asking them to anticipate how beneficial, enjoyable, supported, motivated and difficult they thought it would be to exercise on their own

over the next 6-8 weeks prior to their surgery. At the pre-surgery timepoint, patients again completed a retrospective motivational evaluation for which they were asked to look back and report how beneficial, enjoyable, supported, motivated and difficult it actually was to complete the exercise program post-NACRT.

Specific Perceived Benefits/Harms and Barriers

Specific perceived benefits/harms of the exercise program were measured at two timepoints, post-NACRT and pre-surgery, using a 19 item questionnaire that listed the main health-related fitness outcomes and patient-reported outcomes assessed in the study [5]. Participants were asked: "what affect, if any, did the exercise program have on each of the following for you during your chemoradiotherapy" at the post-NACRT time point; and "what affect, if any, did the exercise program have on each of the following for you after the completion of your chemoradiotherapy and prior to your surgery" at the pre-surgery time point. Evaluation for all items was on a 7-point scale ranging from 1-3 (very much-somewhat-slightly worse) to 4 (no change) to 5-7 (slightly-somewhat-very much improved).

Specific perceived barriers were also measured at post-NACRT and pre-surgery using a 16 item questionnaire that listed the anticipated side effects from chemoradiotherapy in addition to common barriers to exercise in cancer survivors that have been identified in previous research [10,11]. At post-NACRT, participants were asked: "how much of a barrier was each of the following for you in trying to do the exercise program during your chemoradiotherapy". At pre-surgery, participants were asked "how much of a barrier was each of the following for you in trying to do the exercise program after the completion of your chemoradiotherapy and prior to surgery". Responses were evaluated on a 7-point scale ranging from 1 (not at all) to 3 (somewhat) to 5 (a fair bit) to 7 (very much).

Statistical Analyses

Changes in motivational outcomes were computed by subtracting the prospective motivational evaluations of the exercise program (i.e., what was anticipated) from the retrospective motivational evaluations of the exercise program (i.e., what was experienced) and analyzed using dependent t-tests. Differences in the specific perceived benefits/harms and barriers of the exercises programs during- and post-NACRT were also analyzed using dependent t-tests. For the specific benefits/harms, we also report the percentage of patients who perceived that a given outcome: (1) improved (score of 5-7); (2) did not change (score of 4) or (3) worsened (score of 1-3) with exercise. For the specific barriers, we report the percentage of patients who perceived that the factor was: (1) not at all (score of 1); (2) somewhat (score of 2-4) or (3) quite a bit (score of 5-7) of a barrier to exercise.

2.4 Results

Participant flow through the trial, participant characteristics, and exercise adherence have been reported elsewhere [5]. Briefly, 45 rectal cancer patients were assessed for eligibility, 32 (71%) were eligible and 18 (56%) were recruited to the study and completed the pre-NACRT questionnaire. The main reasons for ineligibility in our study were significant medical contraindications to exercise. Patients refused participation in our study mostly because they were afraid it would be "too much" during NACRT (n=5). Other reasons for refusal included feeling overwhelmed (n=3), working (n=3), living out of town (n=1) and not interested (n=2). Study participants had a mean age of 57.5 (range 34-73), were predominantly male (66.7%), Caucasian (94.4%), married (66.7%), not working (55.5%) and overweight/obese (88.9%). In terms of the medical profile, 72.2% had stage IIIB rectal cancer and 2 patients had an ostomy. Seventeen (94%) patients completed the post-NACRT questionnaire; one patient withdrew from

the study because they found it too difficult to keep up with the medical appointments and exercise sessions. Fourteen (75%) patients completed the pre-surgery questionnaire; 2 patients were withdrawn from the study (heart attack and emergency surgery) and 2 patients were loss to follow-up (too stressful and did not return questionnaire). The median attendance for the supervised exercise sessions was 83%. The mean duration of each supervised exercise session was 40 minute ± 9 minutes and moderate-intensity aerobic exercise was achieved 100% of the time. After NACRT and prior to surgery, the mean total aerobic exercise minutes was 222 ± 144 minutes with 10 of the 14 (71%) patients still on trial meeting the aerobic exercise goal of ≥ 150 minutes/week. Most of the exercise after NACRT was unsupervised: only two patients opted to continue with a combination of supervised/unsupervised exercise.

Motivational Outcomes

The prospective and retrospective motivational evaluations of the supervised aerobic exercise program during NACRT are presented in **Table 2-1**. There were statistically significant improvements in perceived enjoyment (mean change = +0.9; 95% CI= 0.3 to 1.4; p=0.003) and perceived difficulty (mean change = -0.6; 95% CI, -1.1 to -0.0; p=0.037) from before to after the supervised exercise program. The prospective and retrospective motivational evaluations of the aerobic exercise program post-NACRT are presented in **Table 2-2**. There was a statistically significant improvement in perceived support (mean change = +0.3; 95% CI, 0.0 to 0.6; p=0.040) from post-NACRT to pre-surgery.

Specific Perceived Benefits/Harms and Barriers

Table 2-3 reports the specific perceived benefits/harms of the exercise program during and after NACRT. The most common perceived benefits for the aerobic exercise program during NACRT were cardiovascular endurance (75%), quality of life (75%) and self-esteem (65%). The

most common perceived harms of the aerobic exercise program during NACRT were fatigue (31%), diarrhea (31%), and skin irritation at the site of irradiation (24%). The most common perceived benefits of the aerobic exercise program post-NACRT were physical functioning (93%), cardiovascular endurance (86%), and quality of life (79%) and the most common perceived harms were fatigue (21%) and hand-foot syndrome (15%). There were no statistically significant differences in the perceived benefits/harms of exercise during and after NACRT.

Table 2-4 reports the specific perceived barriers to the exercise program during and post-NACRT. When combining the percentage of patients who reported that a factor was "quite a bit" a barrier and "somewhat" a barrier, the most common perceived barriers during NACRT were side effects from chemoradiotherapy (88%), fatigue (76%), and diarrhea (71%). The most common barriers post-NACRT were lack of motivation (79%), fatigue (57%), and feeling sick (50%). There was a statistically significant reduction in the perception of side effects from chemoradiotherapy as a barrier to exercise during NACRT compared to post-NACRT (mean change =-1.5; CI,-3.0 to -0.0; p= 0.050). Conversely, too busy/lack of time significantly increased as a barrier to exercise from during NACRT to post-NACRT (mean change = +0.6; CI=0.1 to 1.1; p=0.026).

2.5 Discussion

Rectal cancer patients anticipated that exercising during NACRT would be quite beneficial and that they would be very much supported. Conversely, however, they anticipated the exercise would only be somewhat enjoyable and would also be somewhat difficult. The anticipation that exercise during NACRT would be difficult and not that enjoyable seems reasonable given the known side effects of this treatment that patients would have been educated about prior to starting NACRT [2,3]. It is unclear, however, why rectal cancer patients would

anticipate that exercise during NACRT would be quite beneficial given there is no evidence of benefit in this clinical setting. One possibility is that our sample may be biased towards patients who believe in the benefits of exercise. A second possibility is that rectal cancer patients may be aware of the documented benefits of exercise in other cancer patient populations and assume these benefits apply to their own disease and treatments. Either way, these data are promising for the recruitment and adherence to exercise interventions of rectal cancer patients initiating NACRT.

Another important finding of our study is that rectal cancer patients reported aerobic exercise during NACRT to be more enjoyable and less difficult than they had anticipated. Improvements in enjoyment and difficulty have also been reported in breast cancer patients following a supervised aerobic exercise intervention [10] and lung cancer patients following a supervised progressive resistance exercise training program [9]. Again, the finding that rectal cancer patients found a supervised exercise program during NACRT to be more enjoyable and less difficult than anticipated may have implications for the recruitment and adherence of patients to future exercise intervention trials in this setting. Perceived enjoyment and difficulty are well-known correlates of exercise adherence [12] and improvements in these variables over the course of NACRT are likely to predict continued exercise adherence. The high level of anticipated benefits and support for exercise prior to NACRT, coupled with improvements in enjoyment and difficulty during NACRT, may explain our 83% median adherence to exercise during NACRT.

Post-NACRT, rectal cancer patients still reported being quite motivated to continue to exercise on their own prior to their surgery. Specifically, patients anticipated that exercise after NACRT and prior to surgery would be quite beneficial, quite enjoyable, quite supported, and

only a little bit difficult. Moreover, perceived support for the unsupervised exercise after NACRT actually improved suggesting that rectal cancer patients received more social support than anticipated during the post-NACRT/pre-surgery phase. One possible explanation for this finding is that, after NACRT, patients may have anticipated the loss of support from the radiation oncologists, exercise trainers, and other rectal cancer patients. It is possible that patients then received more support than anticipated from their spouses and/or the study coordinator, who followed up with patients weekly by telephone or email to support patients in meeting the exercise goal.

In terms of specific benefits, rectal cancer patients perceived that exercising during and after NACRT improved health-related fitness outcomes (e.g., cardiovascular endurance, physical functioning, and muscular strength), psychosocial outcomes (e.g., self-esteem, anxiety, depression and stress), and quality of life which are well-documented outcomes in the exercise oncology literature for other patient groups [13,14]. Interestingly, few rectal cancer patients perceived that exercise was beneficial for the prevention or management of treatment side effects during or after NACRT. In fact, several symptoms were perceived to have worsened from the exercise during NACRT including fatigue (31%), diarrhea (31%), and radiation dermatitis (24%). Although fatigue was one of the most commonly reported perceived harms of exercising during NACRT, it was also reported as a perceived benefit by 50% of patients, suggesting the potential complexity of exercise effects on fatigue in this clinical setting. Randomized controlled trials are needed to evaluate the effects of exercise on side effects from NACRT.

As expected, the most common perceived barriers to exercising during NACRT were side effects from chemoradiotherapy including fatigue and diarrhea. This is not surprising considering that both these symptoms worsened during NACRT [5]. After NACRT, side effects from

chemoradiotherapy were still reported as a barrier to exercise, however, there was a significant decline in the perceived impact of this barrier. This finding suggests that lingering side effects from chemoradiotherapy may still interfere with a patient's ability to exercise after NACRT. Nevertheless, lack of motivation became the most common reported barrier suggesting that self-motivation may be a challenge for patients exercising on their own after NACRT.

Disease- and treatment related side effects have previously been reported as the main barriers to exercise during treatments in colorectal, breast, and lymphoma patients and these trials have identified a need to implement strategies to overcome these barriers [11,10,15]. Despite implementing some of these strategies in our trial (i.e. well located bathroom facilities at our fitness centre and prescribing moderate-intensity exercise), diarrhea and fatigue still emerged as significant barriers to exercise. Future trials should continue to explore different strategies to help minimize these barriers and improve exercise adherence.

In terms of the important medical outcomes, 81% of patients reported that exercising during NACRT did not affect their ability to complete NACRT. This finding suggests that rectal cancer patients believe that exercise neither helped nor harmed their ability to complete NACRT. Nevertheless, two exercise trials in breast cancer patients have reported that exercise improved chemotherapy completion rate [16,17] and this treatment outcome should be tracked in future trials. Conversely, 86% of patients reported that the exercise program post-NACRT helped them prepare for surgery. Some evidence is available to support this perception as a recent systematic review has suggested that exercise may improve surgical outcomes in cancer patients [18]. Following-up rectal cancer patients for surgical outcomes will be important in this clinical setting as has been done by West et al. [19]. If future exercise trials show improvements in these

treatment outcomes, these benefits would likely be the most important factors motivating rectal cancer patients to exercise during and after NACRT.

The present study has important strengths including being the first to explore the motivational basis of exercise in rectal cancer patients during and after NACRT, the use of a validated theoretical model to evaluate motivation, the assessment of these motivational outcomes both prospectively and retrospectively, and the assessment of specific benefits/harms and barriers to exercise. Limitations include the small sample size, some loss to follow-up, and the lack of a comparison group. Future trials with larger sample sizes should explore differences in motivation, perceived benefits/harms and barriers to exercise according to factors including age, disease stage, body weight, and exercise adherence. Another limitation of our study is the lack of comparison between patients who participated in the study and those who did not. To characterize the nature of the selection bias, if possible, future trials should consider collecting some demographic and medical data on patients who refuse study participation.

In conclusion, rectal cancer patients starting an aerobic exercise program during NACRT reported being quite motivated, and anticipated that the exercise program would be quite beneficial and well-supported. Nevertheless, they also believed the exercise program would be somewhat difficult and only somewhat enjoyable. Fortunately, rectal cancer patients found the exercise program to be more enjoyable and less difficult than anticipated which may influence recruitment and adherence rates in future trials. Moreover, rectal cancer patients perceived that an aerobic exercise intervention both during and immediately after NACRT improved health-related fitness outcomes and psychosocial outcomes; however, there was some indication they perceived it may have worsened some of the side effects from NACRT. Furthermore, rectal cancer patients felt that exercise during NACRT did not affect their ability to complete NACRT,

however, they felt exercise after NACRT may have helped them prepare for surgery. Of course, only randomized controlled trials targeting these outcomes can provide definitive answers to the benefits and harms of exercise in this clinical setting. Such trials will need to address the most commonly reported barriers to exercise during and after NACRT to facilitate the testing of exercise interventions in this clinical setting and to ultimately move this research into clinical practice.

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Table 2-1. Changes in motivational outcomes for the supervised aerobic exercise intervention during neoadjuvant chemoradiotherapy in rectal cancer patients (n=17).

Variable	Pre-NACRT Prospective	Post-NACRT Retrospective	Pre- to post- NACRT
	Mean (SD)	Mean (SD)	Mean Change [95% CI]
Beneficial	4.2 (0.7)	4.4 (0.6)	0.2 [-0.2 to 0.6]
Enjoyable	3.4 (0.7)	4.3 (0.8)	0.9 [0.3 to 1.4]
Supported	4.6 (0.8)	4.4 (1.0)	-0.2 [-0.4 to 0.1]
Motivated	3.9 (1.1)	4.1 (0.8)	0.2 [-0.2 to 0.6]
Difficult	2.8 (0.8)	2.2 (1.0)	-0.6 [-1.1 to -0.0]

Abbreviation: NACRT, neoadjuvant chemoradiotherapy. Evaluations for all questions were on a 5 point scale (1=not at all, 2=a little bit, 3=somewhat, 4=quite a bit, 5=very much).

Table 2-2. Changes in motivational outcomes for the unsupervised aerobic exercise intervention after neoadjuvant chemoradiotherapy and before surgery in rectal cancer patients (n=14).

Variable	Post-NACRT Prospective	Pre-surgery Retrospective	Post-NACRT to Pre-surgery
	Mean (SD)	Mean (SD)	Mean Change [95% CI]
Beneficial	4.3 (0.6)	4.4 (0.5)	0.1 [-0.2 to 0.5]
Enjoyable	3.8 (0.7)	3.9 (0.8)	0.1 [-0.4 to 0.6]
Supported	4.4 (0.6)	4.7 (0.5)	0.3 [0.0 to 0.6]
Motivated	3.9 (0.7)	4.0 (0.7)	0.1 [-0.4 to 0.6]
Difficult	2.2 (0.9)	2.1 (0.8)	-0.1 [-0.6 to 0.4]

Abbreviation: NACRT, neoadjuvant chemoradiotherapy. Evaluations for all questions were on a 5 point scale (1=not at all, 2=a little bit, 3=somewhat, 4=quite a bit, 5=very much).

Table 2-3. Specific perceived benefits and harms of participating in an aerobic exercise intervention during and after neoadjuvant chemoradiotherapy in rectal cancer patients.

Variable	During NACRT (N=17)				Post-NACRT/pre-surgery (n=14)			
	Mean (SD)	Percentage improved[1]	Percentage no change[2]	Percentage worsened[3]	Mean (SD)	Percentage improved[1]	Percentage no change[2]	Percentage worsened[3]
Cardiovascular endurance[4]	5.4 (1.0)	75.0	25.0	0.0	5.6 (1.3)	85.7	7.1	7.1
Physical functioning[4]	5.1 (0.9)	62.5	37.5	0.0	5.6 (1.2)	92.9	0.0	7.1
Muscular strength[4]	4.6 (0.7)	56.3	37.5	5.6	4.9 (1.1)	57.1	35.7	7.1
Quality of life[4]	5.1 (0.8)	75.0	25.0	0.0	5.4 (0.9)	78.6	21.4	0.0
Fatigue[4]	4.3 (1.3)	50.0	18.8	31.3	5.0 (1.4)	64.3	14.3	21.4
Sleep quality[4]	4.5 (0.9)	50.0	37.5	12.5	4.7 (0.8)	50.0	50.0	0.0
Depressed feelings[4]	4.5 (0.8)	31.3	68.8	0.0	4.6 (0.9)	35.7	64.3	0.0
Anxious feelings[4]	4.3 (1.0)	25.0	62.5	12.5	4.5 (1.0)	35.7	57.1	7.1
Stress	4.4 (0.9)	23.5	70.6	5.9	4.7 (1.0)	42.9	57.1	0.0
Self-esteem	4.9 (1.0)	64.7	29.4	5.9	4.8 (1.0)	50.0	50.0	0.0
Body weight/shape[4]	4.8 (1.0)	50.0	43.8	6.3	4.6 (0.9)	35.7	64.3	0.0
Diarrhea[5]	3.7 (1.0)	6.3	62.5	31.3	4.4 (1.3)	23.1	69.2	7.7
Abdominal pain/cramps[6]	3.9 (0.8)	5.9	76.5	17.6	4.4 (1.0)	23.1	69.2	7.7
Skin irritation at irradiated site[6]	3.7 (0.7)	0.0	76.5	23.5	4.0 (0.4)	7.7	84.6	7.7
Tingling/numbness/peeling (hands & feet)[6]	3.8 (0.5)	0.0	88.2	11.8	4.0 (0.7)	7.7	76.9	15.4
Nausea/vomiting[6]	4.0 (0.4)	5.9	88.2	5.9	4.4 (1.0)	15.4	84.6	0.0
Ability to complete chemoradiotherapy[7]	4.4 (0.9)	18.8	81.3	0.0	---	---	---	---
Illness or injury[6]	4.1 (0.3)	11.8	88.2	0.0	4.3 (0.9)	15.4	84.6	0.0
Preparation for surgery	---	---	---	---	5.6 (1.0)	85.7	14.3	0.0

Abbreviation: NACRT, neoadjuvant chemoradiotherapy. [1]Percentage improved = 5-7. [2]Percentage no change = 4. [3]Percentage worsened = 1-3. [4]During NACRT n=16, post-NACRT/pre-surgery n=14. [5]During NACRT n=16, post-NACRT/pre-surgery n=13. [6]During NACRT n=17, post-NACRT/pre-surgery n=13. [7]During NACRT n=16.

Table 2-4. Specific perceived barriers to participating in an aerobic exercise intervention during and after neoadjuvant chemoradiotherapy in rectal cancer patients.

Variable	During NACRT (n=17)				Post-NACRT/pre-surgery (n=14)			
	Mean (SD)	Percentage not at all[1]	Percentage somewhat[2]	Percentage quite a bit[3]	Mean (SD)	Percentage not at all[1]	Percentage somewhat[2]	Percentage quite a bit[3]
Medical appointments	1.3 (1.0)	88.2	5.9	5.9	1.4 (0.8)	78.6	21.4	0.0
Lack of motivation	2.0 (1.2)	47.1	47.1	5.9	2.1 (1.0)	21.4	78.6	0.0
Travelling to the fitness centre	1.3 (0.6)	76.5	23.5	0.0	---	---	---	---
Too busy/lack of time	1.3 (0.6)	76.5	23.5	0.0	1.9 (1.4)	50.0	42.9	7.1
Feeling tired or fatigued	2.7 (1.4)	23.5	58.8	17.6	1.9 (1.0)	42.9	57.1	0.0
Side effects of chemoradiotherapy	3.9 (2.1)	11.8	47.1	41.2	2.3 (1.9)	64.3	7.1	28.6
Diarrhea	3.1 (1.9)	29.4	41.2	29.4	2.1 (1.8)	57.1	28.6	14.3
Abdominal pain/cramps	2.7 (1.8)	35.3	47.1	17.6	1.6 (1.0)	64.3	35.7	0.0
Skin irritation at irradiated site	1.7 (1.3)	70.6	23.5	5.9	1.5 (1.2)	78.6	14.3	7.1
Tingling/numbness/peeling (hands & feet)	1.9 (1.6)	64.7	29.4	5.9	1.6 (1.2)	71.4	21.4	7.1
Nausea/vomiting	1.7 (1.3)	76.5	17.6	5.9	1.3 (0.6)	85.7	14.3	0.0
Pain/soreness	2.6 (1.5)	29.4	52.9	17.6	1.6 (1.2)	64.3	28.6	7.1
Feeling sick	2.6 (1.9)	47.1	29.4	23.5	2.1 (1.8)	50.0	35.7	14.3
Illness or injury	1.5 (1.2)	82.4	11.8	5.9	1.4 (1.2)	85.7	7.1	7.1
Vacation	---	---	---	---	2.4 (2.1)	50.0	35.7	14.3
Bad weather	---	---	---	---	1.9 (1.4)	57.1	35.7	7.1
Lack of exercise supervision	---	---	---	---	1.5 (1.0)	78.6	21.4	0.0

Abbreviation: NACRT, neoadjuvant chemoradiotherapy.
[1]Percentage not at all = 1.
[2]Percentage somewhat = 2-4.
[3]Percentage quite a bit = 5-7.

CHAPTER 3: PAPER 2

Predictors of adherence to aerobic exercise in rectal cancer patients during and after neoadjuvant chemoradiotherapy

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3.1 Abstract

This pilot study explored predictors of adherence to exercise during and after neoadjuvant chemoradiotherapy (NACRT) in rectal cancer patients. Eighteen rectal cancer patients were prescribed 3 supervised aerobic exercise sessions/week during NACRT followed by ≥150 min/week of unsupervised aerobic exercise after NACRT. Although not statistically significant, adherence to supervised exercise during NACRT was meaningfully better for patients who were women (d=0.82; P=.12), younger (d=-0.62; P=.30), married (d=0.62; P=.42), with better mental health (r=0.32; P=.21), fewer diarrhea symptoms (r=0.48; P=.052), and higher anticipated enjoyment (r=0.31; P=.23), support (r=0.32; P=.22), and motivation (r=0.31; P=.23). After NACRT, adherence was significantly better for patients who reported worse mental health (r=-0.56; P=.046) and meaningfully better for patients who were women (d=0.54; P=.38), better educated (d=0.77; P=.22), had no comorbidities (d=-0.63; P=.17), and exercised at baseline (d=1.05; P=.12). Demographics, tumor side effects, and motivational variables may predict adherence to exercise during and after NACRT.

3.2 Introduction

Patients with locally advanced rectal cancer normally receive 5-6 weeks of neoadjuvant chemoradiotherapy (NACRT) followed by surgery 6-8 weeks later (Cravo et al., 2014). Although NACRT improves local disease control and possibly survival, it is also associated with side effects which may impede physical functioning and quality of life (QoL) as well as treatment completion, treatment response, and long-term prognosis (Sauer et al., 2004; Sauer et al., 2012). Exercise is an effective strategy for managing symptoms during cancer treatment (Mishra et al., 2012) and may even improve treatment completion rates (Courneya et al., 2007; Van Vulpen et al., 2016; van Waart et al., 2015), treatment response (Courneya et al., 2009), and long-term disease free survival (Courneya et al., 2014). No studies to date, however, have been conducted in rectal cancer patients during and after NACRT.

We previously conducted a phase I study testing the feasibility and safety of aerobic exercise during and after NACRT (Morielli et al., 2016b). In our primary paper, we reported that supervised aerobic exercise during NACRT followed by unsupervised aerobic exercise after NACRT was feasible and safe (Morielli et al., 2016b). Moreover, in a secondary paper, patients reported aerobic exercise during NACRT to be more enjoyable and less difficult than anticipated (Morielli et al., 2016a). Patients also identified potential barriers to supervised aerobic exercise during NACRT (e.g. treatment side effects, fatigue, and diarrhea) and unsupervised aerobic exercise after NACRT (e.g. lack of motivation, fatigue, and feeling sick) (Morielli et al., 2016a). Clearly, adherence is a critical factor in assessing the effectiveness of any exercise intervention for cancer patients. Here, we report the predictors of adherence to the supervised aerobic exercise during NACRT and unsupervised aerobic exercise after NACRT.

3.3 Methods

The methods for this study have been reported elsewhere (Morielli et al., 2016b). In brief, the study was a prospective, single-arm intervention study with assessments at baseline (i.e., pre-NACRT), immediately post-NACRT, and pre-surgery (about 6-8 weeks after NACRT). Eligibility criteria included rectal cancer patients scheduled to receive long-course NACRT followed by definitive surgery.

Exercise Intervention

Details of the exercise intervention have been described elsewhere (Morielli et al., 2016a; Morielli et al., 2016b). Briefly, the supervised aerobic exercise program began at the initiation of NACRT and continued during NACRT. The unsupervised aerobic exercise program began after NACRT until 1-2 weeks before surgery. During NACRT, the primary goal of the exercise intervention was to attend 3 sessions per week for the 6 weeks of NACRT. After NACRT, patients were asked to complete 150 minutes of moderate-intensity aerobic exercise per week.

Measures

Exercise Adherence

Exercise adherence during NACRT was assessed as the percentage of the 18 supervised sessions attended. After NACRT, exercise adherence was assessed as the number of aerobic exercise minutes per week using the Godin Leisure Time Exercise Questionnaire (GLTEQ) (Godin & Shephard, 1985) and were calculated as follows: moderate aerobic exercise minutes per week + 2 x vigorous aerobic exercise minutes per week.

Predictor Variables

Demographic and behavioral variables were assessed at baseline using self-report. Assessments of health-related fitness and patient-reported outcomes were made at baseline and

post-NACRT (Morielli et al., 2016b). A submaximal treadmill protocol was used to estimate functional aerobic capacity (VO_2 max) (Morielli et al., 2016b). QoL was assessed by the Medical Outcomes Study short form survey (SF-36) (Ware et al., 2007), fatigue was assessed by the Functional Assessment of Cancer Therapy- Fatigue (FACT-F) (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997), diarrhea was assessed by the FACT-Diarrhea (FACT-D) (Cella & Nowinski, 2002), and stress was assessed by the Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983). A higher score on the SF-36, FACT-F, and the FACT-D scales indicated better functioning. A higher score on the PSS indicated more perceived stress.

Assessment of motivational constructs were also made at baseline and post-NACRT based on the theory of planned behavior (TPB) (Ajzen, 1991). A detailed description of how these constructs were evaluated has been presented elsewhere (Morielli et al., 2016a).

Statistical Analyses

We used Mann-Whitney U tests to compare differences in adherence based on the dichotomized demographic, behavioral, and health predictors and Spearman's rank-order correlations to examine associations between continuous psychosocial and motivational predictors and adherence. Our phase I study was not powered to assess adherence predictors, therefore, we did not expect statistically significant findings based on a standard p value of $<.05$. Consequently, we interpreted our results for their potential meaningfulness based on at least a medium standardized effect size of $d \geq 0.50$ or r of ≥ 0.30. All analyses were conducted using SPSS® 23.

3.4 Results

Flow of participants through the trial has been reported elsewhere (Morielli et al., 2016b). In brief, 18 (56%) rectal cancer patients were recruited. At the post-NACRT timepoint, health-

related fitness data were obtained from 15 patients (89%) and patient-reported data were obtained from 17 patients (94%). At the pre-surgery timepoint, health-related fitness data and patient-reported data were obtained from 14 patients (78%). For the patients included in the current analysis, mean adherence to the supervised exercise sessions during NACRT was 77% (SD = 19%, range = 33% to 100%) and the mean number of aerobic exercise minutes per week post-NACRT was 160 (SD = 67 minutes, range = 60 to 270 minutes).

Predictors of Adherence to Supervised Exercise During NACRT

Associations between the various predictors and adherence to the supervised exercise during NACRT are presented in **Table 3-1** (demographic and health) and **Table 3-2** (psychosocial and motivational). Although not statistically significant, adherence during NACRT was meaningfully better for patients who were women (d= 0.82; P=.12), younger (d=-0.62; P=.30), married (d=0.62; P=.42), with better mental health (r=0.32; P=.21), fewer symptoms of diarrhea (r=0.48; P=.052), and who anticipated more enjoyment (r=0.31; P=.23), support (r=0.32; P=.22), and motivation (r=0.31; P=.23).

Predictors of Adherence to Unsupervised Exercise Post-NACRT

Associations between the various predictors and adherence to the unsupervised exercise post-NACRT are presented in **Table 3-3** (demographic and health) and **Table 3-4** (psychosocial and motivational). Adherence to the unsupervised exercise was significantly better in patients who reported worse mental health (r= -0.56, P=.046). Although not statistically significant, adherence was meaningfully better for patients who were women (d= 0.54; P=.38), better educated (d= 0.77; P=.22), had no comorbidities (d=-0.63; P=.17), and were aerobic exercisers at baseline (d=1.05; P=.12).

3.5 Discussion

A novel finding of our study was that patients who experienced more severe diarrhea at baseline had lower exercise adherence. Diarrhea is a symptom of rectal cancer itself and one of the potential major adverse effects of NACRT. In our primary paper, we found that diarrhea worsened during NACRT (Morielli et al., 2016b). Additionally, in our secondary paper, we reported that 71% of patients identified diarrhea as a potential barrier to exercise during NACRT (Morielli et al., 2016a). Although strategies to overcome this barrier have been identified (e.g., exercising close to bathroom facilities) (Courneya et al., 2005; Morielli et al., 2016a), diarrhea may be a significant factor limiting exercise adherence during NACRT.

Better mental health was positively associated with exercise adherence during NACRT but negatively associated with exercise adherence after NACRT. One possible explanation for this paradoxical finding is that rectal cancer patients who had better mental health after NACRT may have felt that they no longer needed to exercise. Another possible explanation is that mental health after NACRT may have been heavily influenced by the treatment experience and, therefore, altered its typical positive association with exercise adherence.

Our finding that motivational variables from the TPB were meaningful predictors of exercise adherence during NACRT is similar to the results from a previous supervised exercise study of colorectal cancer survivors mostly on treatments (Courneya et al., 2004). In the current study, however, we did not observe any meaningful or significant associations between motivational variables and adherence to the unsupervised exercise in the post-NACRT phase. This finding is unusual for unsupervised exercise and may be the result of our small sample size or the novel clinical setting.

The main limitation of our study is the small sample size which precludes us from making any definitive statements on the predictors of exercise adherence. Moreover, we did not collect information on treatment toxicity or environmental factors (Loh, Chew, & Lee, 2011a, 2011b) which may be important predictors of exercise adherence both during and after NACRT. Finally, our preliminary comparison of exercise predictors during and after NACRT may have been confounded by differences in the exercise program (i.e., supervised versus unsupervised).

In summary, we examined the predictors of adherence to exercise during and after NACRT in rectal cancer patients. Our results suggest that demographic variables, tumor/treatment side effects, and motivational variables may be important predictors of adherence to aerobic exercise in this clinical setting. The results also suggest that the predictors of exercise adherence during and post-NACRT may differ. Larger studies are needed to confirm our results. Understanding the predictors of exercise adherence in this clinical setting is critical to inform future exercise trials and, ultimately, clinical practice should it be warranted.

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Table 3-1. Associations of demographic and health variables with adherence to supervised aerobic exercise during neoadjuvant chemoradiation in rectal cancer patients (n=17). [a]

Variable[b]	Mean % ± SD[c]	d	*P*
Sex			
Male (n=12)	72 ± 21	0.82	.12
Female (n=5)	88 ± 11		
Age			
<60 years (n=7)	84 ± 12	-0.62	.30
≥ 60 years (n=10)	72 ± 23		
Marital Status			
Not married (n=6)	69 ± 26	0.62	.42
Married (n=11)	81 ± 15		
Education			
< College (n=10)	76 ± 22	0.15	.84
≥ College (n=7)	79 ± 17		
Employment Status			
Not working (n=10)	77 ± 22	-0.05	.69
Working full or part time (n=7)	76 ± 17		
Annual Income			
< 60,000 (n=6)	76 ± 17	0.00	.78
≥ 60,000 (n=10)	76 ± 22		
Comorbidities			
None (n=7)	80 ± 18	-0.31	.56
1 or more (n=10)	74 ± 21		
Body Mass Index (kg/m^2)			
<30.0 (n=11)	74 ± 22	0.41	.61
≥ 30.0 (n=6)	82 ± 14		
VO_2 max (ml/kg/min)			
<25 (n=8)	83 ± 13	-0.15	1.00
≥25 (n=7)	80 ± 18		
Smoking Status			
Never smoked (n=7)	81 ± 24	-0.36	.20
Ex/current smoker (n=10)	74 ± 17		
Baseline aerobic exerciser			
No (n=13)	78 ± 21	-0.21	.61
Yes (n=4)	74 ± 17		

[a] Abbreviation: VO_2 max, maximal oxygen uptake.
[b] All variables assessed at baseline (pre neoadjuvant chemoradiation).
[c] Supervised goal=18 sessions.

Table 3-2. Associations of baseline psychosocial and motivational variables with adherence to supervised aerobic exercise during neoadjuvant chemoradiation in rectal cancer patients (n=17).

Variable[a]	r	*P*
Psychosocial		
Physical health	0.25	.34
Mental health	0.32	.21
Fatigue	0.27	.30
Diarrhea	0.48	.052
Stress	-0.15	.58
Motivational		
Beneficial	0.24	.35
Enjoyable	0.31	.23
Support	0.32	.22
Motivation	0.31	.23
Difficulty	0.04	.88

[a] All variables assessed at baseline (pre neoadjuvant chemoradiation). Higher scores equal better psychosocial functioning or more motivation except for stress and difficulty.

Table 3-3. Associations of demographic and health variables with adherence to unsupervised aerobic exercise after neoadjuvant chemoradiation and before surgery in rectal cancer patients (n=13). [a]

Variable[b]	Mean % ± SD[c]	d	*P*
Sex			
Male (n=9)	149 ± 57	0.54	.38
Female (n=4)	185 ± 90		
Age			
<60 years (n=5)	162 ± 93	-0.05	.94
≥ 60 years (n=8)	159 ± 51		
Marital Status			
Not married (n=4)	183 ± 97	-0.48	.53
Married (n=9)	151 ± 53		
Education			
< College (n=6)	133 ± 74	0.77	.22
≥ College (n=7)	184 ± 54		
Employment Status			
Not working (n=7)	149 ± 84	0.38	.42
Working full or part time (n=6)	174 ± 41		
Annual Income			
< 60,000 (n=4)	143 ± 93	0.42	.49
≥ 60,000 (n=8)	171 ± 60		
Comorbidities			
None (n=6)	183 ± 61	-0.63	.17
1 or more (n=7)	141 ± 69		
Body Mass Index (kg/m^2)			
<30.0 (n=8)	171 ± 82	-0.42	.67
≥ 30.0 (n=4)	143 ± 38		
VO_2 max (ml/kg/min)			
<25 (n=6)	167 ± 84	0.18	.91
≥25 (n=4)	179 ± 51		
Smoking Status			
Never smoked (n=6)	177 ± 39	-0.47	.25
Ex/current smoker (n=7)	146 ± 84		
Baseline aerobic exerciser			
No (n=9)	139 ± 59	1.05	.12
Yes (n=4)	209 ± 63		
Exercise Adherence during NACRT			
<85% (n=7)	159 ± 75	0.05	.72
≥ 85% (n=6)	162 ± 62		

[a] Abbreviation: VO_2 max, maximal oxygen uptake.
[b] All variables assessed at baseline (pre neoadjuvant chemoradiation) except body mass index and VO_2 max which were assessed at post neoadjuvant chemoradiation.
[c] Unsupervised goal=150 min/wk.

Table 3-4. Associations of post neoadjuvant chemoradiation psychosocial and motivational variables with adherence to unsupervised aerobic exercise after neoadjuvant chemoradiation and before surgery in rectal cancer patients (n=13).

Variable[a]	r	*P*
Psychosocial		
Physical health	-0.26	.40
Mental health	-0.56	.046
Fatigue	-0.28	.36
Diarrhea	0.03	.91
Stress	-0.00	.99
Motivational		
Beneficial	-0.15	.62
Enjoyable	-0.22	.48
Support	0.17	.58
Motivation	0.22	.48
Difficulty	-0.10	.74

[a] All variables assessed at baseline (pre neoadjuvant chemoradiation). Higher scores equal better psychosocial functioning or more motivation except for stress and difficulty.

CHAPTER 4: PAPER 3

Exercise during and after neoadjuvant rectal cancer treatment (the EXERT trial): Study protocol for a randomized controlled trial

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4.1 Abstract

Background: Standard treatment for locally advanced rectal cancer includes 5-6 weeks of neoadjuvant chemoradiotherapy (NACRT) followed by total mesorectal excision 6-8 weeks later. NACRT improves local disease control and surgical outcomes but also causes side effects including fatigue, diarrhea, hand-foot-syndrome, and physical deconditioning that may impede quality of life (QoL), treatment completion, treatment response, and long-term prognosis. Interventions to improve treatment outcomes and manage side effects that are safe, tolerable and low-cost are highly desirable. Exercise has been shown to improve some of these outcomes in other cancer patient groups but no study to date has examined the potential benefits (and harms) of exercise training during and after NACRT for rectal cancer. **Methods:** The Exercise During and After Neoadjuvant Rectal Cancer Treatment (EXERT) trial is a prospective, two-armed, phase II randomized controlled trial designed to test the preliminary efficacy of exercise training in this clinical setting and to further evaluate its feasibility and safety. Participants will be 60 rectal cancer patients scheduled to receive long-course NACRT followed by total mesorectal excision. Participants will be randomly assigned to exercise training or usual care. Participants in the exercise training group will be asked to complete 3 supervised high-intensity interval training sessions/week during NACRT and ≥ 150 minutes/week of unsupervised moderate-to-vigorous intensity continuous exercise training after NACRT prior to surgery. Participants in the usual care group will be asked not to increase their exercise from baseline. Assessments will be completed pre-NACRT, post-NACRT, and pre-surgery. The primary endpoint will be cardiorespiratory fitness (VO_2 peak) at the post-NACRT timepoint assessed by a graded exercise test. Secondary endpoints will include functional fitness assessed by the Senior's Fitness Test, QoL assessed by the European Organisation of Research and Treatment of Cancer, and symptom

management assessed by the M.D. Anderson Symptom Inventory. Exploratory clinical endpoints will include treatment toxicities, treatment completion, treatment response, and surgical complications. **Discussion:** If the preliminary findings of EXERT are positive, additional research will be warranted to confirm if exercise is an innovative treatment to maintain QoL, manage side effects, and/or improve treatment outcomes in rectal cancer patients.

4.2 Background

Current standard treatment for locally advanced rectal cancer (stages II and III) includes long-course (5-6 weeks) neoadjuvant chemoradiotherapy (NACRT) followed by surgical resection using total mesorectal excision 6-8 weeks later [1]. When compared to postoperative chemoradiotherapy, NACRT improves local recurrences rates and may improve surgical outcomes in some patients [2, 3]. Unfortunately, NACRT causes acute toxicities including fatigue, diarrhea, hand-foot-syndrome, hematologic toxicity, cardiotoxicity, and physical deconditioning that can cause declines in quality of life (QoL) [4] and may even impede treatment completion, treatment response, and long-term prognosis. Safe, tolerable, and low-cost interventions to manage these side effects and improve treatment outcomes in this clinical setting are highly desirable. We propose that an exercise training intervention initiated during NACRT in patients with rectal cancer may improve cardiorespiratory fitness, symptom management, QoL, treatment completion, treatment response, surgical complications, and possibly even survival **(Figure 4-1)**.

Exercise has been shown to manage some side effects and improve QoL in several cancer patient groups receiving adjuvant therapy [5]. Moreover, limited research has suggested that exercise during chemotherapy for some cancer patient groups may improve chemotherapy completion rates [6-8], treatment response [9], and even long-term survival [10]. Additionally, there is some evidence that pre-operative exercise may improve fitness and surgical outcomes in cancer patients [11]. Finally, preliminary evidence has suggested that exercise is feasible and safe in the neoadjuvant setting [12].

Despite the emerging evidence for the benefits of exercise in some cancer patient groups receiving some treatment protocols, only preliminary research has examined exercise in rectal

cancer patients during and after NACRT. Similar to drug trials, exercise trials have demonstrated that research in one cancer patient/treatment group rarely generalizes to another cancer patient/treatment group [13]. Preliminary research suggests that exercise initiated immediately *after* NACRT is feasible and may improve cardiorespiratory fitness [14], which has prompted a phase II trial in this clinical space [15]. Furthermore, two phase I studies [16, 17], including one from our group [16], have demonstrated the preliminary feasibility and safety of exercise *during* NACRT for rectal cancer patients. Finally, one ongoing randomized controlled trial is examining the feasibility of an unsupervised walking program both during and after NACRT (ISRCTN62859294). Here, we propose the Exercise During and After Neoadjuvant Rectal Cancer Treatment (EXERT) trial which, to our knowledge, is the first phase II trial designed to examine the preliminary efficacy of exercise training in rectal cancer patients during and after NACRT.

Study Objectives

Primary Objective

The primary objective of the EXERT trial is to examine the effects of a supervised high-intensity interval training (HIIT) program, compared to usual care, on cardiorespiratory fitness during NACRT.

Secondary Objectives

The secondary objectives of the EXERT trial are to (1) compare an unsupervised moderate-to-vigorous intensity continuous exercise training program after NACRT to usual care on cardiorespiratory fitness, (2) compare the supervised HIIT program during NACRT and unsupervised continuous exercise training program after NACRT on functional fitness, QoL, and symptom burden, (3) establish the feasibility and safety of the supervised HIIT program during

NACRT, and (4) investigate the motivational outcomes and determinants of exercise during and after NACRT.

Exploratory Objectives

The exploratory objectives of the EXERT trial are to compare a supervised HIIT program during NACRT followed by an unsupervised moderate-to-vigorous intensity continuous exercise training program after NACRT to usual care on clinical outcomes including treatment toxicities, treatment completion, treatment response, and surgical complications.

4.3 Methods/Design

Study Design

The EXERT trial will be a single centre, prospective, two-armed, phase II randomized controlled trial conducted in Edmonton, Alberta. The EXERT trial has been approved by the Health Research Ethics Board of Alberta- Cancer Committee and all participants will be required to provide written informed consent. The proposed participant flow through the study is shown in **Figure 4-2**. Health-related fitness outcomes and patient-reported outcomes will be assessed at baseline (0-7 days before starting NACRT), post-NACRT (0-7 days after completing NACRT), and pre-surgery (7-14 days before the planned surgery date). The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure for the EXERT trial is shown in **Figure 4-3**.

Eligibility Criteria

Men and women will be eligible for the trial if they (1) are ≥ 18 years old, (2) are scheduled to received standard NACRT consisting of 5-6 weeks of radiotherapy (45-54 Gy) with concurrent chemotherapy (oral capecitabine or intravenous 5-fluorarcil) followed by total mesorectal excision (3), receive medical clearance to participate in the study as determined by

their treating oncologist, the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+), and a Certified Exercise Physiologist, (4) are able to complete the pre-NACRT graded exercise test, (5) are not currently engaging in any regular vigorous-intensity exercise and/or ≥ 150 minutes of moderate-intensity exercise/week, (6) are able to provided written informed consent and complete questionnaires in English and, (7) are willing to be randomized to exercise training or usual care (no exercise) for 12 weeks.

Recruitment

Prospective patients will be approached by the treating radiation oncologist and study coordinator at the time of their initial radiation consultation. The study coordinator will follow-up with eligible patients by phone and schedule interested patients for pre-NACRT testing. This recruitment strategy was effective in our feasibility study with 18 of 32 patients (56%) being recruited over a 6 month period [16].

Randomization and Blinding

After completing all baseline assessments, patients will be randomly assigned to either the exercise training group or usual care group in a 1:1 ratio using block randomization. A research assistant, not otherwise involved in the trial, will generate the block sizes and randomization sequence using a computer-generated random allocation sequence which will be concealed from the study coordinator recruiting patients. Given the nature of the intervention, it is not possible to blind the investigators or participants to group allocation. Additionally, due to logistical challenges at our facility, it is difficult to blind outcome assessors to group allocation for the primary outcome of cardiorespiratory fitness and the secondary outcomes of functional fitness. Nevertheless, fitness outcome assessors will follow a detailed protocol and be trained in the importance of standardizing outcome assessments and avoiding bias. Moreover, outcome

assessors will not review the metabolic data during the cardiorespiratory fitness test, and the criteria for achieving peak volume of oxygen consumption (VO_2 peak) will undergo an independent review. Finally, outcome assessors will be blinded to group assignment for the exploratory outcomes of treatment toxicities, treatment completion, treatment response, and surgical complications which will be assessed by medical staff not otherwise involved in the study.

Intervention

For patients randomized to the exercise training group, the intervention will be divided into two phases: (1) during NACRT and (2) post-NACRT. During NACRT, all of the exercise sessions will be supervised by a Certified Exercise Physiologist. We previously determined that it was feasible for patients to attend supervised exercise sessions at our fitness centre (within a 5 minute walk from the cancer centre) since they were already coming to the cancer centre 5 days/week for radiation treatment [16]. During NACRT, patients will be asked to complete 18 supervised HIIT sessions (i.e. 3 session/week for 6 weeks) and to continue with any light-to-moderate intensity exercise they were performing at baseline. We selected a HIIT program for evaluation because of its ability to maximize cardiorespiratory fitness improvements over a short period of time [18]. Moreover, HIIT has previously demonstrated safety and feasibility in clinical populations including patient with cardiometabolic disease [19], diabetes [20], and during adjuvant chemotherapy in patients with mixed cancers [21]. HIIT is characterized by relatively short bursts of vigorous intensity exercise, interspersed by periods of rest or light intensity exercise for recovery. There are an endless number of possible combinations that can make up a HIIT program; however, HIIT typically refers to exercise intensities corresponding to ≥85% of peak heart rate or ≥80% of VO_2 peak [19]. We have designed the HIIT program in the

EXERT trial to closely match a previously published HIIT program which has demonstrated feasibility, safety, and greater improvements in cardiorespiratory fitness in patients with coronary artery disease [22].

In our phase I study, we demonstrated an excellent median attendance rate of 83% to 3 sessions/week of moderate-intensity continuous exercise training during NACRT [16]. Moreover, no adverse events were observed and our evaluation was that even higher intensity exercise training would be feasible in this clinical setting. Nevertheless, the safety and feasibly of HIIT during NACRT in rectal cancer patients has yet to be established and is a key objective of our study.

In our feasibility study, the most frequently used modality was the treadmill (67.4% of sessions) [16]. Thus, the HIIT program will consist of uphill treadmill walking. Each HIIT session will start with a 5 minute warm-up at a workload that elicited 30-40% of VO_2 peak during the baseline graded exercise test. Patients will complete 2-minute, high-intensity intervals at a workload that elicited 85% of VO_2 peak during the baseline graded exercise test. Between the high-intensity intervals, the active-recovery intervals will consist of 2 minutes at a workload that elicited 40% of VO_2 peak during the baseline graded exercise test. Each HIIT exercise session will end with a 5 minute cool-down totaling 40 minutes/session. The number of HIIT intervals will begin at 5 and progress by 1 every second session up to 8 intervals (**Table 4-1**).

Prior to each exercise session, an exercise specialist will assess blood pressure and heart rate and ask patients to report any immediate symptoms. Additionally, body temperature will be assessed in patients reporting any signs or symptoms of a fever. If body temperature is ≥ 38 degrees Celsius, patients will be instructed not to exercise that day. For each supervised session, the exercise specialist will record attendance and the workload (i.e. treadmill speed and incline),

RPE (Borg 0-10), and heart rate for each high-intensity interval. Optimal adherence to the supervised exercise sessions will be facilitated by scheduled appointments, flexibility in scheduling the exercise sessions (i.e. according to patients' radiation sessions), immediate follow-up and re-booking of missed sessions, personable exercise trainers, and free parking. In our feasibility study, we identified the most common barriers to exercising during NACRT as side effects from chemoradiotherapy (88%), fatigue (76%) and diarrhea (71%) [23]. In the EXERT trial, we will optimize adherence to the supervised exercise sessions by modifying each session according to any immediate symptoms or side effects patients are experiencing.
If a patient is experiencing immediate side effects that hinder their ability to complete the high-intensity intervals at the prescribed workload, the fitness attendant will modify the exercise session according to what the patient is able and willing to do. Options for modifying the exercise dose will include either reducing the workload of the high-intensity intervals, reducing the number of high-intensity intervals, or both. All reasons for dose modification will be noted.

After NACRT, patients will be asked to complete at least 150 minutes of unsupervised moderate-to-vigorous intensity continuous exercise training training/week (current Canadian Physical Activity Guidelines). In our phase I study, it was feasible for patients to achieve 150 minutes of mostly unsupervised moderate-intensity exercise/week after NACRT. Although local patients in our pilot study were offered a supervised exercise program after NACRT, only 2 out of 16 patients expressed interest in continuing with supervised exercise in this phase and patients mainly achieved their weekly exercise minutes by walking outdoors or by using pre-existing home exercise equipment (e.g. treadmill, elliptical, and upright bike). For this reason, we felt it would be difficult to deliver a standardized and replicable HIIT program after NACRT. Moreover, in our phase I study, cardiorespiratory fitness improved by 2.4 ml/kg/min from post-

NACRT to pre-surgery suggesting that an unsupervised moderate-intensity continuous exercise training program may be effective at improving cardiorespiratory fitness after NACRT and prior to surgery in rectal cancer patients. Finally, after our experience in the phase I study, we felt that it would be feasible and safe for rectal cancer patients to complete moderate-to-vigorous intensity continuous exercise in this phase and may result in greater improvements in cardiorespiratory fitness. Nevertheless, one of the goals of the EXERT trial is to further establish the feasibility and safety of continuous exercise training after NACRT and to determine its preliminary efficacy at improving outcomes for rectal cancer patients.

After NACRT, the exercise will be individualized according to patients post-NACRT graded exercise test (i.e. heart rate that corresponded with approximately 46-91% of VO_2 peak) [24]. Patients will be provided with a heart rate monitor and will also be instructed on how to use RPE and the talk-test to determine the intensity of their exercise sessions. Patients will be provided with examples of how to complete the exercise (e.g. 30 minutes, 5 days/week; 50 minutes, 3 days/week). Moreover, patients will be instructed that, the exercise completed in this phase should be in addition to what they were already doing at baseline. Finally, patients will receive printout materials with instructions on how to complete the exercise in the post-NACRT phase as well an exercise log to help them keep track of their exercise. After NACRT, optimal adherence will be achieved using a more formal behavioral support program based on the theory of planned behavior [25]. The study coordinator will maintain weekly contact with each patient via telephone and offer behavioral support sessions consisting of standard behavioral change techniques including goal setting, planning, self-monitoring, and overcoming barriers.

Usual Care Group

Patients randomized to the usual care group will receive standard medical care which includes meeting with a dietician weekly to ensure adequate caloric and nutrient intake. Patients in the usual care group will be asked not to increase their physical activity/exercise levels during or after NACRT. Exercise is not currently part of standard care for these patients at our center and patients do not receive any exercise recommendations. After the pre-surgery assessment, patients in the usual care group will be offered a copy of the Canadian Physical Activity Guidelines and encouraged to initiate an exercise program after they recover from surgery and receive medical clearance from their doctor.

Outcome Measures

Primary Outcome Measure

We selected *cardiorespiratory fitness* as the primary endpoint for the EXERT trial because there is clinical equipoise as to whether 6 weeks of HIIT during NACRT is sufficient to meaningfully improve cardiorespiratory fitness. Moreover, cardiorespiratory fitness is an established surrogate for some patient-reported outcomes and clinical outcomes [9, 26-29]. Our primary measure of cardiorespiratory fitness, VO_2 peak, will be assessed by the modified Bruce graded exercise test on a treadmill with direct measures of cardio-respiratory variables using a metabolic measurement system (Parvo Medics TrueOne® 2400; Sandy, UT) [30, 31]. The modified Bruce treadmill protocol was designed for use in high-risk and elderly individuals. Briefly, the protocol will start at 1.7 mph and 0% grade and will progress every 3 minutes until the patient reaches volitional fatigue or if any exercise contraindications occur. During the test, heart rate will be monitored continuously and recorded every minute and blood pressure, oxygen saturation, and rating of perceived exertion will be measured and recorded in the last minute of

every stage. Immediately after the test, patients will complete a 5 minute active recovery (1.7 mph and 0% grade). During the active recovery, heart rate, blood pressure, and oxygen saturation will continue to be monitored and recorded at 1 minute and 5 minutes.

Secondary Outcome Measures

Functional fitness will be assessed by the Senior's Fitness Test which measures basic mobility-related parameters associated with functional abilities in the everyday living of older adults [32, 33]. The Senior's Fitness Test consists of six items including the 30-second chair stand (assessment of lower body strength), the arm curl (assessment of upper body strength), the chair sit-and-reach (assessment of lower body flexibility), the back scratch (assessment of upper body flexibility), the 8-foot up-and-go (assessment of agility and dynamic balance), and the six-minute walk (assessment of aerobic endurance).

Quality of life will be assessed by the widely used and validated European Organisation of Research and Treatment of Cancer (EORTC) core 30-item questionnaire (QLQ-C30) version 3.0 [34]. We selected the EORTC QLQ-C30 because it assesses symptoms, physical function, psychosocial function, and overall QoL [35]. The EORTC QLQ-C30 is composed of five multi-item functional scales (physical, cognitive, role, emotional, and social), three multi-item symptom scales (fatigue, nausea and vomiting, and pain), five single-item symptom scales (dyspnea, insomnia, loss of appetite, constipation, and diarrhea), a single-item financial impact scale, and a two-item global health and QoL scale. Additionally, the EORTC-QLQ-CR29 (colorectal cancer) will be used to assess QoL. The EORTC QLQ-CR29 has demonstrated acceptable validity and reliability for its supplemental use with the QLQ-C30 to assess the QoL of colorectal cancer patients during treatment [36]. The EORTC QLQ-CR29 contains 29 questions and evaluates urinary dysfunction, gastrointestinal symptoms, body image, separate

concerns for persons with or without a stoma, and sexual function (separate scale for men and women). Items for both questionnaires are evaluated using a 1 week time frame (i.e. “during the past week”) on a 4-point scale (“not at all”, “a little”, quite a bit”, very much”), except for the global health scale of the QLQ-30, which is measured on a 7-point scale ranging from “very poor to “excellent”. For both the QLQ-C30 and QLQ-CR29, a higher score on the functional scales indicates better functioning, whereas a higher score on the symptom scales indicates worse symptoms.

Overall symptom burden will be assessed by the M.D. Anderson Symptom Inventory (MDASI) [37]. We selected the MDASI because it is brief and easy to use, and captures the most frequently reported disease- and treatment-related symptoms. The MDASI scale consists of 13 core symptom items (pain, fatigue, nausea, disturbed sleep, distress (emotional), shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling) and 6 interference items (general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life). In addition to the 13 core symptoms, we will incorporate 4 additional symptoms that are specifically relevant in this clinical setting: mouth sores, hand-foot-syndrome, diarrhea, and skin reaction at the site of irradiation.

Exercise motivation will be assessed using the Theory of Planned Behaviour (TPB) [25]. The key TPB constructs including attitudes, subjective norms, intention, and perceived behavioral control will be assessed using standardized items [38]. At the pre-NACRT timepoint, all patients will be asked to prospectively evaluate their motivation for the HIIT program. After NACRT, patients randomized to the exercise group will be asked to retrospectively evaluate their motivation for the HIIT program during NACRT and their prospective motivation for the exercise program post-NACRT. Before surgery, patients in the exercise group will be asked to

evaluate their retrospective motivation for the exercise program post-NACRT, and all patients will be asked to evaluate their prospective motivation for exercising after surgery. All questions will be evaluated on a 5-point scale ranging from 1 ("not at all") to 5 ("very much").

Feasibility and Safety

The feasibility and safety of the exercise intervention will be determined based on eligibility rate, recruitment rate, exercise adherence rate, assessment rate, and adverse events. The willingness of rectal cancer patients to be randomized to a supervised HIIT program during NACRT is unknown, however, based on the results of our feasibility study, we anticipate a recruitment rate ≥ 50% [16]. Moreover, we do not know the willingness of patients in the usual care group to return for all follow-up assessments, however, based on the results of our feasibility study, we anticipate a follow-up assessment rate ≥ 80% at each time point [16].

Exercise adherence during NACRT will be assessed by the number of exercise sessions attended out of 18 as well as adherence to the workload and duration of the high-intensity intervals. Based on the results from our phase I study [16], we anticipate a median attendance rate to the supervised exercise training during NACRT ≥ 80%. Exercise adherence to the unsupervised exercise training after NACRT will be assessed by self-report using the Godin Leisure-Time Exercise Questionnaire (GLTEQ) [39]. Based on our previous results [16] we anticipate that the mean number of moderate-to-vigorous intensity exercise minutes post-NACRT will be ≥ 222 per week. Safety will be assessed by monitoring any serious adverse events that occur during exercise testing or the supervised exercise sessions. No serious exercise-related adverse events were observed in our previous study [16].

Exploratory Outcome Measures

Treatment toxicities will be assessed by clinical nurses on a weekly basis during NACRT using the National Cancer Institute Common Toxicity Criteria for Adverse Events Version 3.0. *Treatment Completion* will be assessed as the number of patients completing 100% of their planned radiation dose within 1 week of the planned completion date using electronic medical records. Additionally, the number of patients receiving ≥ 80% of their planned chemotherapy dose will be recorded. *Treatment Response* will be assessed by pathologic complete response as reported by the pathologist after reviewing the surgical sample. *Surgical outcomes and complications* will be obtained from medical records.

Baseline Descriptive Variables

Demographic variables will be collected from the baseline questionnaire and will include age, sex, marital status, education, income, employment status, and ethnicity. *Behavioral variables* will include smoking and physical activity. Physical activity (PA) will be assessed using the GLTEQ [39]. All participants will complete the GLTEQ at baseline (PA in the past month), post-NACRT (unsupervised PA in the exercise training group; all PA in the usual group), and pre-surgery (all PA in both the exercise training and usual care groups). *Medical variables* will be abstracted from medical records at baseline and will include disease stage, chemotherapy protocol, and ostomy. Comorbidities and a list of medications will be collected in the baseline questionnaire.

Body composition/anthropometry will be assessed by height, weight, and waist and hip circumference [40, 41].

Sample Size

Based on our feasibility study recruiting 18 patients in six months, we anticipate recruiting 60 patients over a 20 month period and randomizing 30 patients to each group. Based on this sample size, our study has 80% power, with a two-tailed alpha <0.05, to detect a clinically meaningful effect of 3.5 ml/kg/min on our primary outcome of VO_2 peak at post-NACRT, assuming a standard deviation of 5.6 ml/kg/min, 10% missing data, and adjustment for baseline value and other prognostic covariates [42]. This power may be sufficient for detecting differences in our secondary patient-reported outcomes if the effects are at least moderate (i.e., a standardized effect sizes of approximately ≥ d=0.60). This power is unlikely sufficient for detecting potentially meaningful differences in any of the exploratory clinical outcomes. Given that the purpose of this phase II trial is to inform phase III trials, the patient-reported and clinical outcomes will be interpreted for potential clinical significance based on the direction and magnitude of numerical differences.

Data Analysis

We will use analysis of covariance (ANCOVA) at both the post-NACRT and pre-surgery timepoints to compare the two groups on all primary and secondary outcomes with adjustment for baseline value of the outcome as well as other potential covariates. All statistical analyses will be based on the intention-to-treat principle and include all patients with baseline and follow-up data. No missing data replacement strategies will be performed for this phase II trial as we anticipate <10% missing data. Chi-square analyses will be used to explore between group differences in the categorical and ordinal clinical outcomes. All analyses will be performed using SPSS (SPSS Inc., Chicago, IL).

4.4 Discussion

NACRT is part of standard care for locally advanced rectal cancer and results in improvements in local recurrence rates and surgical outcomes. Furthermore, about 10-20% [43, 44] of patients achieve a pathologic complete response to NACRT which is associated with better disease control and surgical outcomes [45]. Moreover, despite advances in supportive care management, NACRT still causes toxicities that can negatively impact outcomes for rectal cancer patients. Interventions to manage side effects, improve QoL and optimize treatment outcomes are needed. Exercise is a low-cost, low-toxicity intervention that improves symptom management, cardiorespiratory fitness, and QoL in several cancer patient groups, however, no definitive studies have examined the impact of exercise on outcomes for locally advanced rectal cancer patients. Loughney et al. [15] are currently conducting a randomized controlled trial in rectal cancer patients focused on the post-NACRT phase and Moug et al. (ISRCTN62859294) are currently examining the effects of an unsupervised walking program during and after NACRT. We propose that an exercise training intervention both during and after NACRT may have additional benefits for symptom management, QoL, treatment outcomes, and possibly even survival **(Figure 4-1)**.

The results from our phase I single arm study demonstrated that rectal cancer patients are willing and able to participate in a supervised moderate intensity continuous exercise training intervention during NACRT followed by an unsupervised moderate intensity continuous exercise training intervention after NACRT [16]. More specifically, we reported an excellent recruitment rate of 56% (18/32 patients) over six months and a follow-up assessment rate of >80% [16]. Moreover, the median attendance rate for the supervised exercise during NACRT was 83%. After NACRT, patients completed an average of 222 ± 155 minutes/week of unsupervised

exercise [16]. No adverse events were observed and our evaluation was that even higher intensity exercise would be feasible in this clinical setting [16]. Despite the exercise intervention, most health-related fitness outcomes and patient-reported outcomes declined during NACRT and recovered after NACRT [16]. Consequently, any benefit from exercise during NACRT is likely related to preventing declines in functioning. Moreover, patients reported they experienced several benefits from exercise (e.g., physical fitness, quality of life, self-esteem) but they also perceived some potential harms (e.g., worsening fatigue, diarrhea, skin irritation, hand-foot syndrome) [23]. We concluded that moderate intensity continuous exercise training during and after NACRT for rectal cancer is feasible and safe, and that phase II randomized controlled trials are needed to establish the benefits (and possible harms) of exercise in this clinical setting [16, 23].

The EXERT trial will be the first to evaluate the efficacy of exercise training for improving outcomes in rectal cancer patients during and after NACRT. Furthermore, the EXERT trial will establish the feasibility and safety of a HIIT program in this unique and challenging clinical setting. To date, most exercise oncology studies have focused on high volume, continuous, moderate-to-vigorous intensity exercise training [46]. HIIT is receiving attention in cancer patients [47-49] because of its ability to generate larger and more rapid improvements in maximal volume of oxygen consumption (VO_2 max) which may be a surrogate for important clinical outcomes such as QoL and survival [9, 26, 28]. Although moderate-intensity continuous exercise training is beneficial for cancer patients, HIIT may be viewed as a potentially "high risk-high reward" exercise training intervention because its greater risk for safety and feasibility challenges may be offset by its greater potential for improved outcomes. Moreover, HIIT may be

especially attractive in clinical settings such as during NACRT or pre-surgery where shorter time frames are available for intervention delivery.

The EXERT trial will also be one of the few exercise oncology trials to examine the impact of exercise in the neoadjuvant setting and one of the few to include clinical cancer outcomes (e.g., treatment completion, pathologic complete response, postsurgical outcomes). In the rectal cancer setting, observational data suggest that cardiorespiratory fitness declines during NACRT and that pre-surgical cardiorespiratory fitness may predict post-surgical complications [29]. Initiating an exercise training intervention during NACRT could potentially optimize improvements in cardiorespiratory fitness which may result in fewer post-surgical complications and better post-surgical recovery when compared to an exercise training intervention initiated after NACRT. Additionally, poor compliance to external beam radiation has been associated with an increased risk of disease recurrence and death [50]. If exercise is effective in managing symptoms and subsequently improving treatment compliance, radiation therapy may be optimized and result in better outcomes in this clinical setting. Finally, tumor hypoxia has been identified as a factor limiting the effectiveness of radiation therapy [51]. Pre-clinical models suggest that exercise may cause favorable changes in the vasculature of solid tumors thereby enhancing tumor oxygenation and possibly the effectiveness of radiation therapy [52-55]. Although these findings are intriguing, they have yet to be replicated in human clinical trials. Nevertheless, these are the outcomes that are most important to patients and clinicians and likely to drive changes in clinical practice.

To summarize, EXERT is the first phase II trial designed to generate preliminary efficacy data on the benefits and harms of exercise training, including clinical outcomes, in rectal cancer patients during and after NACRT. Additionally, EXERT will also establish the feasibility and

safety of a supervised HIIT program in rectal cancer patients during NACRT. If the EXERT trial shows that exercise is safe, tolerable and produces meaningful improvements in cardiorespiratory fitness, symptom management, QoL, and/or clinical outcomes, larger phase II and III trials designed to target these outcomes will be necessary to determine if exercise should be integrated in standard clinical care for this patient population.

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Table 4-1. High-intensity interval training program during neoadjuvant chemoradiotherapy in the EXERT Trial.

Session	Interval Period			Recovery Period			Total Duration Minutes
	No.	Duration Minutes	Intensity % VO_2 peak[1]	No.	Duration Minutes	Intensity % VO_2 peak[1]	
1-2	5	2	85	4	2	40	28
3-4	6	2	85	5	2	40	32
5-6	7	2	85	6	2	40	36
7-18	8	2	85	7	2	40	40

[1]Prescribed according to workload (treadmill speed and incline) that elicited 85% of VO_2 peak (interval period) and 40% of VO_2 peak (recovery period) during baseline graded exercise test.
Note: All HIIT Sessions Start with a 5 minute warm-up and end with a 5 minute cool-down.

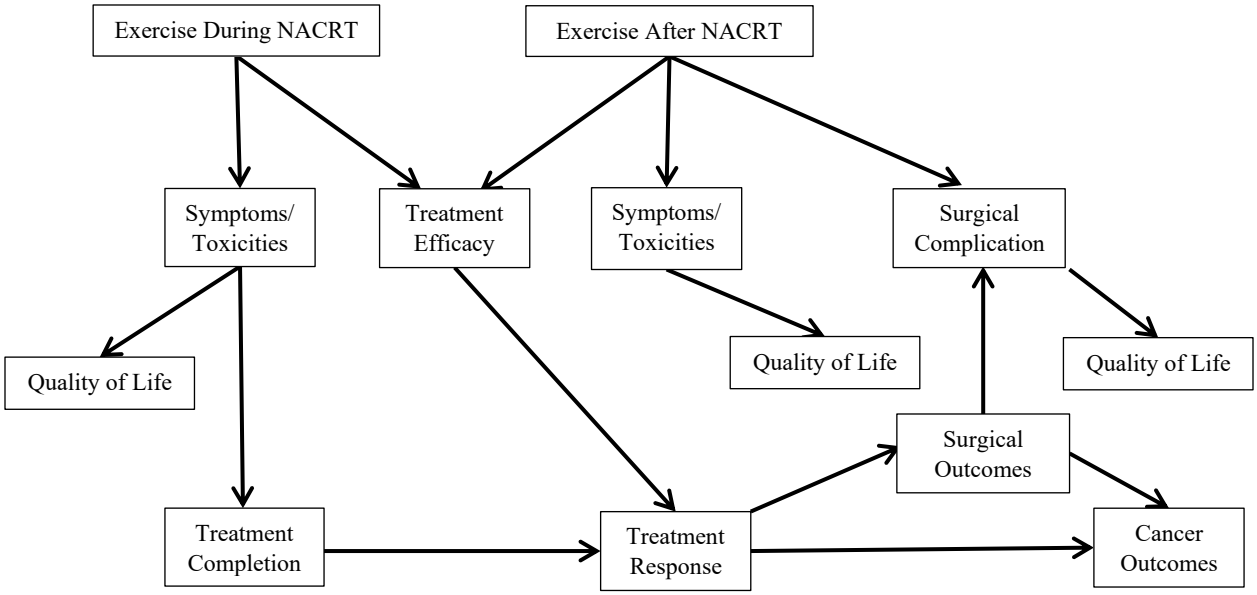

Figure 4-1. Proposed effects of exercise during and after neoadjuvant chemoradiotherapy in rectal cancer patients.

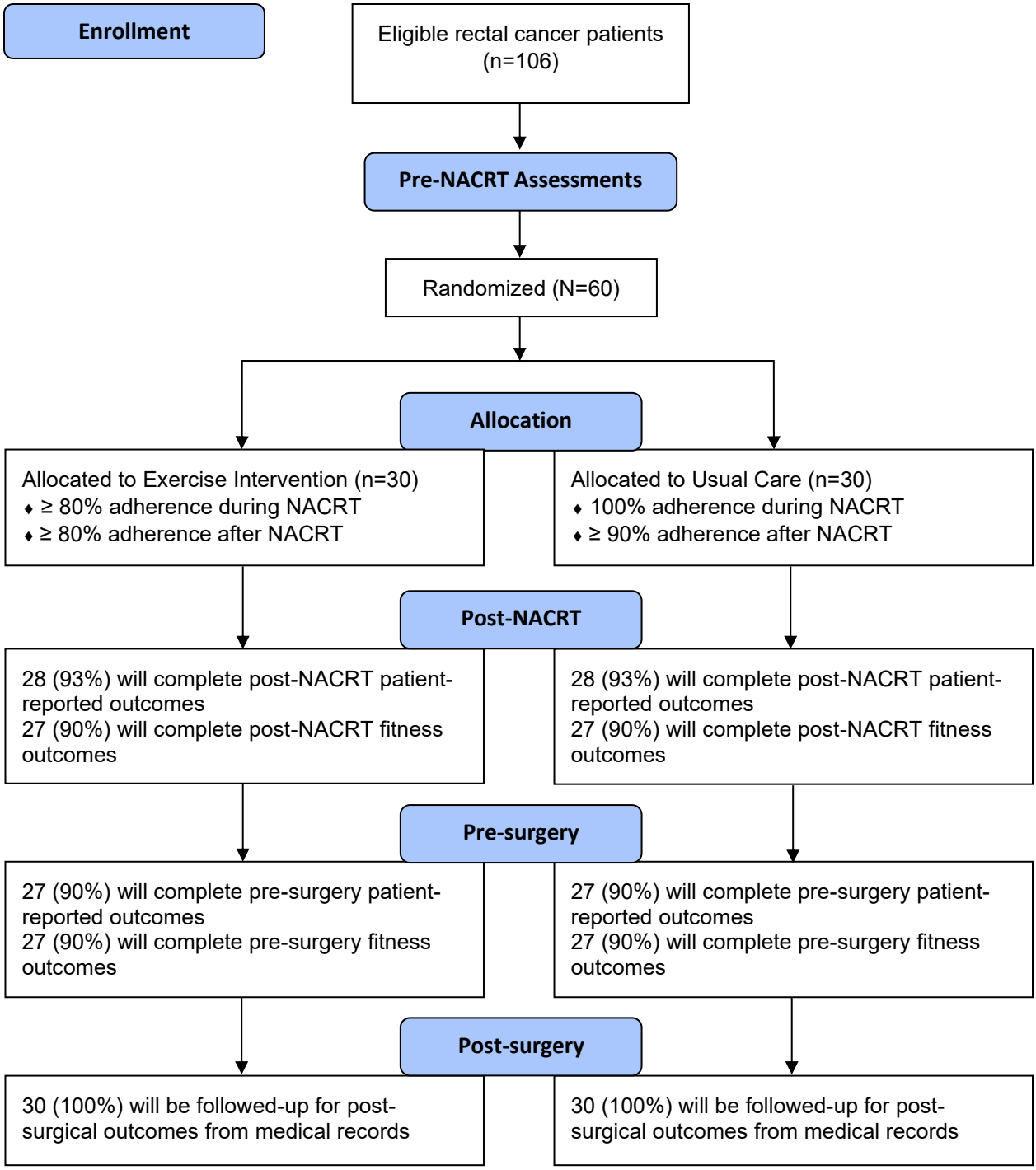

Figure 4-2. Proposed flow of participants through the EXERT Trial.

	STUDY PERIOD						
	Enrolment & Baseline Assessment	**Allocation**	**Post-allocation**			**Close-out**	
TIMEPOINT	$-t_1$	*0*	t_1	t_2	t_3	t_4	t_5
	Pre-NACRT	***Pre-NACRT***	***Exercise during NACRT***	***Post-NACRT Assessment***	***Exercise post-NACRT***	***Pre-surgery Assessment***	**Post-surgery follow-up**
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Randomization		X					
INTERVENTIONS:							
Exercise Training			←	—	→		
Usual Care			←	—	→		
ASSESSMENTS:							
Primary outcome: *Cardiorespiratory fitness.*	X			X		X	
Secondary outcomes: *Functional fitness, quality of life, symptom burden, and exercise motivation.*	X			X		X	
Feasibility and safety outcomes	X	X	X	X	X	X	X
Exploratory outcomes: *Treatment toxicities, treatment completion, treatment response, and surgical outcomes and complications.*			X	X	X	X	X

Figure 4-3. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure for the EXERT Trial.

CHAPTER 5: PAPER 4

Feasibility, safety, and preliminary efficacy of exercise during and after neoadjuvant chemoradiation for rectal cancer: The EXERT randomized controlled trial

5.1 Abstract

Background: Neoadjuvant chemoradiation (NACRT) improves outcomes for rectal cancer patients; however, there are dose-limiting toxicities and only a 15-27% pathologic complete response (pCR) rate. Exercise may help manage toxicities and improve treatment response in this clinical setting but feasibility and early efficacy have not been demonstrated. EXERT was a phase II trial designed to establish the feasibility and safety of exercise in this clinical setting and provide the first evidence of clinical activity. **Methods**: Rectal cancer patients scheduled to receive NACRT were randomly assigned to usual care (n=18) or exercise (n=18) involving supervised exercise during NACRT and unsupervised exercise after NACRT. The primary outcome was cardiorespiratory fitness (VO_2 peak). Clinical outcomes included treatment toxicities, treatment completion, and treatment response. **Results**: Median attendance at supervised exercise sessions during NACRT was 82%, and median self-reported exercise minutes/week post-NACRT was 90 minutes. From baseline to post-NACRT, VO_2 peak increased by 0.4 $ml \cdot kg^{-1} \cdot min^{-1}$ in the exercise group and decreased by 0.8 $ml \cdot kg^{-1} \cdot min^{-1}$ in the usual care group (p=0.47). There were no significant differences between groups for grade 3/4 toxicities or treatment completion. The number of patients achieving a pCR or near pCR was 56% in the exercise group compared to 18% in the usual care group (p=0.020). **Conclusions**: Exercise during and after NACRT is feasible for some rectal cancer patients and may improve pCR despite limited fitness improvements. Larger trials are warranted to confirm if exercise is an effective intervention for improving treatment outcomes in this clinical setting.

5.2 Introduction

Long-course (5-6 weeks) neoadjuvant chemoradiation (NACRT) followed by surgical resection using total mesorectal excision (TME) 6-8 weeks later remains a standard treatment for stage II/III rectal cancers. NACRT results in tumor downsizing which improves the chances of negative resection margins and sphincter sparing surgery. Unfortunately, only 15-27% of patients achieve a pathologic complete response (pCR) which has been associated with better survival (1) and the possibility of avoiding surgery altogether (2). Moreover, NACRT may cause acute toxicities that can negatively impact quality of life (3) and impede treatment tolerance. Interventions to manage toxicities and improve treatment response in this clinical setting are highly desirable. We have previously highlighted the clinical and biological pathways via which exercise may improve outcomes for rectal cancer patients receiving NACRT (4).

Despite the evidence for benefit of exercise in other cancer patient groups (5-9), only preliminary research has been conducted in the neaodjuvant rectal cancer setting (10-16). We designed the Exercise During and After Neoadjuvant Rectal Cancer Treatment (EXERT) Trial as a phase II randomized controlled trial to further establish the feasibility and safety of exercise in this clinical setting and to provide the first evidence of clinical activity. We hypothesized that a supervised high-intensity interval training (HIIT) program during NACRT followed by ≥150 minutes/week of unsupervised moderate-to-vigorous-intensity continuous exercise after NACRT would be feasible, safe, and produce meaningful improvements in health-related fitness and clinical outcomes compared to usual care.

5.3 Methods

Detailed methods for the EXERT Trial (NCT03082495) have been reported elsewhere (4).

Setting and Participants

Participants were recruited from the Cross Cancer Institute in Edmonton, Alberta, Canada. The trial was approved by the Health Research Ethics Board of Alberta-Cancer Committee and conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants prior to enrollment. Rectal cancer patients were eligible for the trial if they were (1) scheduled to receive long-course NACRT followed by TME, (2) ≥18 years old, (3) medically cleared, (4) not currently exercising, (5) English-speaking (6) able to complete the baseline exercise test, and (7) willing to be randomized.

Design and Procedures

The study was a single-center, phase II randomized controlled trial. Eligible patients were approached by their radiation oncologist and the study coordinator at the time of their initial radiation consultation. Interested patients were scheduled for baseline testing. After baseline assessments, patients were randomly assigned to either the exercise group or usual care group in a 1:1 ratio using a computer-generated program with random blocks of 4 or 6. The allocation sequence was generated independently and concealed from the study coordinator who assigned participants to groups. Participants and interventionists were not blinded to group assignment. Outcome assessors were not blinded to group assignment for the health-related fitness assessments; however, they were blinded for clinical outcome assessments.

Neoadjuvant Chemoradiation Protocol

Radiation therapy was delivered at 1.8-2.0 Gy on weekdays for a total of 25-30 fractions over 5-6 weeks and a total dose of 45-54 Gy. Concurrent chemotherapy consisted of either oral capecitabine (825 mg/m^2 twice per day) or continuous intravenous 5-fluorouracil (equivalent to 1200 mg/m^2 five days per week).

Intervention

During NACRT, participants in the exercise group were asked to complete 3 supervised HIIT sessions/week. The details and rationale for the selected HIIT program have been reported elsewhere (4). Briefly, HIIT sessions consisted of 2-minute, high-intensity intervals completed at 85% of VO_2 peak interspersed with 2 minutes of active recovery completed at 40% of VO_2 peak on a treadmill. Each HIIT session started with a 5-minute warm-up and ended with a 5-minute cool-down at 30-40% of VO_2 peak. The number of HIIT intervals started with 5 and progressed by 1 every second session until participants reached 8 intervals. The total duration of the exercise sessions progressed from 28 to 40 minutes. Exercise sessions were modified according to participants ability and motivation.

After NACRT, participants were asked to complete 150 minutes of unsupervised, moderate-to-vigorous-intensity continuous exercise/week in accordance with Canadian guidelines (17). A certified exercise specialist provided participants with verbal instructions and printout materials on how to achieve the target exercise duration and intensity. The study coordinator followed-up with participants weekly by phone to support patients in meeting the exercise goal.

Usual care participants were asked not to change their activity levels for the duration of the study. At the end of the study, all trial participants were offered a copy of the Canadian

guidelines and encouraged to contact the study coordinator for exercise guidance once they had recovered from surgery.

Sample Characteristics

Baseline demographic and behavioral variables were assessed by self-report. Medical variables were abstracted from medical records. Baseline physical activity was assessed using self-report (18). Body composition was estimated from height and weight (19, 20).

Outcome Measures

Health-related fitness assessments were completed at baseline, post-NACRT, and pre-surgery. Treatment toxicities, treatment completion, and treatment response were abstracted from medical records.

Feasibility and Safety Outcomes

Feasibility was determined based on eligibility rate, recruitment rate, follow-up assessment rate, and exercise adherence rate. The main measure of exercise adherence during NACRT was attendance (attended exercise sessions/planned exercise sessions). Adherence to unsupervised exercise after NACRT was assessed by self-report (18). Safety was assessed by tracking adverse events related to exercise.

Primary Outcome

We selected *cardiorespiratory fitness* as the primary endpoint because it provides a bridge between the feasibility and efficacy goals of this study. Improved cardiorespiratory fitness provides an indication of the patient's ability and willingness to perform the HIIT program (feasibility) and has also been associated with improved clinical outcomes in other cancer patients (efficacy) (21-24). Cardiorespiratory fitness (VO_2 peak) was defined as the highest value of oxygen consumption measured during the modified Bruce treadmill graded exercise test with

direct measures of gas exchange and ventilation on a metabolic measurement system (Parvo Medics TrueOne® 2400; Sandy, UT, USA).(25, 26) Details of the protocol have been described elsewhere (4).

Secondary Outcomes

Functional fitness was assessed by the Senior's Fitness Test (27, 28) which has been described in detail elsewhere (4). Other pre-specified secondary outcomes not reported here include *quality of life*, *symptom burden*, *exercise motivation,* and *surgical outcomes*.

Clinical Outcomes

Treatment toxicities were assessed weekly during NACRT by clinical nurses who graded symptoms using the National Cancer Institute Common Toxicity Criteria for Adverse Events Version 4.03 (CTCAE v4.03). Laboratory findings were abstracted by the study coordinator who transformed the blood parameters into toxicity grades according to the CTCAE v4.03. *Treatment completion*, including the planned versus actual radiation and chemotherapy schedules and dosages, were abstracted from medical records. *Treatment response* was abstracted from the surgical pathology report in which pathologists reported tumor regression score according to the American Joint Committee on Cancer Staging Manual (8^{th} Edition).

Statistical Analyses and Sample Size Calculation

Based on our phase I study (16), we planned to recruit 60 patients over a 20-month period. With 30 participants per group, our study would have 80% power, with a two-tailed alpha < 0.05, to detect a clinically meaningful effect of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ for our primary outcome of VO_2 peak post-NACRT, assuming a standard deviation of 5.6 $ml \cdot kg^{-1} \cdot min^{-1}$, 10% missing data, and adjustment for baseline value and select covariates (29). This power was unlikely to be sufficient for detecting between-group differences in clinical outcomes. As the purpose of this

phase II trial was to determine the preliminary efficacy of exercise in this setting, clinical outcomes were interpreted for both statistical and clinical significance.

We used analysis of covariance (ANCOVA) to compare the two groups on continuous health-related fitness outcomes at both the post-NACRT and pre-surgery timepoints with adjustment for age, sex, and baseline value of the outcome. All patients with available baseline and follow-up data were analyzed according to group assignment. No missing data strategy was employed and no adjustments were made for multiple testing.

Clinical outcomes were categorized based on accepted cut-points. For treatment toxicities, we analyzed the number of patients with any grade 2 toxic events (yes vs. no) and the number of patients with any grade 3/4 toxic events (yes vs. no). For treatment completion, we analyzed the number of patients completing 100% of their planned radiation dose within 1 week of the planned completion date (yes vs. no), and the number of patients receiving ≥80% of their planned chemotherapy dose (yes vs. no). Treatment response was analyzed as the number of patients achieving a pCR/near pCR vs. pPR. Chi-squared analyses were used to compare between-group differences for the clinical outcomes and followed the intention-to-treat principle. All analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL, USA).

5.4 Results

Feasibility and Safety Outcomes

Flow of patients through the trial is reported in **Figure 5-1**. From June 2017 to August 2019 we assessed 205 rectal cancer patients for eligibility of which 131 (64%) were eligible and 36 (27%) were randomized (18 in each group). For the primary outcome, VO_2 peak at the post-NACRT timepoint, data were available in 25 of 36 (69%) participants. For the clinical outcomes,

data were available on all participants except for pathologic response wherein one patient in the usual care group did not have surgery.

The median exercise attendance rate during NACRT was 82% (interquartile range 65-95%). The most common reason for missed sessions among all participants was unwillingness to come to our facility on a day when they did not have radiation treatment (statutory holidays or scheduled machine maintenance). Most exercise sessions (74%) took place after radiation treatment.

After NACRT, self-report exercise data was collected from 15 of 18 (83%) participants in the exercise group and 14 of 18 (78%) participants in the usual care group. In the exercise group, 7/15 (47%) participants reported completing ≥ 150 minutes of aerobic exercise/week. The median total aerobic exercise minutes/week post-NACRT was 90 minutes (interquartile range 0-233 minutes) in the exercise group compared with 40 minutes (interquartile range 0-105 minutes) in the usual care group (p=0.15). No serious adverse events were observed during exercise testing or the supervised HIIT sessions.

Sample Characteristics

The baseline profile of participants is presented in **Table 5-1 and Table 5-2**. Participants had a mean age of 57±12 years, 67% were men, 61% were current or ex-smokers, and 67% were overweight or obese. A total of 22 (61%) participants had stage III disease. There were slightly more patients with clinical T4, N2, and M1 stage disease in the usual care group compared to the exercise group. Given that clinical stage is a predictor of treatment response (30-32), we conducted an additional logistic regression analysis to examine the effects of exercise on pCR/near pCR adjusting for baseline clinical disease stage. The mean duration between

chemoradiation and surgery was 69 days in the exercise group and 65 days in the usual care group (between-group difference 5 days, 95% CI, -3 to 12; p=0.20).

Primary and Secondary Outcomes

Between-group differences in health-related fitness outcomes at the post-NACRT and pre-surgery timepoints are presented in **Table 5-3** and **Table 5-4** respectively. From baseline to post-NACRT, the primary outcome of VO_2 peak increased by 0.4 $ml \cdot kg^{-1} \cdot min^{-1}$ in the exercise group and decreased by 0.8 $ml \cdot kg^{-1} \cdot min^{-1}$ in the usual care group (adjusted between-group mean difference, 0.9 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% CI, -1.6 to 3.3; p=0.47). From baseline to pre-surgery, VO_2 peak decreased by 0.2 $ml \cdot kg^{-1} \cdot min^{-1}$ in the exercise group and did not change in the usual care group (p=0.73). No statistically significant between-group differences were observed for any of the secondary fitness outcomes.

Clinical Outcomes

Treatment Toxicities

Treatment toxicities are reported in **Table 5-5**. Lymphocytopenia was the only reported grade 3/4 toxicity and no difference between groups was observed (n=12, exercise; n=13, usual care; p=0.72). Thirteen participants (72%) in the exercise group experienced a grade 2 toxicity compared to 9 (50%) in the usual care group (p=0.17).

Treatment Completion

Participants in both groups received 100% full-dose radiation therapy (i.e. 45-54 Gy in 25-30 fractions) without any breaks >5 days (p=1.00). The number of participants receiving >80% full-dose chemotherapy was 16 (89%) in the exercise group and 18 (100%) in the usual care group (p=0.15). The reasons for receipt of <80% full-dose chemotherapy in the exercise group were neutropenia and diarrhea.

Treatment Response

In the exercise group, the pathologic response was complete in 39% (7/18), near complete in 17% (3/18), and partial in 44% (8/18) of participants. In the usual care group, the pathologic response was complete in 12% (2/17), near complete in 6% (1/17), and partial in 82% (14/17) of participants. The number of participants achieving a pCR/near pCR was significantly higher in the exercise group (10/18=56%; 95% CI, 31% to 79%) compared to the usual care group (3/17=18%; 95% CI, 4% to 43%) (p=0.020). After adjusting for baseline clinical stage, participants in the exercise group were still more likely to achieve a pCR/near pCR (odds ratio, 8.1; 95% CI, 1.5 to 44.0; p=0.016). **Figure 5-2**.

5.5 Discussion

To our knowledge, EXERT is the first randomized controlled trial to demonstrate the feasibility and early efficacy of exercise during and after NACRT for rectal cancer. Consistent with our hypothesis, the EXERT Trial demonstrated acceptable eligibility, recruitment, and adherence to the supervised HIIT program during NACRT; however, the unsupervised exercise program after NACRT was only feasible in a subset of patients. Contrary to our primary hypothesis, the HIIT program during NACRT did not meaningfully improve cardiorespiratory fitness, treatment toxicities, or treatment completion rates. Nevertheless, exercise during and after NACRT significantly improved the rate of pCR/near pCR.

Based on data from our phase I trial, we had anticipated recruiting 60 patients in 18 months; however, we recruited 36 patients in 26 months after which the trial was stopped because of a time limitation. Although there are no studies with which to directly compare our results, the 64% eligibility rate in the current trial is higher than the eligibility rate for supervised exercise trials during treatment in other cancer types (33%-41%) (21, 33-35). In the only other report

from a randomized exercise intervention trial during NACRT, Moug et al. (15) reported a 61% recruitment rate for a home-based walking intervention. Although our 27% recruitment rate is lower than the 61% recruitment rate reported by Moug et al. (15), it is consistent with other randomized exercise oncology trials in patients on treatment (21, 33) and may reflect our supervised program versus their home-based program. Nevertheless, it is clear that multicenter trials will be required for larger phase II or III trials in this clinical setting.

The assessment follow-up rates for physical fitness were lower than the rate reported for other cancer patient groups participating in exercise interventions during treatment (89-91%) (21, 33) and prior to surgery (100%) (10); however, this may not be critical if future trials are designed to target cancer efficacy endpoints. The median adherence rate of 82% for the supervised HIIT sessions during NACRT appears acceptable based on large exercise trials during adjuvant cancer treatment (21, 33, 34). Although self-report exercise minutes post-NACRT were numerically higher in the exercise group, most participants failed to meet the exercise prescription. Overall, these data suggest that exercise during and after NACRT is feasible for some rectal cancer patients although strategies to improve exercise adherence post-NACRT are needed.

Contrary to our hypothesis, the supervised HIIT program during NACRT did not improve cardiorespiratory fitness. It is possible that the overall training stimulus of 5-6 weeks was insufficient to counteract the expected declines in cardiorespiratory fitness during NACRT. This explanation is further supported by the null findings in the 6-minute walk test. We cannot comment on the effects of the unsupervised moderate-to-vigorous continuous training program after NACRT because of the high number of missed fitness tests and modest adherence in this phase of the trial.

Despite our small sample size, and no change in fitness, treatment toxicities, or treatment completion, participants in the exercise group experienced a significantly higher rate of pCR/near pCR that was triple the rate of the usual care group. This effect remained after adjusting for imbalances in baseline clinical disease stage, suggesting the possibility that exercise acted as a "radiosensitizer".

The potential interactions between exercise and cancer treatment efficacy are complex; nevertheless, there are several biologically plausible mechanisms. For example, evidence from pre-clinical studies has demonstrated that exercise improves intratumor perfusion and oxygen delivery both acutely (i.e., via increased blood flow to the tumor) (36) and chronically (i.e. via improved vascularization and normalization) (37). Hypoxic tumors are more resistant to radiation therapy (38), thus, it is plausible that exercise-mediated reductions in tumor hypoxia may improve the effectiveness of radiation therapy. Moreover, HIIT is capable of inducing angiogenesis in skeletal muscle within 4 weeks (39) and, given that physiologic factors limiting VO_2 are multifactorial, it is possible that the training stimulus in the EXERT Trial was sufficient to produce improvements in the tumor microenvironment but not in cardiorespiratory fitness.

Clinical trials examining the effect of exercise on treatment response are limited; however, West et al. (40) reported an association between exercise and tumor regression following NACRT. Moreover, in an exploratory subgroup analysis of the HELP Trial (8), a 12 week supervised aerobic exercise intervention in lymphoma patients receiving chemotherapy resulted in a numerically superior pCR rate (46.4%) compared to usual care (30.8%).

Our study has strengths and limitations. EXERT is the first randomized trial to demonstrate the effects of exercise during and after NACRT on a meaningful cancer efficacy endpoint. Strengths of our study include the clinically relevant endpoints, the supervised exercise

during NACRT, the prospective collection of data, and the excellent quality of clinical outcome data. One limitation of our study is the small sample size that resulted from slower than expected accrual. The small sample size may have limited our ability to detect meaningful differences in some outcomes and increased the likelihood that our positive finding for pCR/near pCR was due to chance. Other limitations of the study include the modest exercise adherence post-NACRT, multiple comparisons without adjustment, the lack of biological markers, and the lack of long-term follow-up.

In conclusion, the EXERT Trial demonstrated the feasibility and early efficacy of an exercise intervention during and after NACRT for rectal cancer. Our finding that exercise may improve treatment response is novel and important given that pCR is associated with better survival and even the possibility of avoiding surgery. Given the limitations of the EXERT trial, exercise warrants further investigation as a novel intervention for improving treatment outcomes in this clinical setting and other clinical settings using neoadjuvant chemoradiation.

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Table 5-1. Baseline characteristics of participants in the EXERT Trial.

Variable	Overall	Exercise	Usual Care
	(N=36)	(n=18)	(n=18)
Demographic profile			
Age, yrs., mean (SD)	57 (12)	56 (14)	58 (9)
Sex, male, n (%)	24 (67)	11 (61)	13 (72)
Married, n (%)	18 (50)	9 (50)	9 (50)
Completed university/college, n (%)	18 (50)	10 (56)	8 (44)
Annual family income ≥100,000/year, n (%)	16 (44)	10 (56)	6 (33)
Employment status			
Employed full/part-time, n (%)	14 (39)	4 (22)	10 (56)
Disability/sick leave, n (%)	13 (36)	8 (44)	5 (28)
Ethnicity, Caucasian, n (%)	31 (86)	15 (83)	16 (89)
Behavioral profile			
Smoking Status			
Current cigarette smoker, n (%)	6 (17)	3 (17)	3 (17)
Former cigarette smoker, n (%)	16 (44)	6 (33)	10 (56)
Physical activity, past month			
Moderate aerobic exercise, min/week, median (ICR)	0 (0-21)	0 (0-24)	0 (0-23)
Vigorous aerobic exercise, min/week, median (ICR)	0 (0)	0 (0)	0 (0)
Resistance exercise, ≥ 2 days/week, n (%)	7 (19)	3 (17)	4 (22)
Medical profile			
Weight, kg, mean (SD)	82.0 (15.9)	79.6 (17.0)	84.5 (14.8)
BMI, kg/m^2, mean (SD)	27.9 (4.9)	27.5 (4.9)	28.3 (4.9)
Overweight, n (%)	11 (31)	5 (28)	6 (33)
Obese, n (%)	13 (36)	7 (39)	6 (33)
Number of comorbidities			
None, n (%)	14 (39)	6 (33)	8 (44)
1-2, n (%)	11 (31)	4 (22)	7 (39)
≥ 3, n (%)	11 (31)	8 (44)	3 (17)
Most common comorbidities[1]			
Hypertension, n (%)	9 (25)	5 (28)	4 (22)
Arthritis, n (%)	8 (22)	5 (28)	3 (17)
Hyperlipidemia, n (%)	7 (19)	3 (17)	4 (22)

Abbreviations : SD, standard deviation; n, number; ICR, interquartile range; kg, kilograms; BMI, body mass index

1 More than one response could be checked

Table 5-2. Baseline disease and treatment characteristics of participants in the EXERT Trial.

Variable	Overall	Exercise	Usual Care
	N=36	n=18	n=18
	n (%)	n (%)	n (%)
Pre-treatment MRI	36 (100)	18 (100)	18 (100)
Clinical T stage			
T2	2 (6)	1 (6)	1 (6)
T3	24 (67)	14 (78)	10 (56)
T4	8 (22)	2 (11)	6 (33)
Unknown	2 (6)	1 (6)	1 (6)
Clinical N stage			
N0	3 (8)	2 (11)	1 (6)
N1	22 (61)	11 (61)	11 (61)
N2	7 (19)	2 (11)	5 (28)
Unknown	4 (11)	3 (17)	1 (6)
Clinical M stage			
M0	31 (86)	16 (89)	15 (83)
M1	3 (8)	0	3 (17)
Unknown	2 (6)	2 (11)	0
Disease Stage			
IIA	3 (8)	2 (11)	1 (6)
IIIA	1 (3)	0 (0)	1 (6)
IIIB	17 (47)	10 (56)	7 (39)
IIIC	5 (14)	2 (11)	3 (17)
IVA	3 (8)	0	3 (17)
Unknown	7 (19)	4 (22)	3 (17)
Diverting ostomy	6 (17)	4 (22)	2 (11)
Planned radiation dose, Gy, mean (SD)	51.8 (2.5)	51.9 (2.5)	51.6 (2.5)
Chemotherapy Protocol			
Oral Capecitabine	34 (94)	18 (100)	16 (89)
Intravenous 5-Fluororacil	2 (6)	0	2 (11)
Distance of tumor from anal verge, cm			
< 5	7 (19)	4 (22)	3 (17)
5-10	18 (50)	8 (44)	10 (56)
> 10	5 (14)	2 (11)	3 (17)
Unknown	6 (17)	4 (22)	2 (11)

Abbreviations: n, number; MRI, magnetic resonance imaging; Gy, gray; SD, standard deviation; cm, centimeters

Table 5-3. Effects of supervised high-intensity interval training during chemoradiation on health-related fitness outcomes postchemoradiation in the EXERT Trial.

	Baseline	Post-NACRT	Baseline to Post-NACRT		
			Mean change	Adjusted between-group difference[1]	
Outcome	Mean (SD)	Mean (SD)	Mean [95% CI]	Mean [95% CI]	*P*
VO_2peak, ml·kg^{-1}·min^{-1}					
Exercise (n=13)	27.3 (6.6)	27.6 (6.7)	0.4 [-1.2, 1.9]	0.9 [-1.6, 3.3]	0.47
Usual Care (n=12)	29.6 (5.3)	28.8 (7.7)	-0.8 [-3.1, 1.5]		
Vo_2peak, L/min					
Exercise (n=13)	2.16 (0.86)	2.15 (0.78)	-0.01 [-0.15, 0.13]	0.04 [-0.17, 0.24]	0.70
Usual Care (n=12)	2.55 (0.52)	2.45 (0.67)	-0.09 [-0.28, 0.09]		
Six-minute walk, m					
Exercise (n=14)	530 (88)	555 (67)	25 [6, 43]	0 [-30, 30]	0.98
Usual Care (n=13)	548 (105)	567 (86)	19 [-17, 56]		
30-second chair stands, n					
Exercise (n=13)	15 (6)	17 (5)	2 [1, 3]	0 [-4, 3]	0.90
Usual Care (n=13)	15 (3)	17 (6)	2 [-1, 5]		
30-second arm curls, n					
Exercise (n=13)	17 (5)	19 (4)	2 [0, 4]	0 [-2, 3]	0.90
Usual Care (n=12)	18 (4)	19 (4)	1 [-1, 3]		
Sit-and-reach, cm					
Exercise (n=14)	-5.0 (13.3)	-5.8 (11.7)	-0.8 [-4.2, 2.7]	-1.4 [-6.2, 3.3]	0.53
Usual Care (n=13)	1.2 (11.3)	1.4 (13.6)	0.2 [-2.9, 3.3]		
Back scratch, cm					
Exercise (n=14)	-8.8 (12.4)	-8.3 (9.9)	0.5 [-4.9, 6.0]	-0.5 [-5.9, 4.9]	0.85
Usual Care (n=14)	-10.4 (15.5)	-8.6 (16.0)	1.8 [0.6, 2.9]		
8-foot up-and- go, s					
Exercise (n=14)	4.5 (0.8)	4.1 (0.5)	-0.4[-0.7, 0.0]	-0.3 [-0.7, 0.0]	0.051
Usual Care (n=13)	4.1 (0.8)	4.2 (0.8)	0.1 [-0.1, 0.4]		

Abbreviations: SD, standard deviation; CI, confidence interval; VO_2, volume of oxygen consumption; ml, milliliters; kg, kilograms; min, minute; L, liters; m, meters; n, number; cm, centimeters; s, seconds

[1] Adjusted for age, sex, and baseline value of the outcome

Note: Complete case analyses were conducted. Discrepancies between sample sizes in Figure 1 and Table 3 are due to unavailable data for a given variable at baseline, post-NACRT, or both timepoints.

Table 5-4. Effects of exercise during and after chemoradiation on health-related fitness outcomes prior to surgery in the EXERT Trial.

	Baseline	Pre-surgery	Baseline to Pre-surgery		
			Mean change	Adjusted between-group difference[1]	
Outcome	Mean (SD)	Mean (SD)	Mean [95% CI]	Mean [95% CI]	*P*
VO_2peak, ml·kg^{-1}·min^{-1}					
Exercise (n=7)	31.3 (4.4)	31.1 (6.2)	-0.2 [-2.4, 2.1]	-0.5 [-3.4, 2.5]	0.73
Usual Care (n=8)	30.2 (6.5)	30.3 (8.2)	0 [-2.4, 2.4]		
Vo_2peak, L/min					
Exercise (n=7)	2.83 (0.68)	2.86 (0.78)	0.03 [-0.29, 0.35]	-0.01 [-0.31, 0.29]	0.93
Usual Care (n=8)	2.59 (0.67)	2.62 (0.75)	0.03 [-0.13, 0.18]		
Six-minute walk, m					
Exercise (n=9)	559 (78)	614 (66)	55 [19, 90]	24 [-33, 82]	0.37
Usual Care (n=8)	556 (101)	581 (129)	25 [-29, 79]		
30-second chair stands, n					
Exercise (n=9)	15 (7)	17 (6)	2 [1, 4]	-1 [-5, 2]	0.41
Usual Care (n=9)	15 (4)	18 (7)	3 [0, 6]		
30-second arm curls, n					
Exercise (n=9)	19 (4)	21 (7)	2 [-2, 6]	-3 [-7, 1]	0.17
Usual Care (n=8)	19 (4)	22 (6)	3 [0, 6]		
Sit-and-reach, cm					
Exercise (n=10)	-5.2 (13.1)	-4.7 (13.6)	0.5 [-6.2, 7.2]	1.9 [-8.1, 11.8]	0.69
Usual Care (n=8)	1.3 (11.7)	0 (19.8)	-1.3 [-9.2, 6.7]		
Back scratch, cm					
Exercise (n=10)	-6.4 (13.8)	-8.1 (10.5)	-1.7 [-10.4, 7.1]	-2.4 [-11.7, 7.0]	0.59
Usual Care (n=7)	-9.6 (12.2)	-8.6 (13.6)	1.0 [-3.9, 5.9]		
8-foot up-and- go, s					
Exercise (n=10)	4.3 (0.5)	3.9 (0.6)	-0.4 [-0.9, 0]	-0.4 [-1.1, 0.2]	0.17
Usual Care (n=8)	4.0 (0.9)	4.2 (1.1)	0.2 [-0.3, 0.7]		

Abbreviations: SD, standard deviation; CI, confidence interval; VO_2, volume of oxygen consumption; ml, milliliters; kg, kilograms; min, minute; L, liters; m, meters; n, number; cm, centimeters; s, seconds

[1] Adjusted for age, sex, and baseline value of the outcome

Note: Complete case analyses were conducted. Discrepancies between sample sizes in Figure 1 and Table 4 are due to unavailable data for a given variable at baseline, pre-surgery, or both timepoints.

Table 5-5. Recorded treatment toxicities in the EXERT Trial.

	Overall	**Exercise**	**Usual Care**	
	N=36	**n=18**	**n=18**	***P***
	n (%)	n (%)	n (%)	
Event[1,2]				
Any grade 2 toxicity	22 (61)	13 (72)	9 (50)	0.17
Any grade 3/4 toxicity[3]	25 (69)	12 (67)	13 (72)	0.72
Anorexia				
Grade 2 toxicity	3 (8)	2 (11)	1 (6)	-
Grade 3/4 toxicity	0	0	0	-
Diarrhea				
Grade 2 toxicity	2 (6)	2 (11)	0	-
Grade 3/4 toxicity	0	0	0	-
Fatigue				
Grade 2 toxicity	9 (25)	6 (33)	3 (17)	-
Grade 3/4 toxicity	0	0	0	-
Hand-foot-syndrome[4]				
Grade 2 toxicity	0	0	0	-
Grade 3/4 toxicity	0	0	0	-
Functional mucositis[4]				
Grade 2 toxicity	1 (3)	1 (6)	0	-
Grade 3/4 toxicity	0	0	0	-
Clinical mucositis[4]				
Grade 2 toxicity	1 (3)	1 (6)	0	-
Grade 3/4 toxicity	0	0	0	-
Nausea				
Grade 2 toxicity	2 (6)	2 (11)	0	-
Grade 3/4 toxicity	0	0	0	-
Pain				
Grade 2 toxicity	3 (8)	3 (17)	0	-
Grade 3/4 toxicity	0	0	0	-
Radiation dermatitis				
Grade 2 toxicity	1 (3)	0	1 (6)	-
Grade 3/4 toxicity	0	0	0	-
Hematologic toxicity				
Anemia				
Grade 2 toxicity	2 (6)	2 (11)	0	-
Grade 3/4 toxicity	0	0	0	-
lymphocytopenia				
Grade 2 toxicity	8 (22)	4 (22)	4 (22)	-
Grade 3/4 toxicity	25 (69)	12 (67)	13 (72)	-
Neutropenia				
Grade 2 toxicity	1 (3)	1 (6)	0	-
Grade 3/4 toxicity	0	0	0	-
Decrease in white blood cells				
Grade 2 toxicity	5 (14)	4 (22)	1 (6)	-
Grade 3/4 toxicity	0	0	0	-

Abbreviations: n, number

[1]Worst reported toxicity during chemoradiation in each participant

[2]Some participants experienced more than one toxicity therefore the totals may exceed 100%

[3]The only reported grade 3/4 toxicity was lymphocytopenia

[4]N=34, n=18; exercise, n=16; usual care

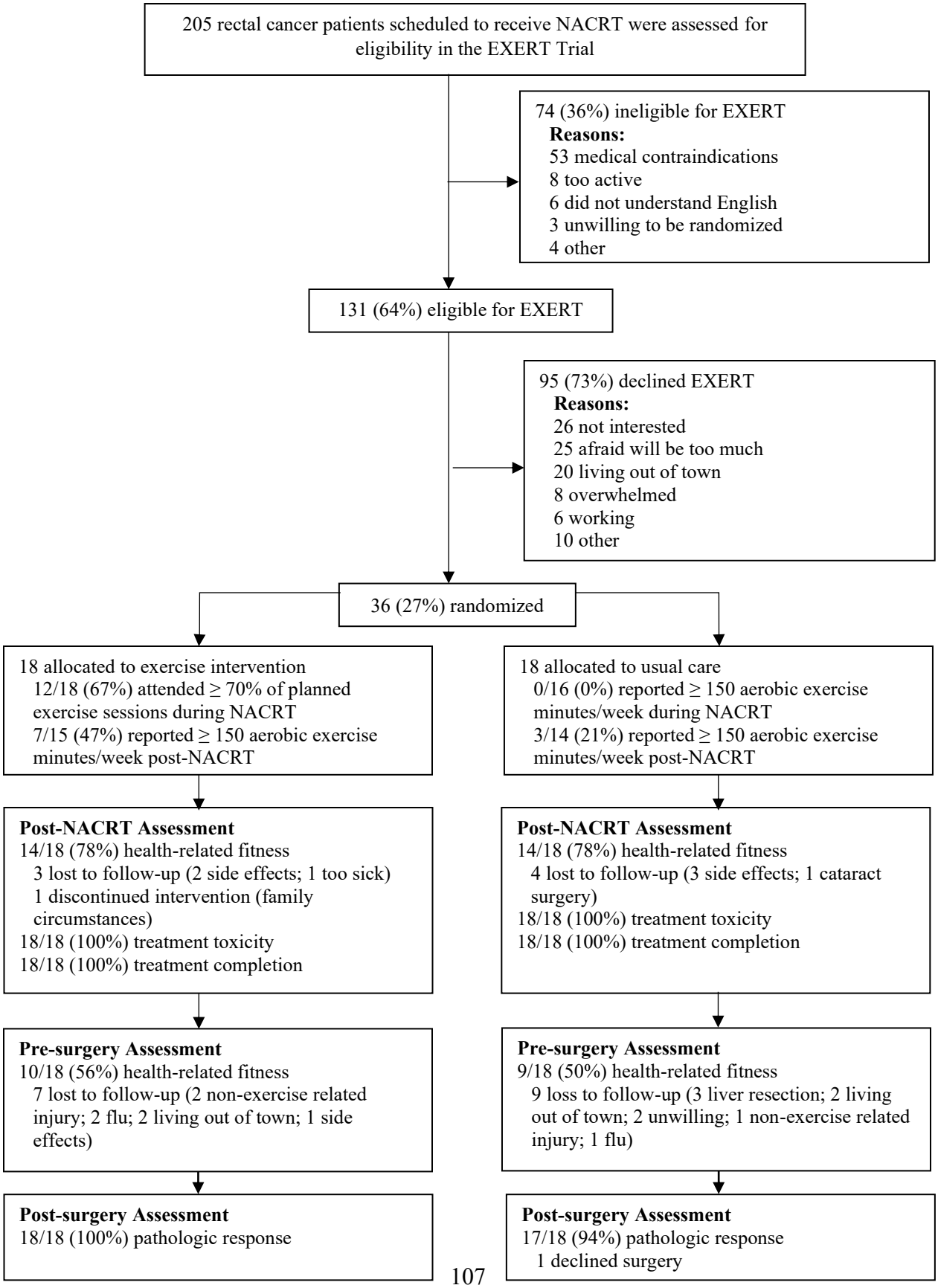
205 rectal cancer patients scheduled to receive NACRT were assessed for eligibility in the EXERT Trial
74 (36%) ineligible for EXERT
Reasons:
53 medical contraindications
8 too active
6 did not understand English
3 unwilling to be randomized
4 other
131 (64%) eligible for EXERT
95 (73%) declined EXERT
Reasons:
26 not interested
25 afraid will be too much
20 living out of town
8 overwhelmed
6 working
10 other
36 (27%) randomized
18 allocated to exercise intervention
12/18 (67%) attended ≥ 70% of planned exercise sessions during NACRT
7/15 (47%) reported ≥ 150 aerobic exercise minutes/week post-NACRT
18 allocated to usual care
0/16 (0%) reported ≥ 150 aerobic exercise minutes/week during NACRT
3/14 (21%) reported ≥ 150 aerobic exercise minutes/week post-NACRT
Post-NACRT Assessment
14/18 (78%) health-related fitness
3 lost to follow-up (2 side effects; 1 too sick)
1 discontinued intervention (family circumstances)
18/18 (100%) treatment toxicity
18/18 (100%) treatment completion
Post-NACRT Assessment
14/18 (78%) health-related fitness
4 lost to follow-up (3 side effects; 1 cataract surgery)
18/18 (100%) treatment toxicity
18/18 (100%) treatment completion
Pre-surgery Assessment
10/18 (56%) health-related fitness
7 lost to follow-up (2 non-exercise related injury; 2 flu; 2 living out of town; 1 side effects)
Pre-surgery Assessment
9/18 (50%) health-related fitness
9 loss to follow-up (3 liver resection; 2 living out of town; 2 unwilling; 1 non-exercise related injury; 1 flu)
Post-surgery Assessment
18/18 (100%) pathologic response
Post-surgery Assessment
17/18 (94%) pathologic response
1 declined surgery

Figure 5-1. CONSORT diagram showing flow of participants through the EXERT Trial.

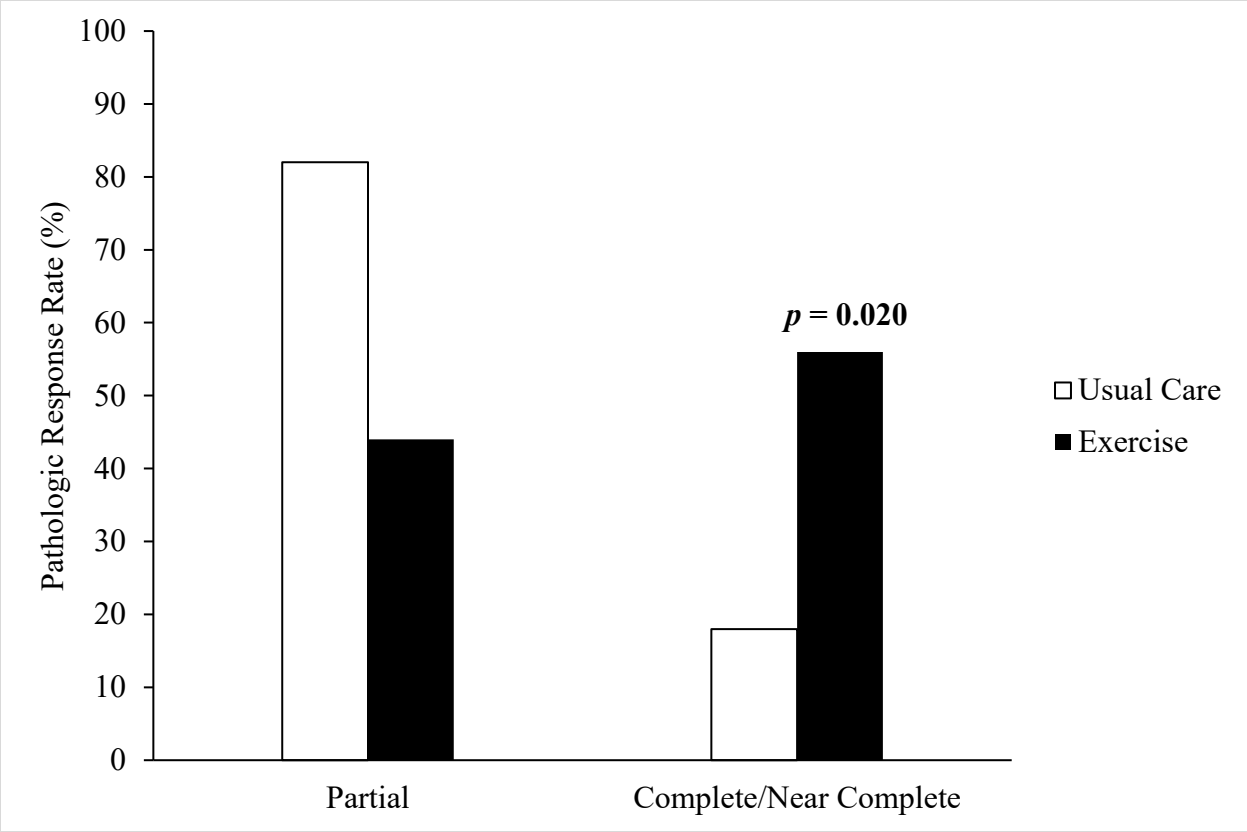

Figure 5-2. The results from the chi-squared analysis for pathologic response rate in the EXERT Trial.

CHAPTER 6: PAPER 5

Effects of exercise during and after neoadjuvant chemoradiation on symptom burden and quality of life in rectal cancer patients

6.1 Abstract

Purpose: To examine the effects of exercise on symptom burden and quality of life (QoL) in rectal cancer patients during and after neaodjuvant chemoradiation (NACRT). **Methods:** Rectal cancer patients (N=36) were randomized to a supervised high-intensity interval training (HIIT) program during NACRT followed by ≥ 150 minutes of unsupervised moderate-to-vigorous intensity continuous exercise/week after NACRT or usual care. Patient-reported outcomes were assessed at baseline, post-NACRT, and pre-surgery including symptom burden (M.D. Anderson Symptom Inventory) and QoL (European Organisation for Research and Treatment of Cancer QLQ- C30 and -CR29). **Results:** Analyses of covariance indicated that during NACRT, exercise significantly worsened stool frequency (adjusted between-group mean difference, 25.8; 95% CI, 4.0 to 47.6; p=0.022; d=0.99), role functioning (adjusted between-group mean difference, -21.3; 95% CI, -41.5 to -1.1; p=0.039; d=-0.90), emotional functioning (adjusted between-group mean difference, -11.7; 95% CI, -22.0 to -1.4; p=0.028; d=-0.80) and cognitive functioning (adjusted between-group mean difference, -11.6; 95% CI, -19.2 to -4.0; p=0.004; d=-0.58) compared to usual care. After NACRT, exercise significantly worsened diarrhea (adjusted between-group mean difference, 1.2; 95% CI, 0.1 to 2.3; p=0.030; d=0.59) and embarrassment (adjusted between-group mean difference, 19.7; 95% CI, 7.4 to 32.1; p=0.003; d=0.68) compared to usual care. **Conclusion:** Exercise may exacerbate some symptoms and worsen QoL during NACRT; however, most negative effects dissipated prior to surgery. Larger trials are necessary to confirm whether exercise has a negative impact on patient-reported outcomes in this clinical setting.

6.2 Introduction

Neoadjuvant chemoradiation (NACRT) is considered a standard treatment option for locally advanced rectal cancer. NACRT improves local disease control (1, 2) and may even eliminate the immediate need for surgery in patients with a complete clinical response (3). Nevertheless, NACRT causes some acute toxicities which may negatively impact patient-reported outcomes including symptoms, functioning, and quality of life (QoL) (4).

Substantive research has demonstrated that exercise interventions during cancer treatment are effective at mitigating some treatment-related side effects and improving QoL (5, 6). Despite the evidence for benefit of exercise, only preliminary research has been conducted in the neaodjuvant rectal cancer setting. Two phase I single-arm exercise trials (7, 8), including one from our group (8), have demonstrated inconsistent results with self-report symptoms, functioning, and QoL either worsening, remaining stable, or improving during NACRT. After NACRT, and prior to surgery, symptoms and QoL mostly appeared to recover or exceed baseline values in these trials (8-10). In the first report from a randomized controlled trial of exercise in rectal cancer patients during and after NACRT, Moug et al. (11) did not observe between-group differences for any patient-reported outcomes from pre-NACRT to pre-surgery when comparing a walking program to usual care. To date, no randomized controlled trials have examined the effects of exercise in this clinical setting on patient-reported outcomes both immediately following NACRT and prior to surgery. Further research is required to determine the potential benefits and harms of exercise for symptom management and QoL in this clinical setting.

We conducted the Exercise During and After Neoadjuvant Rectal Cancer Treatment (EXERT) Trial, a phase II randomized controlled trial, to further examine the feasibility and safety of exercise in this clinical setting and to provide the first evidence of efficacy. We

previously reported that a high-intensity interval training (HIIT) program during NACRT followed by ≥ 150 minutes of unsupervised moderate-to-vigorous intensity continuous exercise/week after NACRT was feasible and safe (12). Moreover, exercise during and after NACRT, compared to usual care, significantly improved the rate of complete/near complete pathologic response despite no improvement in cardiorespiratory fitness (12). Here, we report the effects of the supervised HIIT program during NACRT and unsupervised moderate-to-vigorous intensity continuous exercise after NACRT on patient-reported outcomes including symptom burden and QoL.

6.3 Methods

Setting and Participants

The EXERT Trial methods have been reported elsewhere (12, 13). Briefly, the EXERT Trial was conducted at the Cross Cancer Institute and Behavioral Medicine Fitness Center at the University of Alberta in Edmonton, Alberta, Canada. The trial was approved by the Health Research Ethics Board of Alberta-Cancer Committee and informed consent was obtained from all trial participants. Rectal cancer patients were eligible if they were (1) scheduled to receive standard long-course NACRT consisting of 5-6 weeks of radiation therapy (45-54 Gy) with concurrent chemotherapy (oral capecitabine or intravenous 5-fluorouracil) followed by total mesorectal excision, (2) ≥ 18 years old, (3) English speaking, (4) medically cleared to participate in the trial (5) not performing any regular exercise, and (6) willing to be randomized.

Design and Procedures

The study was a prospective, two-armed, phase II randomized controlled trial with assessment of health-related fitness outcomes and patient-reported outcomes at three timepoints: (1) baseline (pre-NACRT), (2) post-NACRT, and (3) pre-surgery. The study coordinator

provided prospective patients with a study information package at the time of their initial radiation consultation which included the baseline questionnaire. The study coordinator followed-up with eligible patients by phone and scheduled those who were interested in participating in the study for baseline fitness testing and asked them to complete the baseline questionnaire and bring it with them to their appointment. This conversation usually took place about 1 week before participants started NACRT.

At the post-NACRT timepoint, participants in the exercise group were provided with a follow-up questionnaire at their last supervised exercise session. For participants in the usual care group, the study coordinator met with them at the cancer center sometime during their last week of radiation treatment and provide them with a follow-up questionnaire. Participants in both groups were asked to complete the questionnaire as soon as possible after their last radiation session and bring the completed questionnaire with them to their post-NACRT fitness assessment. If participants were unable or unwilling to complete the fitness assessments at the post-NACRT timepoint, they were asked to complete the questionnaire and return it by mail.

At the pre-surgery timepoint, participants in both groups were asked to complete a follow-up questionnaire during their study visit for the final fitness assessments. In instances where participants were unable or unwilling to complete the pre-surgery fitness assessments, they were still asked to complete the questionnaire. If participants were agreeable, the study coordinator mailed out the questionnaire with a pre-paid return envelope approximately 2 weeks prior to the participants scheduled surgery date.

Randomization and Blinding

After baseline assessments, participants were randomly assigned in a 1:1 ratio to exercise or usual care using a computer-generated program with random blocks of 4-6. The allocation

sequence was generated by a research assistant not involved in the study and was concealed from the study coordinator who assigned participants to groups. It was not possible to blind participants or interventionists to group assignment; therefore, participants were not blinded to group assignment when completing the patient-reported outcomes.

Intervention

The exercise intervention has been described in detail elsewhere (12, 13). Briefly, during NACRT participants randomized to exercise were asked to complete 3 supervised HIIT sessions/week at the Behavioral Medicine Fitness Center which is within walking distance from the cancer center where participants were already coming 5 days/week for radiation treatment. HIIT sessions were performed on a treadmill and mostly involved uphill treadmill walking. More specifically, each HIIT session consisted of 2-minute high-intensity intervals performed at a workload corresponding to 85% of VO_2 peak interspersed with 2-minute low-intensity active recovery intervals performed at a workload corresponding to 30% of VO_2 peak. The number of HIIT intervals started at 5 and progressed by 1 every second sessions up to 8 intervals. The total duration of each exercise sessions progressed from 28 minutes to 40 minutes (including a 5-minute warm-up and a 5-minute cool-down). All exercise sessions were supervised by qualified exercise specialists who, when necessary, modified the exercise session according to participants ability and willingness. After NACRT, when participants were no longer coming to the cancer center daily for radiation treatment, participants in the exercise group were asked to complete ≥ 150 minutes of unsupervised moderate-to-vigorous intensity continuous exercise/week. Participants received verbal instructions (and printout materials) on how to complete the unsupervised exercise. Moreover, qualified exercise personnel phoned participants weekly to support them in meeting the exercise goal.

Usual care participants were asked to maintain their baseline physical activity levels for the duration of the trial. At the end of the study, participants in both groups were offered a copy of the Canadian Physical Activity Guidelines and encouraged to contact the study coordinator for exercise recommendations once they had recovered from surgery and received medical clearance from their physician.

Assessment of Patient-Reported Outcomes

Patient-reported outcome measures and the rationale for their selection have been reported elsewhere (13). *Overall symptom burden* was assessed using the M.D. Anderson Symptom Inventory (MDASI) (14). Briefly, The MDASI assesses the severity of 13 core cancer-specific disease- and treatment-related symptoms (pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness or tingling). For this study, we included 4 additional symptoms identified during our experience in the phase I trial (mouth sores, hand-foot syndrome, diarrhea, and skin irritation). The MDASI also assesses the degree to which symptoms interfere with various aspects of a patients' life (general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life). All items on the MDASI have a 24-hour recall period and are rated on an 11-point scale ranging from 0 (symptoms not present/did not interfere) to 10 (symptoms as bad as you can imagine/interfered completely).

Quality of life (QoL) was assessed using the European Organisation of Research and Treatment of Cancer (EORTC) core 30-item questionnaire (QLQ-C30) version 3.0 which has demonstrated repeated reliability and validity (15). The EORTC QLQ-C30 comprises 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, nausea and vomiting, and pain), 5 single-item symptom scales (dyspnea,

insomnia, appetite loss, constipation, and diarrhea), a single-item financial impact scale, and a 2-item global health and QoL scale. Additionally, a summary score calculated from the mean of the five functional and eight symptom scales has demonstrated responsiveness (16). The QLQ-C30 was supplemented with the QLQ-CR29 (colorectal). Briefly, the QLQ-CR29 comprises 19 single-item scales and 4 multi-item scales assessing symptoms and functional issues related specifically to colorectal cancer. Five of the scales (problems caring for stoma, male sexual interest, impotence, female sexual interest, and dyspareunia) are not reported here due to a low response rate. Both the QLQ-C30 and QLQ-CR29 have a 1 week recall period and are rated on a 4-point Likert scale. Raw scores are transformed to scores ranging from 0-100 where higher scores on the functional scales indicate better functioning, while higher scores on the symptom scales indicate worse symptoms.

Statistical Analyses

Based on our phase I study, we anticipated recruiting 60 patients in 20 months. With 30 patients per group and adjustment for baseline value and select covariates, our study would have 80% power (two-tailed alpha <0.05) to detect a difference of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ for our primary outcome of VO_2 peak post-NACRT, assuming a standard deviation of 5.6 $ml \cdot kg^{-1} \cdot min^{-1}$. This level of power is equivalent to a standardized effect size of $d = 0.63$ and may be sufficient for detecting moderate standardized effect sizes (i.e. $d \geq 0.60$) for the patient-reported outcomes analyzed in this paper. Given that the purpose of this trial was to inform larger trials, the patient-reported outcomes were interpreted for both statistical significance and potential clinical significance, where possible. For symptom burden, we used a between-group difference of 1 point as the minimally important difference (MID) (17). For the QLQ-C30 and -C29, we used a between-group difference of 10 points as the MID (18, 19).

We used analysis of covariance (ANCOVA) to compare the two groups on continuous patient-reported outcomes at both the post-NACRT and pre-surgery timepoints with adjustment for age, sex, and baseline value of the outcome. All patients with available baseline and follow-up data were analyzed according to group assignment. No missing data strategy was utilized, and no adjustments were made for multiple testing. All analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL, USA).

6.4 Results

Flow of participants through the trial has been reported elsewhere (12). Briefly, we recruited 36 patients and randomized 18 to each group over a period of 26 months. At the post-NACRT timepoint, patient-reported data was available in 16/18 (89%) participants in the exercise group and 16/18 (89%) participants in the usual care group. At the pre-surgery timepoint, patient-reported data was available in 15/18 (83%) participants in the exercise group and 14/18 (78%) participants in the usual care group.

Demographic and medical data have been reported elsewhere (12). The mean age of participants was 57 ±12 years, 67% were men, 50% were married, 67% were overweight or obese, and 61% had comorbidities. For disease and treatment variables, 22 (61%) participants had stage III disease, 6 (17%) had a diverting ostomy, and most (34/36) received oral capecitabine (versus intravenous 5-fluoracil) as their chemotherapy regimen.

Feasibility outcomes, health-related fitness outcomes, and clinical outcomes from the EXERT Trial have been reported (12). Briefly, median attendance to the supervised HIIT sessions during NACRT was 82% (interquartile range 65-95%). After NACRT, participants in the exercise group completed a median of 90 minutes (interquartile range 0-233 minutes) of unsupervised moderate-to-vigorous intensity continuous exercise/week compared with 40

minutes (interquartile range 0-105 minutes) in the usual care group (p=0.15). Exercise did not significantly or meaningfully improve VO_2 peak at the post-NACRT timepoint (p=0.47) or the pre-surgery timepoint (p=0.73). There were also no between-group differences for treatment toxicities or treatment completion rates. Exercise did significantly increase the rate of complete/near complete pathologic response compared to usual care (56% vs. 18%; p=0.020).

Effects of Exercise During NACRT on Symptom Burden and Quality of Life

Between-group differences for symptom burden and QoL at the post-NACRT timepoint are presented in **Tables 6-1 and 6-2**, respectively. Exercise significantly worsened stool frequency (adjusted between-group mean difference, 25.8; 95% CI, 4.0 to 47.6; p=0.022; d=0.99) compared to usual care. Exercise also produced a MID for more sleep disturbance (adjusted between-group mean difference, 1.5; 95% CI, -0.1 to 3.2; p=0.07; d=0.57), worse skin reaction (adjusted between-group mean difference, 1.5; 95% CI, -0.6 to 3.5; p=0.15; d=3.08), pain (adjusted between-group mean difference, -16.2; 95% CI, -1.6 to 34.0; p=0.07; d=0.68), and sore skin (adjusted between-group mean difference, 24.9; 95% CI, -0.1 to 49.9; p=0.051; d=0.97) compared to usual care. There was no between-group difference for overall symptom severity (adjusted between-group mean difference, 0.3; 95% CI, -0.5 to 1.1; p=0.48; d=0.26). Conversely, exercise produced a MID for worse symptom interference (adjusted between-group mean difference, 1.6; 95% CI, 0.0 to 0.3; p=0.056; d=0.85).

Exercise significantly worsened role functioning (adjusted between-group mean difference, -21.3; 95% CI, -41.5 to -1.1; p=0.039; d=-0.90), emotional functioning (adjusted between-group mean difference, -11.7; 95% CI, -22.0 to -1.4; p=0.028; d=-0.80), and cognitive functioning (adjusted between-group mean difference, -11.6; 95% CI, -19.2 to -4.0; p=0.004; d=-0.58) compared to usual care. Exercise also produced a MID for worse physical functioning

(adjusted between-group mean difference, -10.0; 95% CI, -20.1 to 0.1; p=0.051; d=-1.20) and social functioning (adjusted between-group mean difference, -13.1; 95% CI, -33.0 to 6.8; p=0.19; d=-0.52) compared to usual care. There was no between-group difference for global health status/QoL (adjusted between-group mean difference, -4.1; 95% CI, -18.3 to 10.2; p=0.56; d=-0.21).

Effects of Exercise After NACRT on Symptom burden and Quality of Life

Between-group differences for symptom burden and QoL at the pre-surgery timepoint are presented in **Tables 6-3 and 6-4**, respectively. Exercise significantly worsened diarrhea (adjusted between-group mean difference, 1.2; 95% CI, 0.1 to 2.3; p=0.030; d=0.59) and embarrassment (adjusted between-group mean difference, 19.7; 95% CI, 7.4 to 32.1; p=0.003; d=0.68) compared to usual care. Exercise also produced a MID for worse insomnia (adjusted between-group mean difference, 14.2; 95% CI, -10.4 to 38.9; p=0.25; d=0.46), diarrhea (adjusted between-group mean difference, 11.2; 95% CI, -6.5 to 28.8; p=0.20; d=0.41), and sore skin (adjusted between-group mean difference, 17.2; 95% CI, -1.4 to 35.9; p=0.07; d=0.67) compared to usual care. There was no between-group difference for overall symptom severity (adjusted between-group mean difference, 0.2; 95% CI, -0.7 to 1.2; p=0.60; d=0.17); however, exercise produced a MID for worse symptom interference (adjusted between-group mean difference, 1.5; 95% CI, -0.4 to 3.5; p=0.12; d=0.80).

Exercise produced a MID for worse role functioning (adjusted between-group mean difference, -10.1; 95% CI, -29.6 to 9.4; p=0.30; d=-0.43) compared to usual care. No other differences were observed for the functional domains of QoL or for global health status/QoL (adjusted between-group mean difference, 3.3; 95% CI, -10.3 to 16.9; p=0.62; d=0.17). The

patterns of change in symptoms and QoL across the intervention are summarized in **Figures 6-1 and 6-2**, respectively.

6.5 Discussion

The purpose of the current report from the EXERT Trial was to examine the preliminary effects of a supervised HIIT program during NACRT and ≥ 150 minutes of unsupervised moderate-to-vigorous intensity continuous exercise/week after NACRT on important patient-reported outcomes. Contrary to other exercise intervention trials during and after cancer treatment, (5, 6, 20, 21), exercise during NACRT appeared to exacerbate several symptoms and worsen functional QoL. After NACRT, most of the negative effects of exercise on symptoms and QoL dissipated; however, some symptoms persisted.

During NACRT, exercise had negative effects on several symptoms (i.e. stool frequency, general pain, skin reaction/sore skin around the anal area, sleep disturbance, and symptom distress) and all functional domains of QoL. The finding that exercise during NACRT increased stool frequency is plausible as exercise studies have demonstrated that exercise reduces transit time in the intestinal track (22, 23). Moreover, several factors may explain the harmful effect of exercise on skin reaction/sore skin around the anal area during NACRT including increased friction from walking and/or jogging, sweating, and more frequent wiping from increased stool frequency. This finding is consistent with our phase I trial (24) in which 24% of participants reported that exercise made skin irritation worse during NACRT. Additionally, worse pain in the exercise group during NACRT could have been attributed to sore skin. Moreover, the finding that exercise negatively impacted sleep during NACRT is inconsistent with other exercise intervention trials which have demonstrated a beneficial effect of exercise on sleep in several

cancer patient groups (25-27). One possible explanation for this finding is that other symptoms including increased stool frequency, sore skin, and pain interfered with sleep.

Despite no between-group differences for overall symptom severity, symptom interference was worse in the exercise group at the post-NACRT timepoint. This may be explained by the 2-3 symptoms which caused patients considerable distress. Overall, between-group differences at the post-NACRT timepoint suggest the possibility that exercise could be exacerbating some symptoms. Nevertheless, the severity of symptoms was mild (< 5 on the MDASI) and not likely to impact clinical decision making related to treatment reductions, delays, or discontinuation. These findings are consistent with our primary paper (12) where we reported more grade 2 toxicities in the exercise group but no differences in treatment completion rates. One possible explanation for the slightly overall negative impact of exercise on toxicities and symptoms could be that exercise is increasing the biologic activity of chemoradiation. Nonetheless, the reliability of these findings is questionable given the small sample size, high variability (indicative of anywhere from a substantial negative effect to a trivial positive effect), and outliers which have the potential to substantially change an outcome. Future exercise intervention trials during NACRT for rectal cancer will need to closely track symptoms.

During NACRT, exercise also had large negative effects on all functional domains of QoL. This finding is inconsistent with a meta-analysis (5) reporting the effects of exercise interventions during active treatment on functional domains of QoL. Moreover, recent meta-analyses (6, 20) have demonstrated a statistically significant, although small, benefit of supervised exercise interventions on physical functioning and QoL both during and after cancer treatment. Nevertheless, the exercise interventions in these trials consisted mainly of moderate-to-vigorous intensity continuous aerobic exercise and the effects of HIIT during active treatment

on patient-reported outcomes remain unclear. In the only report from a HIIT intervention during active treatment with assessments of patient-reported outcomes to date, an 8 week supervised HIIT program, compared to general education and phone calls, did not improve functional QoL in small-cell lung cancer patients receiving targeted therapy (28). It is possible that worse symptoms negatively impacted the functional status of participants in the exercise group during NACRT. Still, there was large variability in the data for functional domains of QoL at the post-NACRT timepoint and these results should be interpreted with caution. Although it is unlikely that the supervised HIIT program during NACRT will improve QoL, larger trials are required to confirm if these negative effects are reliable.

After NACRT, most of the negative effects of exercise on symptoms and QoL appeared to dissipate. Nevertheless, the exercise group did report worse diarrhea, embarrassment, sore skin, insomnia, and symptom distress at the pre-surgery timepoint. The finding that exercise may have caused more diarrhea after NACRT is in contrast to a recent meta-analysis assessing the impact of exercise intervention trials on cancer-related symptoms which found no beneficial or harmful effect of exercise on diarrhea (29). Conversely, there are reports of exercise-induced diarrhea among elite athletes, especially marathon runners, with probable causes including mechanical, ischemic, and nutritional factors (30). Although it is unlikely that the exercise intensity and duration in the EXERT Trial caused gastrointestinal ischemia, it is possible that the impact of walking and/or jogging moved the bowels around. Considering this finding, it is not surprising that participants in the exercise group also experienced more embarrassment related to their bowel movements as several patients experienced urgencies during and immediately after exercise.

The possible explanations for higher rates of sore skin, insomnia, and symptom distress in the exercise group after NACRT are similar to during NACRT. Toxicities from radiation can worsen for up to two weeks after treatments are completed; therefore, it is possible for exercise after NACRT to have harmful effects on symptoms. Moreover, the negative effects of exercise on symptoms during NACRT may have hindered their recovery after NACRT. Nevertheless, exercise during and after NACRT did not have any lasting negative effects on QoL at the pre-surgery timepoint. Moreover, the negative effects of exercise on QoL during NACRT may have blunted improvements after NACRT. Additionally, the unsupervised nature of the exercise program may not have been sufficient to produce improvements in QoL at the pre-surgery timepoint (6, 20). Again, the reliability of these findings are questionable and larger, more definitive trials are required to confirm these results.

The overall strengths and limitations of the EXERT Trial have been described elsewhere (12). Strengths of the current report include being the first to examine the effects of exercise on patient-reported outcomes at both the post-NACRT and pre-surgery timepoints in a randomized controlled trial, extensive assessment of important patient-reported outcomes using validated measures, and the use of disease-specific measures with clinical utility. The main limitation of our study is the small sample size which resulted from our slower than anticipated accrual and affects the reliability and generalizability of our findings. Moreover, we were only powered to detect large effects of exercise and we may have failed to identify other symptoms that could reasonably be influenced by exercise (e.g. fatigue, anxiety, distress, hand-foot syndrome). Additional limitations include the large number of analyses conducted for the patient-reported outcomes (>100) with no adjustment for multiple testing, and the determination of the MID for

the MDASI which was generalized from a validation study completed in patients with malignant pleural mesothelioma.

In conclusion, preliminary results from the EXERT Trial suggest that exercise may exacerbate some symptoms and worsen QoL during NACRT; however, most of these effects appear to dissipate prior to surgery. Larger trials are needed to establish whether exercise has negative effects on symptoms and QoL in this clinical setting. If these negative effects are confirmed in a larger trial, then exercise may be contraindicated during NACRT for rectal cancer, assuming no other clinical benefit. As previously noted, however, we have reported that exercise may have a clinical benefit in this setting in the form of an improved pathologic complete/near complete response. If this clinical benefit is confirmed in a larger trial, then the modest symptom exacerbation from exercise during NACRT may be considered tolerable.

6.6 References

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Table 6-1. Effects of supervised high-intensity interval training during chemoradiation on symptom burden postchemoradiation in the EXERT Trial.

	Baseline	Post-NACRT	Baseline to Post-NACRT			
			Mean Change	Adjusted between-group difference[3]		
MDASI items	Mean (SD)	Mean (SD)	Mean [95% CI]	Mean [95% CI]	*P*	*d*
Symptom severity[1]						
Exercise (n=16)	1.3 (0.8)	1.9 (1.6)	0.7 [0.1, 1.3]	0.3 [-0.4, 1.0]	0.38	0.32
Usual Care (n=16)	1.1 (1.1)	1.5 (1.0)	0.4 [-0.2, 1.0]			
Symptom interference[2]						
Exercise (n=16)	1.6 (1.6)	3.7 (2.6)	2.1 [0.6, 3.6]	1.6 [0.0, 3.3]	0.056	0.85
Usual Care (n=16)	1.3 (1.9)	1.9 (1.9)	0.7 [-0.7, 2.0]			
Core symptoms						
Pain						
Exercise (n=16)	1.8 (2.8)	3.9 (3.2)	2.2 [0.4, 4.0]	0.6 [-1.4, 2.6]	0.57	0.23
Usual Care (n=16)	1.6 (2.7)	3.3 (2.4)	1.7 [0.1, 3.3]			
Fatigue						
Exercise (n=16)	2.8 (1.9)	4.0 (2.4)	1.2 [-0.4, 2.8]	0.1 [-1.6, 1.8]	0.89	0.05
Usual Care (n=16)	1.9 (1.8)	3.3 (2.3)	1.4 [0.4, 2.5]			
Nausea						
Exercise (n=16)	0.3 (0.6)	1.2 (2.3)	0.9 [-0.2, 2.0]	0.8 [-0.5, 2.2]	0.2	0.72
Usual Care (n=16)	0.8 (1.5)	0.5 (1.2)	-0.3 [-1.2, 0.7]			
Disturbed sleep						
Exercise (n=15)	3.5 (3.1)	4.6 (3.5)	1.1 [-0.4, 2.7]	1.5 [-0.1, 3.2]	0.07	0.57
Usual Care (n=16)	1.4 (1.9)	1.7 (1.4)	0.3 [-0.6, 1.1]			
Distress						
Exercise (n=16)	2.6 (2.3)	2.0 (2.2)	-0.6 [-2.0, 0.9]	0.1 [-1.4, 1.6]	0.94	0.05
Usual Care (n=16)	1.9 (2.2)	1.8 (1.9)	-0.1 [-1.5, 1.2]			
Shortness of breath						
Exercise (n=16)	0.8 (1.2)	0.9 (1.6)	0.2 [-0.8, 1.1]	0.1 [-0.9, 1.1]	0.84	0.10
Usual Care (n=16)	0.4 (0.8)	0.7 (1.1)	0.3 [-0.4, 0.9]			
Difficulty remembering						
Exercise (n=16)	1.0 (1.4)	1.1 (1.4)	0.1 [-0.4, 0.7]	0.2 [-0.6, 0.9]	0.64	0.12
Usual Care (n=16)	1.3 (1.9)	1.1 (1.0)	-0.2 [-1.0, 0.6]			
Lack of appetite						
Exercise (n=16)	0.9 (1.6)	2.0 (1.9)	1.1 [0.0, 2.1]	0.5 [-0.8, 1.7]	0.46	0.25
Usual Care (n=16)	1.4 (2.5)	1.6 (2.2)	0.3 [-1.2, 1.7]			
Drowsiness						
Exercise (n=16)	2.2 (2.0)	3.1 (2.2)	0.9 [-0.6, 2.4]	0.4 [-1.1, 1.9]	0.59	0.17
Usual Care (n=16)	2.1 (2.9)	2.6 (2.1)	0.5 [-1.2, 2.2]			
Dry mouth						
Exercise (n=16)	0.9 (1.1)	1.1 (1.3)	0.2 [-0.5, 0.9]	-0.5 [-1.8, 0.9]	0.46	-0.28
Usual Care (n=16)	1.4 (2.3)	1.8 (2.5)	0.4 [-0.9, 1.8]			
Sadness						
Exercise (n=16)	1.7 (1.7)	1.4 (1.9)	-0.3 [-1.5, 0.8]	-0.3 [-1.7, 1.2]	0.72	-0.17
Usual Care (n=16)	1.6 (1.7)	1.6 (2.0)	-0.1 [-1.5, 1.3]			
Vomiting						
Exercise (n=16)	0.0	0.0	-	-0.1 [-0.2, 0.1]	0.31	-0.27
Usual Care (n=16)	0.2 (0.5)	0.1 (0.3)	-0.1 [-0.5, 0.2]			
Numbness or tingling						
Exercise (n=16)	0.5 (1.0)	0.4 (1.8)	-0.1 [-0.8, 0.7]	0.0 [-0.8, 0.8]	0.98	0.00
Usual Care (n=16)	0.6 (1.9)	0.4 (0.7)	-0.2 [-1.0, 0.6]			

Table 6-1. Effects of supervised high-intensity interval training during chemoradiation on symptom burden postchemoradiation in the EXERT Trial (continued).

Additional symptoms						
Mouth sores						
Exercise (n=16)	0.2 (0.4)	0.1(0.3)	-0.1 [-0.4, 0.1]	-0.1 [-0.4, 0.2]	0.70	-0.24
Usual Care (n=16)	0.1 (0.5)	0.1 (0.5)	0.0 [-0.4,0.4]			
Hand-foot syndrome						
Exercise (n=16)	0.2 (0.8)	0.9 (2.0)	0.7 [-0.5, 1.9]	0.7 [-0.4, 1.9]	0.22	1.40
Usual Care (n=16)	0.0	0.3 (0.8)	0.3 [-0.2, 0.7]			
Skin reaction						
Exercise (n=16)	0.2 (0.5)	3.8 (3.1)	3.6 [1.9, 5.2]	1.5 [-0.6, 3.5]	0.15	3.08
Usual Care (n=16)	0.1 (0.5)	2.1 (2.7)	2.0 [0.7, 3.3]			
Diarrhea						
Exercise (n=16)	2.1 (2.6)	2.6 (2.7)	0.6 [-1.6, 2.7]	0.4 [-1.4, 2.2]	0.65	0.20
Usual Care (n=16)	1.1 (1.5)	2.3 (2.2)	1.1 [-0.4, 2.6]			

Abbreviations: SD, standard deviation; CI, confidence interval

[1] Average of the 17 symptom items

[2] Average of the 6 interference items

[3] Adjusted for age, sex, and baseline value of the outcome

Table 6-2. Effects of supervised high-intensity interval training during chemoradiation on quality of life postchemoradiation in the EXERT Trial.

	Baseline	Post-NACRT	Baseline to Post-NACRT			
			Mean Change	Adjusted between-group difference[1]		
EORTC QLQ-C30	Mean (SD)	Mean (SD)	Mean [95% CI]	Mean [95% CI]	*P*	*d*
Summary score*						
Exercise (n=16)	78.3 (12.9)	69.6 (15.7)	-8.7 [-17.5, 0.1]	-9.2 [-19.2, 0.7]	0.07	*-0.73*
Usual Care (n=16)	85.0 (12.6)	81.4 (10.7)	-3.7 [-11.0, 3.7]			
Global health status/QoL*						
Exercise (n=16)	64.6 (22.3)	58.9 (25.2)	-5.7 [-18.4, 6.9]	-4.1 [-18.3, 10.2]	0.56	*-0.21*
Usual Care (n=16)	71.9 (16.9)	67.7 (16.9)	-4.2 [-13.2, 4.9]			
Physical functioning*						
Exercise (n=16)	92.5 (6.8)	80.0 (16.5)	-12.5 [-22.0, -3.0]	-10.0 [-20.1, 0.1]	0.051	*-1.20*
Usual Care (n=16)	91.7 (10.5)	90.4 (10.3)	-1.3 [-8.4, 5.9]			
Role functioning*						
Exercise (n=16)	79.2 (28.2)	53.1 (32.3)	-26.0 [-44.7, -7.4]	-21.3 [-41.5, -1.1]	0.039	*-0.90*
Usual Care (n=16)	88.5 (19.9)	79.2 (23.2)	-9.4 [-20.6, 1.8]			
Emotional functioning*						
Exercise (n=16)	77.1 (13.4)	74.2 (18.5)	-2.9 [-11.6, 5.9]	-11.7 [-22.0, -1.4]	0.028	*-0.80*
Usual Care (n=16)	83.3 (15.5)	89.1 (11.3)	5.7 [-1.1, 12.6]			
Cognitive functioning*						
Exercise (n=16)	82.3 (19.7)	79.2 (15.5)	-3.1 [-9.8, 3.5]	-11.6 [-19.2, -4.0]	0.004	*-0.58*
Usual Care (n=16)	84.4 (22.3)	91.7 (10.5)	7.3 [-2.9, 17.5]			
Social functioning*						
Exercise (n=16)	65.6 (28.8)	52.1 (33.3)	-13.5 [-32.8, 5.7]	-13.1 [-33.0, 6.8]	0.19	*-0.52*
Usual Care (n=16)	84.4 (19.7)	75.0 (18.3)	-9.4 [-19.6, 0.9]			
Fatigue						
Exercise (n=16)	30.6 (14.9)	46.5 (27.0)	16.0 [-0.8, 32.7]	7.9 [-6.8, 22.7]	0.28	*0.43*
Usual Care (n=16)	21.5 (21.6)	35.4 (13.6)	13.9 [5.4, 22.4]			
Nausea and vomiting						
Exercise (n=16)	3.1 (6.7)	7.3 (12.1)	4.2 [-3.4, 11.8]	3.1 [-4.3, 10.5]	0.40	*0.30*
Usual Care (n=16)	5.2 (11.7)	4.2 (7.5)	-1.0 [-7.1, 5.0]			
Pain						
Exercise (n=16)	24.0 (29.2)	42.7 (37.0)	18.8 [1.9, 35.6]	16.2 [-1.6, 34.0]	0.07	*0.68*
Usual Care (n=16)	18.8 (19.1)	24.0 (18.2)	5.2 [-6.4, 16.8]			
Dyspnea						
Exercise (n=16)	14.6 (17.1)	10.4 (16.0)	-4.2 [-16.9, 8.6]	0.6 [-11.9, 13.2]	0.92	*0.04*
Usual Care (n=16)	4.2 (11.4)	8.3 (14.9)	4.2 [-4.7, 13.0]			
Insomnia						
Exercise (n=16)	45.8 (36.3)	45.8 (38.2)	0.0 [-19.5, 19.5]	6.9 [-15.0, 28.9]	0.52	*0.22*
Usual Care (n=16)	27.1 (21.8)	27.1 (27.8)	0.0 [-11.2, 11.2]			
Appetite loss						
Exercise (n=16)	16.7 (21.1)	27.1 (25.0)	10.4 [-7.6, 28.4]	9.4 [-8.7, 27.5]	0.30	*0.38*
Usual Care (n=16)	14.6 (29.7)	16.7 (27.2)	2.1 [-19.9, 24.0]			
Constipation						
Exercise (n=16)	12.5 (20.6)	14.6 (17.1)	2.1 [-10.0, 14.2]	0.7 [-15.6, 17.0]	0.93	*0.03*
Usual Care (n=16)	20.8 (26.9)	18.8 (29.7)	-2.1 [-18.6, 14.4]			
Diarrhea						
Exercise (n=16)	31.3 (31.0)	39.6 (34.9)	8.3 [-16.4, 33.0]	6.1 [-16.0, 28.1]	0.58	*0.22*
Usual Care (n=16)	14.6 (21.0)	33.3 (17.2)	18.8 [2.9, 34.6]			

Table 6-2. Effects of supervised high-intensity interval training during chemoradiation on quality of life postchemoradiation in the EXERT Trial (continued).

Financial difficulties						
Exercise (n=16)	25.0 (28.5)	29.2 (36.3)	4.2 [-8.6, 16.9]	-5.0 [-20.7, 10.8]	0.52	*-0.18*
Usual Care (n=16)	22.9 (29.1)	31.3 (35.4)	8.3 [-1.9, 18.6]			
EORTC QLQ-CR29						
Urinary frequency						
Exercise (n=16)	37.5 (26.9)	51.0 (26.2)	13.5 [-8.7, 35.8]	2.5 [-17.4, 22.4]	0.80	*0.10*
Usual Care (n=16)	27.1 (22.7)	47.9 (25.7)	20.8 [7.7, 34.0]			
Urinary incontinence						
Exercise (n=16)	8.3 (19.2)	12.5 (20.6)	4.2 [-6.8, 15.2]	-1.7 [-14.9, 11.5]	0.79	*-0.11*
Usual Care (n=16)	2.1 (8.3)	10.4 (20.1)	8.3 [-1.9, 18.6]			
Dysuria						
Exercise (n=16)	4.2 (11.4)	25.0 (35.5)	20.8 [3.8, 37.8]	-6.0 [-26.2, 4.3]	0.55	*-0.56*
Usual Care (n=16)	2.1 (8.3)	27.1 (25.0)	25.0 [12.9, 37.1]			
Abdominal pain						
Exercise (n=16)	20.8 (31.9)	27.1 (30.4)	6.3 [-14.5, 27.0]	-0.7 [-20.4, 19.0]	0.94	*-0.03*
Usual Care (n=16)	12.5 (20.6)	25.0 (22.8)	12.5 [-1.8, 26.8]			
Buttocks pain						
Exercise (n=16)	27.1 (32.7)	56.3 (41.7)	29.2 [6.8, 51.5]	10.2 [-15.8, 36.2]	0.43	*0.34*
Usual Care (n=16)	27.1 (27.8)	45.8 (34.2)	18.8 [2.9, 34.6]			
Bloating						
Exercise (n=16)	22.9 (23.5)	25.0 (25.8)	2.1 [-13.1, 17.3]	1.7 [-16.4, 19.7]	0.85	*0.07*
Usual Care (n=15)	24.4 (26.6)	24.4 (23.5)	0.0 [-17.1, 17.1]			
Blood/mucus in stool						
Exercise (n=16)	40.6 (36.0)	30.2 (28.0)	-10.4 [-36.7, 15.9]	3.3 [-17.6, 24.3]	0.75	*0.11*
Usual Care (n=16)	28.1 (24.1)	26.0 (25.8)	-2.1 [-15.8, 11.6]			
Dry mouth						
Exercise (n=16)	20.8 (29.5)	16.7 (17.2)	-4.2 [-19.9, 11.6]	-7.5 [-23.8, 8.8]	0.35	*-0.29*
Usual Care (n=16)	16.7 (24.3)	22.9 (29.1)	6.3 [-7.1, 19.6]			
Hair loss						
Exercise (n=16)	0.0 (0.0)	18.8 (32.1)	18.8 [1.6, 35.9]	11.5 [-3.9, 26.9]	0.14	-
Usual Care (n=16)	0.0 (0.0)	6.3 (13.4)	6.3 [-0.9, 13.4]			
Taste						
Exercise (n=16)	6.3 (13.4)	20.8 (26.9)	14.6 [-1.3, 30.4]	8.1 [-8.2, 24.4]	0.32	*0.76*
Usual Care (n=16)	2.1 (8.3)	10.4 (16.0)	8.3 [0.4, 16.3]			
Anxiety*						
Exercise (n=16)	52.1 (24.2)	58.3 (25.8)	6.3 [-11.2, 23.7]	4.1 [-12.7, 21.0]	0.62	*0.15*
Usual Care (n=16)	58.3 (31.0)	56.3 (20.1)	-2.1 [-18.6, 14.4]			
Weight*						
Exercise (n=16)	68.8 (28.5)	81.3 (24.2)	12.5 [1.5, 23.5]	8.8 [-4.2, 21.9]	0.18	*0.34*
Usual Care (n=16)	77.1 (23.5)	77.1 (23.5)	0.0 [-15.9, 15.9]			
Body image*						
Exercise (n=16)	79.2 (19.0)	75.0 (22.8)	-4.2 [-14.0, 5.7]	3.2 [-10.4, 16.8]	0.63	*0.19*
Usual Care (n=16)	94.4 (11.5)	85.4 (19.3)	-9.0 [-16.6, -1.5]			
Flatulence						
Exercise (n=16)	29.2 (36.3)	22.9 (26.4)	-6.3 [-23.7, 11.2]	-3.1 [19.0, 12.8]	0.69	*-0.09*
Usual Care (n=16)	31.3 (33.3)	27.1 (21.8)	-4.2 [-19.9, 11.6]			
Fecal incontinence						
Exercise (n=16)	22.9 (29.1)	20.8 (26.9)	-2.1 [-15.8, 11.6]	9.1 [-11.7, 29.9]	0.38	*0.35*
Usual Care (n=15)	20.0 (24.6)	11.1 (27.2)	-8.9 [-32.5, 14.7]			

Table 6-2. Effects of supervised high-intensity interval training during chemoradiation on quality of life postchemoradiation in the EXERT Trial (continued).

Sore skin						
Exercise (n=16)	25.0 (31.0)	66.7 (36.5)	41.7 [21.7, 61.7]	24.9 [-0.1, 49.9]	0.051	*0.97*
Usual Care (n=16)	16.7 (21.1)	39.6 (34.9)	22.9 [3.8, 42.1]			
Stool frequency						
Exercise (n=16)	34.4 (30.7)	55.2 (36.9)	20.8 [-1.5, 43.2]	25.8 [4.0, 47.6]	0.022	*0.99*
Usual Care (n=16)	25.0 (19.2)	29.2 (21.5)	4.2 [-9.8, 18.1]			
Embarrassment						
Exercise (n=16)	27.1 (32.7)	35.4 (39.4)	8.3 [-10.6, 27.2]	9.8 [-12.8, 32.5]	0.38	*0.34*
Usual Care (n=16)	18.8 (27.1)	22.9 (26.4)	4.2 [-16.2, 24.5]			

Abbreviations: SD, standard deviation; CI, confidence interval; QoL, quality of life

[1] Adjusted for age, sex, and baseline value of the outcome

*Functional Scales

Note: for the functional scales, higher scores indicated better functioning (i.e. a positive between-group difference was indicative of better functioning in the exercise group). For the symptom scales, higher scores indicated worse symptoms (i.e. a positive between-group difference indicated worse symptoms in the exercise group).

Table 6-3. Effects of exercise during and after chemoradiation on symptom burden prior to surgery in the EXERT Trial.

	Baseline	Pre-Surgery	Baseline to Pre-Surgery			
			Mean Change	Adjusted between-group difference[3]		
MDASI items	Mean (SD)	Mean (SD)	Mean [95% CI]	Mean [95% CI]	*P*	*d*
Symptom severity[1]						
Exercise (n=15)	1.1 (0.8)	1.4 (1.3)	0.3 [-0.4, 1.0]	0.3 [-0.5, 1.0]	0.48	*0.32*
Usual Care (n=14)	1.2 (1.1)	1.1 (0.7)	-1.1 [-0.6, 0.4]			
Symptom interference[2]						
Exercise (n=15)	1.3 (1.4)	2.7 (3.1)	1.4 [-0.6, 3.3]	1.5 [-0.4, 3.5]	0.12	*0.80*
Usual Care (n=14)	1.8 (2.4)	1.0 (1.3)	-0.9 [-2.4, 0.6]			
Core symptoms						
Pain						
Exercise (n=15)	1.3 (2.2)	1.4 (2.1)	0.1 [-0.8, 1.0]	0.5 [-0.6, 1.6]	0.38	*0.19*
Usual Care (n=14)	1.8 (2.8)	1.2 (1.5)	-0.6 [-1.8, 0.6]			
Fatigue						
Exercise (n=15)	2.9 (1.9)	3.5 (2.9)	0.6 [-1.0, 2.2]	0.6 [-1.2, 2.4]	0.50	*0.32*
Usual Care (n=14)	2.0 (1.9)	2.5 (1.3)	0.5 [-0.6, 1.6]			
Nausea						
Exercise (n=15)	0.3 (0.6)	0.9 (2.1)	0.6 [-0.6, 1.8]	0.5 [-0.8, 1.8]	0.42	*0.45*
Usual Care (n=14)	0.9 (1.6)	0.5 (1.2)	-0.4 [-1.0, 0.3]			
Disturbed sleep						
Exercise (n=14)	2.9 (3.1)	2.4 (2.8)	-0.5 [-2.6, 1.6]	-0.3 [-2.2, 1.5]	0.72	*-0.11*
Usual Care (n=14)	1.6 (1.9)	2.1 (1.8)	0.5 [-0.6, 1.6]			
Distress						
Exercise (n=15)	2.1 (2.0)	2.5 (2.9)	0.4 [-1.3, 2.1]	-0.1 [-1.8, 1.6]	0.88	*-0.05*
Usual Care (n=14)	2.1 (2.3)	2.4 (1.6)	0.2 [-0.9, 1.3]			
Shortness of breath						
Exercise (n=15)	0.3 (0.6)	1.0 (2.0)	0.7 [-0.4, 1.8]	0.3 [-1.1, 1.8]	0.63	*0.29*
Usual Care (n=14)	0.5 (0.9)	0.7 (1.4)	0.2 [-0.8, 1.2]			
Difficulty remembering						
Exercise (n=15)	0.9 (1.5)	1.6 (2.4)	0.7 [-0.5, 1.8]	0.4 [-0.9, 1.7]	0.51	*0.25*
Usual Care (n=14)	1.4 (2.1)	1.2 (1.7)	-0.1 [-1.0, 0.7]			
Lack of appetite						
Exercise (n=15)	0.8 (1.4)	1.3 (2.1)	0.5 [-0.4, 1.4]	0.9 [-0.1, 2.0]	0.08	*0.45*
Usual Care (n=14)	1.6 (2.7)	0.6 (1.5)	-0.9 [-1.8, -0.1]			
Drowsiness						
Exercise (n=15)	1.9 (1.8)	2.5 (3.2)	0.6 [-1.2, 2.4]	0.0 [-1.8, 1.9]	0.97	*0.00*
Usual Care (n=14)	2.2 (3.1)	2.1 (1.9)	-0.1 [-2.1, 1.9]			
Dry mouth						
Exercise (n=15)	0.7 (1.0)	0.7 (1.7)	0.0 [-0.8, 0.8]	-0.3 [-1.7, 1.1]	0.70	*-0.17*
Usual Care (n=14)	1.9 (2.5)	1.5 (2.0)	-0.4 [-1.8, 0.9]			
Sadness						
Exercise (n=15)	1.7 (1.7)	2.3 (2.4)	0.5 [-0.8, 1.9]	0.1 [-1.4, 1.5]	0.92	*0.06*
Usual Care (n=14)	1.7 (1.9)	2.0 (1.9)	0.3 [-0.4, 0.9]			
Vomiting						
Exercise (n=15)	0.0 (0.0)	0.7 (2.6)	0.7 [-0.8, 2.1]	0.4 [-1.0, 1.8]	0.58	*1.09*
Usual Care (n=14)	0.2 (0.6)	0.1 (0.3)	-0.1 [-0.5, 0.2]			
Numbness or tingling						
Exercise (n=15)	0.3 (0.8)	0.4 (0.7)	0.1 [-0.6, 0.7]	0.1 [-0.9, 1.1]	0.86	*0.06*
Usual Care (n=14)	1.1 (2.3)	0.3 (1.9)	-0.4 [-1.7, 0.8]			

Table 6-3. Effects of exercise during and after chemoradiation on symptom burden prior to surgery in the EXERT Trial (continued).

Additional Symptoms						
Mouth sores						
Exercise (n=15)	0.2 (0.4)	0.1 (0.3)	-0.1 [-0.3, 0.1]	0.1 [-0.1, 0.2]	0.41	*0.24*
Usual Care (n=14)	0.1 (0.5)	0.0 (0.0)	-0.1 [-0.5, 0.2]			
Hand-foot syndrome						
Exercise (n=15)	0.2 (0.8)	0.2 (0.6)	0.0 [-0.6, 0.6]	0.1 [-0.3, 0.5]	0.65	*0.20*
Usual Care (n=14)	0.0 (0.0)	0.1 (0.4)	0.1 [-0.1, 0.4]			
Skin reaction						
Exercise (n=15)	0.2 (0.6)	0.8 (1.6)	0.6 [-0.1, 1.3]	0.5 [-0.6, 1.5]	0.37	*1.03*
Usual Care (n=14)	0.1 (0.5)	0.4 (1.1)	0.2 [-0.5, 0.9]			
Diarrhea						
Exercise (n=15)	1.9 (2.6)	1.5 (1.8)	-0.5 [-2.4, 1.5]	1.2 [0.1, 2.3]	0.030	*0.59*
Usual Care (n=14)	1.3 (1.5)	0.4 (0.8)	-0.9 [-1.7, 0.0]			

Abbreviations: SD, standard deviation; CI, confidence interval

[1] Average of the 17 symptom items

[2] Average of the 6 interference items

[3] Adjusted for age, sex, and baseline value of the outcome

Table 6-4. Effects of exercise during and after chemoradiation on quality of life prior to surgery in the EXERT Trial.

	Baseline	Pre-surgery	Baseline to Pre-surgery			
			Mean Change	Adjusted between-group difference[1]		
EORTC QLQ-C30	Mean (SD)	Mean (SD)	Mean [95% CI]	Mean [95% CI]	*P*	*d*
Summary score*						
Exercise (n=15)	81.4 (9.6)	81.3 (16.2)	-0.1 [-9.5, 9.4]	-4.4 [-14.5, 5.7]	0.38	*-0.35*
Usual Care (n=14)	83.9 (13.4)	87.0 (8.4)	3.1 [-3.5, 9.7]			
Global health status/QoL*						
Exercise (n=15)	66.7 (19.4)	73.3 (18.7)	6.7 [-5.7, 19.0]	3.3 [-10.3, 16.9]	0.62	*0.17*
Usual Care (n=14)	70.8 (17.8)	71.4 (18.1)	0.6 [-11.6, 12.7]			
Physical functioning*						
Exercise (n=15)	93.8 (5.9)	91.1 (15.9)	-2.7 [-11.2, 5.9]	-2.0 [-12.8, 8.9]	0.71	*-0.24*
Usual Care (n=14)	91.4 (11.2)	92.9 (10.3)	1.4 [-6.1, 9.0]			
Role functioning*						
Exercise (n=15)	84.4 (19.4)	78.9 (29.2)	-5.6 [-24.9, 13.8]	-10.1 [-29.6, 9.4]	0.30	*-0.43*
Usual Care (n=14)	88.1 (21.1)	90.5 (19.3)	2.4 [-5.0, 9.8]			
Emotional functioning*						
Exercise (n=15)	77.2 (13.9)	79.4 (19.6)	2.2 [-6.9, 11.4]	0.0 [-11.2, 11.2]	1.0	*0.0*
Usual Care (n=14)	83.9 (17.1)	82.7 (8.9)	-1.2 [-10.0, 7.6]			
Cognitive functioning*						
Exercise (n=15)	84.4 (20.4)	82.2 (24.0)	-2.2 [-11.4, 6.9]	-3.5 [-15.1, 8.2]	0.54	*-0.18*
Usual Care (n=14)	83.3 (23.6)	85.7 (12.8)	2.4 [-7.5, 12.3]			
Social functioning*						
Exercise (n=15)	68.9 (26.6)	75.6 (25.1)	6.7 [-13.3, 26.6]	-3.3 [-23.0, 16.5]	0.74	*-0.13*
Usual Care (n=14)	85.7 (20.5)	82.1 (21.1)	-3.6 [-15.6, 8.5]			
Fatigue						
Exercise (n=15)	31.1 (15.3)	34.1 (27.0)	3.0 [-13.2, 19.2]	6.6 [-11.0, 24.1]	0.45	*0.36*
Usual Care (n=14)	22.2 (22.2)	23.8 (15.6)	1.6 [-10.2, 13.4]			
Nausea and vomiting						
Exercise (n=15)	4.4 (9.9)	7.8 (25.9)	3.3 [-7.2, 13.9]	2.9 [-11.9, 17.7]	0.69	*0.28*
Usual Care (n=14)	6.0 (12.4)	4.8 (10.2)	-1.2 [-11.5, 9.1]			
Pain						
Exercise (n=15)	15.6 (20.4)	17.8 (24.0)	2.2 [-11.7, 16.1]	8.5 [-6.7, 23.8]	0.26	*0.36*
Usual Care (n=14)	20.2 (19.8)	9.5 (15.6)	-10.7 [-22.4, 1.0]			
Dyspnea						
Exercise (n=15)	11.1 (16.3)	11.1 (20.6)	0.0 [-9.9, 9.9]	1.0 [-11.1, 13.2]	0.86	*0.07*
Usual Care (n=14)	4.8 (12.1)	4.8 (12.1)	0.0 [-7.5, 7.5]			
Insomnia						
Exercise (n=15)	37.8 (35.3)	40.0 (42.2)	2.2 [-20.3, 24.8]	14.2 [-10.4, 38.9]	0.25	*0.46*
Usual Care (n=14)	26.2 (23.3)	19.0 (21.5)	-7.1 [-18.3, 4.0]			
Appetite loss						
Exercise (n=15)	17.8 (21.3)	13.3 (27.6)	-4.4 [-22.7, 13.8]	1.9 [-15.3, 19.1]	0.82	*0.08*
Usual Care (n=14)	16.7 (31.4)	9.5 (15.6)	-7.1 [-25.9, 11.6]			
Constipation						
Exercise (n=15)	6.7 (13.8)	6.7 (13.8)	0.0 [-9.9, 9.9]	-5.6 [-26.0, 14.9]	0.58	*-0.24*
Usual Care (n=14)	23.8 (27.5)	19.0 (31.3)	-4.8 [-24.5, 15.0]			
Diarrhea						
Exercise (n=15)	26.7 (25.8)	20.0 (27.6)	-6.7 [-31.0, 17.7]	11.2 [-6.5, 28.8]	0.20	*0.41*
Usual Care (n=14)	21.4 (24.8)	11.9 (16.6)	-9.5 [-28.7, 9.6]			

Table 6-4. Effects of exercise during and after chemoradiation on quality of life prior to surgery in the EXERT Trial (continued).

Financial difficulties						
Exercise (n=15)	20.0 (21.1)	17.8 (27.8)	-2.2 [-13.2, 8.7]	-7.0 [-24.1, 10.1]	0.41	*-0.26*
Usual Care (n=14)	23.8 (30.5)	28.6 (34.2)	4.8 [-8.0, 17.5]			
EORTC QLQ-CR29						
Urinary frequency						
Exercise (n=15)	36.7 (26.1)	37.8 (16.0)	1.1 [-12.6, 14.8]	7.7 [-5.6, 21.0]	0.24	*0.32*
Usual Care (n=14)	23.8 (21.4)	27.4 (20.3)	3.6 [-7.9, 15.0]			
Urinary incontinence						
Exercise (n=15)	6.7 (18.7)	2.2 (8.6)	-4.4 [-10.9, 2.1]	1.5 [-1.6, 4.6]	0.34	*0.10*
Usual Care (n=14)	4.8 (12.1)	0.0 (0.0)	-4.8 [-11.8, 2.2]			
Dysuria						
Exercise (n=15)	4.4 (11.7)	8.9 (26.6)	4.4 [-10.9, 19.8]	9.0 [-6.2, 24.1]	0.23	*0.85*
Usual Care (n=14)	2.4 (8.9)	0.0 (0.0)	-2.4 [-7.5, 2.8]			
Abdominal pain						
Exercise (n=15)	15.6 (24.8)	15.6 (27.8)	0.0 [-20.9, 20.9]	11.5 [-3.2, 26.2]	0.12	*0.45*
Usual Care (n=14)	11.9 (21.1)	2.4 (8.9)	-9.5 [-21.3, 2.2]			
Buttocks pain						
Exercise (n=15)	22.2 (27.2)	20.0 (24.6)	-2.2 [-17.0, 12.5]	4.6 [-12.7, 22.0]	0.59	*0.15*
Usual Care (n=14)	28.6 (28.8)	19.0 (25.2)	-9.5 [-23.5, 4.5]			
Bloating						
Exercise (n=15)	20.0 (21.1)	13.3 (16.9)	-6.7 [-19.1, 5.8]	3.5 [-9.3, 16.3]	0.58	*0.15*
Usual Care (n=14)	28.6 (25.7)	14.3 (17.1)	-14.3 [-28.8, 0.3]			
Blood/mucus in stool						
Exercise (n=15)	38.9 (34.3)	16.7 (17.8)	-22.2 [-42.2, -2.3]	2.2 [-9.8, 14.2]	0.71	*0.07*
Usual Care (n=14)	25.0 (27.5)	11.9 (15.2)	-13.1 [-24.5, -1.7]			
Dry mouth						
Exercise (n=15)	20.0 (30.3)	8.9 (15.3)	-11.1 [-26.2, 4.0]	-8.7 [-22.8, 5.5]	0.22	*-0.34*
Usual Care (n=14)	21.4 (24.8)	19.0 (25.2)	-2.4 [-14.2, 9.5]			
Hair loss						
Exercise (n=15)	0.0 (0.0)	15.6 (21.3)	15.6 [3.7, 27.4]	4.4 [-12.5, 21.3]	0.60	-
Usual Care (n=14)	0.0 (0.0)	11.9 (21.1)	11.9 [-0.3, 24.1]			
Taste						
Exercise (n=15)	4.4 (11.7)	13.3 (21.1)	8.9 [-2.1, 19.8]	3.4 [-11.4, 18.2]	0.64	*0.32*
Usual Care (n=14)	2.4 (8.9)	9.5 (20.4)	7.1 [-4.0, 18.3]			
Anxiety*						
Exercise (n=15)	48.9 (24.8)	53.3 (30.3)	4.4 [-15.1, 24.0]	-7.4 [-26.7, 11.8]	0.43	*-0.27*
Usual Care (n=14)	59.5 (32.5)	66.7 (22.6)	7.1 [-6.3, 20.6]			
Weight*						
Exercise (n=15)	73.3 (28.7)	75.6 (29.5)	2.2 [-15.5, 20.0]	-10.9 [-29.2, 7.2]	0.23	*-0.42*
Usual Care (n=14)	78.6 (24.8)	88.1 (16.6)	9.5 [-4.5, 23.5]			
Body image*						
Exercise (n=15)	79.3 (16.7)	77.0 (25.4)	-2.2 [-18.2, 13.8]	-0.3 [-20.9, 20.2]	0.97	*-0.02*
Usual Care (n=14)	94.4 (12.1)	81.0 (20.2)	-13.5 [-24.5, -2.5]			
Flatulence						
Exercise (n=14)	28.6 (36.6)	21.4 (16.6)	-7.1 [-25.9, 11.6]	-5.8 [-18.4, 6.9]	0.36	*-0.17*
Usual Care (n=13)	33.3 (36.0)	30.8 (21.4)	-2.6 [-19.9, 14.8]			
Fecal incontinence						
Exercise (n=15)	17.8 (21.3)	13.3 (16.9)	-4.4 [-16.3, 7.4]	0.8 [-13.4, 15.0]	0.91	*0.03*
Usual Care (n=13)	20.5 (25.6)	15.4 (22.0)	-5.1 [-23.2, 13.0]			

Table 6-4. Effects of exercise during and after chemoradiation on quality of life prior to surgery in the EXERT Trial (continued).

Sore skin						
Exercise (n=15)	22.2 (30.0)	31.1 (29.5)	8.9 [-7.4, 25.2]	17.2 [-1.4, 35.9]	0.07	*0.67*
Usual Care (n=13)	17.9 (22.0)	12.8 (16.9)	-5.1 [-21.3, 11.0]			
Stool frequency						
Exercise (n=15)	30.0 (26.1)	25.6 (25.1)	-4.4 [-18.6, 9.7]	2.0 [-14.0, 17.9]	0.80	*0.08*
Usual Care (n=13)	21.8 (19.7)	21.8 (19.7)	0.0 [-13.6, 13.6]			
Embarrassment						
Exercise (n=15)	24.4 (32.0)	22.2 (20.6)	-2.2 [-17.0, 12.5]	19.7 [7.4, 32.1]	0.003	*0.68*
Usual Care (n=13)	20.5 (29.0)	2.6 (9.2)	-17.9 [-37.4, 1.5]			

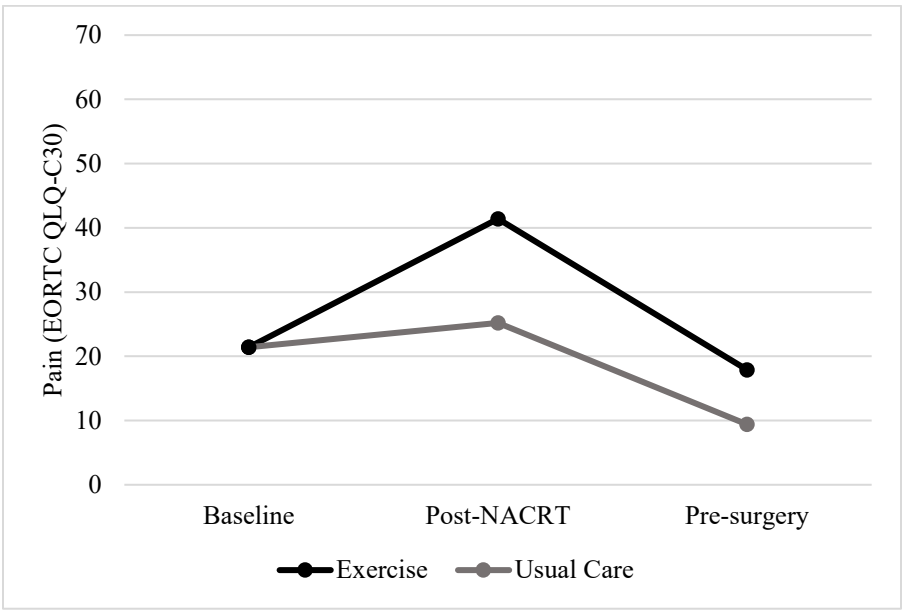
Abbreviations: SD, standard deviation; CI, confidence interval; QoL, quality of life

[1] Adjusted for age, sex, and baseline value of the outcome

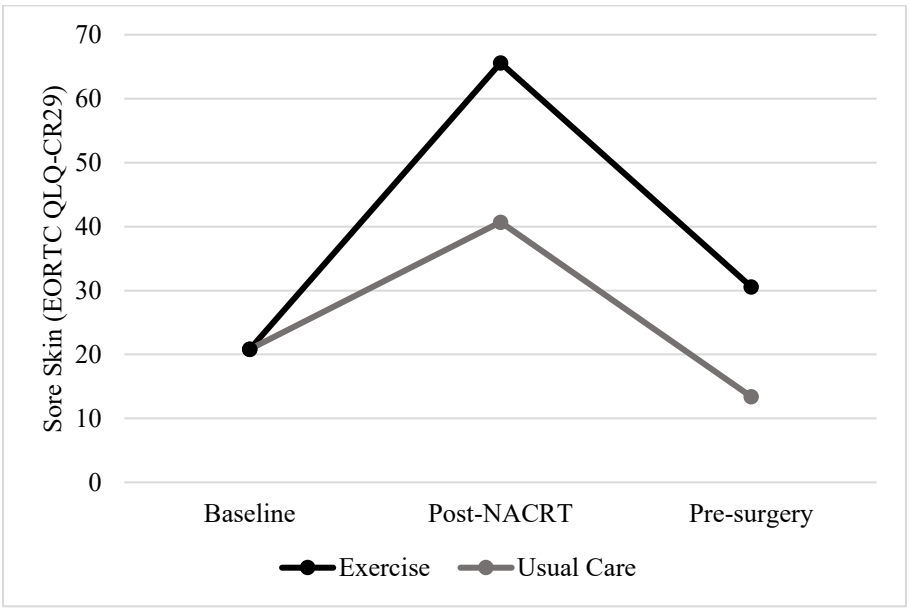
*Functional Scales

Note: for the functional scales, higher scores indicated better functioning (i.e. a positive between-group difference was indicative of better functioning in the exercise group). For the symptom scales, higher scores indicated worse symptoms (i.e. a positive between-group difference indicated worse symptoms in the exercise group).

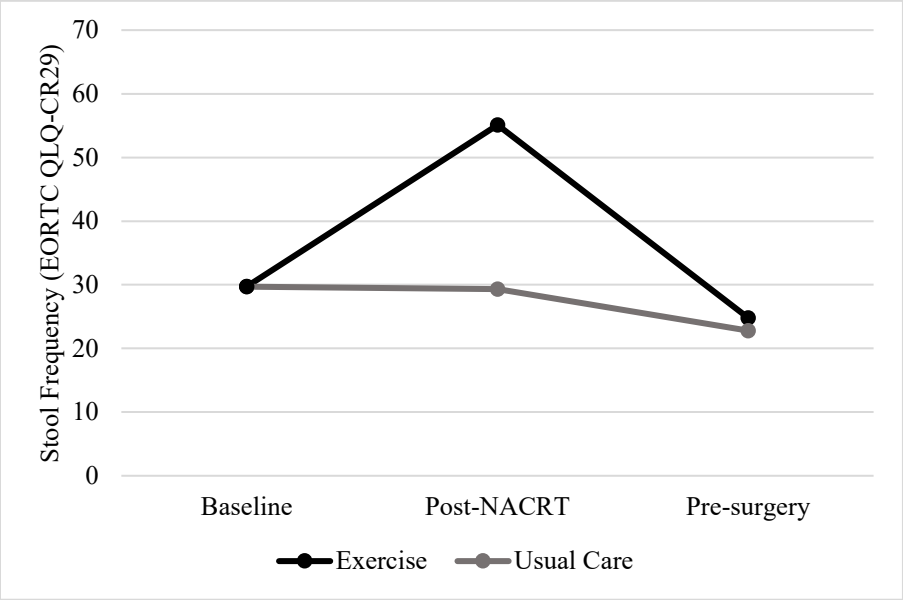
A


70
60
50
40
30
20
10
0
Pain (EORTC QLQ-C30)
Baseline
Post-NACRT
Pre-surgery
Exercise
Usual Care

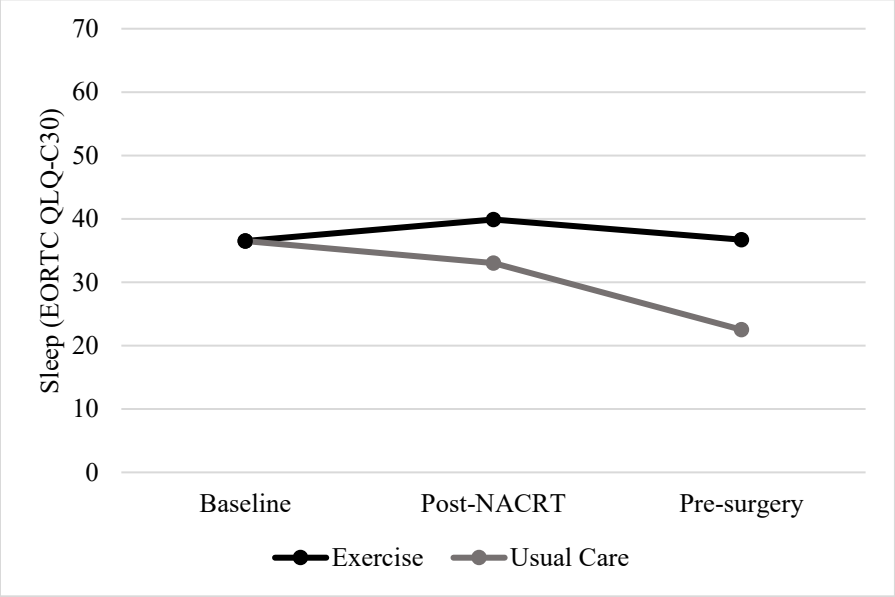
B


70
60
50
40
30
20
10
0
Sore Skin (EORTC QLQ-CR29)
Baseline
Post-NACRT
Pre-surgery
Exercise
Usual Care

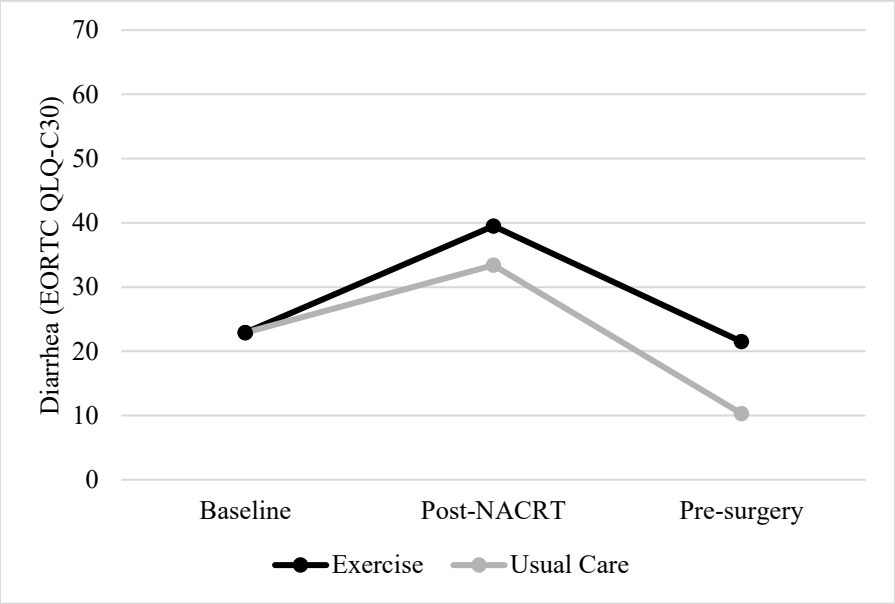
C


70
60
50
40
30
20
10
0
Stool Frequency (EORTC QLQ-CR29)
Baseline
Post-NACRT
Pre-surgery
Exercise
Usual Care

D


70
60
50
40
30
20
10
0
Sleep (EORTC QLQ-C30)
Baseline
Post-NACRT
Pre-surgery
Exercise
Usual Care

E



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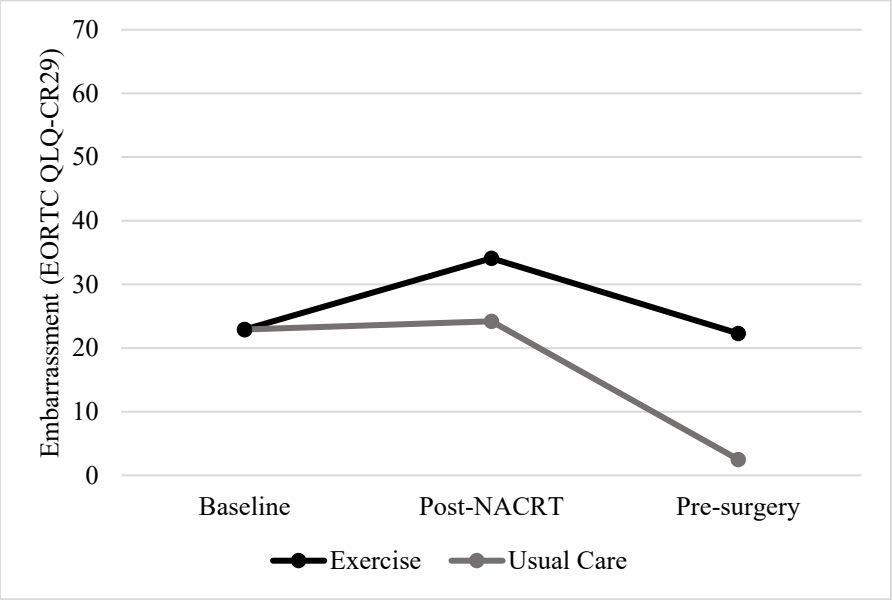
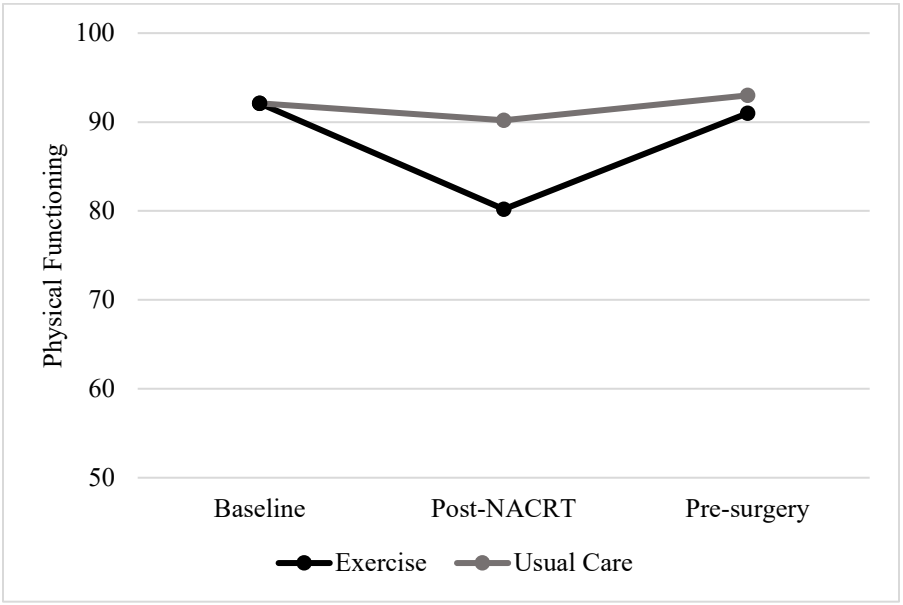
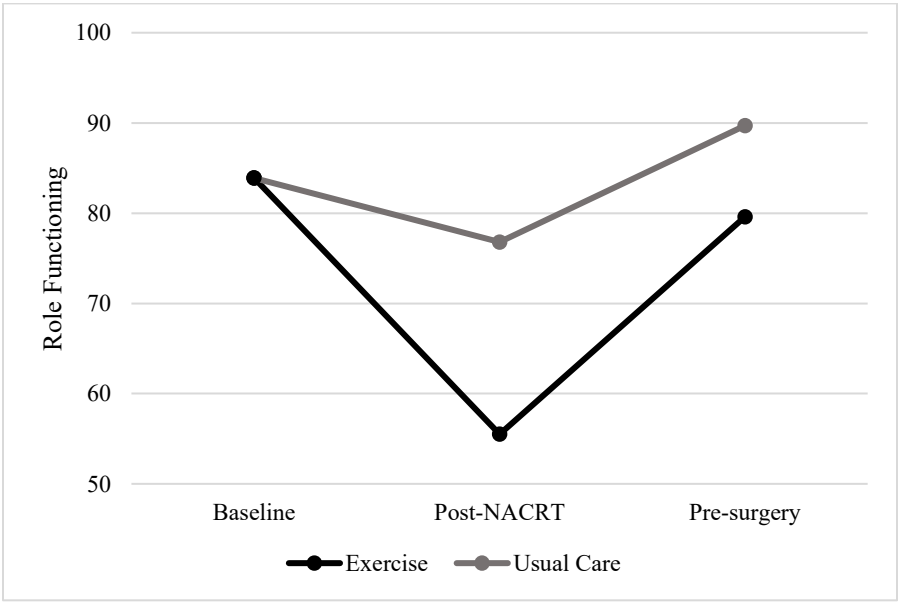


Figure 6-1. Effects of exercise during and after neoadjuvant chemoradiation on (a) pain, (b) sore skin, (c) stool frequency, (d) sleep, (e) diarrhea, and (f) embarrassment. Post-NACRT and pre-surgery means are adjusted for baseline value of the outcome, age, and sex.

A


100
90
80
70
60
50
Physical Functioning
Baseline
Post-NACRT
Pre-surgery
Exercise
Usual Care

B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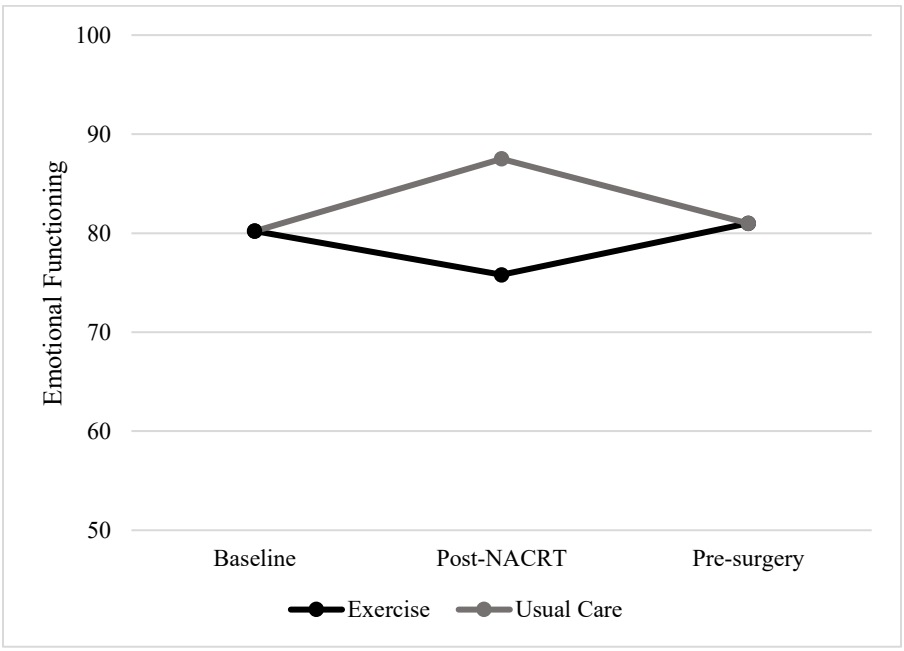
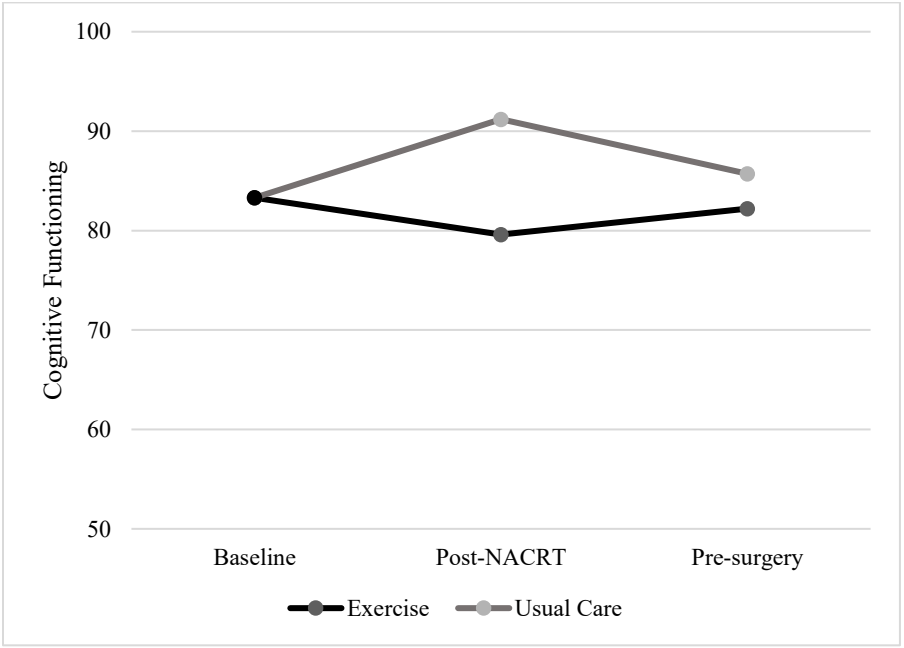
90
80
70
60
50
Role Functioning
Baseline
Post-NACRT
Pre-surgery
Exercise
Usual Care

C


100
90
80
70
60
50
Emotional Functioning
Baseline
Post-NACRT
Pre-surgery
Exercise
Usual Care

D


100
90
80
70
60
50
Cognitive Functioning
Baseline
Post-NACRT
Pre-surgery
Exercise
Usual Care

E

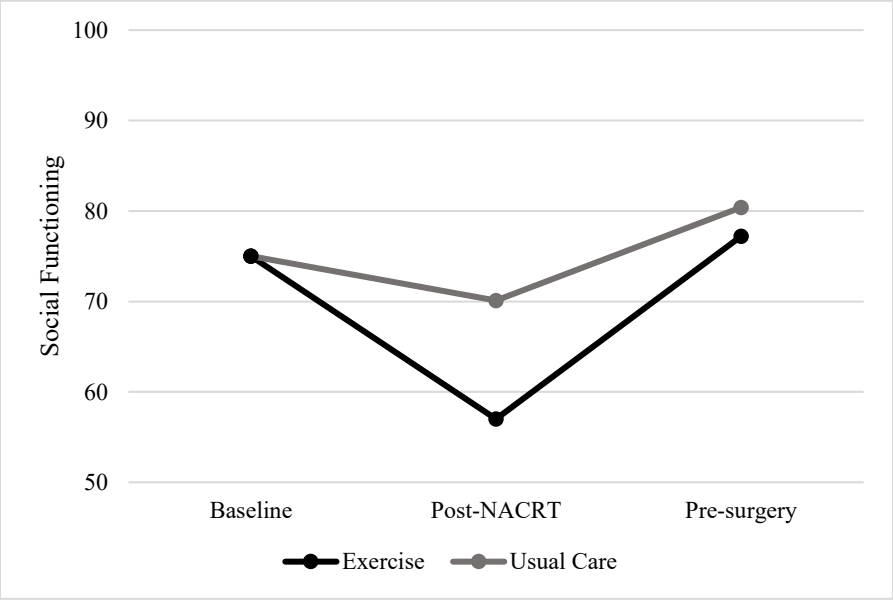


Figure 6-2. Effects of exercise during and after neoadjuvant chemoradiation on (a) physical functioning, (b) role functioning, (c) emotional functioning, (d) cognitive functioning, and (e) social functioning. Post-NACRT and pre-surgery means are adjusted for baseline value of the outcome, age, and sex.

CHAPTER 7: DISCUSSION

7.1 Overview

The overall purpose of this dissertation was to further establish the feasibility and safety of exercise in rectal cancer patients during and after NACRT and to examine the preliminary effects of exercise on outcomes in this clinical setting. The results from **Chapters 2 and 3** were generated from data collected during my master's thesis and helped inform the design and execution of the EXERT Trial. Briefly, in **Chapter 2** rectal cancer patients reported that participation in a supervised aerobic exercise program during NACRT was more enjoyable and less difficult than initially perceived. Moreover, participants perceived many possible benefits of exercise during and after NACRT (e.g. cardiovascular endurance, physical functioning, quality of life, and self-esteem); however, they also perceived some possible harms including fatigue, diarrhea, skin irritation, and hand-foot-syndrome. Furthermore, during NACRT, the most common perceived barriers to exercise were side effects from NACRT; however, after NACRT, lack of motivation was the most common barrier to exercise. **Chapter 3** identified the potential determinants of exercise adherence during and after NACRT. Although no significant associations were observed during NACRT, several variables including demographics, treatment-related side effects, and motivational outcomes meaningfully predicted exercise adherence. After NACRT, worse mental health was a significant predictor of exercise adherence and several other factors were meaningfully associated with exercise adherence. Together, the results from **Chapters 2 and 3** helped facilitate recruitment and exercise adherence during and after NACRT in the EXERT Trial. Moreover, the potential harms of exercise identified in **Chapter 2** were closely tracked in the EXERT Trial.

Overall, the EXERT Trial demonstrated the feasibility and safety of a supervised HIIT program during NACRT followed by ≥ 150 minutes of moderate-to-vigorous intensity

continuous exercise after NACRT (**Chapter 5**). Exercise did not improve health-related fitness outcomes, treatment toxicities, or treatment completion rates; however, the exercise group experienced a significantly better rate of pCR/near pCR compared to usual care (**Chapter 5**). Moreover, exercise exacerbated some symptoms and QoL during NACRT; however, most of the negative effects of exercise dissipated at the pre-surgery timepoint (**Chapter 6**).

7.2 Strengths and Limitations

The strengths and limitations of each paper that comprise the main body of this dissertation have been discussed in their respective chapters. Here, I will expand on the main strengths and limitations of the EXERT Trial. A major strength of the EXERT Trial was its novelty. EXERT was the first randomized controlled trial to examine the effects of exercise training on various outcomes in rectal cancer patients during and after NACRT. To date, most exercise oncology research has been conducted in breast and prostate cancer. However, differences among cancer patient groups exist according to disease, treatment, and individual factors; therefore, it is important that exercise intervention trials in oncology evaluate the unique considerations for exercise feasibility, safety, and potential benefit by clinical setting. Secondly, EXERT was one of the few exercise oncology trials to include clinical outcomes (i.e. treatment completion and treatment response). Limited research has demonstrated that exercise may improve chemotherapy completion rates in early stage breast cancer patients (1). It is possible that exercise may improve treatment completion rates by mitigating some dose-limiting treatment toxicities. Additionally, exploratory analyses from large randomized controlled trials indicate that exercise during chemotherapy may improve survival outcomes in breast cancer and lymphoma (2-4). Pre-clinical studies support several biologically plausible mechanisms via which exercise may improve the effectiveness of cancer therapies (e.g. alterations in tumor

vascularization, perfusion, metabolism, and immune response) (5). Clinical outcomes are extremely important to cancer patients and clinicians and, given the possible benefit of exercise, it is imperative that exercise intervention trials include these outcomes. A third novel aspect of the EXERT Trial was the exercise intervention. Most exercise research in the oncology setting has focused on moderate-to-vigorous intensity continuous aerobic exercise training (6). However, HIIT is gaining attention as an effective and time-efficient intervention for improving health outcomes in oncology (7, 8).

A further strength of this dissertation was the incremental research process used to design and implement the EXERT Trial. Findings from the phase I trial helped to inform the design of the phase II trial. Moreover, I was able to use my experiences from the phase I trial to improve the conduct of the phase II trial. The high-quality design and conduct of the EXERT Trial provided the most comprehensive and robust evaluation to date of exercise in this clinical setting. The EXERT Trial was high-quality based on its use of a randomized controlled design, supervised exercise during NACRT, gold standard measures of health-related fitness, validated patient-reported outcome measures, and clinically important endpoints. Moreover, the trial was thoughtfully conducted and included thorough participant instruction, documentation, and follow-up. The neaodjuvant rectal cancer setting was ideal to test the effects of a rigorous exercise intervention on a clinically relevant endpoint as patients were undergoing 5-6 weeks of daily radiation therapy at the cancer center which was within walking distance from the supervised exercise facility. Additionally, all patients were scheduled to undergo surgery with an opportunity to assess response to the treatment.

Despite the strengths of the EXERT Trial, there are several limitations that should be considered when interpreting the findings and planning future research. The main limitation of

the EXERT Trial was the small sample size which resulted from slower than expected recruitment. Smaller randomized trials usually have limited power to detect a statistically significant effect. Furthermore, a statistically significant effect is more likely to be due to chance because (a) groups may be unbalanced at baseline for known and unknown confounding and/or prognostic variables and (b) the results are fragile (i.e. only a small number of participants' status would need to change for the outcome to change from significant to non-significant). Therefore, it is possible that the positive findings for pCR and the negative findings for some symptoms and QoL were due to chance. Conversely, the significant loss to follow-up for VO_2 peak at both the post-NACRT (31%) and pre-surgery (58%) timepoints may have further hindered the ability to detect a meaningful effect of exercise for this particular outcome.

Another important limitation is the potential self-selection bias for participation in exercise research. Based on our 27% recruitment rate, the sample in EXERT was not representative of the general population in this clinical setting and this limits the generalizability of our findings. Additionally, outcome assessors, interventionists, and participants were not blinded to group assignment which could have introduced bias for the health-related fitness and patient-reported outcome results. In exercise trials, it is not possible to blind interventionist or participants to group assignment. Moreover, in the EXERT Trial it was not logistically feasible to blind the outcome assessors for the health-related fitness outcomes.

The unsupervised exercise program after NACRT was another limitation of the EXERT Trial. In oncology, supervised exercise trials, compared to unsupervised, yield greater improvements in physical fitness and patient-reported outcomes (9-11). Additionally, we relied on self-report exercise adherence data after NACRT which is subject to recall and reporting

biases. Although exercise specialists carefully reviewed participants responses in the EXERT Trial, the reliability of these data are questionable.

Lastly, the EXERT Trial could have benefited from the inclusion of biological markers (e.g. angiogenesis markers, immune cells, inflammatory markers, and metabolic factors) to help explain the biological mechanisms underpinning the relationship between exercise and treatment response.

7.3 Future Research Directions

The findings from the EXERT Trial provide valuable insight into the design and conduct of future exercise trials in the neaodjuvant rectal cancer setting. Most importantly, larger phase II/III trials are required to establish whether exercise has a positive effect on treatment response and a negative effect on symptoms and QoL in this clinical setting. Therefore, it will be vital for future research to address the challenges of recruiting rectal cancer patients to exercise intervention trials during NACRT. Implementation of a multicenter trial is one way to address this issue; however, this will not address the limited generalizability of the findings. Further strategies are needed to facilitate the recruitment of patients in this clinical setting. Some of the main reasons for refusal in the EXERT Trial were “not interested”, “afraid will be too much”, and “living out of town”. The potential for exercise to improve treatment response is likely to be a strong motivator for patients. Nevertheless, some patients may not want to participate in a randomized controlled trial knowing that they may not receive a potentially superior treatment (i.e. exercise). Thus, it will be important for researchers to explain to patients that although promising, these findings are preliminary and that their participation in this research will help to confirm (or disprove) these findings. Moreover, a better understanding of the motivational outcomes (e.g. participants’ enjoyment, difficulty) related to the exercise program in the EXERT

Trial may facilitate recruitment. This data has been collected and will be reported in future papers. To further address concerns for patients who live out of town and will be commuting daily (Monday to Friday) for radiation treatment whose main concern is time, researchers may be able to work with local cancer treatment centers to accommodate patients' preferred time of day for treatment. If these strategies are not successful, future research may need to consider remote delivery of supervised exercise or a combination of face-to-face and remote (to reduce the burden of extra visits). Finally, to characterize the selection bias and develop strategies to broaden the reach of our exercise intervention trials, future research should consider collecting demographic, medical, and behavioral data on patients who are not eligible or refuse study participation.

Another important feasibility consideration is exercise adherence. The median attendance rate (82%) for the supervised HIIT sessions during NACRT was acceptable; however, if exercise does have a clinical benefit in this setting future research should look for strategies to optimize exercise adherence and maximize benefit. The most common reason for missed supervised exercise sessions in the EXERT Trial was patients' unwillingness to come to the fitness center on days they were not receiving radiation therapy. Again, it may be possible to convince patients to exercise if there is a clinical benefit. Moreover, exercise specialists can consider viable options for making up these sessions (e.g. possible back-to-back sessions or virtual delivery). Treatment-related side effects were the second most common reason for missed supervised exercise sessions during NACRT and may be hard to address in future trials. Furthermore, a common pitfall in exercise oncology research is reporting attendance rate but not any modifications to the planned exercise sessions. This may be less of a concern for exercise interventions in the survivorship phase of the cancer trajectory; however, it is reasonable to assume that

modifications according to immediate symptoms and side effects will be required during active treatment. Exercise dose modifications are an important aspect of the feasibility of exercise interventions during cancer treatment and should be reported in future trials. After NACRT, exercise adherence to the unsupervised exercise was suboptimal despite providing behavioral support. Strategies to further support patients in meeting the exercise prescription after NACRT may include supervised exercise sessions, remote delivery, and teaming up with community fitness centers. Data on exercise dose modifications during NACRT and the predictors of exercise adherence during and after NACRT has been collected and will be reported in a future paper to help inform the design of larger trials.

A further feasibility consideration is the rate of assessment completion. For physical fitness outcomes, the loss to follow-up rate was > 20% for both the VO_2 peak test and 6-minute walk test-a more feasible test of cardiorespiratory endurance for older frail adults- at both the post-NACRT and pre-surgery timepoints. Moreover, the reasons for missed testing were all medical in nature and will not be possible to address in future trials. Thus, it is unlikely that measures of cardiorespiratory fitness will be feasible in this clinical setting. Nonetheless, cardiorespiratory fitness may not be an important measure for inclusion in future trials with a cancer outcome as the primary endpoint. For patient-reported outcomes, the assessment completion rate was acceptable a both timepoints (< 20% loss to follow-up); however, strategies to optimize completion of these measures could include online delivery and completion. Lastly, the EXERT Trial demonstrated the feasibility of collecting clinical outcomes including treatment toxicities, treatment completion rates, and treatment response rates in this setting. Nevertheless, future trials should consider collecting treatment toxicities prospectively, and central review of cancer efficacy endpoints to ensure consistency.

The EXERT Trial provided the first evidence to suggest a clinical benefit of exercise in this setting. Interestingly, this finding occurred despite no between-group differences in cardiorespiratory fitness, treatment toxicities, or treatment completion rates. It was reasonable to assume that if the exercise stimulus (i.e. HIIT program) during NACRT was sufficient to produce improvements in VO_2 peak then it was likely sufficient to produce improvements in the tumor microenvironment. However, in the EXERT Trial, treatment response occurred in the absence of improvements in cardiorespiratory fitness.

Physiological factors limiting VO_2 max are multifactorial and include those involved in central blood flow (e.g. cardiac output, hemoglobin), peripheral blood flow (e.g. capillary density, oxygen diffusion and extraction), muscle metabolism (e.g. mitochondria size and number, energy stores and substrate availability), and ventilation (e.g. minute ventilation) (12). Exercise training produces positive adaptations in several of these factors and ultimately improves VO_2 peak; however, cancer treatments can negatively impact several of the physiological factors limiting VO_2 max. It is possible that any positive physiological adaptations to exercise were cancelled out by the negative effects of chemoradiation, especially given the short timeframe during NACRT (i.e. 5-6 weeks). Furthermore, the measure of cardiorespiratory fitness in EXERT was VO_2 peak which has slightly different criteria than VO_2 max. VO_2 peak in EXERT was determined as the highest value of oxygen consumption measured during a graded exercise test to volitional exhaustion. Moreover, achievement of ≥ 2 secondary criteria (i.e. respiratory exchange ratio > 1.05, >7 on the 10-point Borg scale, and within 5 bpm of age-predicted maximal heart rate) was used to confirm VO_2 peak. However, treatment-related side effects may have interfered with patients' perception of volitional exhaustion and the secondary criteria; therefore, VO_2 peak may not be a valid measure of cardiorespiratory fitness in this

clinical setting. It was difficult to comment on the effects of the unsupervised exercise program after NACRT because of the high number of missed fitness tests and modest adherence to the exercise in this phase of the trial.

The potential interactions between exercise and cancer treatment efficacy are complex. Briefly, exercise in the neaodjuvant cancer setting may have an additive, sensitizing, synergistic, or even antagonistic effect. There are several plausible biological mechanisms that could explain the relationship between exercise and treatment response in this clinical setting including systemic adaptations and changes in the tumor microenvironment. Acutely, exercise training may increase tumor blood perfusion and oxygenation whereas, chronic exercise training may induce positive systemic changes (e.g. improved immune function, metabolism, reduced inflammation) and intratumoral changes (e.g. improved tumor vascularization and normalization, enhance immunogenicity, and improve metabolism) (13, 14). Future trials should consider including correlative biological markers. This would provide insight into the mechanisms underlying the effects of exercise on treatment response and the development of more targeted exercise prescriptions.

The exercise program in the EXERT Trial was just one of many possible exercise prescriptions and the optimal exercise prescription (i.e. frequency, intensity, timing, and type) for improving treatment response in this clinical setting is unknown. For example, if an acute bout of exercise does considerably increase tumor blood flow and reduce tumor hypoxia, then exercise immediately before radiation therapy may be more beneficial. Contrarily, if factors improving treatment response are primarily driven by the chronic effects of exercise then the timing of the exercise relative to treatment may be less important. Moreover, if the acute effects of exercise are driving this effect, a feasible daily exercise intervention may be optimal whereas, an earlier

intervention (e.g. initiated at diagnosis) may be more beneficial if the chronic effects of exercise are driving this response. Additional factors that may influence the effects of exercise on treatment response that should be considered in the design of future trials include the location of the tumor (i.e. gastrointestinal track) and individual factors (i.e. biomarkers).

In the context of the current exercise oncology literature, it was reasonable to assume that exercise may improve treatment response by mitigating treatment-related side effects and possibly improving treatment completion rates. However, improvements in treatment response in the EXERT Trial occurred in the absence of any improvements in treatment toxicities or treatment completion rates. In fact, these outcomes were trending in the wrong direction in the EXERT Trial and future exercise trials should continue to track these as safety outcomes.

Larger phase II/III trials are warranted to confirm the clinical benefit of exercise on treatment response in this clinical setting. These studies should also include long-term survival endpoints (i.e. disease-free survival and overall survival). Moreover, these trials should continue to track patient-reported outcomes to confirm whether exercise has a negative effect on symptom and QoL in this clinical setting. Furthermore, exercise trials to explore the potential benefit of exercise on treatment response in other neaodjuvant cancer settings is warranted.

On a final note, exercise during and after NACRT has the potential to improve surgical outcomes for rectal cancer patients including blood loss, duration of the surgery, quality of the surgery, length of hospital stay, and postsurgical complications. The collection of this data was pre-specified in the EXERT Trial; however, it was beyond the scope of this dissertation. I will be abstracting this data from patients' medical records and analyzing it in the future.

7.4 Practical Implications

Research on the effects of exercise in the neoadjuvant rectal cancer setting is preliminary in nature; however, this dissertation reports novel findings that may have important future practical implications. Most notably, exercise appeared to improve treatment response in this clinical setting. If larger trials confirm this positive effect of exercise on treatment response, the potential benefit to patients could be immense. Clinical trials of medical interventions (i.e. chemotherapy) to improve tumor response to NACRT and delay or possibly even avoid surgery are ongoing (15) with the hope of reducing the morbidity associated with surgery including permanent colostomy bags. Exercise could provide a less resource intensive and toxic approach for improving tumor response to NACRT. Contrarily, in the absence of any clinical benefit, exercise may be contraindicated in this clinical setting, assuming the negative effects of exercise on symptoms and QoL are confirmed. For now, patients in the neoadjuvant rectal cancer setting seeking exercise guidance should be informed about the potential benefit and harms of exercise during and after NACRT.

7.5 Conclusions

The purpose of this dissertation was to further establish the feasibility and safety of exercise during and after neaodjuvant rectal cancer treatment and to provide the first evidence of preliminary efficacy. Overall, this dissertation demonstrated the feasibility and safety of a supervised HIIT program during NACRT and ≥150 minutes of unsupervised moderate-to-vigorous intensity continuous exercise/week after NACRT. Most notably, this dissertation identified a possible beneficial effect of exercise on treatment response. Furthermore, exercise appeared to exacerbate symptoms and QoL during NACRT; however, most of these effects appeared to dissipate prior to surgery. These findings are important and warranted further

investigation in larger phase II/III trials. Finally, both the strengths and limitations of the EXERT Trial provide valuable insight into the design and conduct of future exercise oncology trials.

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APPENDIX A: TRIMODAL THERAPY FOR RECTAL CANCER

Trimodal Therapy for Rectal Cancer

Neoadjuvant Chemoradiation

The use of preoperative (vs. postoperative) chemoradiation (CRT) is largely a result of the German Rectal Cancer Trial (1, 2). In this study, 823 patients with stage II-III rectal cancer were randomly assigned to preoperative or postoperative CRT. The treatment regimen was similar in both groups and consisted of 50.4 Gy in 28 fractions of radiation (patients in the postoperative group received an additional 5.4 Gy boost) with concurrent 5-FU (1000 mg/m^2 daily for 5 days, during the first and fifth weeks of radiation). Patients in the preoperative group underwent a TME 6 weeks after completing CRT. All patients received 4 cycles of adjuvant 5-FU (500 mg/m^2, 5 times per week, every 4 weeks). Patients in the preoperative group started adjuvant chemotherapy 4 weeks after surgery whereas, patients in the postoperative group started adjuvant chemotherapy 4 weeks after the completion of CRT. The preoperative CRT resulted in significantly lower 5-year (6% vs. 13%, p=0.006), and 10-year (7% vs. 10%, p=0.048) local recurrence rates. There were no significant differences in the 5-year or 10-year overall survival rates. The preoperative CRT resulted in a higher rate of sphincter-preserving surgeries (39% vs. 19%, p=0.004). Additionally, there were fewer grade 3 and 4 acute toxicities (27% vs. 40%, p=0.001) and long-term toxicities (14% vs. 24%, p=0.01) in the preoperative group.

The theoretical advantages of NACRT include: (1) sterilization of the mesorectal lymphatic channels helping to prevent spreading of tumor cells during mesorectal dissection, (2) reducing the tumor size, (3) exclusion of the small bowel from the radiation field (the small bowel often becomes tethered in the pelvis after surgery which would increase toxicity if radiation is given post-operatively), (4) improved response of well-oxygenated tumor, and (5) better functioning of the neorectum (which is not subjected to radiation) (3).

Radiation Therapy

External beam radiation therapy is the primary radiation technique used in the neoadjuvant rectal cancer setting. The utility of three-dimensional conformal radiation therapy (3DCRT), a specific form of external beam radiation, has been established for rectal cancer (4). Briefly, in 3DCRT the beams of radiation are shaped to match the target volume thereby reducing the amount of healthy tissue being exposed to radiation. Moreover, intensity modulated radiation therapy (IMRT) is emerging as a radiation technique that may conform more tightly to the target volume and further reduce toxicity. There are two accepted preoperative radiation regimens to treat locally advanced rectal cancer. Short-course radiation delivers 5 Gy/day for 5 days, while long-course (i.e. 5-6 weeks) radiation delivers 1.8-2.0 Gy/day over 25-28 days on weekdays with concurrent chemotherapy. To date, two randomized controlled trials have compared these two regimens (5, 6). Long-course NACRT appears to improve tumor downstaging, pCR, and negative circumferential resection margins compared to short-course radiation alone. The current data does not show a significant difference in terms of local recurrence rates, overall survival or QoL between the two approaches. Although the optimal regimen is still being debated, long-course NACRT appears to be the preferred approach worldwide.

Despite advancing technology, radiation to the pelvis is still associated with acute and late toxicities including diarrhea, enteritis, fatigue, skin erythema, pain, micturition problems, bowel obstructions, bowel dysfunction, sexual dysfunction, and second cancers (7, 8). Moreover, some of these side effects can cause a decline in QoL during treatment and prolong surgical recovery times (7). New technologies are being investigated to try and reduce these treatment related side effects and improve adherence to the treatment regimen.

Chemotherapy

The rationale for the addition of chemotherapy to long-course radiation is that it may act as a radiosensitizer which could potentially improve tumor downsizing, tumor downstaging, rates of sphincter preserving surgery, and rates of pCR (9). The current data have shown that, when compared to radiation alone, the addition of chemotherapy to preoperative long-course radiation significantly improves local disease control for patients with locally advanced rectal cancer (10). Sensitizing preoperative radiation with concurrent infusion 5-FU (continuous or bolus) or oral capecitabine (825 mg/m^2 twice daily), which is enzymatically converted into 5-FU, are both currently accepted regimens (4, 11). The NSABP R-04 trial randomized 1,608 patients to either intravenous 5-FU or oral capecitabine and found no difference in terms of pCR rates, local recurrence or disease-free survival (12). Additionally, a phase III German trial demonstrated that capecitabine was non-inferior to bolus 5-FU in terms of local recurrence rates and 5-year overall survival (13). Acute side effects of preoperative chemotherapy in this clinical setting include fatigue, diarrhea, hand-foot syndrome, neutropenia, cardiotoxicity, proctitis, and oral mucositis.

Surgery

The current recommendation is for rectal cancer patients to undergo surgery approximately 6-8 weeks after completing NACRT (14). Delaying surgery appears to allow tumor regression, as the tumor continues to shrink after the completion of NACRT. A longer radiation-surgery interval however, is associated with increased morbidity and mortality (15, 16). Surgery is the definitive treatment for rectal cancer, as no other intervention has a high chance of definitively eradicating the cancer (4, 9). The standard surgical procedure is a TME which involves the radical resection of the rectum. This surgical approach reduces the likelihood of

having pathologic involvement of the radial margins and, subsequently reduces the rate of local recurrence (17, 18). The two most common TME procedures performed are the lower anterior resection (LAR) and the abdominoperineal resection (APR). An LAR is typically performed for tumors in the upper third of the rectum and is anal sphincter sparing while an APR is usually performed for tumors in the lower third of the rectum and involves the removal of the anus (including the sphincter muscle) necessitating a permanent ostomy.

Despite advancements in surgical techniques, complications and late adverse effects from surgery can still occur. Some of the late adverse effects include bowel dysfunction, urinary dysfunction, and sexual dysfunction which may worsen QoL in these patients (19). Of note, approximately 15-27% of patients may achieve pCR after NACRT and current research is investigating whether surgery can be delayed or avoided in these patients with the goal of reducing surgery-related toxicities (20, 21).

Adjuvant Chemotherapy

Currently, 4-6 months of postoperative chemotherapy is indicated in all locally advanced rectal cancer patients regardless of the results from their pathology (22). For now, once a patient is scheduled to receive long-course NACRT they are committed to subsequent surgery and adjuvant chemotherapy. The benefits of adjuvant chemotherapy in patients who received NACRT remains controversial however (23), and the current recommended regimens are based on adjuvant trials for colon cancer.

To summarize, NACRT followed by TME and adjuvant chemotherapy is the most common treatment option for the management of locally advanced rectal cancer. Although this regimen has resulted in better local and distant disease control there is still concern that some

patients are being overtreated. These treatments are continuing to be refined to optimize outcomes including morbidity, QoL, and survival in rectal cancer patients.

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APPENDIX B: BOOK CHAPTER

Effects of exercise on cancer treatment completion and efficacy

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Abstract

Exercise during cancer treatments improves physical fitness, symptoms, and quality of life in several cancer patient groups; however, its effects on treatment completion and response are largely unknown. Here, we review the preclinical and clinical evidence of the potential effects of exercise on cancer treatment completion and efficacy. We first propose a framework to highlight the clinical pathways via which exercise during cancer treatment may impact cancer outcomes. We also discuss the potential complex interactions between exercise and cancer treatment efficacy. In terms of cancer treatment completion rates, there is preliminary evidence that exercise may improve chemotherapy completion in early stage breast cancer patients; however, very little research has examined other cancer treatment modalities or patient groups. In terms of cancer treatment efficacy, preclinical studies have demonstrated that exercise alone may have positive, neutral, or even negative direct antitumor effects. Moreover, when combined with a chemotherapy agent, exercise may enhance or interfere with treatment efficacy. Several clinical trials have demonstrated that exercise during chemotherapy may improve treatment outcomes; however, these trials were not designed to answer this question. Further research is needed to determine whether exercise during cancer treatment has any meaningful effects on cancer treatment completion and efficacy.

Cancer is a complex disease that has many different treatment options including surgery, chemotherapy, radiation therapy, hormone therapy, and immunotherapy. In many cases, individuals will receive a combination of these treatments either concurrently or sequentially. The effectiveness of these treatments depends largely on their substantive completion which, unfortunately, is not always optimal. Cancer treatments are often reduced, interrupted or discontinued because of substantial toxicities and/or side effects including hematologic toxicities, neurotoxicity, cardiotoxicity, pain, and fatigue. Interventions to manage toxicities and improve treatment completion would be beneficial and could ultimately lead to better disease control and survival. Evidence from multiple clinical exercise intervention trials has demonstrated that exercise is effective at mitigating some cancer treatment-related side effects and, therefore, may improve treatment completion rates (**Figure 1**). The first purpose of this chapter is to examine the potential impact of exercise during cancer treatments on the completion rates of various cancer treatment modalities.

Even if completed, however, cancer treatments are not always effective. Some individuals achieve substantial benefit, some modest benefit, and some no benefit at all. Interventions to improve the efficacy of cancer treatments would also be highly beneficial to patients. Emerging evidence from preclinical studies supports several biologically plausible mechanisms via which exercise may improve the efficacy of cancer therapies or exhibit direct effects on tumor growth and metastases (**Figure 1**). The second purpose of this chapter is to examine the effects of exercise during cancer treatments on treatment response and disease outcomes.

Treatment Completion

Chemotherapy

The effectiveness of chemotherapy is dose dependent and any reductions and/or delays can undermine treatment efficacy [1, 2]. Chemotherapy dose intensity represents the amount of drug delivered per unit of time and is expressed in mg/m^2/week [3]. Although clinical thresholds may vary by cancer type, disease stage, and treatment regimen, evidence from clinical trials in breast cancer and lymphoma suggests that maintenance of ≥ 85% of the planned chemotherapy dose intensity is associated with better outcomes [4-6]. Chemotherapy can cause substantial toxicities and side effects that result in modifications to the planned regimen in the form of dose reductions or dose delays.

In clinical practice, adverse effects of cancer treatments are assessed using the Common Terminology Criteria for Adverse Event Reporting (CTCAE). The CTCAE defines an adverse event as either an unfavorable and/or unintentional sign (e.g. abnormal laboratory finding or abnormal finding on examination) or symptom (e.g. fatigue, pain, and neuropathy). Furthermore, symptoms are evaluated for their degree of interference with activities of daily living. Consequently, the decision to modify the planned chemotherapy regimen is based on both clinical and patient-reported factors. The severity of a sign or symptom is graded from 1 (mild) to 5 (death) with grades 3 (severe) or 4 (life-threatening) most often being an indication to modify the planned chemotherapy dosage. Exercise has been identified as an effective strategy for managing some toxicities and side effects and improving quality of life during adjuvant chemotherapy in several cancer patient groups [7], consequently, it is possible that exercise may also improve adherence to chemotherapy treatments.

Bland et al. [8] recently conducted a systematic review examining the effects of exercise on chemotherapy completion rates. In their review, they identified 7 randomized controlled trials with chemotherapy completion as an outcome, two of which reported significant findings [9, 10]. In the START trial [9], women with early stage breast cancer undergoing adjuvant chemotherapy were randomized to either supervised aerobic exercise training, supervised resistance exercise training, or usual care. Resistance exercise training was statistically superior to usual care for improving chemotherapy completion rate (89.8% in the resistance training group vs. 84.1% in the usual care group; p=.033). Aerobic exercise training was numerically superior to usual care (87.4%). Additional non-significant between-group differences were observed for the number of patients receiving ≥ 85% of their planned chemotherapy dose (65.9% in the usual care group vs. 78.0% in the resistance training group, and 74.4% in the aerobic training group). Moreover, the usual care group received more granulocyte colony-stimulating factor than the resistance exercise training group which possibly worked against an even larger effect. In ancillary analyses, exercise adherence in both the aerobic and resistance training groups was associated with receiving a higher dose of planned chemotherapy. Moreover, improvements in lean body mass in the resistance exercise training group, compared to the usual care group, were associated with a higher percentage of patients completing ≥ 85% of their planned chemotherapy dose. Reasons for dose reductions were not reported in the START trial.

In the PACES trial [10], women with early stage breast cancer were randomly assigned to three groups including a low-intensity home-based exercise program, a supervised moderate-to high-intensity combined resistance and aerobic exercise program, or usual care. Significantly fewer women in the supervised combined resistance and aerobic exercise program required chemotherapy dose modifications (12%) compare to both the home-based exercise program

(34%) and usual care (34%). Moreover, the average dose reductions were 10% in both exercise programs compared to 25% in the usual care group. The main reasons for dose adjustment across all groups were neuropathies (31%), myelosuppression (11%), febrile neutropenia (11%), and nausea and vomiting (11%). Statistical differences between the groups were not reported, however, the rates of dose reductions for febrile neutropenia were numerically higher in the usual care group (n=6) compared to both the low-intensity exercise group (n=0) and the moderate-to-high intensity exercise group (n=2).

It is important to note that in all the trials reviewed by Bland et al. [8], chemotherapy completion was a secondary or exploratory outcome. Thus, these trials were not designed to determine if exercise may improve chemotherapy completion rates. Nevertheless, this preliminary evidence is encouraging and, as Bland et al. [8] pointed out, more research into the mechanisms through which exercise training may improve chemotherapy completion rates is needed. Moreover, Sanft et al. are currently conducting the first lifestyle intervention with chemotherapy completion as the primary outcome [11]. The LEANER study is examining the effects of a healthy diet and exercise, compared to usual care, on chemotherapy completion rate in women with early stage breast cancer.

Although limited, studies examining the predictors of treatment toxicity and chemotherapy completion rates in large clinical trials have identified non-modifiable (e.g. age and disease stage) and modifiable (e.g. body mass index, body surface area, performance status, and the presence of comorbidities) variables in some cancer types [12-15]. Researchers in the field of exercise oncology are especially interested in identifying and studying modifiable factors that may be positively influenced by exercise. For example, low muscle mass and functional

fitness are emerging as potentially important determinants of chemotherapy treatment toxicity and/or treatment completion rates [16, 17].

Mechanisms of exercise-mediated improvements in chemotherapy toxicity and completion

Sarcopenia (low skeletal muscle mass) and sarcopenic obesity (low skeletal muscle mass and excessive adipose tissue) have been identified as determinants of chemotherapy treatment toxicity across several cancer types and chemotherapy agents [16]. Most chemotherapy regimens are prescribed according to total body surface area. Body surface area is a function of height and weight and does not account for individual differences in body composition. Pharmacokinetics (i.e. drug distribution and metabolism) are driven by blood flow and perfusion and occur in lean tissue (primarily in highly perfused organs such as the liver, heart, and kidneys and in smaller quantities in muscle). Thus, in theory, the volume through which a drug can be distributed is reduced in someone with less muscle mass thereby increasing their risk of developing dose limiting toxicities in the blood (i.e. a higher plasma concentration of the drug) and in highly perfused organs.

Christensen et al. recently described cancer drug distribution in untrained vs. trained individuals [18]. Their model suggests that when two individuals with the same body surface area receive the same dose of chemotherapy, the drug will be distributed to a smaller area in the untrained individual (low muscle mass, high fat mass) compared to the trained individual (high muscle mass, low fat mass) making the untrained individual more likely to experience treatment toxicities. In addition to sarcopenia, poor functional fitness has recently been associated with completing fewer cycles of chemotherapy in advanced non-small cell lung cancer [17]. Treatment toxicities and reasons for dose modifications were not reported. There is considerable overlap between sarcopenia and poor functional fitness, and muscle mass and strength are key

components. Although muscle mass, muscle strength, and physical functioning are interrelated, it is unclear which of these should be the target of exercise interventions designed to improve treatment toxicity and completion for cancer patients. Interestingly, resistance training in the START trial and combined resistance and aerobic exercise training in the PACES trial were superior to usual care at improving chemotherapy completion rates. Moreover, in the START trial, improvements in lean body mass were associated with chemotherapy completion rates ≥85%. It is unclear if this association was mediated by reductions in treatment toxicity as reasons for treatment modifications were not closely tracked in the START trial, however, it is unlikely that other factors would have strongly influenced the decision to modify treatments.

In addition to the chronic effects of exercise training on muscle mass, Christensen et al. [18] noted that during an acute bout of exercise, blood perfusion in skeletal muscle increases substantially which could add to the volume through which chemotherapy drugs may be distributed thereby reducing toxicity in the blood and other organs. This mechanism suggests that exercise training involving large muscle groups during chemotherapy infusion may be most effective at mediating treatment toxicities. To date, two pilot studies have reported the feasibility and safety of aerobic exercise during chemotherapy infusion [19, 20]. Kirkham et al. [21] are currently examining the impact of a single bout of exercise 24 hours prior to chemotherapy infusion on treatment toxicity and treatment response in women with breast cancer receiving anthracycline [21]. Their rationale is based on pre-clinical evidence of a cardioprotective effect and a pilot randomized controlled trial demonstrating the feasibility of the exercise intervention [22-25]. Moreover, the same group is studying the effects of caloric restriction and a moderate intensity exercise session during chemotherapy infusion on tumor response in breast cancer patients with metastatic disease [26].

More recently, Christensen et al.[18] have suggested that exercise may reduce chemotherapy treatment toxicities via improvements in immune function. Acutely, exercise training causes an increase in circulating immune cells. Moreover, it has been suggested that the acute release of immune cells stimulated by exercise may provide a feedback response to the bone marrow to produce new immune cells further helping the body's defense mechanisms [18]. Exercise-mediated improvements in immune function could reduce hematologic toxicities which are a common reason for dose modifications across different cancer types and chemotherapy regimens. Several studies have examined the impact of exercise on immune function in cancer patients during (and after) chemotherapy and have found mixed results: some findings have indicated no change and others have indicated improvements in immune function parameters [27]. Nonetheless, these early results suggest the possibility of immune function mediated improvements in chemotherapy completion rates in cancer patients engaging in an exercise training program.

Radiation Therapy

Similar to chemotherapy, the effectiveness of external beam radiation therapy is dependent on receiving the treatments as planned. Although limited, research from large clinical studies suggests that local disease control and overall survival decrease as the total treatment time to complete treatment increases. In head and neck cancer and cervical cancer, each day of treatment interruption has been associated with approximately a 1% reduction in local control [28, 29]. Moreover, delays exceeding 5 days (i.e. 1 week as radiation therapy is normally delivered on weekdays only) have been associated with reduced local control and survival in uterine cervix squamous cell cancer [30]. In general, adherence to the planned number of radiation fractions is high, nevertheless, toxicities of grade 3 or 4 (e.g. fatigue, dermatologic, and

hematologic toxicities) can cause a reduction, delay, or discontinuation of radiation therapy. The severity of the side effects, and consequently adherence to radiation therapy, may vary according to cancer type, treatment timing, treatment regimen, and individual factors. To date, very few exercise intervention trials have been conducted during radiation therapy and none have reported on radiation therapy completion rates [31-35].

A recent systematic review and meta-analysis examining the effects of exercise interventions during adjuvant radiation therapy for breast cancer found that supervised combined aerobic and resistance training improves fatigue [33]. Moreover, Rogers et al. have demonstrated that resistance training during radiation therapy for head and neck cancer improves fatigue, and functional fitness compared to no exercise [31]. Whether exercise mediated improvements in side effects from radiation therapy translate into improvements in treatment adherence remains unknown. One ongoing phase II trial that will report on this issue is the EXERT trial [36], a randomized controlled trial comparing high-intensity aerobic exercise to usual care in rectal cancer patients receiving neoadjuvant combined chemotherapy and radiation therapy. Treatment toxicity and treatment completion are prespecified as exploratory outcomes in the EXERT trial.

Hormone Therapy

Hormone therapy is commonly prescribed to treat hormone-dependent breast and prostate cancers. These treatments significantly improve long-term survival, however, adverse effects including hot flashes, arthralgia, fatigue, changes in mood, and bone loss often result in suboptimal treatment adherence. Reviews of both clinical trials and clinical practice settings have found that up to 50% of breast cancer survivors on either tamoxifen or an aromatase inhibitor (AI) do not take their drug as prescribed or discontinue therapy altogether [37]. Moreover, treatment side effects (e.g. menopausal symptoms and arthralgia) are strongly

associated with adherence to the treatments [37]. Very few studies have examined the effects of exercise in breast cancer patients on hormone therapy. In the HOPE trial, Irwin et al. [38] examined the effects of a 1-year exercise program consisting of 2 supervised resistance training sessions per week and 150 minutes per week of unsupervised aerobic exercise, compared to usual care, on the severity of arthralgia in women receiving AIs. Joint pain severity and interference improved in the exercise group, however, there was no statistically significant difference between the exercise group (80%) and the usual care group (76%) for adherence to daily AI therapy. The HOPE trial was not designed to examine AI treatment adherence, therefore, studies are needed to directly examine this question.

To date, numerous studies have examined the effects of exercise in men with prostate cancer receiving androgen deprivation therapy (ADT), however, none have reported on adherence to ADT. Although clinical trials have reported a low percentage of grade 3 and grade 4 toxicities caused by ADT [39, 40], treatment side effects including muscle loss, fatigue, changes in mood, sexual dysfunction, and weight gain appear to influence the receipt of long-course (vs. short-course) ADT in practice [41]. The side effects associated with ADT can negatively impact the quality of life of men with prostate cancer [40] which may influence their decision to continue with the treatments. Moreover, it is possible that some of the risks associated with ADT (e.g. cardiovascular events) may influence a physician's recommendation to initiate (and continue) with ADT based on comorbidities and age [41]. The effects of exercise on ADT adherence is an important question that should be addressed in future exercise trials.

Immunotherapy

Immunotherapy is emerging as a promising treatment for cancer that has been associated with improved disease outcomes in metastatic melanoma, non-small cell lung cancer, head and

neck squamous cell cancer, renal cell cancer, bladder cancer, colorectal cancer, and hematologic cancers [42]. Many different types of immunotherapy are used to treat cancer including monoclonal antibodies, immune checkpoint inhibitors, conjugated monoclonal antibodies and non-specific immunotherapy. The most common grade 3-4 toxicities associated with immunotherapy are driven by autoimmunity and include skin reactions (rash, itching), fatigue, pneumonitis, diarrhea, and loss of appetite [42]. The effects of exercise on side effects from immunotherapy and ability to complete these treatments are unknown but they are important research questions as exercise may be beneficial but could also be harmful (i.e. worsen symptoms).

Treatment Efficacy

The ability of cancer treatments to eradicate cancer cells is of uttermost importance to clinicians and patients. The effectiveness of cancer treatments will vary based on cancer type, stage at diagnosis, tumor biology, as well as individual factors. The 5 year relative survival rate for all cancers is 69% and survival is highest for prostate cancer (98%) and lowest for pancreatic cancer (9%) when all stages of the disease are combined [43]. It has been proposed that exercise training may enhance the efficacy of standard cancer treatments including chemotherapy, radiation therapy, and immunotherapy through a series of systemic and local (i.e. tumor microenvironment) physiological adaptations which ultimately could improve the delivery and cytotoxic effect of cancer treatment.

The potential impact of exercise on cancer treatment response is complex and is dependent on whether exercise may have direct effects on tumor growth and/or metastases (**Figure 2**). Under a scenario where exercise is known to have its own positive direct effects on tumor growth or metastases (i.e., exercise is an active single agent), exercise may interfere with

cancer treatment efficacy (i.e., an antagonistic effect), have no additional effect on treatment efficacy (i.e., a redundant effect), or enhance treatment outcomes in a manner consistent with the known independent effects (i.e., additive effect) or in a manner that is larger than the known independent effects (i.e., a synergistic effect). Under a scenario where exercise is known to have no direct effects on tumor growth or metastases, exercise may interfere with cancer treatment efficacy (i.e., an antagonistic effect), have no effect on treatment efficacy (i.e., an inert effect), or enhance treatment efficacy (i.e., a sensitizing effect). Finally, under a scenario where exercise is known to actually have a negative direct effect on tumor growth or metastases (i.e., exercise makes the cancer grow or spread more quickly), exercise may reduce treatment outcomes in a manner consistent with the known independent effects (i.e. subtractive effect) or interfere with treatment efficacy in a manner that is larger than the known independent effects (i.e. an antagonistic effect), have no effect on treatment efficacy (i.e. neutralizing effect), or enhance treatment efficacy (i.e. sensitizing effect).

Chemotherapy

Several characteristics of the tumor microenvironment (TME) lead to chemotherapy resistance. Most notably, the TME is characterized by abnormal vascularization and poor blood perfusion which impairs the delivery of anti-cancer drugs. Exercise training stimulates angiogenesis and improves blood flow (via NO- and VEGF- mediated pathways) which have broad-reaching effects (not limited to the skeletal muscle) and therefore has the potential to induce favorable changes in the TME. Evidence from pre-clinical studies suggests that repeated bouts of aerobic exercise improve TME vascularization and normalization as demonstrated by a reduction in tumor hypoxia [44, 45]. However, studies examining whether or not these changes translate into therapeutic benefit are mixed [46-49]. Jones et al. [46] randomly assigned female

mice injected with MDA-MB-231 breast carcinoma cells to doxorubicin only, moderate-intensity aerobic exercise only, doxorubicin plus moderate-intensity aerobic exercise, or control. Survival rate significantly improved in the doxorubicin only and the doxorubicin plus exercise groups, compared to the control group. Additionally, exercise only had no effect, compared to control (i.e. neutral effect), on survival rates. Interestingly, doxorubicin plus exercise not only had no additional benefit on survival compared to doxorubicin only, it actually made the outcomes worse (i.e., a possible antagonistic effect).

Sturgeon et al. [47] examined the effects of low-intensity aerobic exercise on doxorubicin efficacy in mice injected with B16F10 melanoma cells in a 4-arm randomized controlled trial (i.e. doxorubicin only, exercise only, doxorubicin plus exercise, control). Tumor volume significantly decreased in both the doxorubicin only and doxorubicin plus exercise groups, compared to the control group with even larger effects observed for the doxorubicin plus exercise group, compared to the doxorubicin only group. Interestingly, exercise alone appeared to have a negative effect, compared to control, on tumor volume however, doxorubicin plus exercise had a sensitizing effect. Betof et al. [48] randomly assigned female mice injected with breast cancer cells to cyclophosphamide only, aerobic exercise only, cyclophosphamide plus aerobic exercise or control. Tumor growth was significantly reduced in the cyclophosphamide plus aerobic exercise group, compared to all other groups. Additionally, cyclophosphamide only and exercise only both significantly reduced tumor growth compared to the control group. Moreover, the magnitude of the individual effects of cyclophosphamide and exercise were approximately the same (around 200 mm^3 tumor size reduction) and the magnitude of the effect of cyclophosphamide plus exercise, was approximately double this effect (around 350-400 mm^3 tumor size reduction), suggesting that the exercise did not interact with the treatment but rather

had an additive effect. More recently, Shadler et al. [49] found that doxorubicin plus moderate-intensity exercise in mice with B16F10 melanoma tumors and gemcitabine plus moderate-intensity exercise in mice with PDAC-4662 pancreatic cancer significantly reduced tumor growth, compared to doxorubicin alone or gemcitabine alone. Exercise only promoted tumor growth in B16F10 melanoma cancer and had no effect on tumor growth in PDAC pancreatic cancer highlighting the complexity of the interaction between exercise and tumor growth. Under both conditions, exercise did not have an additive effect however, the combination of chemotherapy and exercise significantly improved treatment efficacy which suggests a sensitizing effect. Additional experiments showed that the delivery of a single dose of doxorubicin (after the last exercise session) to the interior of the B16F10 tumors was significantly increased in the mice that exercised compared to controls. Moreover, administration of doxorubicin immediately before a single bout of exercise did not improve the levels of the doxorubicin in the B16F10 tumors compared to controls. Taken together, these results suggest that the chronic effects of exercise on tumor vascularization and normalization may have a more significant impact on tumor blood perfusion than a single acute bout of exercise.

Emerging evidence from pre-clinical studies suggests many other biologically plausible systemic adaptations including changes in immune function, inflammation, metabolism, and sex hormones, which may mediate changes in the tumor microenvironment and subsequently influence chemotherapy treatment efficacy or have direct effects on treatment response [50-52].

Very few clinical studies have examined the impact of exercise on chemotherapy response. In a subgroup analysis of patients receiving chemotherapy in the HELP trial [53] (a randomized controlled trial comparing usual care to 12 weeks of supervised exercise in lymphoma cancer survivors) the complete response rate was 46.4% (13/28) in the exercise group

compared to 30.8% (8/36) in the usual care group. Although these findings were non-significant, they are noteworthy despite the small sample size. Lymphoma patients receiving chemotherapy all have multiple existing tumors, therefore, the possible mechanisms of improved vascularization and perfusion of the tumors applies in this clinical setting. In the neoadjuvant breast cancer setting, Jones et al. have demonstrated that aerobic exercise in conjunction with chemotherapy modulates systemic factors including endothelial progenitor cells, plasma cytokines, and plasma angiogenic factors which may enhance the effectiveness of anti-cancer drugs [54].

Moreover, exploratory long-term follow-up data from large exercise clinical trials suggests that exercise in the adjuvant chemotherapy setting may improve treatment response including disease-free survival (DFS) and overall survival (OS) in breast cancer survivors [55, 56] and progression-free survival in lymphoma cancer survivors [57]. In the previously mentioned START trial [55], the aerobic exercise training group and the resistance exercise training group were combined and compared to the usual care group on longer-term cancer outcomes. After a median follow-up of 89 months, there were 25/160 (15.6%) DFS events in the exercise groups compared to 18/82 (22%) in the control group. Eight-year DFS was 82.7% in the exercise groups compared to 75.6% in the control group. There were 20 (12.5%) recurrence-free interval (RFI) events in the exercise groups and 17 (20.7%) in the control group. The eight-year RFI incidence rate was 12.6% in the exercise groups and 21.6% in the control group. Although none of these observed effects were statistically significant, the magnitude of the effects could be meaningful. Moreover, exercise appeared to have a stronger effect on DFS (borderline significant effect) and RFI (significant effect) in women who received ≥85% of their planned chemotherapy which suggests that improved chemotherapy completion rate may not be

the sole explanation for the improved outcomes. Finally, eight-year overall survival was 91.2% in the exercise groups compared to 82.7% in the control group (HR, 0.60; 95% CI, 0.27–1.33).

In Australia, data from the Exercise for Health Trials were combined to examine their effects on survival outcomes [56]. Briefly, both trials were randomized and compared the effects of an 8 month pragmatic exercise intervention on function, side effects, and quality of life, compared to usual care, however, one trial was conducted in an urban setting and delivered either face-to-face or by telephone (randomized comparison) whereas the other trial was conducted in a rural setting and delivered by telephone [58, 59]. After a median follow-up of 8.3 years, there were more DFS events in the usual care group (23/130, 17.7%) compared to the exercise group (25/207, 12.1%) (adjusted HR: 0.65, 95% CI 0.36-1.17, p=0.15). Although not statistically significant, there were 10 (7.7%) breast cancer-specific deaths in the usual care group compared to 10 (4.8%) in the exercise group. Furthermore, there were significantly more OS events in the usual care group (15/130, 11.5%) compared to the exercise group (11/207, 5.3%). Of note, the sample included women receiving a mix of adjuvant cancer treatments including chemotherapy, radiation therapy, hormone therapy, and Herceptin. Although the groups were somewhat balanced at baseline for treatment types, it is unclear if all participants were receiving adjuvant treatment.

In longer-term follow-up of the HELP trial [57], patients who received supervised exercise (including those in the control group who crossed-over), had an adjusted 5 year progression-free survival of 68.5% compared to 59.0% for the group that received no supervised exercise (HR=0.70, 95% CI=0.35-1.39, p=0.31). Furthermore, exercise adherence in both the START and HELP trials was not optimal suggesting the potential for even larger effects with

improved adherence. Nevertheless, the data from these studies provide support for trials with adequate sample size to detect differences in treatment efficacy outcomes.

The nature of the effects of exercise on treatment efficacy is difficult to disentangle in human clinical trials because (a) it is often unknown whether exercise has direct effects on tumor growth and metastases in humans and (b) it is often impossible to randomize cancer patients to exercise alone. Consequently, if exercise during cancer treatment improved cancer outcomes it would be unclear if it were a sensitizing, synergistic, or additive effect. Animal studies can answer these questions more clearly but their generalizability to clinical contexts is obviously limited.

Radiation Therapy

Tumor hypoxia has been identified as a key factor limiting the effectiveness of radiation therapy as radiation cannot induce tumor cell DNA damage without sufficient oxygen [60, 61]. The characteristics of the TME that cause chemotherapy drug resistance also cause tumor hypoxia, and pre-clinical studies have demonstrated that repeated bouts of exercise improve the delivery of oxygen to the interior of the tumor through the same mechanisms as chemotherapy drug delivery (i.e. angiogenesis and improved blood perfusion) [44, 62]. Moreover, McCullough et al. demonstrated that a single bout of exercise improved intratumoral blood perfusion by 200% and subsequently reduced tumor hypoxia by 50% in a preclinical orthotopic prostate cancer model [45]. This response is somewhat unexpected given what we know about the redirection of blood flow to active skeletal muscle during exercise. Wiggins et al. have suggested that this response may be explained by tumor vessels inability to respond to vasoconstrictive signals and therefore benefiting from the increase in cardiac output and oxygen supply that occur during exercise [63]. To date, very little is known about how exercise may mediate the response to

radiation therapy in patients and no exercise intervention trials have included radiation response as an outcome.

Hormone Therapy

It is unclear if exercise can improve the efficacy of hormone therapy. It is possible, however, that exercise may have an added benefit in women with hormone sensitive breast cancer. Higher levels of physical activity after a breast cancer diagnosis have been associated with a lower risk of recurrence [64]. In postmenopausal women, moderate-intensity exercise, compared to control, decreases circulating levels of sex hormones including oestrogens and androgens with even larger effects observed when fat loss is achieved [65]. Therefore, it is possible that exercise may reduce recurrence in women with breast cancer by improving circulating hormone levels and/or inducing fat loss. The effects of exercise on hormone treatment efficacy in men with prostate cancer are unknown.

Immunotherapy

As noted earlier, several types of immunotherapy exist and are associated with positive outcomes for patients. Through complex mechanisms, immunotherapies help the immune system detect and destroy cancer cells thereby stopping or slowing the growth of cancer and preventing the development of metastatic disease. Moreover, conjugated monoclonal antibodies can be used to help deliver radiation or chemotherapy to the cancer cells. Exercise training induces systemic changes in circulating immune cells, however, the impact of these changes on the TME and immunotherapy is unclear. Some groups have proposed that exercise mediated changes in the TME may improve response rates to immunotherapy through various pathways. For instance, as Aschcraft et al. [50] and Christensen et al. [18] have pointed out, exercise mediated improvements in tumor hypoxia and tumor metabolism may improve immune cell infiltration

and ultimately the delivery and effectiveness of checkpoint inhibitors. Contrarily, Hojman et al. [51] have pointed out the potential negative effects of exercise on response to certain types of immunotherapy (e.g. anti-angiogenic therapies) where the goal of treatment is to reduce blood flow to the tumor. To date, no exercise studies have examined the impact of exercise on response to immunotherapy in cancer patients; however, given the strong rationale for benefit or harm, preclinical and clinical studies are warranted.

Summary and Future Directions

Treatment Completion

Chemotherapy, radiation therapy, hormone therapy, and immunotherapy cause toxicities which may interfere with patients' ability and willingness to successfully complete their treatments. Exercise appears to mitigate some of the side effects of cancer treatments and may improve treatment completion rates. Treatment-related side effects which result in dose modifications will vary according to cancer type, treatment timing (neoadjuvant vs. adjuvant), treatment regimen (e.g. radiation alone vs. radiation in combination with chemotherapy, chemotherapy alone vs. chemotherapy in combination with immunotherapy), and individual factors. Therefore, it is imperative that research examine the effects of exercise on treatment completion rates in various clinical cancer settings. To date, there is some evidence that exercise may improve chemotherapy completion rates, however, the data are restricted to early stage breast cancer patients. Moreover, sarcopenia is emerging as a determinant of dose-limiting treatment toxicities across various cancer types and chemotherapy drugs and may be an important target for future exercise intervention trials. Nevertheless, much more research on the determinants of chemotherapy treatment completion in various cancer settings are needed in order to develop targeted exercise interventions. Moreover, this research needs to be expanded to

other cancer treatment modalities including radiation therapy, hormone therapy, and possibly immunotherapy where dose-limiting toxicities and the safety of exercise may differ. For example, exercise has the potential to make dermatologic toxicities from radiation therapy worse depending on the site that is being irradiated and the type of exercise prescribed. Additionally, exercise intervention studies designed to compare the effects of different types of exercise (i.e. resistance vs. aerobic vs. combined vs. usual care) on cancer treatment completion are warranted. Finally, more research is needed to determine the optimal timing of exercise relative to cancer treatment. For example, is exercising during chemotherapy infusion or immediately prior to radiation therapy safe and feasible and does it improve dose-limiting treatment toxicities?

Treatment Efficacy

Although multiple pre-clinical studies have shown that exercise training regulates several of the pathways involved in chemotherapy resistance, research demonstrating that these improvements translate into therapeutic benefit is limited and even less is known about the potential impact of exercise on treatment efficacy for other cancer treatment modalities including radiation therapy and immunotherapy. The effects of exercise on cancer treatment response may be impacted by the location of the tumor, the timing of the intervention relative to treatment (i.e. before, during, or after), the treatment regimen, and individual factors (i.e. biomarkers).

Consideration should be given to how we measure treatment efficacy in exercise intervention trials. For one, the outcomes will differ based on the timing of the intervention. In the neoadjuvant and metastatic settings where the goal of treatment is to shrink the tumor(s), response to the treatment might be evaluated using tumor volume or clinical downsizing. In the adjuvant setting where the goal is to eradicate residual tumor cells, survival-related outcomes with longer-term follow-up will be required. The use of traditional efficacy endpoints (e.g. DFS,

PFS, OS) to assess cancer treatment response rates in exercise intervention trials poses similar limitation to clinical trials. For example, a large sample size is required, and the longer-term follow-up is often confounded by exercise crossover.

Moreover, measuring the effects of exercise on treatment response may be challenging as exercise has the potential to mediate traditional efficacy endpoints independently of its interaction effect with cancer treatments (see Figures 1 and 2). Exercise, as an adjuvant therapy, may control cancer progression/recurrence through its direct effects on tumor growth and metastases or by interacting with existing cancer treatments. Distinguishing between an additive effect and interaction effect of exercise on these traditional efficacy endpoints is difficult as it would require a factorial design with four groups (i.e., drug only, exercise only, both, and neither). Research in pre-clinical models supports the possibility of additive, sensitizing, and synergistic effects of exercise on disease outcomes. Designing similar trials in humans will require "window of opportunity" studies where a new treatment is compared to placebo/no treatment with additional randomization to exercise versus no exercise.

It may be feasible to examine the effects of exercise on treatment response in the neoadjuvant setting, however, it will still be unclear if the effect is additive, sensitizing, synergistic, or even antagonistic. Moreover, it may be feasible to study the direct effects of exercise on disease progression in the active surveillance setting (e.g. prostate and colon cancer). As illustrated by the animal studies reviewed in this chapter, the potential interactions between exercise and treatment response are complex and we cannot assume that exercise will be beneficial. At a minimum, exercise intervention trials during cancer treatment should be tracking treatment response to ensure that exercise is not negatively impacting cancer treatment response rates.

Another important consideration for exercise trials is the timing of the exercise relative to cancer treatment. If an acute bout of exercise does substantially increase tumor blood perfusion and reduce tumor hypoxia then exercising immediately before or after, or even during cancer treatment may be optimal. While exercising during a chemotherapy infusion seems feasible, it is unclear if exercising during, or even immediately before, radiation therapy is feasible. It is also possible that the acute effects of exercise may not significantly improve blood perfusion and that changes may be driven by the chronic effects of exercise training. If that is the case, then the timing of the exercise relative to treatment delivery may not be as critical.

Finally, given the challenges of designing resistance training exercise interventions in rodents, the effects of this exercise modality on the TME are unknown. Nevertheless, resistance training has the potential to induce favorable changes that could lead to improvements in the effectiveness of cancer treatments. For example, resistance training has the potential to optimize changes in body composition which could lead to better drug distribution and hence effectiveness. Much more work is needed before we can start to examine the optimal exercise prescription (i.e. frequency, intensity, duration, and type) for improving cancer treatment response rates.

Conclusion

Exercise is an effective strategy for improving physical fitness, symptoms, and quality of life in several cancer patient groups. Nonetheless, it is unclear if exercise can improve treatment and disease outcomes. This chapter highlights preliminary research demonstrating the potential for exercise mediated improvements in treatment completion and treatment efficacy. Moreover, multiple pre-clinical studies have shown that exercise has direct effects on tumor growth and

disease progression. Although this research is promising, no study to date has been designed to answer the questions related to treatment completion and efficacy in actual patients.

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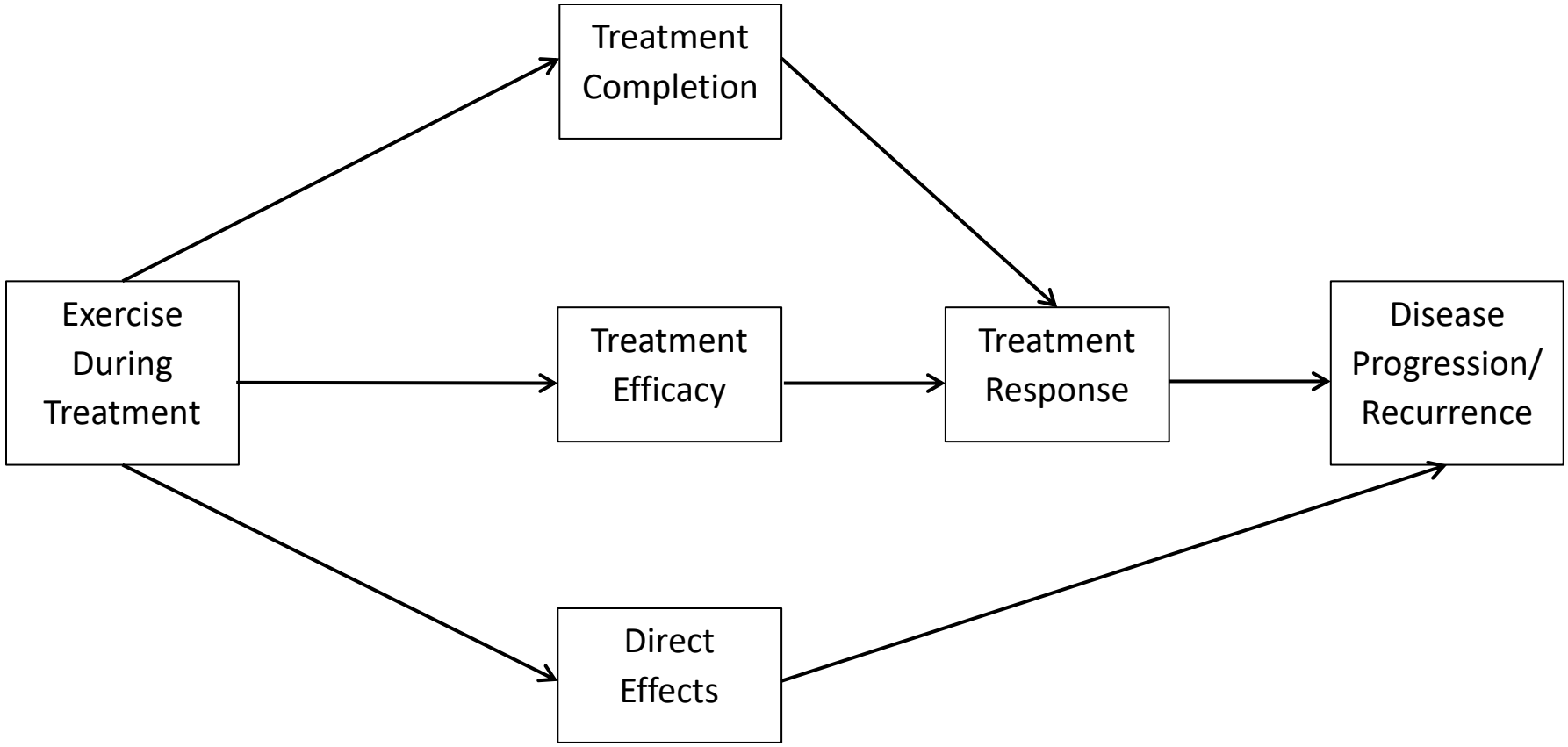

Figure 1. Proposed Clinical Pathways of Exercise During Cancer Treatment on Treatment and Disease Outcomes.

			Cancer Treatment Efficacy (ES=4)		
			Reduced	**Unchanged**	**Enhanced**
Exercise Direct Effect	**Negative**	(ES=-4)	Subtractive (ES=0-3) Antagonistic (ES<0)	Neutralized (ES=4)	Sensitizing (ES>4)
	Neutral	(ES=0)	Antagonistic (ES<4)	Inert (ES=4)	Sensitizing (ES>4)
	Positive	(ES=4)	Antagonistic (ES<4)	Redundant (ES=4)	Additive (ES=5-8) Synergistic (ES>8)

Figure 2. Possible Effects of Exercise During Cancer Treatment on Treatment Efficacy. Notes: ES= hypothetical effect size.

APPENDIX C: EXERCISE INTERVENTIONS IN THE NEOADJUVANT RECTAL CANCER SETTING

Exercise Interventions in the Neoadjuvant Rectal Cancer Setting

To date, seven pilot exercise studies have been conducted in the neoadjuvant rectal cancer setting including five single-arm trials (1-5), one non-randomized controlled trial (6), and one randomized controlled trial (7). Of note, one of the single-arm trials was my master's thesis project (1).

Study sample sizes ranged from 10-48 participants. The mean age of participants ranged from 54 to 65 years with one trial (6) only reporting the mean age of participants by group (64 exercise; 72 control). The percentage of male participants range from 25%-85%. The exercise intervention was conducted exclusively during NACRT in one trial (3), exclusively after NACRT in another trial (6), and both during and after NACRT in all other trials (1, 2, 4, 5, 7). Exercise programming and duration varied considerably across studies. The single-arm study by Alejo et al. (3) was a 6 week behavioral intervention conducted during NACRT and consisted of weekly face-to-face educational sessions, 5 of which included an exercise component (either aerobic, resistance, flexibility, or a combination of the three), lasting from 45-60 minutes. The exercise intervention in the single-arm study by Heldens et al. (2) was conducted both during and after NACRT and consisted of twice-weekly supervised combined aerobic (treadmill and cycle ergometer) and resistance training (3 sets of 15 repetition for 3 exercises including leg press, chest press, and lateral pulldown) performed at moderate-intensity (Borg > 13) for a total duration of 45-60 minutes per session. Although unclear, the reports from Singh et al. (4, 5) appear to be from a single trial with some participants completing the exercise intervention for 10 weeks during NACRT and others completing the exercise intervention for 16 weeks (during and after NACRT). The exercise intervention in this study included twice-weekly 60-minute supervised sessions consisting of combined aerobic (60%-80% estimated heart rate maximum)

and resistance exercise (2-4 sets performed at 6-12 repetition maximum for major muscle groups) and an additional 15 minutes of unsupervised aerobic exercise performed ≥ 2 days/week. In my master's thesis study (1), participants were asked to complete thrice-weekly 50-minute supervised moderate-intensity aerobic exercise sessions during NACRT and 150 minutes/week of moderate-intensity aerobic exercise after NACRT. The exercise intervention in the non-randomized controlled study by West et al. (6) was conducted for 6 weeks immediately post-NACRT and consisted of thrice-weekly 40-minute supervised moderate-to-vigorous-intensity aerobic exercise sessions. In the only report from a randomized controlled trial in this setting to date, Moug et al. (7) compared a home (telephone-guided) walking program (gradual progression to 3000 steps/day) to usual care during and after NACRT.

Feasibility assessments included eligibility, recruitment, exercise adherence, and follow-up assessment rates. The screening process was different among the trials and eligibility rate ranged from 26%-89% (1, 4, 5, 7), with no report of eligibility rate in three trials (2, 3, 6). Recruitment rate ranged from 52%-71% and was not reported in one trial (6). Exercise adherence was reported as attendance (range 74%-96% of planned exercise sessions) (1-3, 5, 6), the number of participants attending more that 60% of their planned sessions (n=8/10, 80%) (4), and the number of completed telephone calls (75%) (7). Follow-up assessment rate was reported in all trials and ranged from 69%-100%. No serious adverse events were observed or reported in any of the studies. Measures of health-related fitness and patient-reported outcomes and the timing of their assessment varied greatly between studies. Three trials assessed outcomes immediately after NACRT (1, 2, 5). Heldens et al. (2) and Singh et al. (5) reported a slight increase in muscular strength during NACRT. Heldens et al. (2) also reported a slight increase above baseline for physical functioning whereas, Singh et al. (5) reported a slight decrease in physical

functioning during NACRT. Moreover, in my master's thesis (1), we reported no change in physical functioning but a slight decrease in cardiorespiratory fitness during NACRT. At the pre-surgery timepoint, health-related fitness outcomes either slightly declined, remained unchanged, or improved from baseline in the single-arm studies (1-4). In the non-randomized controlled trial by West et al. (6), VO_2 peak improved by 2.7 $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI, 1.2 to 4.9) in the exercise group and declined by 1.3 $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI, -3.1 to 0.6) in the control group from week 0 to 6 post-NACRT. The adjusted between-group mean difference for VO_2 peak was 3.9 $ml \cdot kg^{-1} \cdot min^{-1}$ (95% CI, 1.5 to 6.3). In the randomized controlled trial by Moug et al. (7) the between-group mean in 6-minute walk distance was 68.5 meters (95% CI, 27.2 to 164.2) at the pre-surgery timepoint. In the single arm trials with assessment of patient-reported outcomes (1, 3-5), findings were mixed with symptoms, functioning, and QoL either declined, remaining stable, or increasing during NACRT (1, 5). At the pre-surgery timepoint, these patient-reported outcomes appeared to return to baseline or slightly increase above baseline values (1, 3, 4). Moug et al. (7) did not detect any between-group differences in patient-reported outcomes at the pre-surgery timepoint in their randomized controlled trial.

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APPENDIX D: EXERT BASELINE QUESTIONNAIRE

Identification #:_____

Date: _____

Exercise During and After Rectal Cancer Treatment

Andria R. Morielli, MSc; Normand Boulé, PhD; Nawaid Usmani, MD; Kurian Joseph, MD; Diane Severin, MD; Keith Tankel, MD; Tirath Nijjar, MD; Alysa Fairchild, MD; Kerry S. Courneya, PhD

BASELINE QUESTIONNAIRE

Instructions

Thank you for agreeing to participate in this study. In this questionnaire, we are going to ask you a series of questions about yourself. Many of the questions ask you about your physical and mental health, and some may be viewed as personal. It is important to answer as many of these questions as possible, however, if you feel uncomfortable answering certain questions please leave them blank. All responses are completely confidential and will never be used in any way that could link them to you. Many of the questions may seem similar but it is important to treat each question separately and provide an answer for each. There are no right or wrong answers and all we ask is that you provide responses that are as honest and accurate as possible. The questionnaire should take about 30 minutes of your time to complete. If you have any questions about completing the questionnaire, please contact Andria Morielli (Study Coordinator) at (780) 492-2829 (call collect from out of town) or morielli@ualberta.ca.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall <u>health</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall <u>quality of life</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ-CR29

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you urinate frequently during the day?	1	2	3	4
32. Did you urinate frequently during the night?	1	2	3	4
33. Have you had any unintentional release (leakage) of urine?	1	2	3	4
34. Did you have pain when you urinated?	1	2	3	4
35. Did you have abdominal pain?	1	2	3	4
36. Did you have pain in your buttocks/anal area/rectum?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had blood in your stools?	1	2	3	4
39. Have you had mucus in your stools?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
40. Did you have a dry mouth?	1	2	3	4
41. Have you lost hair as a result of your treatment?	1	2	3	4
42. Have you had problems with your sense of taste?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4
44. Have you worried about your weight?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you been feeling less feminine/masculine as a result of your disease or treatment?	1	2	3	4
47. Have you been dissatisfied with your body?	1	2	3	4
48. Do you have a stoma bag (colostomy/ileostomy)? (please circle the correct answer)	Yes		No	

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
Answer these questions ONLY IF YOU HAVE A STOMA BAG:				
49. Have you had unintentional release of gas/flatulence from your stoma bag?	1	2	3	4
50. Have you had leakage of stools from your stoma bag?	1	2	3	4
51. Have you had sore skin around your stoma?	1	2	3	4
52. Did frequent bag changes occur during the day?	1	2	3	4
53. Did frequent bag changes occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your stoma?	1	2	3	4
55. Did you have problems caring for your stoma?	1	2	3	4
Answer these questions ONLY IF YOU DO NOT HAVE A STOMA BAG:				
49. Have you had unintentional release of gas/flatulence from your back passage?	1	2	3	4
50. Have you had leakage of stools from your back passage?	1	2	3	4
51. Have you had sore skin around your anal area?	1	2	3	4
52. Did frequent bowel movements occur during the day?	1	2	3	4
53. Did frequent bowel movements occur during the night?	1	2	3	4
54. Did you feel embarrassed because of your bowel movement?	1	2	3	4
During the past 4 weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
For men only:				
56. To what extent were you interested in sex?	1	2	3	4
57. Did you have difficulty getting or maintaining an erection?	1	2	3	4
For women only:				
58. To what extent were you interested in sex?	1	2	3	4
59. Did you have pain or discomfort during intercourse?	1	2	3	4

M.D. Anderson Symptom Inventory (MDASI)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										**As Bad As You Can Imagine**
1. Your **pain** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
2. Your **fatigue (tiredness)** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
3. Your **nausea** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
4. Your **disturbed sleep** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
5. Your feelings of being **distressed (upset)** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
6. Your **shortness of breath** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
7. Your problem with **remembering things** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
8. Your problem with **lack of appetite** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
9. Your feeling **drowsy (sleepy)** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
10. Your having a **dry mouth** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
11. Your feeling **sad** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
12. Your **vomiting** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
13. Your **numbness or tingling** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
14. Your **mouth sores** at their WORST?	0	1	2	3	4	5	6	7	8	9	10
15. Your **hand-foot syndrome** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
16. Your **skin reaction** at its WORST?	0	1	2	3	4	5	6	7	8	9	10
17. Your **diarrhea** at its WORST?	0	1	2	3	4	5	6	7	8	9	10

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following ***items in the last 24 hours:***

	Did Not Interfere										**Interfered Completely**
18. **General activity?**	0	1	2	3	4	5	6	7	8	9	10
19. **Mood?**	0	1	2	3	4	5	6	7	8	9	10
20. **Work (including work around the house)?**	0	1	2	3	4	5	6	7	8	9	10
21. **Relations with other people?**	0	1	2	3	4	5	6	7	8	9	10
22. **Walking?**	0	1	2	3	4	5	6	7	8	9	10
23. **Enjoyment of life?**	0	1	2	3	4	5	6	7	8	9	10

Godin Leisure-Time Exercise Questionnaire

For this next question, we would like you to recall the amount of exercise you have done during the past month.

When answering these questions please:

- only count exercise sessions that lasted 10 minutes or longer in duration.
- only count exercise that was done during free time (i.e., not occupation or housework).
- note that the main difference between the first three categories is the intensity of the endurance (aerobic) exercise and the fourth category is for strength (resistance) exercise.
- please write the average frequency on the first line and the average duration on the second.
- if you did not do any exercise in one of the categories, please write in "0".

Considering a typical week (7 days) over the PAST MONTH how many times on the average did you do the following kinds of exercise?

		Times Per Week	Average Duration
a.	VIGOROUS/STRENUOUS EXERCISE (HEART BEATS RAPIDLY, SWEATING) (e.g., running, aerobics classes, cross country skiing, vigorous swimming, vigorous bicycling).	_____	_____
b.	MODERATE EXERCISE (NOT EXHAUSTING, LIGHT PERSPIRATION) (e.g., fast walking, tennis, easy bicycling, easy swimming, popular and folk dancing).	_____	_____
c.	LIGHT/MILD EXERCISE (MINIMAL EFFORT, NO PERSPIRATION) (e.g., easy walking, yoga, bowling, lawn bowling, shuffleboard).	_____	_____
d.	RESISTANCE/STRENGTH EXERCISE (e.g., lifting weights, push ups, sit ups, therabands).	_____	_____

Exercise Motivation

The following questions ask you to rate how you feel about exercising during your chemoradiation. Please pay careful attention to the words and descriptions for each scale and circle the number that best represents how you feel.

How beneficial do you think it will be to exercise during your chemoradiation?

1	2	3	4	5
not at all	a little bit	somewhat	quite a bit	very much

How enjoyable do you think it will be to exercise during your chemoradiation?

1	2	3	4	5
not at all	a little bit	somewhat	quite a bit	very much

How supportive do you think family/friends will be of you exercising during your chemoradiation?

1	2	3	4	5
not at all	a little bit	somewhat	quite a bit	very much

How motivated are you to exercise during your chemoradiation?

1	2	3	4	5
not at all	a little bit	somewhat	quite a bit	very much

How difficult do you think it will be to exercise during your chemoradiation?

1	2	3	4	5
not at all	a little bit	somewhat	quite a bit	very much

How much control do you think you will have over exercising during your chemoradiation?

1	2	3	4	5
not at all	a little bit	somewhat	quite a bit	very much

How confident are you that you will be able to exercise during your chemoradiation?

1	2	3	4	5
not at all	a little bit	somewhat	quite a bit	very much

Demographic and Medical Information

This part of the questionnaire is needed to help understand the characteristics of the people participating in the study. For this reason it is very important information. All information is held in strict confidence and its presentation to the public will be group data only.

1. Age: _____

2. Sex: Male _____ Female_____

3. Current Marital Status: Never Married _____ Married _____ Common Law _____
Separated _____ Widowed _____ Divorced _____

4. Education (Please check highest level attained):
_____ Some High School _____ Completed High School _____ Some University/College
_____ Completed Univ/Coll _____ Some Graduate School _____ Completed Grad School

5. Annual Family Income: < 20,000 _____ 20-39,999 _____ 40-59,999 _____
60-79,999 _____ 80-99,999 _____ > 100,000 _____

6. Current Employment Status: Disability _____ Retired _____ Part Time _____
Homemaker _____ Full Time _____ Sick Leave _____

7. What is your primary ethnic origin or race (please circle)?
White Black Hispanic Asian Aboriginal Other _____

8. Which of the following best describes your current smoking status?
____ Never Smoked ____ Ex-Smoker ____ Current Smoker

9. Has a doctor or nurse ever told you that you had any of the following conditions? (check all that apply):

High blood pressure	_____No	_____Yes	High cholesterol	_____No	_____Yes
Heart attack	_____No	_____Yes	Stroke	_____No	_____Yes
Emphysema	_____No	_____Yes	Chronic bronchitis	_____No	_____Yes
Diabetes	_____No	_____Yes	Other cancer	_____No	_____Yes
Angina (chest pains)	_____No	_____Yes	Arthritis	_____No	_____Yes

Any other long term health condition? _____

10. In the past month, was your ability to exercise limited by a health condition, injury, or disability?

1	2	3	4	5
No, Not at All	A Little	Somewhat	Quite a lot	Completely

11. Are you currently taking any medications for health problems? (e.g., for anxiety, depression, blood pressure, constipation, pain, to help with sleep, etc.).

What is the medication?	What is it for? (e.g., blood pressure, anxiety)
1. _____	_____
2. _____	_____
3. _____	_____

Others? _____

Anything else you would like to tell us? On this final page, please feel free to make any comments concerning your rectal cancer, your treatments, the questionnaire, the exercise study, or anything else you think may be helpful to us. All comments are welcome.

Thank you very much for your participation in this research project. Please place the completed questionnaire in the envelope provided and bring it to your scheduled fitness test.