Prehabilitation in Colorectal Cancer Surgery

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ABSTRACT

Prehabilitation is a preoperative intervention that aims to prevent or attenuate treatment-related functional decline and its consequences. Given the complex nature of the functional impairment of cancer patients undergoing surgery, our research group has conceptualized prehabilitation as multidisciplinary intervention, including exercise training with both endurance and resistance components, nutritional counseling with protein supplementation, and anxiety reducing strategies. In this thesis, the study population consists in patients undergoing elective colorectal surgery for non-metastatic cancer.

Including four original trials and one review article, this dissertation is meant to provide a solid scientific proof in this new and fast growing field. These studies: i) demonstrate that prehabilitation is effective in preventing perioperative functional decline; ii) establish that patients with low physical status, at high-risk for poor surgical outcome, respond to greater extend to prehabilitation; iii) find an association between improved preoperative physical fitness and lower severity of postoperative complications; iv) objectively define functional the trajectory along the whole perioperative period; and v) show that high-intensity interval training is the optimal strategy to improve cardiorespiratory fitness after surgery.

Taken together, conclusive evidence is provided that physical functioning could be preserved and optimized during cancer care using prehabilitation, with proven effects in high-risk population, surgical morbidity, and whole-body metabolism. I think is that this scientific finding will foster further research in the topic, and promote the implementation of evidence-based principles into cancer care.

RÉSUMÉ

Les patients atteints du cancer sont à risque de subir un déclin de leur fonction physique suite à leur opération. La préhabilitation est une intervention préopératoire qui vise à prévenir ou atténuer la détérioration liée à un traitement. Il s'agit d'une intervention multidisciplinaire comprenant trois volets: le conditionnement physique (entrainement aérobique et musculaire), un suivi en nutrition avec suppléments en protéine, ainsi que des sessions de relaxation pour réduire le niveau d'anxiété. La population cible de cette thèse sont les patients en attente d'une chirurgie colorectale élective pour cancer non-métastasique.

Comprenant quatre études et un article de synthèse, l'objectif de cette dissertation est de fournir une preuve scientifique solide dans ce nouveau domaine croissant. Ces études : i) démontrent que la préhabilitation est efficace dans la prévention du déclin fonctionnel periopératoire, ii) établissent que les patients en piètre état physique sont à risque élevé d'un résultat chirurgical défavorable, iii) trouvent une association entre une santé physique préopératoire améliorée et une sévérité moindre dans les complications postopératoires, iv) définissent objectivement la trajectoire de fonction physique au cours de la période periopératoire, et v) démontrent que

l’entrainement à intervalle à haute-intensité est la modalité la plus efficace dans l’amélioration de la santé cardiorespiratoire après l’opération.

En ce qui est des soins offerts aux patients atteints du cancer, des preuves montrent qu’il est possible de préserver et d’optimiser la fonction physique en ayant recours à la préhabilitation, avec des effets prouvés dans la population à risque élevé, la morbidité chirurgicale, et le métabolisme du corps. Je pense que ces résultats de recherche vont encourager davantage de recherche dans ce domaine, et vont promouvoir l’implantation de ces principes dans les soins du cancer.

TABLE OF CONTENTS

LIST OF COMMON ABBREVIATIONS

6MWD, 6-minute walk distance

6MWT, six-minute walk test

ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program

ACSM, American College of Sports Medicine

ASA, American Society of Anesthesiologists physical status

AT, anaerobic threshold

BMI, Body Mass Index

CCI, Comprehensive Complication Index

CHAMPS, Community Healthy Activities Model Program for Seniors questionnaire

CI, confidence interval

CO_2, carbon dioxide

CPET, cardiopulmonary exercise testing

CR-POSSUM, Colorectal Possum Score

DASI, Duke Activity Score Index

ECG, Electrocardiogram

ERAS, Enhanced Recovery After Surgery

ESPEN, European Society for Clinical Nutrition and Metabolism

FC, functional capacity

GEE, generalized estimating equation

HADS, Hospital Anxiety and Depression Scale questionnaire

HIIT, high intensity interval training

IQR, interquartile ranges

MCID, minimal clinically important difference

MCS, 36-Item Short-Form Health Survey Mental Component Summary

METs, metabolic equivalents

MICT, moderate intensity continuous training

MNA, Mini Nutritional Assessment

MUHC, McGill University Health Centre

NRI, Nutritional Risk Index

NRS-2002, Nutritional Risk Screening 2002

O_2, oxygen

PCS, 36-Item Short-Form Health Survey Physical Component Summary

PG-SGA, Patient-Generated Subjective Global Assessment

PNR, Prospective Non-randomized Trial

RCRI, Revised Cardiac Risk Index

RCT, Randomized Controlled Trial

REB, Research Ethic Board

SD, standard deviation

SF-36, 36-Item Short-Form Health Survey

TNM, Tumor Node Metastasis Classification.

$\dot{V}O_2$, oxygen uptake

LIST OF FIGURES

LIST OF TABLES

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Most importantly, my warmest and heartfelt gratitude goes to the many women and men suffering from cancer who participated in my clinical trials, providing their valuable time and effort during such a difficult moment of their life. Their altruism, willingness, and resilience are indelible and moving lessons for me, for which I will be forever thankful.

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THESIS FORMAT

This is a manuscript-based thesis comprised of six chapters, five of which include the text of research papers, either published or submitted to peer-reviewed journals during my student journey at McGill University. Chapter 1 presents the theoretical background of multimodal prehabilitation, and provides a comprehensive review of the relevant literature on the topic. This is review article published in *European Journal of Surgical Oncology* in July 2018. Following chapters present research findings, which constitute an original contribution to the field. Chapter 2 provides data on clinical proof of efficacy of prehabilitation, analyzing our cohort of patients over a 5-year period. This paper was published in *Acta Oncologica* in February 2017. Chapters 3 and 4 address two main knowledge gaps, testing efficacy of prehabilitation in elderly and deconditioned patients, and its impact on postoperative complications. These papers were published in *Surgery* in October 2016, and in *Acta Oncologica* in February 2019. Chapter 5 aims at expanding the current knowledge in the topic, using a randomized controlled design to compare two different modalities of preoperative training programs, and assess their effect on perioperative exercise capacity. This manuscript was submitted for publication. To facilitate the appraisal of the coherent and unifying flow through the whole thesis, a concise preface introduces all manuscript-based chapters. To conclude, Chapter 6 includes a general discussion of the thesis findings and provides thoughts for future directions.

LIST OF ORIGINAL MANUSCRIPTS

This thesis includes the publications of five original manuscripts; four published, one submitted for publication.

1. **Minnella EM**, Awasthi R, Gillis C, Fiore J Jr, Liberman AS, Charlebois P, Stein B, Bousquet Dion G, Feldman LS, Carli F. *Patients with poor baseline walking capacity are most likely to improve their functional status with multimodal prehabilitation*. Surgery. 2016 Oct; 160(4):1070-9.
2. **Minnella EM**, Bousquet-Dion G, Awasthi R, Scheede-Bergdahl C, Carli F. *Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience*. Acta Oncol. 2017 Feb;56(2):295-300.
3. **Minnella EM**, Carli F. *Prehabilitation And Functional Recovery For Colorectal Cancer Patients.* Eur J Surg Oncol. 2018 Jul;44(7):919-926.
4. **Minnella EM**, Liberman AS, Charlebois P, Stein B, Scheede-Bergdahl C, Awasthi R, Gillis C, Bousquet-Dion G, Ramanakuma AV, Pecorelli N, Feldman LS, Carli F. *The impact of improved functional capacity before surgery on postoperative complications: a study in colorectal cancer.* Acta Oncol. 2019 Feb 6:1-6. doi: 10.1080/0284186X.2018.1557343.
5. **Minnella EM**, Ferreira V, Awasthi R, Charlebois P, Stein B, Liberman SA, Scheede-Bergdahl C, Morais JA, Carli F. *Effect of training intensity on*

perioperative exercise capacity: a randomized controlled trial in multimodal prehabilitation for colorectal surgery. Submitted.

AUTHOR CONTRIBUTIONS

Chapter 1

Minnella EM, Carli F. *Prehabilitation And Functional Recovery For Colorectal Cancer Patients.* Eur J Surg Oncol. 2018 Jul;44(7):919-926.

I wrote the manuscript, conducted the literature review, and proposed the original clinical pathway. Francesco Carli supervised the work and edited the manuscript.

Chapter 2

Minnella EM, et al. *Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience*. Acta Oncol. 2017 Feb;56(2):295-300.

I had a primary role in the conception and design of the study, and analysis and interpretation of data.

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R Awasthi: Patients' recruitment and acquisition of data; C Gillis: Analysis and interpretation of data; C Scheede-Bergdahl: Patients' recruitment and acquisition of data; G Bousquet-Dion: Patients' recruitment and acquisition of data; F Carli: Conception and design, patients' recruitment, analysis and interpretation of data.

Chapter 3

Minnella EM, Patients with poor baseline walking capacity are most likely to improve their functional status with multimodal prehabilitation. Surgery. 2016 Oct; 160(4):1070-9.

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Awasthi R: Patients' recruitment and acquisition of data; Gillis C: Patients' recruitment and acquisition of data; Fiore J Jr: Patients' recruitment and interpretation of data; Liberman AS: Patients' recruitment and interpretation of data, Charlebois P: Patients' recruitment and interpretation of data; Stein B: Patients' recruitment and interpretation of data; Bousquet Dion G: Patients' recruitment and interpretation of data; Feldman LS: design of the study, and interpretation of data; Carli F: conception and design of the study, and interpretation of data.

Chapter 4

Minnella EM, et al. *The impact of improved functional capacity before surgery on postoperative complications: a study in colorectal cancer.* Acta Oncol. 2019 Feb 6:1-6. doi: 10.1080/0284186X.2018.1557343.

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Chapter 5

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Preface to chapter 1

This chapter presents the background knowledge upon which multimodal prehabilitation is grounded. It starts highlighting, in surgical care, the central importance of optimizing functional capacity, defined as "the degree to which an individual can perform chosen roles without limitation in three key domains: physical, social, and psychocognitive".[1] Then, I illustrate the conceptual frame underpinning the multidisciplinary approach of prehabilitation. Although the fundamental principles of exercise, nutrition, and psycho-social interventions are similar regardless of different clinical settings, there are unique features and considerations in the perioperative management of surgical adult patients, which are worthily explored in detail.

The chapter continues with a proposal of a preoperative clinical pathway which includes prehabilitation. The goal is to implement a structured screening of relevant risk factors to guide personalized interventions. Trying to implement an evidence-based practice,[2] I used three information sources:

- best available scientific evidence,
- clinical expertise developed over a 5-year experience in high-volume center,
- patients' expectations, values, and motivations.

With this pathway, I propose to screen every surgical patient using simple, quick, and validated tools. Once identified, only patients at high postoperative risk are targeted for further tests, and eventually prescribed with a prehabilitation program. Since its publication in July 2018, continuing feedback from colleagues and recent advance have contributed to refine this pathway. For instance, the subjectively reported metabolic equivalents (METs)[3] was replaced by the Duke Activity Score Index (DASI)[4] as screening tool of the physical function. This revision followed a recent work by Wijeysundera and collegues,[5] that showed that a mere estimation of functional capacity based on patient-reported data is not accurate. Despite this steady update, the pathway I present in this first chapter and, even more important, its underling rationale are still valid, and currently adopted by the Prehabilitation Unit at MUHC.

The chapter ends with a comprehensive review of the existing literature on the topic, outlining differences between studies in term of design, interventions, outcome measures, protocol adherence, and results.

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CHAPTER 1

Prehabilitation and functional recovery for colorectal cancer patients.

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1.1 Abstract

Cancer and its treatments are associated with functional decline that has impactful consequences on quality of life, and care continuum. Thus, optimizing perioperative functional capacity has been identified as a research and clinical priority in cancer care. The process of enhancing physical fitness before an operation to enable the patient to withstand the stress of surgery has been termed prehabilitation. Main elements are preoperative exercise, nutrition therapy, and anxiety-reduction techniques. Given the growing body of evidence on prehabilitation efficacy, this narrative review will summarize the rational underlying preoperative interventions, and propose a structured clinical pathway aimed at optimizing preoperative functional capacity.

1.2 Introduction

Surgery is a major stressor. The response of the body to injury consists in an ancestral systemic reaction aimed to maintain vital functions and restore homeostasis.[1] Stress response is normally adaptive and time-limited, and it is assumed to provide a survival advantage.[2,3] However, a prolonged activation of this pathway, even after the removal of the noxious stimulus, may contribute to worsen clinical and functional status. During the initial phase, activation of the hypothalamic-pituitary axes and the innate immune system promote fast availability of energetic substrates, minimize excessive inflammation, and preserve vascular tone. In contrast, the late phase is associated with uncontrolled catabolism and resistance to anabolic signals, increased oxidative potential that lead to tissue damage, development of weakness and/or myopathy, and increased susceptibility to infection.

Unlike trauma and critical illness, elective surgery is a 'scheduled stress'. Thus, the idea of preventing or attenuating the stress response and its consequences has attracted medical science for a century.[4] Considerable progress has been made in recent years towards improving surgical care, and ERAS represents a unique milestone in that direction.[5,6] Only in the recent past, however, there has been appropriate attention to the clinical impact of reduced functional capacity on care continuum.[7,8] Indeed, the main determinants of functional capacity (physical, nutrition, and psychological status), identified as risk factors for poor surgical outcome, are potentially modifiable conditions.[9]

This awareness has caused a conceptual shift away from attempting to restore functional capacity after surgery towards preventive strategies.[10]

Prehabilitation is a multidisciplinary intervention that aims at using the preoperative period to prevent or attenuate the surgery-related functional decline and its consequences. Multimodal prehabilitation includes exercise training, nutritional therapy, and anxiety reduction strategies. Despite an incomplete and still evolving understanding, a mounting clinical evidence developed in last 5 years allows us for the development of a rational preoperative approach aiming at attenuating surgical-related functional decline. This narrative review will summarize the rational of preoperative interventions, explain how prehabilitation could impact upon current practice, outline our thoughts on preoperative pathway, review the evidence, and speculate upon how care will further evolve.

1.3 The prehabilitation approach

Colorectal cancer is associated with both unhealthy lifestyle attitude (low physical activity and poor food intake) and pathological organ response to specific interventions (exercise intolerance and metabolic dysfunction). Multimodal prehabilitation aims at assessing for these specific conditions and intervening in high-risk population. This approach is supported by emerging evidence of effectiveness in selected, deconditioned patients.[11,12] Figure 1 shows our proposal for a rational preoperative approach in the context of multimodal prehabilitation. Limited surgical or perioperative society guidelines exist on how to optimally screen, assess, and intervene on surgical patients' physical status; thus, we suggest a practical pathway that attempts to meet the needs of majority of patients. The counseling and the consequent interventional strategies should be run by specialized healthcare providers, such dieticians, psychologists, exercise physiologists, physiotherapists and sport specialists. The treatment of special conditions goes beyond the purpose of this review, and the care pathway of each patient must be planned and personalized. For instance, in the nutrition session we propose a classical optimal carbohydrates/fat ratio whereas it is known that a higher fat intake would be beneficial in some weight-losing cancer patients with insulin resistance.[13]

Aiming at increasing the quality of perioperative care by accelerating recovery, prehabilitation should be integrated into best perioperative management and ERAS pathway, representing its clinical and scientific development. Thus, clinical elements of usual preoperative care (such as risk assessment, medication management, perioperative blood management, and smoking cessation) and ERAS pathway (such as minimally invasive surgical approach when feasible, multimodal analgesia, minimized blood loss and perioperative fluid administration, preoperative oral carbohydrate loading, early oral nutrition, respiratory physiotherapy, and early mobilization) are not further explained in this paper. In our 3-step approach*, all patients* should be screened before surgery, and further tests and intervention should involve high-risk population:

1. *Screening*. Its main purpose is to predict the probability of poor outcome, and whether specific interventions could modify this risk. *All patients* should be screened preoperatively.

2. *Assessment*. This is a detailed examination of functional variables by an expert clinician, dietitian, kinesiologist/physiotherapist, or nurse. It is a time and resource-consuming process and should involve only high-risk population identified with screening tools. Mandatory elements are comprehensive history, exercise and dietary habits, functional evaluation in form of signs/symptoms, and laboratory or clinical testing results. A detailed description of a physical, nutritional, and psychological assessment goes beyond the purpose of this review.

3. *Intervention*. Training and nutritional program need to be personalized and prescribed based on specific assessments, ensuring high quality clinical standard and patients'

safety. Specific interventions such as physical therapy in patients with severely impaired cognition/motion, or nutritional therapy in severely compromise oral intake require special consideration.

Why Exercise?

Poor physical fitness carries an impressive worldwide burden.[14] Interest in cancer rehabilitation has grown exponentially during last decades, addressing the urgent demand of improving quality of life in a growing population of survivors. The novel approach of prehabilitation focuses the ability of exercise to deliver a physiologic stress that causes an adaptive response in all organs and tissue, thus improving the ability to withstand the incoming stress of surgery.[15]

Cardiorespiratory fitness is determined by the capacity to meet the increase in oxygen consumption during daily activities, exercise, and stress conditions. The ability to both deliver and utilize oxygen and substrates could be impaired by cancer and its treatments, such as surgery, chemotherapy, radiotherapy, and hormone therapy.[16] In this setting, the potential role of exercise to revert or treat this condition is now a proof of concept.[17] In contrast, the potential impact on immune-modulation is poorly understood and more controversial, since both anti- and pro-inflammatory mediators could be stimulated by different exercise interventions.[18] Although aerobic training is the single most studied intervention,[19] both resistance and endurance exercise promote a synergistic effect on tissue protein synthesis and aerobic capacity, and should be included in a preoperative programme.[20-22] Older adults should perform 150 minutes of moderate-intensity physical activity a week or 75 minutes of vigorous-intensity activity, and strengthening activities involving major muscle groups should be performed on at least 2 days per week.[23]

Screening. Self-reported functional capacity could be evaluated with patient's history, and expressed in metabolic equivalents (METs), where 1 MET is the resting oxygen consumption. Climbing a flight of stairs or walking up a hill are activities associated with METs > 4, and they are considered a 'safe' threshold below which postoperative complications are more likely to occur.[24] Validated tools to assess perioperative risk of major cardiac complications are: Revised Cardiac Risk Index,[25] ACS NSQIP MICA,[26] and ACS NSQIP Surgical Risk Calculator.[27] A simple, objective, and inexpensive measure of functional capacity is the six-minute walk test, that measures the distance covered over 6 minutes at a brisk pace. Although it is an easy test, a high-quality, standardized protocol should be always followed.[28] A six-minute walking distance below 400 meters is an indicator of impaired mobility, limited independence, and poor surgical outcome.[29-31] Recent findings show how this threshold could be used to identify the target population for prehabilitation intervention.[11]

Assessment & Intervention. Endurance and strength tests should be utilized to both assess physical status and prescribe exercise. Cardio Pulmonary Exercise Testing

(CPET) is the gold standard to evaluate functional capacity and therapeutic response in numerous medical and surgical settings.[32] CPET metabolic cart measures gas exchange and ventilation parameters, allowing the evaluation of oxygen consumption during a ramped incremental exercise. CPET provides recognized clinical measure of surgical outcome in colorectal cancer, and it is a valuable tool to guide prehabilitation.[33]

The physical intervention of multimodal prehabilitation is exercise training. Although it seems to be a simple concept, it needed to be properly defined and recognized as a “planned, structured, repetitive, and purposive in the sense that the improvement or maintenance of one or more components of physical fitness is the objective”.[34] For instance, giving advice of walking is not prescribing exercise. Delivering a behavioral intervention is a complex process that relies on patients’ volitional effort, and the researcher/clinician should promote and facilitate both the personal commitment and the quality of the intervention. In our experience, main elements are the close monitoring of the adherence to prescription, the encouragement of the compliance to the program, the continuous feed-back to patients’ effort, and the introduction of supervised training session.

When designing a training program, it is recommended to follow the international recognized guidelines.[35] There are three main categories of exercise (aerobic, resistance and flexibility training), that complement each other, and lead to a comprehensive functional outcome improvement. Aerobic training, involving large muscle groups that use oxygen-supplied energy, is the cornerstone intervention for increasing aerobic capacity.[19] Stationary and recumbent-type bikes, stair climbing machines and treadmills are the most common used equipment. The duration depends upon the intensity of the activity, but each bout should last 10 minutes' at least. Exercise intensity and module, in form of either moderate intensity continuous or high intensity interval training, should be based on CPET-derived variables, ensuring an individualized protocol for each participant.[8,33] In resistance training, muscles work against an applied force or weigh aiming at improving strength. Eccentric resistance exercise at high intensity is most beneficial,[36] although not always feasible in unfit patients. Stretching and strengthening exercise, warm-up and cool-down activities should always be performed in a training session.

Why Nutrition?

Malnutrition, affecting two in three patient, is one of the most impactful and undertreated oncologic condition.[37,38] It is associated with higher risk of surgical complication, longer hospital length of stay, low tolerance to adjuvant therapy, higher rate of mortality, and increased health-care costs.[39-43] Both tumor and surgery cause a systemic inflammation response that can alter insulin and anabolic resistance, energy expenditure rate, patterns of hormonal secretion, and lipolysis/proteolysis pathway. Clinical sequelae include anorexia, poor appetite, weight loss, and muscle mass wasting, and could lead to condition such as cachexia or sarcopenia. Furthermore, medical treatments and tumor-mass effect could alter food intake and/or absorption because of dysphagia (for oral ulcers, difficult chewing, or xerostomia), taste alteration, nausea, vomiting, constipation or diarrhea, abdominal discomfort, and motility disorders. Older age, impaired physical function, and gastrointestinal tract cancer are additional nutritional risk factors.[44] The clear and consistent relationship between nutrition, cancer and surgery is the rational for proactive preoperative intervention. However, despite the strong evidence, the support from surgeons, and the evident cost-effectiveness, only 1 in 5 patients receive any preoperative dietary intervention, and only 1 in 5 hospitals have screening processes.[45-47] In the last decades, significant progress has been made in the field of metabolism, and a cultural shift evolves from nutrition as a baseline support to a therapeutic intervention; thus, we strongly believe in the need of implementing this knowledge into an evidence-based nutrition approach in major surgery.

Screening. From a practical point of view, the use of parameters such as BMI, involuntary weight loss or BMI-adjusted weight loss,[48] and plasma albumin levels remains unquestioned in nutritional screening; however, Patient-Generated Subjective Global Assessment (PG-SGA) and Nutritional Risk Screening 2002 (NRS-2002) are the most appropriate tool to identify the presence of undernutrition or the risk of developing undernutrition, and to start nutritional therapy.[49] Second line tools are Mini Nutritional Assessment (MNA), MNA short form,[50] Nutritional Risk Index (NRI).[51]

Assessment & Intervention. Cancer-associated malnutrition may result from A) reduced dietary intake or unmatched energy expenditure, and/or deficiency of B) protein or C) other macronutrients. The nutrient-based intervention of multimodal prehabilitation addresses all these points from the assessment phase to the intervention:

A) Meet energy requirement. Energy requirement is the amount of macro- and micronutrients needed to meet daily expenditure, maintain energy store, and promote physiologic metabolic processes. Energy requirement in patients with cancer is extremely variable,[52] and one in four patient with gastro-intestinal cancer shows a hypermetabolic state.[53] Thus, formula such as Harris and Benedict equations is not accurate, and resting energy expenditure should be determined with indirect calorimetry and adjusted for the additional exercise and physical activity prescribed. Hypermetabolism, considered as an early marker of cancer cachexia, is a central nutritional target, since it is associated with negative energy balance, weight loss, systemic inflammation, and alteration of performance status.[54] Insidiously, it occurs in patients with a good physical status,[54] then its early detection is extremely important. Waiting for validated targeted therapy,[55] we strongly suggest utilizing indirect calorimetry to personalize preoperative caloric intake.

B) High protein diet. In view of altered muscle protein metabolism, protein intake adequacy is key component of prehabilitation. Protein synthesis could be increased with amino acids supplementation in patient with cancer,[56,57] and high protein intake could improve the whole-body net protein balance during acute stress.[58,59] Based on this rationale and following current international guidelines,[60,61] dietary therapy in prehabilitation aims to achieve a daily protein intake of 1.5 g/kg of ideal body weight.

Good quality proteins from poultry, fish, dairy, eggs, and plant represent the first-line source, whereas supplementations should be prescribed only if needed. Whey protein or essential amino acids such as leucine are strong anabolic triggers, and should be preferred over other supplemental protein source.[62,63] In presence of moderate-advanced chronic kidney disease (and no ongoing dialysis), protein intake should not be > 1.0 g/kg/d.[64] Although hypothesized to exert a positive effect on tumor grow and host metabolism, specific regimens such as caloric restriction, ketogenic diet or pharmacological intervention still lack of clinical evidence, and are not currently included in prehabilitation.[65-67]

C) *Balanced meal*. The third element of nutritional intervention aims at guaranteeing an adequate intake and proportion of all macronutrients. A balanced meal is defined by with a 2:1:2 ratio between starches, meat (or alternative protein sources) and vegetables. Patients should be taught basic dietary suggestions, e.g. limiting the intake of high-fat foods, preferring whole-grain products, limiting sugar-rich foods with poor nutritional value, limiting alcohol intake, or eating meals at regular hours with proper interval.[68] All patients should receive nutritional education, and should be able to estimate the size a serving.

Why Anxiety Coping Strategies?

Psychological distress drives an impressive burden in oncologic care, and cancer patients often experience anxiety, depression, low self-esteem and fears of recurrence and death.[69] International studies reported rates of emotional distress in cancer patients ranging from 35% to 45%.[70] The reason for detecting and intervening on psychosocial disorders is not only limited to the relief of a mood distress and the consequent improvement in quality of life.[71] Preoperative anxiety and depression have negative impact on wound healing, infection rate, length of hospital stay, and adherence to medical treatment.[72-75] Based on this evidence, a growing interest on psychological issues in cancer care has developed. Unfortunately, primary concern focuses on cancer survivors after treatment. Once again, our clinical model proposes a cultural shift aiming at preventing rather than cure the functional impairment associated with cancer and its treatments, including psychological distress. Recent findings suggest that anxiety, rather than depression, should be the target of clinical efforts aimed at improving its recognition and treatment.[76]

The psychological component of multimodal prehabilitation is a nonpharmacological, cognitive-behavioral intervention. The aim is reducing anxiety symptoms and cancer-related distress by promoting an active-behavioral and active-cognitive coping within the relative short time allowed before surgery. During a single psychosocial visit, patients are encouraged to disclose personal beliefs and understanding about cancer and surgery, to reframe thoughts and experience to more positive interpretations, to reduce maladaptive lifestyle modifications. Furthermore, relaxation and imagery techniques are taught to the patients, such as passive breathing exercise accompanied by either passive or active muscle relaxation, simple meditation skills, and guided imagery. Patients are encouraged to participate in their favorite daily activities, and to do not avoid social contact. Psychotherapy, anxiolytic medications, and hypnosis are specific approaches that go beyond the purpose of prehabilitation, and are therefore not included.

Why Exercise + Nutrition + Relaxation? When 1+1+1=4

The short answer is that a multi-driven functional impairment needs to be addressed by a multimodal therapeutic strategy. Improving exercise tolerance in oncology patients is a unique challenge that goes beyond cardiopulmonary physiology, as cancer is a systemic disease affecting nervous, immune, endocrine, and cognitive systems. Thus, although there are no clinical studies comparing unimodal vs. multimodal approach, there is a strong rational for combining exercise training, nutritional therapy and anxiety reduction interventions.

The key target of conditioning interventions is the muscle system. Since it represents both a store and a source of key macronutrients, skeletal muscle has a critical role in whole body homeostasis.[77] Thus, maintenance of skeletal muscle not only allows locomotion and preserves functional independence, but also confers protection from adverse effects of metabolic dysfunction. Patients with colorectal cancer show:

- increased muscle protein breakdown;
- normal muscle protein synthesis in a fasted-state; *but,*
- impaired muscle protein synthesis in response to amino acid infusion alone, or exercise alone.[78,79]

This is the result of an inflammation state associated with cancer, that produces a systemic metabolic alteration. Furthermore, surgery induces an acute on chronic inflammatory response that further accelerate this response, leading to an uncontrolled catabolism and resistance to anabolic signals.[80-82] Collectively, this desensitization to both nutrient- and physical-driven anabolic stimuli regulating muscle metabolism likely promotes an impactful functional impairment. On this basis, the well-known synergism between exercise and hyperproteic diet appears to be essential in the attempt to address the complex pathophysiology of the functional decline in colorectal cancer patients, and to overcome the state of anabolic resistance.[83] The impact of psychological distress on adherence to intervention and mood attitude speaks to the synergic effect of anxiety-reducing intervention and physical and nutritional therapy.

1.4 State of Evidence

Although prehabilitation is not a new concept, trials on structured preoperative intervention aiming at improving perioperative functional capacity emerged only in the last decade. Table 1 and table 2 summarize main characteristics of studies on surgical prehabilitation.[84-92] These trials included patients with colorectal cancer scheduled for surgery, and involved at least one of the multimodal components, exercise, nutrition, and/or anxiety-reduction techniques.

Over the last years, there has been a shift from a home-based to supervised training sessions; from unimodal to multimodal approach; and from a daily moderate activity to a 3 times per week moderate-high intensity exercise. Probably because of all the above changes, adherence to the intervention rises, and measure outcomes becomes clinically significant. Although the impressive difference among studies, in term of study design and outcome, this evidence constitutes the proof of concept of the efficacy of prehabilitation in optimizing functional capacity.

Although prehabilitation is an effective intervention, a recent study we conducted showed that 41% of participant did not improve their physical fitness.[93] Non-response to exercise is a common finding in medical research, and could be explained by several mechanisms, such as age, gender, disease stage, comorbidity, type of exercise and dietary intervention, genetic, epigenetic and metabolic traits.[94,95] Further research is required to identify these patients, and personalize an effective intervention.

1.5 Future Directions and Opportunities for Research.

- *Short-term surgical outcome.* Despite some recent evidence and a strong rational,[12,96] a definitive association between prehabilitation and 'traditional' short-term postsurgical outcome (e.g. 30-day mortality, postoperative major complication, intensive care admission, reoperation, readmission, or length of stay) has yet to be shown.

- *Target frail and elderly with co-morbidities.* Although cancer incidence is higher in elderly, the proportion of patients with a cancer diagnosis undergoing surgery declines with age.[97] One of the main reason for this exclusion is low physical fitness, independently associated with worst surgical outcome.[98] Enhancing functional capacity before surgery could address this issue increasing the numbers of candidates eligible for curative-intent resection.

- *Early adjuvant chemo-radiotherapy.* Postoperative functional impairment is associated with delayed chemotherapy, and patients who received chemotherapy ≥8 weeks postoperatively have worse local and distant recurrence rates and worse overall survival.[99] The role of prehabilitation in shortening the waiting time for adjuvant therapy should be investigated.

- *Long term health-related factors.* It is widely recommended that cancer survivors should engage in regular physical activity and adopt a proper diet.[100] Even if it known that longstanding exercise intervention may promotes life-style change, the role of prehabilitation has not been addressed yet.

- *Long term cancer outcome.* After completion of the main treatment, exercise positively influences disease progression and tumor recurrence.[101] Whether prehabilitation could impact on cancer outcome is not known.

- *Improved oxygen consumption and in vivo proliferation capacity of cancer cells.* High rate non-oxidative breakdown of glucose is the key energetic pathway linked to cancer cell proliferation.[102] Thus, it is widely accepted that cancer metabolism relies primarily on glucose delivery, and occurs in low-oxygen environment. However, a recent theory postulated that tumors are glycolytic because are hypoxic in vivo.[103] To the same extent, branched-chain amino acids support cancer energetic and biosynthetic demands.[104,105] Clinical consequences of one-month preoperative conditioning program (aimed at improving whole oxygen uptake capacity and increasing protein intake) on tumor microenvironments, energy metabolism, and proliferation capacity needs to be elucidated.[106]

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Both authors contributed to conception and design of the present work; and draft, reviewed, and approved the last version of the paper.

1.7 Tables

Table 1.1. Characteristic of studies on prehablitation in colorectal cancer. PNR, prospective non-randomized trial; RCT, randomized controlled study.

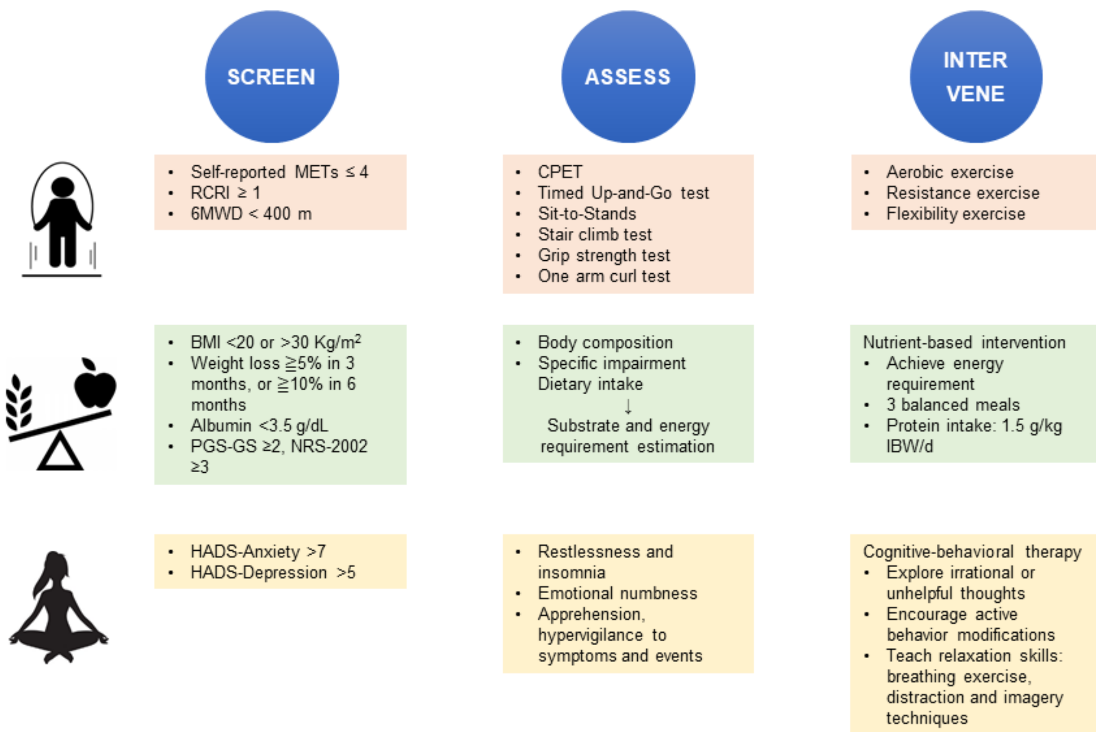
Study	Design	Sample Size, n Prehab (Control)	Intervention			Duration, wk	Exercise		Compliance, %
			Exercise	Nutrition	Anxiety		Frequency, d/wk	Supervision	
Kim DJ, 2009 [84]	RCT	14 (7)	✓ moderate→high	✗	✗	4	7	No	74
Carli F, 2010 [85]	RCT	58 (54)	✓ moderate→high	✗	✗	6	7	No	16
Li C, 2013 [86]	PNR	42 (45)	✓ moderate	✓	✓	4	3	No	45
Gillis C, 2014 [87]	RCT	38 (39)	✓ moderate	✓	✓	4	3	No	78
West MA, 2015 [88]	PNR	22 (13)	✓ high interval	✗	✗	6	3	Yes	96
Gillis C, 2015 [89]	RCT	22 (21)	✗	✓	✗	4	-	-	94
Heldens A, 2016 [90]	PNR	9 (0)	✓ moderate	✗	✗	5.5	2	Yes	96
Loughney L, 2017 [91]	PNR	23 (10)	✓ high interval	✗	✗	6	3	Yes	-
Bousquet-Dion, 2018 [92]	RCT	37 (26)	✓ moderate	4	✓	4	3-4	1 d/w	98

Table 1.2. Outcome Measure. 6MWD, 6-min walking distance; $\dot{V}O_2$ AT / peak, oxygen consumption at the anaerobic threshold / at peak exercise; $\dot{V}O_2max$, maximal oxygen consumption

Study	Functional Measure	Functional PreOp Change	Functional PostOp Change	Complication
Kim DJ, 2009 [84]	$\dot{V}O_2max$	0.5 (4.2) mL/kg/min	✗	✗
Carli F, 2010 [85]	6MWD	- 10.6 (7.3) m	-34.4 (9.9) m	No difference
Li C, 2013 [86]	6MWD	42 (41) m	37 (70) m	No difference
Gillis C, 2014 [87]	6MWD	25.2 (50.2) m	23.4 (54.8) m	No difference
West MA, 2015 [88]	① $\dot{V}O_2AT$ ② $\dot{V}O_2peak$	① 2.12 [1.3-2.9] ② 2.65 [1.2-4.1] mL/kg/min	✗	✗
Gillis C, 2015 [89]	6MWD	20.8 (42.6) m	18.6 (65.1)	No difference
Heldens A, 2016 [90]	6MWD	9%	↓	✗
Loughney L, 2017 [91]	Daily Steps	22%	✗	✗
Bousquet-Dion, 2018 [92]	6MWD	21 (47) m	20 (54) m	No difference

1.8 Figure

Figure 1.1 Proposed clinical pathway for preoperative functional optimization of patients undergoing colorectal cancer surgery. 6MWD, 6-min walking distance; BMI, body mass index; CPET, Cardiopulmonary exercise testing; HADS, Hospital Anxiety and Depression Scale questionnaire; Anxiety and Depression sub-scale; IBW, ideal body weight; METs, metabolic equivalent; NRS-2002, Nutrition Risk Screening 2002; PG-SGA, Patient-Generated Subjective Global Assessment; RCRI, Revised Cardiac Risk Index.



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Preface to chapter 2

As explained in the previous chapter, the hypothesis underling prehabilitation is that the synergistic effect of physical, dietary, and psychological interventions would lead to a preoperative improvement in physical status, which would serve as a buffer against functional decline after surgery. Emerging evidence shows that prehabilitation can be beneficial. Nonetheless, as highlighted in previous chapter, current studies have several limitations, such as:

- small sample size,
- poorly described or unimodal intervention,
- inconsistent outcome measures,
- and missing outcome data after surgery.

For these reasons, meta-analysis has limited application in this topic, since combining data from these trials would lead to poor quality results. Nevertheless, at this stage, a strong proof of concept on the efficacy of prehabilitation is mandatory and should constitute the first step of this dissertation.

In the attempt to address the above-mentioned limitations, we intended to perform an analysis on a large cohort of surgical patients. Including 185 participants, this is the largest study population analyzed in prehabilitation setting, aimed at providing a strong evidence on the ability of multimodal prehabilitation to improve perioperative functional capacity in patients undergoing colorectal cancer surgery.

CHAPTER 2

Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a 5-year research experience.

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2.1 Abstract

Background

Multimodal prehabilitation is a preoperative conditioning intervention in form of exercise, nutritional assessment and whey protein supplementation, and anxiety-coping technique. Despite recent evidence suggesting that prehabilitation could improve functional capacity in patients undergoing colorectal surgery for cancer, all studies were characterized by a relatively small sample size. The aim of this study was to confirm what was previously found in three small population trials.

Methods & Materials

Data of 185 participants enrolled in a pilot single group study and 2 RCTs conducted at the McGill University Health Centre from 2010 to 2015 were reanalyzed. Subjects performing trimodal prehabilitation (exercise, nutrition and coping strategies for anxiety) were compared to the patients who underwent the trimodal program only after surgery (rehabilitation/control group). Functional capacity was assessed with the six-minute walk test (6MWT), a measure of the distance walked over six minutes (6MWD). A significant functional improvement was defined as an increase in 6MWD from baseline by at least 19 meters. Changes in 6MWD before surgery, at four and eight weeks were compared between groups.

Results

Of the total study population, 113 subjects (61%) underwent prehabilitation. Changes in 6MWD in the prehabilitation group were higher compared to the rehabilitation/control group during the preoperative period (30.0 (SD 46.7) m vs. -5.8 (SD 40.1) m, $p<0.001$), at 4 weeks (-11.2 (SD 72) m vs. -72.5 (SD 129) m, $p<0.01$), and at 8 weeks (17.0 (SD 84.0) m vs. -8.8 (SD 74.0) m, $p=0.047$). The proportion of subjects experiencing a significant preoperative improvement in physical fitness was higher in those patients who underwent prehabilitation (68 (60%) vs 15 (21%), $p < 0.001$).

Conclusion

In large secondary analysis, multimodal prehabilitation resulted in greater improvement in walking capacity throughout the whole perioperative period when compared to rehabilitation started after surgery.

2.2 Introduction

Improving physical capacity is beneficial in almost all health and medical conditions, and strong evidence supports the relation between functional capacity and postoperative outcome.[1,2] Thus, enhancing cardiorespiratory fitness during the preoperative period has an intuitive appeal. In recent years, clinical trials have shown that increasing physical status before surgery is feasible in different settings, and through a wide spectrum of preoperative interventions.[3,4] A recent systematic review by Singh and colleagues on the impact of presurgical exercise demonstrated a potential benefit on postoperative short-term outcomes, such as muscle strength and physical fitness. Out of 18 studies three were randomized controlled trials in patients with colorectal cancer fitting the criteria for inclusion in the study. Two studies used structured, home-based intense aerobic exercise together with resistance exercise before surgery, and the third one aerobic exercise only. In the former two studies the preoperative intense exercise protocol lead to increased oxygen peak by 12%, but no improvement in functional walking capacity was shown after surgery. The authors also reported 16% compliance to the intense exercise. In view of these unexpected results these same authors subsequently conducted other trials using a multimodal prehabilitation protocol which included moderate structured, 4-week, home-based aerobic and resistance exercise, nutritional counselling and supplementation and psychological support, and they were able to demonstrate surgery significant improvement in preoperative and postoperative functional capacity.[5] However, each of these studies included a small sample of patients.

The present study was therefore set up to reanalyze the result of three studies conducted over a period of five years in a single center using a multimodal prehabilitation. The primary objective was to confirm that prehabilitation is associated with a better functional outcome before and after surgery in a large population undergoing colorectal surgery for cancer.

2.3 Method

Protocol design and study population

This study is a reanalysis of prospectively collected data from all consecutive participants enrolled in three consecutive studies: one published single group pilot study,[4] followed by one published RCT,[3] and subsequently by one recently completed RCT (GEN11-004). The trials were all approved by the institutional ethics board and conducted at the McGill University Health Centre (Montreal, Quebec, Canada) over the period 2010-2015. Eligible patients were 18 years of age or older scheduled for resection of colorectal cancer at any stage. Exclusion criteria were morbid conditions that absolutely contraindicated exercise, severely impaired ambulation, simultaneously participation to a pharmacotherapy trial, and inability to provide an informed consent. Surgical interventions were performed by three fellowship-trained colorectal surgeons, and all patients were treated according to an enhanced recovery program as a standard of perioperative care.[6] Participants were assigned to receive the multimodal prehabilitation program either before (prehabilitation group) or after surgery (rehabilitation/control group). Functional capacity was assessed with the six-minute walk test (6MWT), which measures the distance walked over six minutes (6MWD). Changes in 6MWD in relation to baseline were compared between groups before surgery, at four and eight weeks after surgery. A clinically meaningful functional improvement has been defined as an increase in 6MWD from baseline by at least 19 meters.[7]

Prehabilitation program

The scientific rational and the detailed description of the program have been published previously.[8] Briefly, prehabilitation is a conditioning intervention that consists of three main components: exercise, nutritional care and anxiety-coping intervention. Comprehensive history, physical assessment and subsequent personalized training design were performed including aerobic, resistance and flexibility static and dynamic balance exercises, either supervised or unsupervised. Endurance training was the core of the program, performed three days a week for 20-30 minute per session. The intensity was set to achieve a moderate continuous training as defined with a Borg scale, a well-validated index that rates the perceived exertion.[9] Resistance exercise was prescribed two times per week, and involved major muscle groups of lower body, chest and core body, and upper body. Stretching and strengthening exercises, warm-up and cool-down activities were performed in each training session. Patients' nutritional intake was assessed, and dietary changes and protein supplementation in order to achieve a total protein intake of 1.5 g/kg/day were prescribed, as recommended by the European Society of Nutrition and Metabolism.[10] A psychological consultation and basic relaxation techniques were provided. All the interventions were conducted by specialist professionals in the different fields, kinesiology, dietetics and psychology. Prehabilitation lasted for four weeks before surgery, and continues after surgery for two months.

Control condition

Patients in the control group started the trimodal conditioning intervention (rehabilitation) after surgery, once they were discharged from hospital.

End Point, Measures and Assessments

The primary outcome was the 6MWD, recorded by a blinded assessor and following a standardized protocol.[11] Walk tests are routinely used by clinicians to evaluate aerobic capacity and therapeutic response for a wide variety of patients and settings. This test is very inexpensive and easy to administer as it requires minimal equipment, space, time and expertise. Moreover, 6MWT has been shown to be strongly correlated with surgical outcome.[12,13] Since the minimal important difference for the 6MWD (i.e. “the smallest change in an outcome measure perceived as beneficial by patients or physicians”) has been estimated at 14 m (95% CI 9-18 m) in colorectal surgical setting,[7] we considered 19 meters to be a meaningful change in functional ability throughout the perioperative period.

Assessments were performed four weeks before surgery (baseline), the day before surgery, and four and eight weeks after surgery. In addition to the 6MWT, a complete anthropometric evaluation was performed together with a self-reported physical activity as evaluated by the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire,[14] well validated in surgical patients.[7,15] Assessment of compliance was based on the diary filled by the patient and the weekly structured telephone calls.

Surgical outcomes as total length of hospital stay and post-surgical complication, graded following Clavien-Dindo classification,[16] were also analyzed.

All patients were undergoing standard clinical care according to an enhanced recovery program (ERAS) instituted since 2008, as previously described.[17]

Statistical Analysis

Statistical analysis was performed with SPSS, version 23 (IBM Corporation). We present descriptive statistics both for the pooled sample and stratified by study such that the reader can validate the appropriateness of the pooling of the data.

For all variables, variance homogeneity and normal distribution were tested with Kolmogorov-Smirnov tests. Data are presented as mean ± standard deviation (SD) or median (interquartile range). Data of the 2 groups were compared at the same time points using $\chi 2$ or Fisher's exact test for categorical data, and Student's t-test or Mann–Whitney U-test for continuous data, as appropriate. The alpha level was set for all comparisons at a p-value threshold of 0.05.

2.4 Results

Patients' Characteristics

A total of 186 participants were enrolled in three prehabilitation trials from October 2010 to August 2015. One hundred eighty-five patients (99%) completed the preoperative physiological assessment, and were included in this study, and of these one hundred thirteen (61%) were in the prehabilitation group, 72 (39%) were in the control group.

The baseline demographic, oncological and surgical characteristics of the patients were similar in the prehabilitation and the control group (Table 1 and 2). However, a higher percentage of patients in the prehabilitation group were older than 75 years old. Moreover, despite the two group had a similar level of functional capacity (baseline 6MWD 428.0 ±105 vs. 436.0 ±94.6 meters, p=0.600), participants in the prehabilitation group had a lower self-reported physical activity (CHAMPS 22.3 [10.0-46.0] vs. 38.5 [14.2-61.6] kcal/kg/week).

Functional Capacity over Time

Functional capacity over time, as measured by 6MWD change in relation to baseline value, is shown in Figure 1. Walking capacity modifications were quantified for three time periods (Table 3). From the first assessment to the day before surgery, there was a statistically significant difference between groups, as the prehabilitation group improved their functional capacity by more than 30 meters on average, whereas the control group stayed around baseline value.

At 4 weeks after surgery, participants in both groups decreased their physical status; however, the rehabilitation/ control group experienced a significant higher reduction, more than 70 meters on average. At eight weeks after surgery, the change in functional capacity was significantly higher in prehabilitation group, whereas the control group changed their functional capacity minimally. A significant preoperative improvement in physical fitness occurred in the prehabilitation group: 68 of 113 patients (60%) gain more than 19 meters in 6MWD preoperatively versus 15 of 72 (21%) in the control group ($p < 0.001$). At four weeks after surgery, 37% in prehabilitation group (38/104, nine lost in follow-up) versus 19% (12/65, seven lost in follow-up) in the control one experienced a significant enhancement in walking capacity ($p=0.015$).

The compliance to the multimodal program of the three studies ranged from 70 to 98% in the preoperative period, and 53 to 72% at four weeks and 53 to 82% at eight weeks. No adverse events were reported.

There were no differences in length of hospital stay or post-surgical complication (Table 2).

Descriptive characteristics by study are displayed in Supplementary Table 1S and shows that studies were relatively comparable in terms of age, gender distribution, BMI and surgical procedures, but that baseline 6MWD was considerably longer in the second and unpublished trials compared to the single group pilot study and the first trial.

2.5 Discussion

This secondary analysis confirmed that a structured multimodal prehabilitation program improved walking capacity before and after surgery for colorectal cancer.

This demonstrates a possible role of enhancing physical fitness preoperatively in increasing the ability to deal with the stress of surgery, and to preserve or restore homeostasis throughout the postoperative period.[18] Indeed, patients in the prehabilitation group recovered their functional capacity faster after surgery, and more than one third experienced a meaningful increase in their walking capacity one month after surgery.

Another element of interest in this study was the high rate of adherence to the preoperative exercise training. This could be due to the constant encouragement given by our research group to the patients, and weekly phone calls. Almost all patients (99%) returned the day before surgery to complete the preoperative assessment. Compliance to treatment declined after surgery (16 lost in follow-up), as a previous study has already shown.[3]

Functional decline after surgery is one of the most known treatment-related adverse effect in medicine,[19] strongly linked with the systemic inflammation induced by the stress response to surgery.[18] Indeed, both groups in this study tended to reduce their cardiorespiratory fitness one month postoperatively. This is a key period in cancer care, since the majority of complications occur within the first 30 days after surgery,[20] and impact on functional and long term outcome.[21] Although physical exercise has been shown to modulate positively inflammation in many chronic diseases,[22] few studies addressed the potential role of preoperative exercise as a therapy for surgery-related functional impairment. Moreover, cancer and anticancer therapies are associated with varying degrees of side effects such as reduced muscle strength, decreased cardiorespiratory fitness, reduced lean body mass, bone loss, severe fatigue, depression, emotional distress and anxiety.[23] Exercise has been suggested as a useful intervention to counteract both tumor and treatment-derived systemic effects, determined either by surgery or chemoradiotherapy.[24,25] In the present study functional capacity decreased after surgery in the prehabilitation group , but significantly less than in the control group implying that prehabilitation could have potential role in limiting the ailments associated with further cancer therapy. Future studies are needed to address volume, intensity and type of exercise training, and whether the accelerated return to baseline function can facilitate the initiation of adjuvant chemotherapy

Ideally, such interventions should be widely accessible to have the largest benefit for patients with varying age and functional status levels. Doubts have arisen about the feasibility of these programs in the surgical population, usually old, weak and untrained. This is particularly true in patients with colorectal cancer, as a result of the high incidence of physical inactivity, nutritional disorders, and cardiovascular and metabolic comorbidities.[26] However, a recent study showed that unfit and old patients benefit the most from prehabilitation by increasing their functional capacity to a greater extent.[27] In this population functional walking capacity can be considered a proxy of independency and mobility, facilitating activities of daily living.

It is now commonly accepted that achieving full recovery after surgery does not only mean being discharged earlier and without complications. In fact, surgery is only one step in cancer care, implying that every effort needs to be made to minimize the burden associated with further therapies. In colorectal cancer patients, a consistent body of evidence shows the negative role of physical inactivity and dietary disorder in cancer recurrence and survival.[26] Therefore the perioperative period may be a key moment to address modifiable risk factors of cancer recurrence and treat surgery-related side effects by promoting prehabilitation integrated in cancer care (Figure 2). Further investigation on the possible impact of prehabilitation on postoperative complication and continuum of cancer care is required. Furthermore, this patient-centered, multidisciplinary and integrated medical care program should start in the preoperative clinic where vulnerable patients are identified, risk stratified and adequately by an interdisciplinary team with the aim of improving surgical outcome and promoting health behavior throughout the continuum of cancer care.

2.6 Acknowledgments

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2.7 Tables

Table 2.1 Demographic and surgical characteristics of patients.

	Prehabilitation (n=113)	Control (n=72)	p-value
Age (years), mean ±SD*	68.5 ±11.8	66.6 ±9.9	0.246
>75 years old, n (%)	40 (35)	13 (18)	0.012
Gender Male, n (%)	69 (61)	46 (64)	0.757
BMI † (kg/m^2), mean ±SD	27.4 ±4.5	28.6 ±4.2	0.076
Obesity (BMI † ≥ 30), n (%)	35 (31)	28 (39)	0.271
ASA‡ III-IV, n (%)	28 (24)	26 (36)	0.135
Charlson Comorbidity Index), median [IQR]§	2.0 [2-3]	2.5 [2-3]	0.839
Cancer stage, n (%)			0.295
0-1	40 (35)	28 (39)	
2	33 (29)	21 (29)	
3	38 (34)	17 (24)	
4	2 (2)	6 (8)	
Laparoscopic approach‖, n (%)	94 (83)	53 (78)	0.434
Type of resection, n (%)			1.000
Colonic surgery	71 (63)	47 (66)	
Rectal surgery	42 (37)	25 (34)	
New stoma formation	29 (26)	15 (21)	0.721
Baseline 6MWD¶ (meters), mean ±SD	428.0 ±105	436.0 ±94.6	0.600

Baseline self-reported physical activity (CHAMPS[#] kcal/kg/week), median [IQR][§]	22.3 [10.0-46.0]	38.5 [14.2-61.6]	0.044

[*]SD = standard deviation, [†]BMI = Body Mass Index, [‡]ASA= American Society of Anesthesiologists physical score, [§]IQR = interquartile range, Laparoscopic procedures converted into open were not considered in this category, [¶] 6MWD = 6-minute walk distance, [#]CHAMPS = Community Healthy Activities Model Program for Seniors.

Table 2.2 Surgical characteristics and outcomes.

	Prehabilitation (n=113)	Control (n=72)	p-value
Laparoscopic approach*, n (%)	94 (83)	53 (78)	0.434
Type of resection, n (%)			1.000
Colonic surgery	71 (63)	47 (66)	
Rectal surgery	42 (37)	25 (34)	
New stoma formation	29 (26)	15 (21)	0.721
Length of Hospital Stay, median [IQR]	4 [3-5]	3 [3-6]	0.806
Grade of complication (Clavien-Dindo classification) ‡, n (%)			0.752
Grade 0	68 (62)	45 (66)	
Grade I	20 (18)	11 (16)	
Grade II	15 (14)	8 (12)	
Grade III	6 (6)	2 (3)	
Grade IV	1 (1)	2 (2)	
Grade V	0(0)	0 (0)	

* Laparoscopic procedures converted into open were not considered in this category, ‡ 7 missing data

Table 2.3 Changes in walking capacity through the perioperative period.

	Prehabilitation (n=113)	Control (n=72)	p-value
Preoperative change (in relation to baseline)			
Six-minute walk distance (meters), mean ±SD*	+30.0 ±46.7	-5.8 ±40.1	<0.001
4-week change (in relation to baseline)			
Six-minute walk distance (meters), mean ±SD	-11.2 ±72.0	-72.5 ±129.0	<0.01
8-week change (in relation to baseline)			
Six-minute walk distance (meters), mean ±SD	+17.0 ±84.0	-8.8 ±74	0.047

*SD = standard deviation

Table 2.4 Supplementary Table 1S. Descriptive statistics of the main variables stratified by original source study.

	Study 1 (n=42)	Study 2 (n=79)			Study 3 (n=64)		
	P	P	C	p value	P	C	p value
	n = 42	n = 39	n = 40		n = 32	n = 32	
Age (years), mean ±SD†	67.4 ± 11	66.5 ± 13.5	66.0 ± 9.0	0.859	72.5 ± 8.8	67.4 ± 11.0	0.039
Male, n (%)	22 (54)	21 (55)	28 (70)	0.242	27 (84)	18 (56)	0.64
Body mass index (kg/m^2), mean ±SD†	27.5 ± 4	26.8 ± 4.6	28.4 ± 4.2	0.111	27.7 ± 4.0	28.8 ± 4.4	0.268
American Society of Anesthesiologists score, n (%)				0.934			0.321
I-II	34 (81)	30 (77)	29 (73)		20 (63)	17 (53)	
III-IV	8 (19)	9 (23)	11 (27)		12 (37)	15 (47)	
Laparoscopic approach, n (%)	34 (81)	35 (89)	32 (80)	0.348	27 (84)	21 (65)	0.541
Colonic resection, n (%)	28 (66)	23 (59)	21 (53)	0.652	23 (72)	22 (69)	0.566
New stoma, n (%)	15 (36)	13 (33)	11 (28)	0.630	4 (13)	4 (13)	1.0
Baseline 6MWD* (meters), mean ±SD†	422 ± 87	416.9 ± 118	424.3 ± 83	0.748	447.3 ±109	450.6 ± 107	0.902
Length of Hospital Stay (day), median [IQR] §	4 [3-6]	4 [3-5]	4 [3-5]	0.159	3 [3-5]	3 [2-4]	0.154

P= prehabilitation group, C= control group, *6MWD= six-minute walk distance, †SD = standard deviation, §IQR = interquartile range.

2.8 Figures

Figure 2.1 The trajectory of the changes in functional capacity through the perioperative period in the prehabilitation and the control groups. Error bars represent the 95% confidence interval. 6MWD = six-minute walk distance.

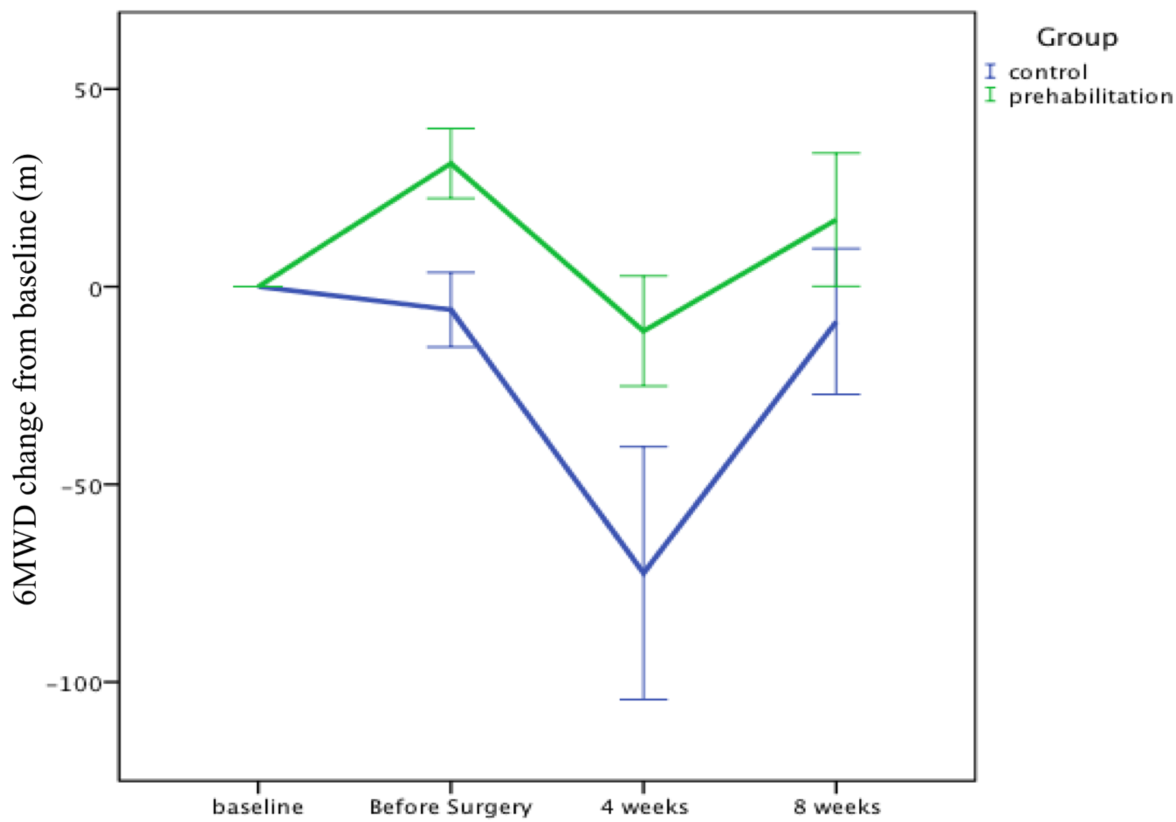
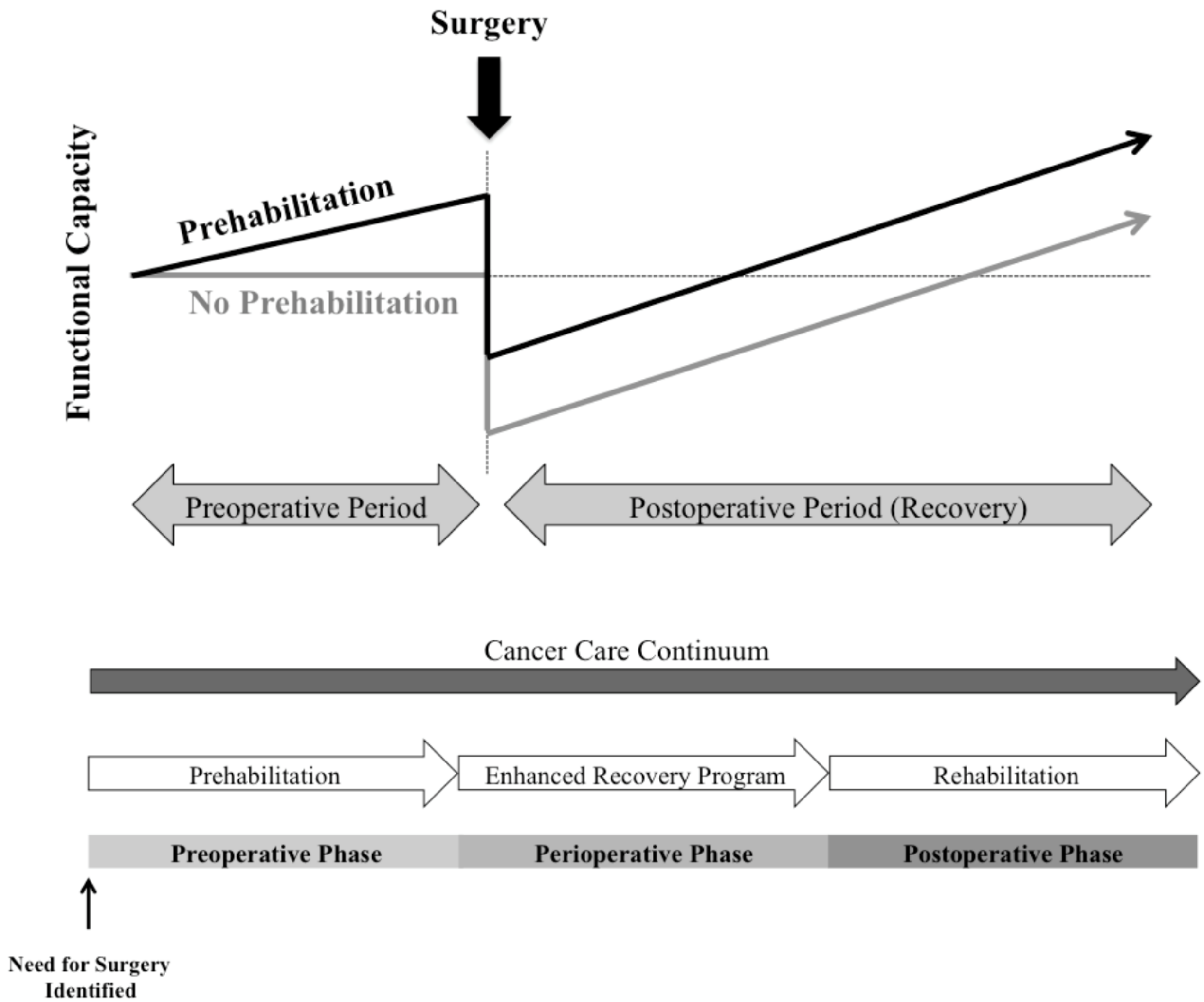


Figure 2.2 Prehabilitation in a continuum of cancer care



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Preface to chapter 3

The previous chapter provides the proof of concept of the efficacy of prehabilitation on optimizing perioperative functional status. This knowledge may have valuable application in older and unfit patients.

Poor physical status is a sign of reduced physiological reserve and impaired ability to compensate for alteration in homeostasis.[1] As a result, even minor stressors cause substantial decline in health status with detrimental effect in quality of life. Not surprising, major surgery is a leading cause of disability and loss of independence in elderly, accounting for new or worsening disability which persists for months.[2] Moreover, perioperative morbidity remains largely clustered in this high-risk population, which makes the availability of effective treatment for such patients crucial.[3]

Considering the increased demand for surgery from an aging population, and their reduced tolerance to treatment, effort should be made in the attempt to target these patients. This strategy may lead to maximize treatment efficacy and optimize resource utilization.

Therefore, after providing supporting data on prehabilitation in general surgical population in chapter 2, the following step consists in testing if prehabilitation could sustain a clinical benefit in patients who would need it the most. Thus, a retrospective analysis of our interventional cohort was conducted, aiming at establishing whether less-fit patients would benefit to a greater extent from prehabilitation compared to patients with no functional impairment.

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CHAPTER 3

Patients with poor baseline walking capacity are most likely to improve their functional status with multimodal prehabilitation

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3.1 Abstract

Background

Evidence suggests that multimodal prehabilitation programs comprising physical activity, nutritional and anxiety coping interventions can improve functional recovery after colorectal cancer surgery; however, such programs may be more clinically meaningful and cost-effective if targeted to specific sub-groups. This study aimed to estimate the extent to which patients with poor baseline functional capacity improve their functional capacity.

Methods

Data of 106 participants enrolled in a multimodal prehabilitation program before colorectal surgery were analyzed. Low baseline functional capacity was defined as a 6-minute walking test distance (6MWD) below 400 meters. Participants were categorized as higher fitness (6MWD ≥400 meters, n=70) or lower fitness (6MWD <400 meters, n=36). Changes in 6MWD over the preoperative period, 4 weeks and 8 weeks after the operation were compared between groups. Secondary outcomes included patient-reported physical activity and health status, postoperative complications, length of stay and readmissions. Less-fit patients were then compared with subjects in the rehabilitation arm of the original studies who had a baseline 6MWD < 400 meters.

Results

Participants with lower baseline fitness had greater improvements in functional walking capacity with prehabilitation compared to patients with higher fitness (+46.5 (SD 53.8) m vs. +22.6 (SD 41.8) m, p=0.012). At 4 weeks postoperatively, patients with lower baseline fitness were more likely to be recovered to their baseline 6MWD than those with higher fitness (74% vs 50%, p=0.029). There were no differences in secondary outcome. Less-fit patients had a higher improvement through all the preoperative period compared to the control group.

Conclusions

Patients with lower baseline walking capacity are more likely to experience meaningful improvement in physical function from prehabilitation before and after colorectal cancer surgery.

3.2 Background

Colorectal cancer is expected to continue to increase as population ages.[1] After colorectal operation, postoperative complications occur in >1 in 4 patients [2] and, even in the absence of complications, surgery is associated with a 20-40% reduction in functional capacity.[3] Especially in the elderly, functional recovery may take up to 6 months, and some patients never return to baseline functioning.[4] This prolonged or incomplete recovery poses a significant health care burden for patients and caregivers and increases time away from work, leisure, family and social activities.[5]

Impaired preoperative physical and morbid conditions are independent factors related to poor operative outcome.[6] Poor cardiorespiratory fitness measured by the gold standard cardiopulmonary exercise testing is associated with increased risk of morbidity.[7] Tests of functional exercise capacity, including the six-minute walk test (6MWT), which measures the distance walked in six minutes (6MWD), correlate with formal exercise testing and also predict complications after colorectal surgery.[8]

Traditionally, interventions to decrease complications and improve functional recovery focus on in-hospital or postoperative care. Actually, the preoperative period may represent a salient opportunity to increase physiological reserve in anticipation of the operative stress, an approach termed “prehabilitation”.[9]

We reported the results of a pilot study[10] and a randomized controlled trial[11] comparing a multimodal prehabilitation intervention, including aerobic and resistance exercise, nutritional counselling and supplementation with whey protein, and anti-anxiety strategies, with the same program begun postoperatively (rehabilitation). A 4-week prehabilitation program in colorectal cancer improved the primary outcome of walking capacity preoperatively and postoperatively; however, this study included patients with a wide range of baseline fitness levels.

As the prehabilitation intervention is resource intensive, targeting at-risk populations would be an attractive strategy to increase its effectiveness. We hypothesized that patients with poor functional exercise capacity would derive the most benefit from prehabilitation. The objective of this study was to estimate the extent to which patients with poor baseline walking capacity (defined as 6MWD <400 meters) benefit from a multimodal prehabilitation program compared to those with higher baseline walking capacity and to determine whether the changes achieved in the preoperative period would continue to be present during the postoperative period. Furthermore, subjects in the interventional group were compared to those in the control groups of the original studies.

3.3 Materials and Methods

Subjects

We re-analyzed the data of 106 participants from the intervention arms of one cohort study [10], one randomized controlled trial (RCT)[11] and one ongoing RCT (ethics approval code GEN11-004). As a control group, we reanalyzed data from participants in the rehabilitation group of the same studies. All participants were adults scheduled for elective colorectal cancer resection at a single institution (Montreal General Hospital, McGill University Health Centre, Montreal, Quebec, Canada) from November 2011 to August 2014. Patients with poor English or French comprehension and premorbid conditions that contraindicated exercise (severe cardiovascular and neuromuscular diseases, only 3 patients) were excluded. All trials were approved by the Research Ethics Board of the McGill University Health Centre, Montreal, Canada.

Study design

Participants of the prehabilitation arms of the original studies were categorized into 2 groups with respect to their baseline walking capacity as measured by the 6MWT, a validated indicator of recovery in colon operation. We defined low functional capacity as a 6MWD less than 400 meters (gait speed below the average of 1.1 m/s) as a cut-off. In older adults, the inability to walk this distance or achieve this gait speed is associated with a higher risk of mortality, cardiovascular disease, limitation in mobility and disability. [12-14] Furthermore, a 6MWD less than 409 m is predictive of a peak oxygen uptake (peak VO_2) below 15 $ml \cdot kg^{-1} \cdot min^{-1}$ measured with cardiopulmonary exercise testing, the gold standard reference for the evaluation of physical fitness.[15] A peak $\dot{V}O_2$ less than this threshold is a well-validated independent predictor of both postoperative morbidity and decreased mid-term survival after elective major surgery.[16-18]

Therefore, the cut-off of 6MWD of 400 m was chosen as an indicator of a level of physiologic reserve less than which mobility and independency are limited and operative complications are more frequent. Patients in group A had a baseline 6MWD above 400 meters, and those in group B had a baseline 6MWD less than 400 meters.

To investigate the role of prehabilitation in improving functional capacity in less-fit patients, changes in 6MWD were compared between participants in Group B and subjects in the rehabilitation arm of the original studies who had a baseline 6MWD less than 400 m (Group C).

Prehabilitation program

All 3 trials investigated the effect of multimodal prehabilitation (exercise, nutrition counselling and protein supplements, and anti-anxiety techniques) on perioperative functional capacity; all the subjects considered in this analysis underwent a similar prehabilitation program, which has previously been described in detail.[19]

Briefly, a certified kinesiology’s assessed and trained each participant following the guidelines of the American College of Sports Medicine.[20] The home-based training alternated aerobic, resistance, and flexibility exercises, up to 50 minutes, 3 times per week. Aerobic exercise (bicycle, walk, swimming) was prescribed based on the rate of perceived exertion measured during the baseline 6MWT. Resistance training exercises targeting major muscle groups were performed using elastic bands.

A registered dietitian estimated macronutrient and energy intake from each participant's food record with validated food exchange lists and composition tables.[21] Whey protein supplementations were prescribed to achieve a total protein intake of 1.2 g/kg/d as per recommendation of the European Society for Clinical Nutrition and Metabolism.[22] A trained psychologist instructed all patients in techniques aimed at decreasing anxiety together with breathing exercises. Patients were also given a compact disc with instructions on how to perform these exercises at home 2 to 3 times per week.

All patients were cared for in an established Enhanced Recovery Program, including multidisciplinary counseling, early return to oral nutrition and mobilization, multimodal analgesia, daily care plans, standardized drain management, and a target discharge of 3 days.[5]

Measures

The primary outcome measure was the 6MWD as measure of functional capacity reflective of activities of daily living. The 6MWT measures the distance that a patient can briskly walk on a flat, hard surface over a period of 6 min (6MWD). It integrates all components of physical activity including balance, speed, muscle force and endurance.[23] Patients could slow down, stop and rest as necessary, and then resume walking as soon as they were able.

Evidence is available supporting the validity of the 6MWT as a measure of postoperative recovery in patients undergoing colorectal operations.[24, 25] The minimal important difference for the 6MWD (i.e. "the smallest change in an outcome measure perceived as beneficial by patients or physicians") has been estimated at 14 m (95% CI 9-18m) in colorectal operation populations; we considered 20m to be a meaningful change.[26] Percentages of age- and gender-specific norms are calculated from the predicted distance using a well validated equation for Canadian population.[27]

Self-reported physical activity was assessed using the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire, a 41-item questionnaire designed to evaluate the effectiveness of interventions aimed at increasing physical activity in the elderly.[28] Subjects report the time spent doing a variety of activities, from which total caloric expenditure per kilogram per week is estimated. Evidence is available supporting its validity as a measure of recovery after abdominal surgery.[29]

The health-related quality of life was assessed using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)[30], a reliable and valid generic index of perceived health status. It incorporates behavioral functioning, subjective well-being, and perceptions of health by assessing 8 health items on a 0–100 scale. Two summary scores can be derived: the physical component summary (PCS) and mental component summary (MCS) scores. A greater score on the SF-36 subscales or component summary measures indicates a better quality of life. Evidence is available supporting its validity as a measure of recovery after colorectal surgery.[31]

To encourage and measure compliance to the program, patients were given a booklet including all instructions and a diary to report activities. In addition, they were contacted once a week by telephone to answer a standardized set of open-ended questions to assess compliance to the frequency, intensity, or duration of exercise, the amount of whey protein taken, and the use of the relaxation methods. Based on the information obtained through telephone and the patient diary, a percentage for compliance was calculated for each component of the program and equally weighted in the determination of overall compliance.

All measurements were taken at 4 weeks before the operation (baseline), the day before the operation (preop), and at 4 weeks and 8 weeks after the operation (4-week and 8-week). Thirty-day postoperative complication rates were graded by severity using the Clavien-Dindo classification.[32]

Statistical analysis

Statistical analyses were performed with Stata 12 (StataCorp LP, College Station, TX). Normality of data distribution was verified visually using histograms. Changes in 6MWD, self-reported physical activity (CHAMPS) scores, SF-36 PCS scores and SF-36 MCS scores over the preoperative period (day of operation – baseline values), at 4 weeks (4-week – baseline values), and at 8 weeks after the operation (8-week – baseline values) were calculated and compared between groups. A complete case analysis without imputation of missing values was conducted given the low rate of missing data for our main outcome of interest (6MWD). Continuous data with normal distribution were reported as mean ± standard deviation (SD) and compared using independent Student t test. Continuous data with non-normal distribution were reported as median [interquartile range (IQR)] and compared using Wilcoxon rank-sum test. Categorical variables were reported as frequency (%) and compared using Fisher exact test.

3.4 Results

Of the 106 participants enrolled in the multimodal prehabilitation program, 70 (66%) had baseline 6MWD above 400 meters (Group A) and 36 (34%) had baseline 6MWD less 400 meters (Group B). The demographic characteristics of these patients are described in Table 1. Participants in Group B were older and had lesser scores of both baseline, self-reported physical activity and baseline physical health-related quality of life. As expected, 6MWD and percent predicted 6MWD were also significantly less in this group. Other demographic and operative characteristics were similar between groups.

During the preoperative prehabilitation period, participants in group B made greater improvements in their 6MWD compared to patients in Group A (+46.5 ±53.8 m vs +22.6 ±41.8 m, p=0.012) (Table 2); 13 patients (36%) in the low fitness group increased their 6MWD to >400m after prehabilitation. At 4 weeks after the operation, patients in Group B were on average recovered to their baseline (prior to prehabilitation) 6MWD (+4.6 ± 59.9 m), while these in Group A tended to remain below their baseline (-22.5 ±77.1 m) (p=0.086).

At 8 weeks after the operation, patients in both groups had achieved a 6MWD that was greater than their baseline 6MWD, but the difference was greater in the Group B patients (+53.0 ±50.4 m vs +12.6 ±59.8 m, p=0.002). Changes in self-reported physical activity (CHAMPS) scores, SF-36 PCS scores and SF-36 MCS scores were similar between the groups at all time periods (Table 2).

The proportion of participants with clinically important improvements (>20m) in 6MWD before surgery was 72% in Group B and 51% in Group A (p=0.06) (Table 3). At 4 weeks after operation, the proportion of patients recovered to baseline 6MWD (within 20 m) was greater in Group B (74% vs 50%, P =0.029). By 8 weeks after surgery, the proportion recovered to baseline 6MWD was similar in the 2 groups. The compliance to the multimodal program of the 3 studies ranged from 70 to 98% in the preoperative period, 53 to 72% at 4 weeks, and 53 to 82% at 8 weeks. There were no differences in clinical outcomes between groups, including hospital length of stay, complications, readmissions and mortality (Table 4).

Among participants enrolled in the control arm of the original studies (rehabilitation), 23 patients had baseline 6MWD less than 400 meters (Group C). No differences were found in baseline characteristics, which included age (Group B 74.7 + 12.8 years vs Group C 71.7 + 7.9 years), body mass index (27.2 + 4.3 vs 29.4), sex (male 47% vs female 56%), cancer stage (stage 3–4, 39% vs 17%), and type of operation (rectal operation, 39% vs 32%) (P ≥ 0.21 each). Subject in Group B achieved a greater preoperative improvement compared to this control population (+46.5 ±53.8 m versus -7.5 ±50.5 m, p <0.01) (Table 5). In the same way, participants in Group B had a greater functional improvement compared to Group C at 4 weeks (+4.6 ±59.9 m versus -29.2 ±66.3, $p=0.065$) and at 8 weeks (+53.0 ±50.4 m vs. +8.3 ±52.6 m, $p=0.004$).

3.5 Discussion

The findings of the present study suggest that for participants enrolled in a multimodal prehabilitation program, those with low baseline functional capacity make greater improvements in functional walking capacity preoperatively and that these changes persist in the early postoperative period. Meaningful improvements from baseline were seen in almost three-quarters of patients with a lesser walking capacity after a 4-week period of prehabilitation.

This supports the hypothesis that patients with less reserve preoperatively have more to gain from prehabilitation efforts aimed at improving physical, nutritional, and mental conditions before an operation compared to patients with greater baseline functional capacity. Furthermore, when we compared changes in walking capacity between less fit patients in the prehabilitation group versus those in the rehabilitation/control group, multimodal prehabilitation shown a positive impact throughout the entire perioperative period.

Based on the understanding that poor baseline functional status and physical performance increase the risk of postoperative complications, evaluation of functional capacity before major operations is recommended for preoperative risk stratification. We chose the 6MWD of less than 400 m to define at-risk patients, which corresponds approximately to a peak VO2 of less than 15 ml O_2 Kg^{-1} min^{-1} measured with cardiopulmonary exercise testing. Using this cut-off, we identified 2 populations with different baseline functional reserves (485.4 +60.9 m vs 308.3 +75.8 m).

Less fit patients were older and had more comorbidities and less self-reported physical activity; but their functional capacity increased by an average of 15% during the 4-week, multimodal prehabilitation program, 3 times greater than the other group. Seventy-two percent of patients with poor baseline physical fitness experienced significant increases in functional walking capacity during the preoperative period, while the others either decreased or remained at the baseline. This group achieved significant improvements even when compared with a control group with similar functional status.

For the elderly, the ability to walk is related to the ability to live in the community and to move without assistance,33 and it must be considered a central operative outcome in this population. As an example, a standard city road (18.3 m width with 0.86 m/s walking speed required)34 would be crossed in time by the majority of our less-fit participants. The less-fit patients increased their 6MWD during the preoperative period by an average of 46 m and therefore their walking speed to 0.98 m/s. At 8 weeks after operation, the increase was of 53 m. This observation supports the role of prehabilitation in helping these patients resume their daily community activities, such as shopping or returning to work after an operation.

Less-fit patients increased their 6MWD preoperatively by an average of 46.5 m, thus approaching a reasonable level of functional capacity. Looking at Group B in detail, only 36% of the less-fit patients increased their 6MWD to greater than the 400 m fitness threshold during the prehabilitation period. Therefore, efforts must be made to optimize even further their functional capacity, possibly by supervising the exercise sessions and monitoring adherence to the protocol.

Attempts were made in these studies to monitor compliance to the 3 elements of the prehabilitation program using self-reported assessment; the overall adherence was >70%, although the majority found it easier to comply with the ingestion of protein supplements. Clearly, efforts must be made to obtain objective measures of adherence to the exercise sessions, and future studies should evaluate the use of interactive sensors capturing physical activity.

In the present study, we wanted to confirm the value of prehabilitation as a way to enhance functional capacity in patients with poor functional reserve before an operation. Because poor functional reserve could be a contraindication for major interventions,[35] prehabilitation could be not only used to improve postoperative outcomes but also to increase access to operations for the elderly. As our population gets older and the incidence of cancer increases with age, this approach could be a key concept in the near future.

All 3 studies were conducted following the implementation of an enhanced recovery program at our institution. Perioperative care was guided by published standardized, evidence-based guidelines following a consensus review on best care for patients undergoing colorectal operations. This standardized approach to clinical care facilitated the introduction of the prehabilitation component within the enhanced recovery process of our patients. The 3 or 4-day duration of hospital stay in both groups reflects the standard duration at our institution and compares favorably with published data.

Despite differences in 6MWD with prehabilitation, improvements were not reflected in patient-reported measures, such as CHAMPS or SF-36. With regard to the self-reported physical activity (CHAMPS), the lack of difference may reflect that the less-fit group, being older, did not need to exert a great deal of physical activity to increase their functional walking capacity as they started well below the 60% of the predicted 6MWD. The physical and mental components of the SF-36 were also not different at any point, which could be explained by the fact that the 6MWT only measures functional walking capacity and no other aspects of health.

No difference was observed between the 2 prehabilitation groups in clinical outcomes, such as duration of hospital stay and 30-day complication rate, but this study was underpowered to detect any potential effect of prehabilitation on these outcomes. Because poor baseline exercise capacity is a risk factor for complications, the finding of no difference in complications between the groups may support a protective effect of prehabilitation. Furthermore, we classified postoperative complications according to the Clavien-Dindo grading which, in spite of being well validated in numerous fields of surgery, may have limited sensitivity to detect between-group differences, as it only takes into account the most severe complication occurred.

While our results are preliminary and require confirmation in larger, randomized studies, they may provide proof of concept that prehabilitation can help unfit patients become stronger before an operation and have a buffer to better withstand the stress of an operation. Future directions of research activity in this group should also focus on identifying strategies to motivate the 30% of patients who did not improve with the multimodal program. Supervised training and personalized programs could be possible modalities of future development within the continuum of cancer care.

3.6 Tables

Table 3.1 Demographic and surgical characteristics of patients with baseline 6MWD* below and above 400 meters.

	Group A 6MWD*≥ 400 m (n=70)	Group B 6MWD< 400 m (n=36)	p-value
Age (years), mean ±SD†	65.3 ±9.6	74.7 ±12.8	<0.001
Male, n (%)	46 (66)	17 (47)	0.094
Body mass index (kg/m^2), mean±SD	27.6 ±4.6	27.2 ±4.3	0.616
American Society of Anesthesiologists score, n (%)			0.099
I-II	56 (80)	23 (64)	
III-IV	14 (20)	13 (36)	
Cancer stage, n (%)			0.849
0	3 (4)	2 (6)	
1-2	34 (49)	20 (56)	
3	30 (43)	12 (33)	
4	3 (4)	2 (6)	
Operative approach, n (%)			1.000
Laparoscopic	65 (93)	33 (92)	
Open	5 (7)	3 (8)	
Type of resection, n (%)			0.101
Colonic surgery	30 (43)	22 (61)	

Rectal surgery	40 (57)	14 (39)	
New stoma	21 (30)	10 (27)	1.000
Baseline 6MWD* (meters), mean ±SD	485.4 ±60.9	308.3 ±75.8	<0.001
Percent predicted 6MWD, mean ±SD	71.3 ±8.8	48.1 ±10.7	<0.001
Baseline self-reported physical activity (CHAMPS‡ kcal/kg/week), median [IQR]§	35.4 [17.5 to 62.2]	11.2 [5.2 to 21.7]	<0.001
Baseline SF-36‖ Physical Component Summary Score, median [IQR] §	53.2 [46.1 to 57.5]	44.3 [39.4 to 51.6]	0.043
Baseline SF-36 Mental Component Summary Score, median [IQR] §	51.9 [44.7 to 58.8]	50.3 [43.9 to 59.9]	0.290

*6MWD= six-minute walk distance, †SD = standard deviation, ‡CHAMPS = Community Healthy Activities Model Program for Seniors, §IQR = interquartile range, ‖SF-36 = 36-Item Short Form Health Survey.

Missing data: CHAMPS =9, SF-36 Physical Component=24, SF-36 Mental Component= 22.

Table 3.2 Changes in self-reported physical activity, physical function and mental function in patients with baseline 6MWD* greater than and less than 400 meters.

	Group A 6MWD* ≥ 400 m (n=70)	**Group B** 6MWD< 400 m (n=36)	p-value
Preoperative change (in relation to baseline)			
6MWD (meters), mean ±SD†	+22.6 ±41.8	+46.5 ±53.8	0.012
Self-reported physical activity (CHAMPS‡, kcal/kg/week), median [IQR] §	+9.5 [-2.1 to 39.2]	+7.0 [-2.5 to 20.0]	0.397
SF-36‖ Physical Component Summary Score, median [IQR]	+1.3 [-0.7 to 5.2]	+0.5 [-2.2 to 6.1]	0.744
SF-36 Mental Component Summary Score, median [IQR]	+1.9 [-1.6 to 6.9]	+1.5 [-3.0 to 3.6]	0.406
4-week change (in relation to baseline)			
Six-minute walk distance (meters), mean ±SD	-22.5 ±77.1	+4.6 ±59.9	0.086
Self-reported physical activity (CHAMPS, kcal/kg/week), median [IQR]	-3.6 [-25.2 to 28.4]	-0.7 [-9.0 to 12.4]	0.621
SF-36 Physical Component Summary Score, median [IQR]	-8.0 [-13.3 to 2.0]	-2.0 [-14.8 to 6.0]	0.536

SF-36 Mental Component Summary Score, median [IQR]	-0.6 [-8.8 to 5.2]	-4.0 [-10.8 to 6.0]	0.714
8-week change (in relation to baseline)			
Six-minute walk distance (meters), mean ±SD	+12.6 ±59.8	+53.0 ±50.4	0.002
Self-reported physical activity (CHAMPS, kcal/kg/week), median [IQR]	+3.3 [-13.6 to 31.7]	+0.7 [-7.4 to16.4]	0.788
SF-36 Physical Component Summary Score, median [IQR]	+2.2 [-2.7 to 8.0]	+0.3 [-5.8 to 8.4]	0.575
SF-36 Mental Component Summary Score, median [IQR]	+4.9 [-2.5 to 11.0]	+2.7 [-7.0 to 8.2]	0.375

[*]6MWD= six-minute walking distance, [†]SD = standard deviation, [‡]CHAMPS: Community Healthy Activities Model Program for Seniors, [§]IQR = interquartile range, [||]SF-36 = 36-Item Short Form Health Survey.

Missing preoperative data: CHAMPS =13, SF-36 Physical Component=28, SF-36 Mental Component= 26.

Missing 4-week data: 6MWD=9, CHAMPS =20, SF-36 Physical Component=30, SF-36 Mental Component= 29.

Missing 8-week data: 6MWD=16, CHAMPS =27, SF-36 Physical Component=40, SF-36 Mental Component= 38.

Table 3.3 Clinically important changes in the 6MWD* in relation to baseline.

	Group A 6MWD≥ 400 m (n=70)	Group B 6MWD< 400 m (n=36)	p-value
Proportion of patients with preoperative improvement in 6MWD* (greater than 20 meters), n (%)	36 (51)	26 (72)	0.060
Proportion of patients returned to baseline 6MWD at 4-weeks after the operation (within 20 m), n (%)	33 (50)	23 (74)	0.029
Proportion of patients returned to baseline 6MWD at 8-weeks after the operation (within 20 m), n (%)	47 (76)	25 (89)	0.166

6MWD= six-minute walking distance

Missing 4-week data = 9

Missing 8-week data = 16

Table 3.4 Postoperative clinical outcomes of patients with baseline 6MWD* greater than and less than 400 m.

	Group A 6MWD*≥ 400 m (n=70)	Group B 6MWD< 400 m (n=36)	p-value
Patients with at least 1 complication within 30 days of surgery, n (%)	23 (33)	12 (33)	1.000
Grade of most severe complication (Clavien-Dindo classification), n (%)			0.237
Grade I	11 (16)	7 (20)	
Grade II	6 (9)	3 (7)	
Grade III	5 (8)	0 (0)	
Grade IV	0 (0)	1 (2)	
Grade V	0(0)	1 (2)	
30-day readmission rate, n (%)	7 (10)	6 (17)	0.358
30-day mortality rate, n (%)	0 (0)	1 (3)	0.340
Length of stay, median [IQR]†	3.5 [3-6]	4 [3-5]	0.626

*6MWD= six-minute walking distance, †IQR = interquartile range

Table 3.5 Changes in physical function in patients with baseline 6MWD* less than 400 m underwent either a prehabilitation intervention (Group B) or not (Group C).

	Group B Intervention (n=36)	Group C Control (n=23)	p-value
Preoperative change (in relation to baseline)			
6MWD (m), mean±SD†	+46.5±53.8	-7.5 ± 50.5	<0.001
4-week change (in relation to baseline)			
6MWD (m), mean±SD	+4.6±59.9	-29.2 ± 66.3	0.065
8-week change (in relation to baseline)			
6MWD (m), mean±SD	+53.0±50.4	+8.3 ± 52.6	0.004

*6MWD= six-minute walking distance, †SD = standard deviation

Missing 4-week data: 6MWD=8.

Missing 8-week data: 6MWD=10.

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Preface to chapter 4

In the previous chapter, prehabilitation appears feasible and promising to contrast surgical-related functional decline in a high-risk population. As stated in Chapter 1, our hypothesis is that prehabilitation would be beneficial not only to prevent or attenuate functional decline, but also its consequences.[1] A main adverse surgical outcome associated with poor physical fitness is higher rate of postoperative complications.[2] Thus, in the attempt to further expand the knowledge of prehabilitation, this chapter focuses on postoperative morbidity.

For decades, literature on quality improvement in surgical oncology has focused on reducing postoperative complications, given their impressive burden for patients and society. Despite continuous advances in perioperative care, one in three patients continues to experience severe complication after colorectal surgery. Targeting postoperative morbidity would be an efficient strategy to simultaneously improve quality of care for patients and reduce health costs.

Since low functional capacity and poor surgical outcome have a well-established relationship in perioperative medicine,[2] a proactive role of preoperative conditioning on risk reduction has a strong rationale. In this study, using our cohort of patients followed over 5 years, I tested the hypothesized of a protective effect of improved preoperative physical status on severe complication after elective colorectal surgery for cancer.

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CHAPTER 4

The impact of improved functional capacity before surgery on postoperative complications: a study in colorectal cancer.

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Disclosure of interest

Authors report no conflicts of interest.

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4.1 Abstract

Background

Poor functional capacity (FC) is an independent predictor of postoperative morbidity. However, there is still a lack of evidence as to whether enhancing FC before surgery has a protective effect on postoperative complications. The purpose of this study was to determine whether an improvement in preoperative FC impacted positively on surgical morbidity.

Methods

This was a secondary analysis of a cohort of patients who underwent colorectal resection for cancer under Enhanced Recovery After Surgery care. FC was assessed with the 6-min walk test, which measures the distance walked in 6 min (6MWD), at 4 weeks before surgery and again the day before. The study population was classified into two groups depending on whether participants achieved a significant improvement in FC preoperatively (defined as a preoperative 6MWD change ≥19 meters) or not (6MWD change <19 meters). The primary outcome measure was 30-day postoperative complications, assessed with the Comprehensive Complication Index (CCI). The association between improved preoperative FC and severe postoperative complication was evaluated using multivariable logistic regression.

Results

A total of 179 eligible adults were studied: 80 (44.7%) improved in 6MWD by ≥19 m preoperatively, and 99 (55.3%) did not. Subjects whose FC increased had lower CCI (0 [0-8.7] vs 8.7 [0-22.6], p=0.022). Furthermore, they were less likely to have a severe complication (adjusted OR 0.28 (95% CI 0.11-0.74), p = 0.010), and to have an ED visit.

Conclusion

Improved preoperative FC was independently associated with lower risk of severe postoperative complications. Further investigation is required to establish a causative relationship conclusively.

4.2 Introduction

Colorectal cancer is the third most common cancer and the second leading cause of cancer death in North America,[1] and surgery is the only curative approach. Despite recent advances in perioperative care,[2] adverse events after elective colorectal surgery affect more than one in three patients.[3] Complications negatively interfere with long-term quality of life,[4] timing of adjuvant chemotherapy,[5] hospital costs,[6] and survival.[7,8] The great burden associated with surgical morbidity prompts research efforts to be directed toward prevention strategies.[9]

Aiming to optimize physical fitness before and after surgery, a preoperative multi-disciplinary intervention called prehabilitation was designed, in which dietary optimization and anti-anxiety strategies are combined with exercise.[10] In the last years, growing evidence has shown a positive impact of prehabilitation on perioperative functional capacity (FC) and postoperative complications.[11,12]

The rational underpinning prehabilitation relies on the potential protective effect of improved physical status toward surgical insults. In fact, poor FC is a well-recognized predictor of higher incidence and severity of postoperative complication.[13,14] Thus, FC has been targeted for specific assessments and interventions aiming at the reduction of postoperative morbidity.[10,15] Nonetheless, although the effect of FC as ‘static’ predictor is established, a direct relationship between significant change in physical status before surgery and postoperative complications has yet to be shown. This represents a main knowledge gap in the fast-growing field of prehabilitation and perioperative medicine, that should be addressed as a research priority.[9]

Therefore, the purpose of the present study was to determine whether an improvement in FC before surgery was associated with a lower severity of complications after elective colorectal resection for cancer.

4.3 Methods

Patient Cohort

Patients of our historical cohort were originally recruited for clinical trials on prehabilitation, from October 2010 to August 2015.[16-18] Eligible participants were 18 years of age or older scheduled for bowel resection for non-metastatic colorectal cancer. Exclusion criteria were morbid conditions that contraindicated exercise, severely impaired ambulation, simultaneously participation to a pharmacotherapy trial, and inability to provide informed consent. A detailed description of the original intervention is elsewhere reported.[19] Briefly, following the initial assessment by kinesiologists, nutritionists and psychology-trained personnel, subjects participated in a structured multimodal intervention which included aerobic and resistance exercise, anti-anxiety techniques, nutrition counselling and whey protein supplements, started either 4 weeks before surgery (prehabilitation group) or after surgery (control group). All studies were conducted at a single research center (McGill University Health Centre, Montreal, Quebec, Canada), and used similar methods, outcome measures and time of assessment. All participants received similar standardized perioperative care, based on the Enhanced Recovery Program established in this institution since 2008.[20] The studies were approved by the McGill Research Ethics Board (McGill University Health Centre, Montreal, Quebec, Canada), and a written informed consent was obtained from all subjects.

Measures

Anthropometric measurements and functional testing were conducted using standardized evaluation techniques,[21] and performed by blinded assessors. FC was assessed with the 6-min walk test (6MWT), in which participants were asked to walk back and forth along a flat hallway over 6 minutes, and the total distance covered (6-min walking distance, 6MWD) was recorded.[21] The 6MWT was performed at four weeks before surgery (Baseline), and on the workday before surgery (Preoperative). Change in 6MWD was defined as the difference between the preoperative and the baseline assessment. The 6MWT was chosen because it is easy to administer, well tolerated, and reflective of cardiorespiratory fitness and daily-living activities, especially in older adults. It is a reliable measure of FC, and it is used to evaluate the impact of interventions in several settings, including colorectal surgery.[22] The minimal clinically important difference (MCID) for 6MWD, defined as "the smallest change in an outcome measure perceived as beneficial by patients or physicians", is estimated at 14 m (95% Confidence Interval 9-18 m).[23] A 6MWD improvement by at least 19 m, above the upper limit of the 95%CI for the MCID, was therefore considered a meaningful change in FC in the present study.

Outcome Measures

The outcome was complications occurring within 30 days after the operation, graded by using the Comprehensive Complication Index (CCI).[24] Complications were predefined (Appendix A), and clinical charts were reviewed by two blinded and independent physicians. For each patient, complications were graded using the CCI®-Calculator (http://www.assessurgery.com), that sums all postoperative complications into a single number from 0 to 100. Length of primary hospital stay, 30-d emergency department visits, and 30-d hospital readmissions were also recorded from the medical record.

Study Design

This is a secondary analysis of prospectively collected data of 186 patients of our historical cohort.[25] This study was meant to assess the relationship between significant change in functional capacity before surgery and severity of complications in the postoperative period. Participants were categorized into two groups according to whether or not their 6MWD increased before surgery (change from baseline to preoperative of <19m vs. ≥19m). As the primary exposure variable was an improvement in preoperative FC, all participants of our historical cohort were included, irrespective of group assignment within the original studies. Sample size and statistical power were calculated in the individual protocols. For this analysis, the power is above conventional threshold of 80% to detect the primary outcomes using bionomical GEE models.

Statistical Analysis

Descriptive statistics such as mean, confidence intervals (CI), median, interquartile ranges [IQR], and frequencies were presented for patient and surgical characteristics. These data were compared between groups, using Chi-square or Fisher's exact test for categorical data, and Student's t-test or Mann–Whitney test for continuous data, based on the data distribution.

In order to test the hypothesis that improved FC is associated with a reduction of the severity of complications after surgery, the CCI is presented both as a continuous and a dichotomous variable, using upper quartile as the cutoff for defining major/severe complication, as described in the literature.[26] Association between gain in the 6MWD and 30 d post-surgical severe complications were tested using logistic regression, and univariable and multivariable logistic regression are presented. Multivariable logistic regression was adjusted for confounding factors known to affect postoperative outcomes such as age, gender, BMI, ASA, study, laparoscopic surgery, tumor stage and presence of rectal tumor.[27] Odds ratios and 95% confidence intervals are presented. All possible interactions were verified during the analysis.

4.4 Results

Participants and surgical characteristics

Among 186 patients of our cohort, 179 (96%) were eligible for this analysis: seven subjects were excluded because of missing data regarding 6MWD (lost at follow-up, n=1) or complications (charts could not be located, n=6).

Baseline characteristics are shown in Table 1. Eighty subjects (45%) increased their 6MWD by ≥19 meters before surgery (group ≥19m), whereas 99 participants (55%) did not (group <19m). There were no significant differences between the two groups in demographic, clinical characteristics or self-reported baseline physical activity. Nonetheless, subjects in the ≥19m group were likely to have a lower walking capacity at baseline (6MWD, 416 (391-440) m versus 443 (424-462) m, p=0.077).

Of our cohort, 111 subjects (62%) had prehabilitation and 68 (38%) were assigned to the control group. In the preoperative period, compliance to the multimodal program of the three studies ranged from 70 to 98%, as reported in each study.[16-18] Surgical characteristics are described in Table 2. There were no differences in the complexity of surgery or intraoperative events.

The impact of functional improvement on complications

Of the study population, 33 (18%) patients had severe complications, defined as CCI >22.6. Overall 30-day complication severity was lower in the ≥19m group compared with the <19m group (CCI 0 [0-8.7] versus 8.7 [0-22.6], p=0.022) (Table 3). The proportion of patients with severe complications was lower in the ≥19m group than the <19m group (25/99 (25%) vs 8/80 (10%), p=0.011).

The multivariable regression analysis revealed that improvement in FC was a strong independent predictor of severe complications (Table 4).[28] The risk of having more severe complications was 71% less likely among those patients who improve their walking capacity in the preoperative period (adjusted OR 0.29 (95% CI 0.11-0.75), p = 0.011).

Secondary outcomes

Patients in the >19m group had less hospital visits after discharge (10 (13%) vs. 25 (25%), p=0.038). There were no significant differences in duration of hospital stay, numbers of readmissions, and in types of complications (Table 5). No patients died during this period.

4.5 Discussion

This secondary analysis shows that a preoperative improvement in functional capacity is strongly associated with lower severity of postoperative complications within 30 d after colorectal resection for cancer.

While preliminary data is mounting that prehabilitation could reduce surgical morbidity,[11,12] the main physio pathological knowledge gap that the present analysis wanted to elucidate was the role of improved preoperative physical fitness on postoperative complications. In addition, a noteworthy point is the positive impact of functional status on emergency visit after discharge. To our knowledge, this is the first study describing a direct association between a change in preoperative walking capacity and surgical morbidity, elsewhere just hypothesized.[9,11,29] We used the Comprehensive Complication Index (CCI) for grading complication, which, compared with other morbidity outcomes based on ordinal scales such as the Clavien-Dindo classification, is more sensitive in detecting treatment effect differences. The 6-min walk test (6MWT) was chosen because is a reliable measure of muscular and aerobic endurance, coordination and gait efficiency. In colorectal surgery, there is evidence supporting 6MWT as an indicator of postoperative recovery,[22] and meaningful change was estimated at 19 meters.[23] The ERAS pathway, well-established in our institution, helped to minimize the variations in postoperative care on surgical outcome. This ensures the quality of the analysis and shows that improving physical status could synergistically improve surgical outcome above and beyond enhanced recovery pathways.

Our study design has limitations that may affect both internal and external validity: retrospective analysis, nonrandomized design, data pooling, and single-center study. Thus, while we showed that improved FC is associated with low severe complication, this does not prove causality, and further investigation is required.

The biological rationale underpinning the results of the present study could be found in the protective role that exercise and nutrition play in the complex network of the stress response to surgery. The degree of preoperative functional capacity reflects the physiological reserve and the ability to meet the increased perioperative energy demands, with the goal to maintain or restore homeostasis.[29] In patients with colorectal cancer, the ability to withstand the stress of surgery may be further impaired by cancer progression, age, anxiety, comorbidities and dietary disorders.[30] Therefore, enhancing physical fitness for surgery through exercise, nutritional and psychological interventions is an attractive strategy to ‘manipulate’ the perioperative period in these patients, with the purpose of minimizing the impact on outcome and accelerating the recovery process. It is worth noting that impaired physical fitness, measured with gait speed, is one of the criteria that defines sarcopenia and frailty. These overlapping clinical entities impose a significant public health burden, which magnitude in oncologic surgery is rising as the number of older persons continues to escalate, along with cancer incidence. These syndromes are characterized by low muscle strength and/or low physical performance, and by progressive loss of functional independence. Not surprisingly, they are associated with postoperative morbidity and mortality after gastro-intestinal surgery.[31,32] This evidence further strengthens the rationale underpinning this analysis, suggesting a key role of impaired functional status in determining an unfavorable postoperative outcome. A proactive and preventive approach to this phenomenon is the mainstay of prehabilitation.

The great burden of surgery on short and long-term outcome has recently prompted research efforts to be directed toward optimization of the clinical care pathway. Moreover, increased life expectancy and better surgical and medical treatment have made it possible for a greater number of old and debilitated patients to be considered for surgical intervention. The present study deals with this new prospective and provides, with all the acknowledged limitations, innovative insight into perioperative management. Considering the growing population of frail patients, we propose to address the decreased functional reserve and resistance for stressors as targets for optimizing surgical outcome. As significant improvements in physical fitness can be achieved in a short period of time,[25] this finding provides a key rational element for prehabilitation to be integrated into oncological care.

In conclusion, this study indicates a strong association between enhanced preoperative physical status and surgical complication in colorectal cancer patients. To this extent, prehabilitation could represent a possible strategy for improving postoperative outcome.

4.6 Acknowledgments

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4.7 Tables

Table 4.1. Patient characteristics

	Preoperative 6MWD change		**p**
	< 19 m **n = 99**	**≥ 19 m** **n = 80**	
Age (years)	67.8 (65.7-69.9)	68.0 (65.2-70.7)	0.861
>75 years old, n (%)	27 (27)	25 (31)	0.621
Male, n (%)	60 (61)	53 (66)	0.553
BMI (kg/m^2)	28.2 (27.3-29.1)	27.3 (26.3-28.3)	0.353
Obesity (BMI ≥ 30), n (%)	32 (32)	28 (35)	0.751
Hemoglobin (g/dL)	13.3 [12.2-14.5]	13.6 [12.3-14.8]	0.942
Albumin (g/L)	40 [38-41]	41 [37-42]	0.304
Current smoker, n (%)	7 (7)	5 (6)	1.0
Medically treated diabetes, n (%)	20 (20)	14 (18)	0.704
Neoadjuvant chemotherapy, n (%)	15 (15)	14 (18)	0.688
Previous abdominal surgery, n (%)	56 (56)	43 (54)	1.0
ASA score, n (%)			0.672
I	9 (9)	6 (8)	
II	58 (59)	54 (67)	
III	30 (30)	19 (24)	
IV	2 (2)	1 (1)	
Charlson Comorbidity Index	3 [2-3]	2 [2-3]	0.105
CR-POSSUM physiologic score	9 [8-10]	9 [7-10]	0.494
CR-POSSUM operative severity	8 [7-11]	7 [7-11]	0.673

Tumor TNM stage			
0 – I	35 (35)	29 (36)	
II	25 (25)	27 (34)	0.582
III	33 (33)	22 (27)	
IV	6 (6)	2 (3)	
Baseline 6MWD (meters)	443 (424-462)	416 (391-440)	0.077
Physical activity (kcal/kg per week)	23.3 [10.5-53.5]	24.3 [10.0-53.0]	0.824

Values are mean (95% CI) or median [IQR], otherwise noted. Abbreviations: 6MWD, Six-minute walk distance; ASA, American Society of Anesthesiologists physical status; BMI, body mass index; CR-POSSUM, Colorectal Possum Score; TNM, Tumor Node Metastasis Classification.

Table 4.2. Operative characteristics.

	Preoperative 6MWD change		p
	< 19 m n = 99	≥ 19 m n = 80	
Procedure performed			0.697
Right hemicolectomy	30 (30)	28 (35)	
Left hemicolectomy	10 (10)	7 (9)	
Subtotal / Total colectomy	4 (4)	1 (1)	
Rectosigmoidectomy	18 (18)	13 (16)	
Low anterior resection	26 (26)	25 (31)	
Abdominoperineal resection	9 (9)	6 (8)	
Transverse colectomy	2 (2)	0 (0)	
Rectal surgery	35 (34)	31 (39)	0.538
Laparoscopic surgical approach	75 (76)	70 (88)	0.056
New stoma formation	25 (25)	19 (24)	0.863
Duration of surgery (minutes), median [IQR]	190 [135-253]	186 [130-245]	0.281
Blood loss (ml), median [IQR]	150 [100-300]	150 [100-300]	0.554
Clinically significant intraoperative complications	5 (5)	6 (8)	0.542

Values are number (%) otherwise noted. Abbreviation: IQR, interquartile range.

[a] Laparoscopic interventions converted into open were not considered in this category

Table 4.3. Postoperative Outcomes.

	Preoperative 6MWD change		p
	< 19 m n = 99	≥ 19 m n = 80	
30-day comprehensive complication index, median [IQR]	8.7 [0-22.6]	0 [0-8.7]	0.022
Participants with at least 1 complication within 30 days	50 (50)	30 (38)	0.097
Length of primary hospital stay (days), median [IQR]	4 [3-6]	3 [3-5]	0.236
30-day ED visit	25 (25)	10 (13)	0.038
30-day hospital readmissions	14 (14)	5 (6)	0.142

Values are number (%) otherwise noted. Abbreviations: ED, Emergency Department; IQR, interquartile range.

Table 4.4. Logistic regression analysis testing the independent association of significant improvement in 6MWD and major postoperative complications.

	Severe Complication CCI ≥ upper quartile					
	Univariate			**Multivariate**		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
6MWD change ≥ 19 m	0.29	0.12-0.72	0.007	0.29	0.11-0.75	0.011
Age, 75+ years old	1.00	0.97-1.03	0.878	1.00	0.96-1.05	0.772
Gender, Male	2.12	0.89-5.02	0.088	2.56	0.99-6.63	0.053
BMI ≥ 30	0.98	0.90-1.07	0.739	0.96	0.87-1.07	0.463
ASA≥ 3	2.27	1.02-5.01	0.042	1.92	0.77-4.78	0.162
Cancer Stage						
1	0.87	0.23-3.18	0.828	0.78	0.18-3.36	0.745
2	0.81	0.26-2.61	0.735	0.76	0.20-2.91	0.689
3	1.12	0.37-2.39	0.834	0.91	0.25-3.31	0.893
4	2.70	0.50-14.52	0.247	2.43	0.32-18.5	0.389
Laparoscopic Surgery	0.46	0.19-1.08	0.074	0.91	0.32-2.57	0.857
Rectal Surgery	2.01	0.91-4.33	0.071	2.27	0.92-5.59	0.531

Abbreviations: 6MWD, Six-minute walk distance; ASA, American Society of Anesthesiologists physical status; BMI, body mass index; CI, confidence interval; OR, odds ratio.

Table 4.5. Type of postoperative complications, n (%)

	Preoperative 6MWD change	
	< 19 m **n = 99**	**≥ 19 m** **n = 80**
Medical Complication	24 (24)	15 (19)
Cardiovascular	6 (6)	1 (1)
Heart failure	3 (3)	1 (1)
Myocardial infarction	1 (1)	0 (0)
Arrhythmias	1 (1)	1 (1)
Deep venous thrombosis	1 (1)	0 (0)
Respiratory	5 (5)	2 (3)
Pneumonia	1 (1)	0 (0)
Pulmonary atelectasis	2 (2)	0 (0)
Pleural effusion	1 (1)	1 (1)
Respiratory failure	2 (2)	2 (3)
Infectious	5 (5)	6 (8)
Urinary tract infection	1 (1)	1 (1)
Wound infection	2 (2)	1 (1)
Intra- or retro-peritoneal infectious	2 (2)	3 (4)
Sepsis	2 (2)	1 (1)
other	1 (1)	0 (0)
Other medical	16 (16)	9 (11)
Acute kidney injury	1 (1)	2 (3)
Urinary retention	5 (5)	2 (3)
Anemia	7 (7)	1 (1)
Nausea/Vomit	1 (1)	2 (3)

Delirium	2 (2)	2 (3)
Pain	1 (1)	1 (1)
Surgical complication	24 (24)	14 (18)
Anastomotic leak	3 (3)	0 (0)
Perforation	1 (1)	1 (1)
Ileus	20 (20)	11 (14)
Wound dehiscence	1 (1)	0 (0)
Bleeding	3 (3)	2 (3)
Other	1 (1)	1 (1)

Values are number (%).Abbreviation: 6MWD, Six-minute walk distance.

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4.9 Appendix

Appendix 4.A DEFINITIONS OF COMPLICATIONS FOR BOWEL SURGERY

INTRAOPERATIVE SIGNIFICANT COMPLICATIONS[1]

- Clinically significant hemorrhage: intraoperative bleeding requiring transfusion of packed red blood cells (PRBC) during surgery or within 24 hours after surgery
- Bowel injury: injury of the small or large bowel requiring intraoperative repair or additional resection.
- Urinary tract injury: injury of the ureter or bladder requiring intraoperative repair
- Vascular injury: injury of any major vessel (e.g. iliac artery or vein) requiring intraoperative repair
- Cardiac or respiratory complications: any cardiovascular (e.g. cardiac arrhythmia, myocardial infarction) or respiratory (e.g. pneumothorax) complication occurring during surgery.
- Aspiration of gastric content: intraoperative pulmonary aspiration of gastric content
- Other: any intraoperative injury to other viscera (e.g. spleen, vagina)

POSTOPERATIVE COMPLICATIONS

MEDICAL

Cardiovascular

- Heart failure: clinical or radiological signs of congestive heart failure and specific treatment initiated.[2]
- Acute myocardial infarction: increase in cardiac biomarker values or characteristic ECG changes or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.[3]
- Cardiac arrhythmia: ECG diagnosis of new arrhythmia requiring at least a pharmacologic intervention.[4]
- Cardiac arrest: cardiopulmonary resuscitation performed.
- Deep vein thrombosis: radiological confirmation of deep vein thrombosis or anticoagulation started due to clinical findings.
- Pulmonary embolism: radiological evidence of pulmonary embolism.
- Cerebrovascular accident: new focal or global neurologic deficit of cerebrovascular cause that persists beyond 24 h or is interrupted by death within 24 h.[5]

Respiratory

- Pneumonia: Hospital acquired pneumonia, defined as presence of lung infiltrate at chest x-ray accompanied with signs of infection and initiation of antibiotic treatment.[6]
- Lobar atelectasis: radiological finding of at least one lobar collapse.[4]
- Pleural fluid: pleural effusion requiring drainage of the pleural cavity.
- Respiratory failure: delayed extubation > 24 hours after primary surgery, or reintubation at any time for ventilatory support.[4]
- Pulmonary edema: clinical signs and radiological confirmation.[7]

Other medical

- Acute Kidney Injury: increase in serum creatinine ×2 from baseline or reduction of glomerular filtration rate greater than 50%.[8]
- Urinary retention: Reinsertion of indwelling urinary catheter after removal attempt or patient discharged with urinary drainage (excluding patients with permanent indwelling urinary catheter).
- Anemia: low serum hemoglobin requiring transfusion of PRBC, unrelated to any identified source of bleeding.
- Hepatic dysfunction: Increased serum bilirubin concentration > 34 μmol/l (2 mg/dl) compared to preoperative value AND elevated liver enzymes AND has NOT undergone a pancreaticobiliary procedure.[4]
- Acute Pancreatitis: diagnosis requires 2 of the following: upper abdominal pain of acute onset often radiating through to the back; increase in serum amylase or

lipase (x3 normal value); cross-sectional abdominal imaging consistent with acute pancreatitis.[9]

- Other gastrointestinal complications: any other complication of the gastrointestinal tract requiring treatment (e.g. blood per rectum, diarrhea, high stoma output).
- Neurological complications: any neurological complication excluding cerebrovascular events or anesthesia-related injuries (e.g. epileptic seizure)
- Psychiatric complications: new psychiatric symptoms including delirium and depression, requiring pharmacological treatment.

INFECTIOUS

- UTI: upper or lower urinary symptoms and urine culture with no more than two species of organisms, at least one of which is a bacteria of ≥105 CFU/ml.[10]
- Wound infection: Purulent drainage, with or without positive culture, from the superficial incision or any sign or symptom of infection (e.g. pain or tenderness, localized swelling, redness) and superficial incision is deliberately opened by the surgeon or attending physician. Not included if part of intra-peritoneal abscess.[11]
- Intra- or retroperitoneal abscess: Radiologic finding of deep collection of pus associated with systemic signs of infection or finding during reoperation.
- Sepsis: at least two SIRS criteria positive and a documented or suspected infection. SIRS criteria are the following: Temperature < 36 or >38 °C; heart rate

>90 beats per minute, respiratory frequency >20 breath per minute, leukocytosis (WBC>12) or leukopenia (WBC<4) AND documented or suspected infection.[12]

- Other infectious complications: any other documented infectious complication (e.g. Clostridium difficile colitis).

SURGICAL

- Anastomotic leak: documentation at reoperation OR documentation by imaging technique (e.g. radiologically, endoscopically) of leakage from the surgical connection between the two bowel ends into the abdomen or pelvis with either spillage and/or fluid collection around the anastomotic site or extravasation through a wound, drain site, or anus.[13] In the case of rectal surgery, a pelvic abscess close to the anastomosis is also considered as anastomotic leakage.[14]
- Bowel perforation: documentation at reoperation OR radiologically of perforation of small or large bowel.[7]
- Mechanical bowel obstruction: documentation at reoperation OR radiologically of mechanical small or large bowel obstruction.
- Wound dehiscence: separation of the abdominal wall muscle fascia large enough to necessitate operative closure of the wound OR incisional hernia diagnosed after primary discharge.[7]
- Bleeding: any postoperative bleeding (e.g. intra-abdominal, gastrointestinal) requiring transfusion of at least 2 PRBC after surgery.[15]

- Ileus (primary postoperative ileus): abdominal distention OR vomiting associated with intolerance of solid food intake or inability to pass gas or stool beyond POD3 (target day for discharge), unrelated to any other ongoing complication.
- Other surgical complications: any other surgical complication necessitating treatment or delaying discharge (e.g. abdominal wall hematoma).

ANESTHESIA-RELATED

- Post-dural puncture headache: persistent headache requiring immobilization, related to puncture of the dura mater during epidural catheter placement
- Epidural hematoma or abscess: radiologically confirmed epidural hematoma or abscess
- Other anesthesia-related complications: any other anesthesia-related complication occurring after surgery (e.g. peripheral nerve injuries).

SYMPTOMS DELAYING DISCHARGE

- Pain: uncontrolled pain requiring prolonged treatment delaying discharge, unrelated to any other complication.

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Preface to chapter 5

As seen in previous chapters, deconditioned patients are the most likely to improve preoperative functional capacity with prehabilitation, which in turn is associated with lower severe complications. This body of evidence calls for better understanding and insight into the metabolic adaptation underpinning such effects, and its possible role in modulating surgical stress response.

From a pathophysiologic perspective, functional capacity reflects the ability of the body to maintain homeostasis in response to a specific stress (surgery, in this case).[1] In our model, we deliver a controlled, physiological stressor (prehabilitation) to trigger a favorable metabolic responce.[2] Although such assumption is biologically plausible, trial with more in-depth assessment of exercise-induced physiologic adaptations needed to be conducted. To fully understand the effect of different exercise protocols on cardiorespiratory and skeletal muscle endurance, we implemented the use perioperative cardiopulmonary exercise testing (CPET). This provides an opportunity “to study the cellular, cardiovascular, and ventilatory systems' responses simultaneously under precise conditions of metabolic stress”.[3]

As the anabolic stimulus delivered depends on the intensity, duration, and mode of exercise prescription, we hypothesized that different exercise protocols could induce different metabolic adaption with impactful consequences on the modulation of surgical stress response. In the following chapter, using a randomized controlled design, two preoperative exercise programs are compared, high intensity interval training (HIIT) and moderate intensity continuous training (MICT), in the context of prehabilitation. This may lead to a better mechanistic understanding of metabolic response to surgery and its potential modulation.

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CHAPTER 5

Effect of training intensity on perioperative exercise capacity: a randomized controlled trial in multimodal prehabilitation for colorectal surgery.

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Conflicts of Interest

Authors declare no competing interests

5.1 Abstract

Background

Multimodal prehabilitation, including exercise training, nutritional therapy and anxiety reduction strategies, is a preoperative intervention that can attenuate surgery-related functional decline. Due to the growing interest in functional status as a targeted surgical outcome, a better understanding of the optimal prescription of exercise is critical. To date, there has been no original comparative research exploring which preoperative exercise protocol is the most appropriate, and how proper individualized care should be conducted. The aim of this study was to compare two different endurance trainings within a four-week, supervised, multimodal prehabilitation for patients with colorectal cancer.

Methods

Forty-two patients were randomly assigned to receive either high intensity interval training (HIIT), or moderate intensity continuous training (MICT), integrated in a 4-week multimodal prehabilitation program. Both groups followed the same supervised resistance training, nutritional therapy, and anxiety reduction intervention. Participants performed four assessments, at baseline, after prehabilitation (just before surgery, preop), and at four and eight weeks after surgery. Changes in oxygen consumption at anaerobic threshold ($\dot{V}O_2AT$) were assessed and compared between groups as a main outcome measure.

Results

Forty-two patients were included in the primary analysis (HIIT n=21 vs. MICT n=21). Both protocols enhanced preoperative $\dot{V}O_2AT$, with no difference between groups: +1.97 (95% IC 0.75-3.19) $ml \cdot kg^{-1} \cdot min^{-1}$ in HIIT vs. +1.71 (0.56-2.85) in MICT, P=0.753. Patients in HIIT group significantly improved their physical fitness at 8 weeks postoperatively: mean 2.50 (95% IC 1.10-3.88) $ml \cdot kg^{-1} \cdot min^{-1}$ in HIIT vs. 0.13 (-1.28, +1.55) in MICT, P= 0.021. No adverse events occurred during the intervention.

Conclusions

Both MICT and HIIT enhanced preoperative functional capacity and prevent postoperative decline. HIIT was most effective in improving physical fitness after surgery.

5.2 Introduction

Surgery, an essential step in oncologic care, often comes at a ‘cost’. A significant proportion of patients suffers from new or worsening physical, nutritional and psychological impairments, with detrimental effect on their independence.[1] In older patients, impactful disability persists as late as 6 months after surgery, not only in instrumental activities of the daily living, but also in basic tasks such as bathing and dressing.[2] This carries an impressive burden on health and social care, considering that surgical volumes are growing rapidly worldwide.[3] Therefore, there is a need to improve cancer care provided to this population, targeting functional capacity as a modifiable clinical, economic, and patient outcome.[4]

Prehabilitation is a multidisciplinary intervention that aims at using the preoperative period to prevent or attenuate treatment-related functional decline and its consequences.[5] Supporting guidelines endorse a multimodal approach, including physical training, diet therapy, and psychological interventions.[5,6] Early result shows that prehabilitation leads to clinically meaningful functional capacity improvements before and after surgery.[7-9] Given this positive finding and the growing clinical interest, further research is critical to investigate the optimal modality of the intervention.[10-12]

With regard to exercise, trials in prehabilitation for colorectal surgery used either high intensity interval training (HIIT), which involves alternating short bursts of high-intensity exercise with recovery periods or light exercise,[13] or moderate intensity continuous training (MICT),[14,15] which implies exercise performed in a continuous manner at a lower intensity. Although HIIT has gained popularity for its superior effects in non-surgical populations,[13,16-20] there are currently no comparative studies evaluating the most appropriate perioperative exercise protocol.

Moreover, there is a need to objectively define the functional trajectory along the whole perioperative period.[2] Cardiopulmonary exercise testing (CPET), analyzing ventilatory gases during exercise, provides an objective, dynamic, and integrative assessment of cardiorespiratory fitness. A variable such as oxygen consumption at anaerobic threshold ($\dot{V}O_2AT$), defining the metabolic rate associated with a submaximal and sustainable exercise, is known to predict postoperative outcome more accurately than subjectively assessed measure of functional capacity.[21,22] Thus, preoperative CPET is extensively used for risk prediction before major surgery and, in the contest of prehabilitation, provides the higher clinical standard for exercise prescription.[6,23] Despite its key role in preoperative medicine, data is missing on exercise capacity after surgery, as high quality measure of functional recovery. There is a need to elucidate whether the intensity of the exercise influences the metabolic reserve as assessed by objectively measured cardiorespiratory fitness.

In the attempt to address these knowledge gaps, this study was designed to compare and quantify the effect of two different exercise programs on perioperative cardiorespiratory fitness. It was hypothesized that, in the context of multimodal prehabilitation, HIIT would be more effective than MICT in optimizing perioperative functional capacity in patients undergoing elective colorectal surgery for cancer.

5.3 Methods

Study Design and Participants

This was a single blinded, pragmatic, randomized controlled study designed to compare two different exercise protocols in the context of multimodal prehabilitation. The trial was conducted at the McGill University Health Centre (MUHC), Montreal, Quebec, Canada, and approved by the McGill University Health Centre Research Ethics Board (15-244-MUHC).

All consecutive patients referred for colorectal cancer resection with a provisional operative date that allowed a four-week intervention were considered for this study. Exclusion criteria were metastatic cancer, age <18 years, ASA >3, or co-morbid conditions that contraindicated oral nutrition or exercise, such as unstable cardiovascular disease, disabling physical and cognitive impairment, and end-stage organ dysfunction. Eligible participants were given appropriate information during their first visit, and written informed consent was obtained before any trial-related activity was commenced.

Approximately four weeks before the scheduled operation, participants attended the Prehabilitation Unit at MUHC, where they met with a physician, a certified kinesiologist, a registered dietitian, and psychology trained personnel for a baseline assessment. Once baseline medical assessment was completed, patients were randomly assigned in a 1:1 ratio to either HIIT or MICT group, using computer-generated blocks of 6, and group assignments were placed in sequentially numbered opaque envelopes. Owing to the behavioral nature of the intervention, health care providers and patients were not blinded, while assessors were not aware of group allocation, and previous scores.

Weekly attendance to the exercise sessions was recorded, and, for each session, adherence to the training module was evaluated as a percentage of the time spent exercising at the prescribed work rate. In addition, patients reported the daily protein intake on a weekly basis. All patients followed the usual preoperative care of our institution, in terms of risk assessment, medication management, perioperative blood management, and smoking cessation as per ERAS guidelines adopted by this institution. Scheduling of surgery was not affected by study, or group assignment.

Interventions: multimodal prehabilitation

Multimodal prehabilitation is a preoperative intervention including exercise training, nutritional therapy and anxiety reducing techniques, aimed at preventing or attenuate surgery-driven functional decline.[24] All activities were completed in dedicated suites at the Prehabilitation Unit at MUHC, by qualified health professionals.

Endurance Exercise: HIIT vs. MICT

Under a one-to-one direct supervision of a staff kinesiologist, patients followed a three-day per week, in-hospital training for four weeks. Exercise was performed between 08:00 am and 01:00 pm, in a well-ventilated room where ambient temperature was kept between 22-26 degrees centigrade. Patients were asked to consume a light meal two hours before the training session.

The two groups differed in the endurance training protocol in terms of intensity, duration and module (Figure 1). Prescriptions were based on cardiopulmonary exercise testing (CPET)-derived variables at baseline, ensuring an individualized protocol for each participant.

In HIIT group, high-intensity bouts, 4 intervals of 2-min, were conducted at 85-90% of work load at peak oxygen consumption (peak $\dot{V}O_2$), and recovery bouts, 4 intervals of 3-min, were conducted at 80-85% of work load at oxygen consumption at anaerobic threshold ($\dot{V}O_2AT$). In MICT group, the intensity was defined as 80-85% of work load at oxygen consumption at anaerobic threshold ($\dot{V}O_2AT$).[25,26] To deliver volume-matched trainings, different durations were prescribed: 40 minutes for MICT, and 30 minutes for HIIT, including 5-min warm-up, and 5-min cool down (Figure 1).

Resistance exercise

Both groups received the identical resistance training program, personalized according to volitional fatigue.[27] At the end of the endurance component, patients rested for ten minutes before starting the resistance exercises, which were also supervised by a kinesiologist. The program included eight exercises targeting major muscle groups (upper limb, trunk, and lower limb), three sets of 8-12 repetitions. Intensity of resistance was based on baseline strength capacity, using the OMNI-Resistance Exercise Scale of perceived exertion.[27] All exercises were performed using body weight and calibrated dumbbells (Bowflex® SelectTech®, Vancouver, WA, US).

Nutrition Intervention

Both groups received identical nutritional intervention. At the time of enrollment, participants completed a 3-day food record, including 2 weekdays and 1 weekend day. Based on dietary habits, medical conditions, anthropometric and functional variables, a certified dietician provided a comprehensive nutrition management program.

A food-based intervention was prescribed to achieve the estimated daily requirement intervening on a caloric intake and meal pattern, and balancing macronutrients composition. Furthermore, a daily protein intake of 1.5 g/kg ideal body weight was prescribed, as per guidelines for surgical patients,[28] and whey protein supplement (Immunocal®, Immunotec®, Vaudreuil, Quebec, Canada) was prescribed, if needed. On training days, patients consumed 20 grams of whey protein supplement following the exercise.

Relaxation Intervention

Both groups received the identical relaxation intervention. Screening for depression and anxiety was performed using the Hospital Anxiety and Depression Scale (HADS) questionnaire.[29] Participants were instructed by psychology-trained personnel on how to reduce anxiety using relaxation techniques, such as imagery and visualization, and deep breathing exercises. A compact disc containing motivation suggestions was also provided to each patient. If needed, referral to psycho-oncology service was recommended, as appropriate.

Outcomes

Patients were asked to attend four assessments: at baseline, before surgery (at the end of prehabilitation), and at four and eight weeks after surgery. All measurements were conducted by assessors who were not aware of group allocations and time-points.

Primary outcome

Main outcomes were preoperative change in oxygen consumption at the anaerobic threshold ($\dot{V}O_2AT$), and at peak exercise (peak $\dot{V}O_2$). Measurements were obtained with CPET (Vmax® Encore, CareFusion, Yorba Linda, CA, USA), following international clinical recommendation.[23,30] Patients were asked to avoid caffeine, alcohol, cigarettes and strenuous exercise as of midnight prior to testing. They were also requested not to consume food two hours before the test. Calibration for flow and gas mixture were performed before each test. Non-invasive blood pressure, heart rate, ECG and pulse oximetry were monitored throughout the test. On an electromagnetically braked cycle ergometer (ViaSprint™ 150P, Vyaire™ Medical Inc, Bitz, Germany), patients performed an incremental exercise until volitional termination, including three min of rest, three min of unloaded cycling warm-up, and five min of recovery.[31] The same ramp slope, tailored to patients' characteristics,[32] was adopted for all assessments, allowing a proper comparison of work rate over time. Ventilation and gas exchange variables were measured at anaerobic threshold and at peak exercise, as appropriate,[21,23] and expressed as absolute value. The $\dot{V}O_2AT$, primary endpoint of this analysis, was defined using the classical three-point discrimination technique,[33] in which modified V-slope method was used to identify the inflection point in the $\dot{V}O_2$ vs. $\dot{V}CO_2$ relation, and changes in ventilatory equivalents and end-tidal partial pressures of O_2 and CO_2 was used to rule out hyperventilation. The peak $\dot{V}O_2$, defined as the highest $\dot{V}O_2$ attained during the rapid incremental exercise, was calculated as an averaged value over 20 seconds. To ensure it represented a physiologically maximal effort, the respiratory exchange ratio at peak had to be above 1.15.[34] This parameter was preferred over age-predicted maximum heart rate because of the high incidence of chronotropic incompetence and beta blockade in the elderly surgical population. All tests were interpreted by two blinded perioperative physicians (E.M.M., and F.C.), and accuracy was ensured by an independent reviewer (V.F.).

Secondary outcomes

Secondary outcomes included functional walking capacity, health-related quality of life and self-reported physical activity. Functional capacity was measured by the six-minute walk test, and properly measured in meters walked over the six-minute period (6MWD).[35] The test has been previously validated in the colorectal surgical population as a measure of exercise tolerance, and ability to endure demanding activities of daily living.[36] A 6MWD improvement by at least 19 meters, above the upper limit of the 95%CI for the minimal clinically important difference,[37] is a meaningful change in colorectal cancer surgery. Self-reported physical activity was measured by the Community Healthy Activities Model Program for Seniors questionnaire (CHAMPS), which allows subjects to estimate the hours spent performing listed activities of various intensities during the previous week.[38] Patient-reported overall health status and quality of life were evaluated with the Short-Form (SF)-36 questionnaire,[39,40] which estimates eight physically and emotionally based domains of well-being.

Statistical Analysis

Sample size

Sample size calculation was based on our main outcome $\dot{V}O_2AT$. Published data shows that surgical population has a mean $\dot{V}O_2AT$ of 12.0 (SD 2.0) $ml \cdot kg^{-1} \cdot min^{-1}$, and significant preoperative improvement set at 1.5 (1.1) $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$.[41] To detect this difference, 16 pairs of subjects were required to reach a power of 0.8, and a type I error probability of 0.05. Assuming a drop-out rate of 0.3, a total recruitment of 42 patients was planned.

Analysis

Baseline participant characteristics were summarized using frequency (percentage) for categorical variables, and median (interquartile range) for continuous variables, as appropriate. Normal distribution was formally assessed using Shapiro–Wilk test and variance using Levene's test.

After a planned interim analysis on preoperative data, significant drop-out was observed. Thus, to appraise the strengths of correlation at the different time points, robust repeated measures modeling with linear mixed models were applied. To assess a binary measurement change, the repeated measure analyses models were fitted by applying generalized estimating equations. Using this analysis, all patients who contribute at least one assessment were included in the primary analysis. Statistical significance was set at P-value below 0.05.

Statistical analyses were performed using SAS 9.4 TS level 1M5 (SAS Institute Inc., Cary, NC).

5.4 Results

Participants

From February 2016 through December 2017, 76 patients were assessed for eligibility, and 42 were enrolled and randomly assigned to either HIIT or MICT group. Baseline demographic and clinical characteristics of the 2 groups appear in Table 1. All participants with a CPET at baseline, 21 per group, were included in the primary analysis (CONSORT diagram, Figure 2). In HIIT and MICT respectively, unattended study visits were: 4/21 (19%) and 1/21 (5%) before surgery, 7/21 (33%) and 8/21 (38%) at 4 weeks after surgery, and 8/21 (38%) and 10/21 (48%) at 8 weeks after surgery. No early termination of CPET protocol was registered for any reason, and measurable AT and peak $\dot{V}O_2$ were obtained in all performed test, according to abovementioned parameters.

Mean adherence to supervised exercise session was 88.5 (SD 19.9)% in HIIT vs. 92.7 (12.1)% in MICT group. Mean adherence to nutrition was 96.6 (SD 7.2)% in the HIT group vs. 98.8 (3.9)% in the MICT group. Mean adherence to training protocol was 89.3 (SD 25)% in HIIT, vs. 96 (7)% in MICT group ($p=0.282$). No exercise-related adverse events were reported.

Change in perioperative exercise capacity

Changes in main functional variables over time are shown in Table 2, and a complete CPET-variable panel appears in Table 3. At baseline, measurements of $\dot{V}O_2$ at AT were comparable between groups: mean 12.33 (95% IC 10.63-14.03) $ml \cdot kg^{-1} \cdot min^{-1}$ in HIIT group vs. 13.81 (12.12-15.50) in MICT (P=0.222). Both groups improved their functional status preoperatively, with no significant difference between them: mean 1.97 (95% IC 0.75-3.19) $ml \cdot kg^{-1} \cdot min^{-1}$ in HIIT vs. 1.71 (0.56-2.85) in MICT (P=0.753). On average, patients in both groups did not experience any decline at 4 weeks after surgery (Table 2, Figure 3).

The increase in $\dot{V}O_2$ at AT from baseline to 8 weeks after surgery was significantly higher for HIIT group compared with MICT (respectively, mean 2.50 (95% IC 1.10-3.88) $ml \cdot kg^{-1} \cdot min^{-1}$ vs. 0.13 (-1.28-1.55), P= 0.021). Absolute value of $\dot{V}O_2$ at AT, and work rate at AT consistently improved and remained higher than baseline throughout the entire preoperative period (Figure 4, Table 3). Changes in peak $\dot{V}O_2$ were not significant when compared between groups over time (Table 2)

Secondary Outcomes

Both groups achieved a clinically meaningful change in 6MWD during the prehabilitation period, and at 8-week after surgery (Table 2); nonetheless, there was no statistical difference in 6MWD between the two groups.

Patients trained with MICT reported a higher physical activity level both preoperatively and at 8 weeks after surgery: CHAMPS, baseline, mean 70.04 (95% IC 34.62-105.46) kcal/kg/week in HIIT group vs. 92.92 (57.95-127.88) in MICT, P=0.364; preoperative, mean 100.43 (95% IC 62.58-138.28) kcal/kg/week in HIIT group vs. 152.76 (117.79-187.72) in MICT, P=0.047; 4-week postoperatively, mean 71.61 (95% IC 29.42-113.80) kcal/kg/week in HIIT group vs. 91.45 (53.70-129.20) in MICT, P=0.488; 8-week postoperatively, mean 66.73 (95% IC 27.93-105.52) kcal/kg/week in HIIT group vs. 144.34 (103.59-185.09), P= 0.0074.

Patients trained with MICT reported a higher score in quality of life at 8 weeks after surgery: SF-36, baseline, mean 81.50 (95% IC 74.04-88.96) in HIIT group vs. 80.12 (72.78-87.47), P=0.795; preoperative, mean 90.96 (95% IC 82.92-98.99) in HIIT group vs. 86.79 (79.44-94.14), P=0.449; 4-week postoperatively, mean 78.94 (95% IC 69.87-87.87) in HIIT group vs. 78.45 (70.43-86.47), P=0.937; 8-week postoperatively, mean 75.57 (95% IC 67.07-84.07) in HIIT group vs. 89.77 (80.75-98.80), P=0.025.

5.5 Discussion

This study on multimodal prehabilitation demonstrated that both HIIT and MICT improved exercise capacity before surgery and prevented postoperative decline. Moreover, patients receiving HIIT sustained a meaningful improvement after surgery.

Exercise prescription is a complex medical process and a clinical study on this topic demands to control several variables. In this study, we aimed to compare HIIT, which involves multiple, near-maximal bursts alternated with active recovery periods, with MICT, that defines an exercise performed in a continuous manner at a lower intensity. To provide high quality personalized medicine, exercise prescription was tailored to the physiological status of each patients, using an objective measure of physical fitness such as CPET.[42] In fact, other parameters, such as age-predicted heart rate, are known to either under or overestimate exercise intensity, in particular for elderly patients undergoing adjuvant therapy.[43] To correctly compare these training modalities, different durations were prescribed to match the total exercise volume, as appropiate.[16,18,44,45] Although evidence on the relative importance of frequency is inconclusive,[46,47] we set a 3-time per week protocol for both groups, in the attempt to match the dose of exercise recommended by American College of Sports Medicine (ACSM).[12] Moreover, the study was designed to avoid all source of experimental and environmental variability, which can bias data on inter- and intra-individual response to exercise: 1. training sessions and tests were always performed in the morning, in a controlled environment; 2. tests were conducted following the same standardized guideline for all patients;[30] 3. the repeated tests used the same protocol over time, ensuring a correct within-subject comparison and 4. consistency in exercise delivery and adherence monitoring were guaranteed by the individual supervision by an exercise specialist.

$\dot{V}O_2$ at AT was chosen as a primary outcome for several physiological, practical, and clinical reasons. First, AT is the metabolic rate that defines a submaximal and sustainable exercise, giving the best objective measure of functional reserve for daily-living activities. Then, AT, if reached during an exercise test, it is never volitionally controlled, which led us to prefer it over peak $\dot{V}O_2$ or 6MWD. Also, it has been used as a predictor of postoperative morbidity and mortality more accurately than other functional variables,[21] strengthening its role as main outcome in perioperative research.

The high compliance to the training sessions (directly monitored by the supervising kinesiologist), and to exercise prescription (89.3 (SD 25)% in HIIT), and the absence of adverse events represent a strength of this study, and demonstrates that even elderly patients can perform high intensity exercise, if appropriately supervised.[48] Interestingly, adherence and dropout rates did not differ by training intensity. The multimodal intervention was here chosen to counteract the whole-body catabolism and anabolic resistance associated with cancer and surgery.[5] To avoid any further confounders, a stringent consistency between groups was ensured for resistance training, dietary therapy, and psychological intervention. Furthermore, a standardized perioperative clinical pathway (ERAS) was followed for all patients, in terms of smoking cessation, glycemic control, medication regimen and anemia management.

Following 4 weeks of prehabilitation, $\dot{V}O_2$ at AT significantly improved in both groups. West and colleagues[41] showed that a preoperative 6-week HIIT program was effective in improving $\dot{V}O_2$ at AT by 2.1 (95% CI 1.3-2.9), in patients scheduled for colorectal cancer resection following neo-adjuvant therapy. The following year, Dunne and colleagues[49] published an RCT showing that a 4-week HIIT program increased $\dot{V}O_2$ at AT by 1.5 (95% CI 0.2-2.9), before liver resection for metastatic colorectal cancer. Our findings are consistent with above mentioned studies using HIIT, and furthermore showed a positive and comparable effect of preoperative MICT. In addition, this study represents the first report exploring and comparing the postoperative impact of these conditioning interventions, showing that at one month after surgery, on average, patients maintained their baseline functional level. As previously hypothesized, the physical improvement achieved before surgery served as a “buffer” against surgically induced functional impairment. This is of importance considering the significant drop in functional capacity previously reported at 4 weeks after colorectal surgery.[2,7,50] HIIT conferred a long-lasting improvement, maintained at two months after surgery, when patients had an exercise capacity even superior to their baseline level (Figure 3, and Table 2). Data on $\dot{V}O_2$ at AT were steadily higher than baseline in HIIT group, and this is corroborated by the consistent improvement in work power produced throughout the entire perioperative period (Figure 4, and Table 3). Since postoperative recovery is the most important patient-centered and clinical outcome, this study may support in favor of

HIIT over MICT. However, the inter-individual response heterogeneity within the same exercise regimen should be emphasized; future studies should be designed to examine response variability, and help individualizing exercise prescription.

Interestingly, change in peak $\dot{V}O_2$ followed different trajectories, increasing before surgery, and returning to baseline level postoperatively, with no difference between HIIT and MICT at any time point. Once again, the fast return to baseline functioning using both training modalities is a valuable and relevant finding of this study.

The significance of this result relies on the role of function as an essential measure of quality in cancer care.[4] A paradigm shift is occurring in surgery and perioperative medicine over last years; while 'traditional' parameters such as 30-day mortality and morbidity remain important, it is becoming clear that also other outcomes define surgical quality. Patients consistently recognize maintaining independence as a main priority, even more important that survivorship.[51] Moreover, functional status plays a key role on the continuity of care of patients suffering from cancer. Thus, maintaining, or even improving physical fitness as early as the first month after surgery could shorten waiting time to adjuvant therapy, improve adherence, and reduce its adverse events.

This study has several limitations. First, significant loss of follow-up was recorded, which limits generalizability. Nonetheless, it is worth highlighting the complexity of the study design for participants that were asked to perform four stress exercise tests over a 3-month perioperative period. Due to power limitation, results on secondary outcomes should be considered preliminary, and the possibility to perform sub-analyses is limited. Furthermore, physical activity outside the hospital was not measured using a tracking device, and we relied on self-reported outcomes. Compliance to nutrition was based solely on protein intake, although patients received a complete dietary intervention.

In conclusion, this study showed safety and efficacy of both moderate continuous and high-intensity interval training in preserving perioperative functional capacity, in the context of multimodal prehabilitation for colorectal cancer surgery. Moreover, high intensity appears to elicit a better resilience to withstand surgery-induced metabolic stress, when compared to work-matched exercise performed at lower intensity. This finding will be useful to build evidence-based pathways in perioperative medicine, and guide future research on physiopathology of stress response to surgery.

5.6 Acknowledgments

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5.7 Tables

Table 5.1. Baseline characteristics.

	HIIT n = 21	**MICT** n = 21
Age, y	67.0 (60-72)	67.0 (50-76)
Sex, n (%)		
Female	11 (52.4)	5 (23.8)
Male	10 (47.6)	16 (76.2)
BMI, kg/m^2	28.6 (23-32)	25.9 (23-34)
Medical history, n (%)		
Cardiovascular disease	2 (9.5)	2 (9.5)
COPD	0 (0)	0 (0)
Medically treated diabetes	3 (14.3)	0 (0)
Current smoker, n (%)	4 (19)	4 (19)
Hemoglobin, g/dL	13.3 (10.9-14.1)	14.1 (12.6-14.9)
Albumin, g/L	41.0 (38.5-44.0)	41.0 (39.5-43.5)
Cancer site, n (%)		
Colon	17 (81)	14 (67)
Rectum	4 (19)	7 (33)
PG-SGA, n (%)		
0-3	13 (62)	12 (57)
4-8	7 (33)	8 (38)
≥9	1 (5)	1 (5)
Neoadjuvant chemotherapy, n (%)	2 (9.5)	6 (28.6)

ASA score, n (%)		
1	1 (5)	4 (19)
2	16 (76)	12 (57)
3	4 (19)	5 (24)
Cancer Stage, n (%)		
I	7 (33)	5 (24)
II	9 (43)	9 (43)
III	5 (24)	7 (33)

Values are median (IQR), otherwise noted. ASA, American Society of Anesthesiologists physical status; BMI, body mass index; PG-SGA, Patient-generated Subjective Global Assessment score.

Table 5.2. Perioperative change in main functional variables, before surgery (PreOp), at 4-week after surgery (4w), at 8-week after surgery (8w), compared with baseline status. Data are mean (95% CI).6MWD, six-min walk distance; AT, anaerobic threshold; $\dot{V}O_2$, oxygen consumption.

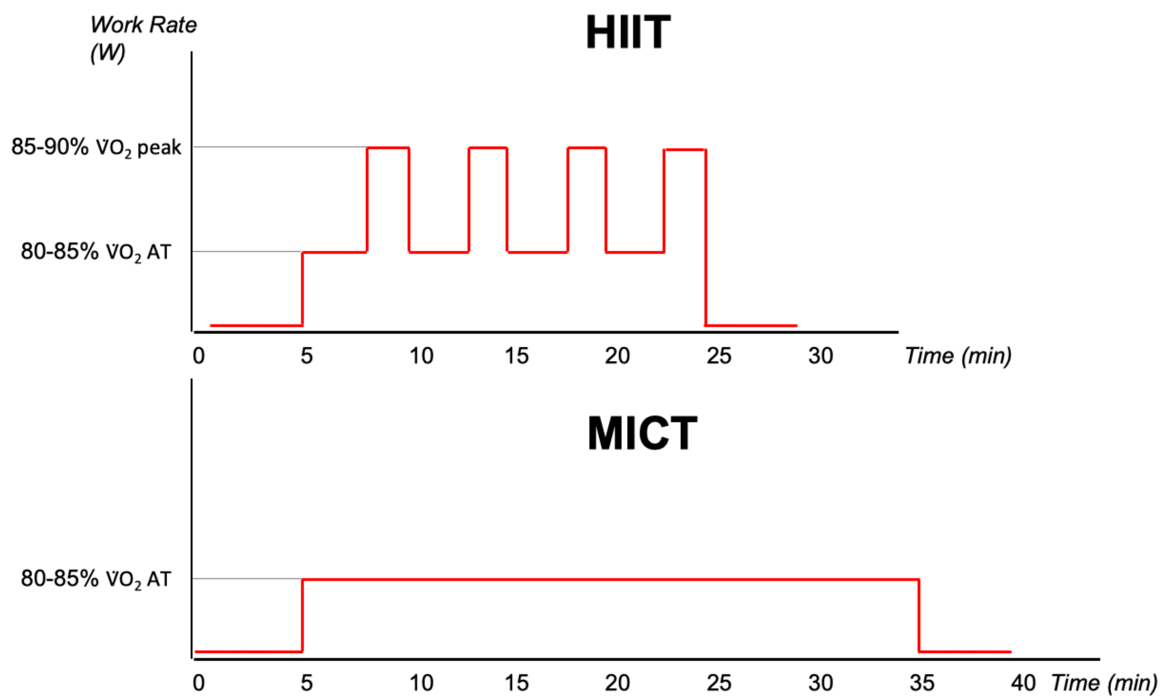
	PreOp			**4-w**			**8-w**		
	HIIT	MICT	P-Value	HIIT	MICT	P-Value	HIIT	MICT	P-Value
$\dot{V}O_2$ at AT, $mL \cdot kg^{-1} \cdot min^{-1}$	1.97 (0.75-3.19)	1.71 (0.56-2.85)	0.753	1.42 (0.07-2.77)	0.19 (-1.11,1.48)	0.191	2.50 (1.10-3.88)	0.13 (-1.28, 1.55)	0.021
$\dot{V}O_2$ peak, $mL \cdot kg^{-1} \cdot min^{-1}$	1.95 (0.71-3.19)	0.44 (-0.71, 1.60)	0.080	-0.52 (-1.92, 0.89)	-0.90 (-2.26, 0.45)	0.692	0.75 (-0.71, 2.21)	-0.27 (-1.78, 1.25)	0.335
Work Rate at AT, W	14.54 (5.51-23.57)	16.64 (8.1625.12)	0.734	8.37 (-1.49, 18.23)	3.96 (-5.50, 13.42)	0.519	11.10 (0.99-21.22)	5.31 (-4.91,15.54)	0.422
Work Rate peak, W	12.79 (4.52-21.05)	8.05 (0.34-15.75)	0.402	-0.228 (-9.75, 9.12)	-8.68 (-17.68, 0.31)	0.196	5.15 (-4.53, 14.84)	-0.155 (10.18-9.87)	0.447
6MWD, m	12.55 (-7.83, 32.92)	18.07 (1.36,37.51)	0.696	10.25 (12.13, 32.63)	12.39 (-8.11, 32.89)	0.888	26.70 (5.18-48.22)	19.48 (2.54, 41.50)	0.640

Table 5.3. CPET-related variables before surgery (PreOp), at 4-week after surgery (4w), at 8-week after surgery (8w). Data are mean (95% CI). AT, anaerobic threshold; $\dot{V}O_2$, oxygen consumption.

	HIIT group n= 21				MICT group n= 21			
	Baseline	PreOp	4-w	8-w	Baseline	PreOp	4-w	8-w
$\dot{V}O_2$ at AT, mL·kg^{-1}·min^{-1}	12.33 (10.63-14.03)	14.35 (12.60-16.10)	13.90 (12.06-15.74)	14.95 (13.08-16.82)	13.81 (12.12-15.50)	15.57 (13.86-17.27)	13.96 (12.16-15.77)	13.83 (11.94-15.72)
$\dot{V}O_2$ at peak, mL·kg^{-1}·min^{-1}	18.53 (15.50-21.56)	20.55 (17.48-23.63)	18.20 (15.05-21.34)	19.44 (16.27-22.60)	21.70 (18.67-24.72)	22.23 (19.19-25.27)	20.62 (17.50-23.73)	21.16 (17.98-24.35)
Work Rate at AT, W	55.50 (41.37-69.63)	70.50 (56.03-84.97)	64.63 (49.60-79.66)	67.35 (52.12-82.57)	65.70 (51.62-79.79)	82.27 (68.11-96.43)	68.66 (53.85-83.47)	69.69 (54.44-85.15)
Work Rate peak, W	97.05 (74.83-119.27)	110.35 (87.86-132.83)	97.61 (74.69-120.53)	102.40 (79.34-125.47)	122.94 (100.76-145.13)	131.41 (109.16-153.66)	113.23 (90.49-135.98)	121.23 (98.06-144.40)
VE/VCO_2 slope	33.94 (31.79-36.10)	33.01 (30.81-35.20)	33.20 (30.95-35.45)	33.23 (30.9-35.50)	31.93 (29.88-34.0)	31.96 (29.9034.02)	33.24 (31.1035.38)	33.73 (31.5135.95)

5.8 FIGURES

Figure 5.1. Graphical representation (upper part) and prescription details (bottom part) of exercise training in HIIT and MICT group. *Duration includes 5-min warm-up, and 5-min cool-down.



	HIIT	MICT
*Duration**	30 min	40 min
Pattern	Interval: 4 high intensity bouts (2 minutes) interspersed by 3-min recovery	Continuous
Intensity	85-90% $\dot{V}O_2$ peak	80-85% $\dot{V}O_2$ AT
Mode	Cycling on electromagnetically braked ergometer at constant pedaling frequency	
Frequency	3 days per week	
Progression	No change over time	

Figure 5.2. Flow chart of enrolment and follow-up (CONSORT).

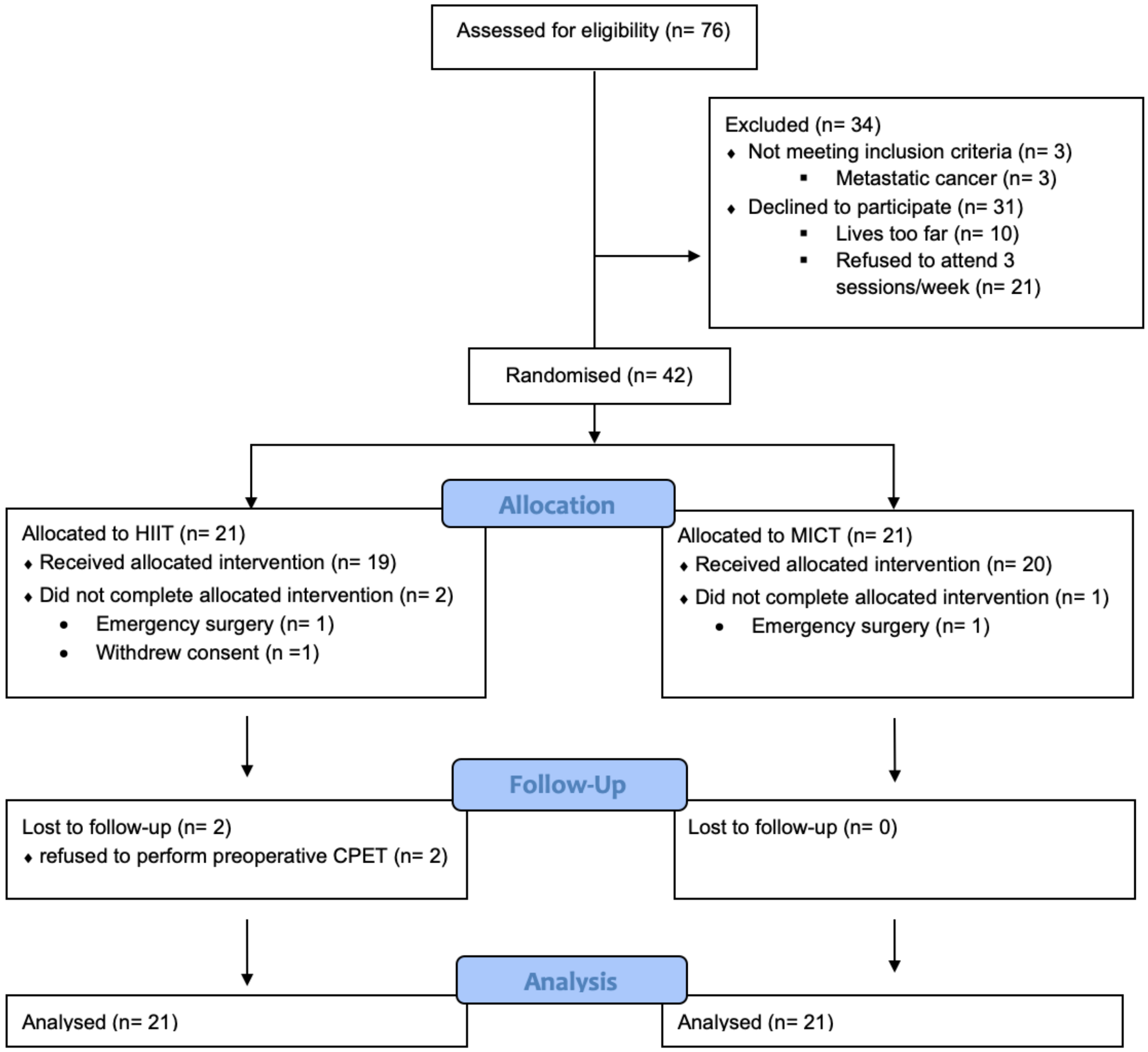


Figure 5.3. Trajectory of Change in Functional Capacity measured with oxygen consumption at the anaerobic threshold ($\dot{V}O_2AT$) and at peak exercise (peak $\dot{V}O_2$). Data are mean, SD.

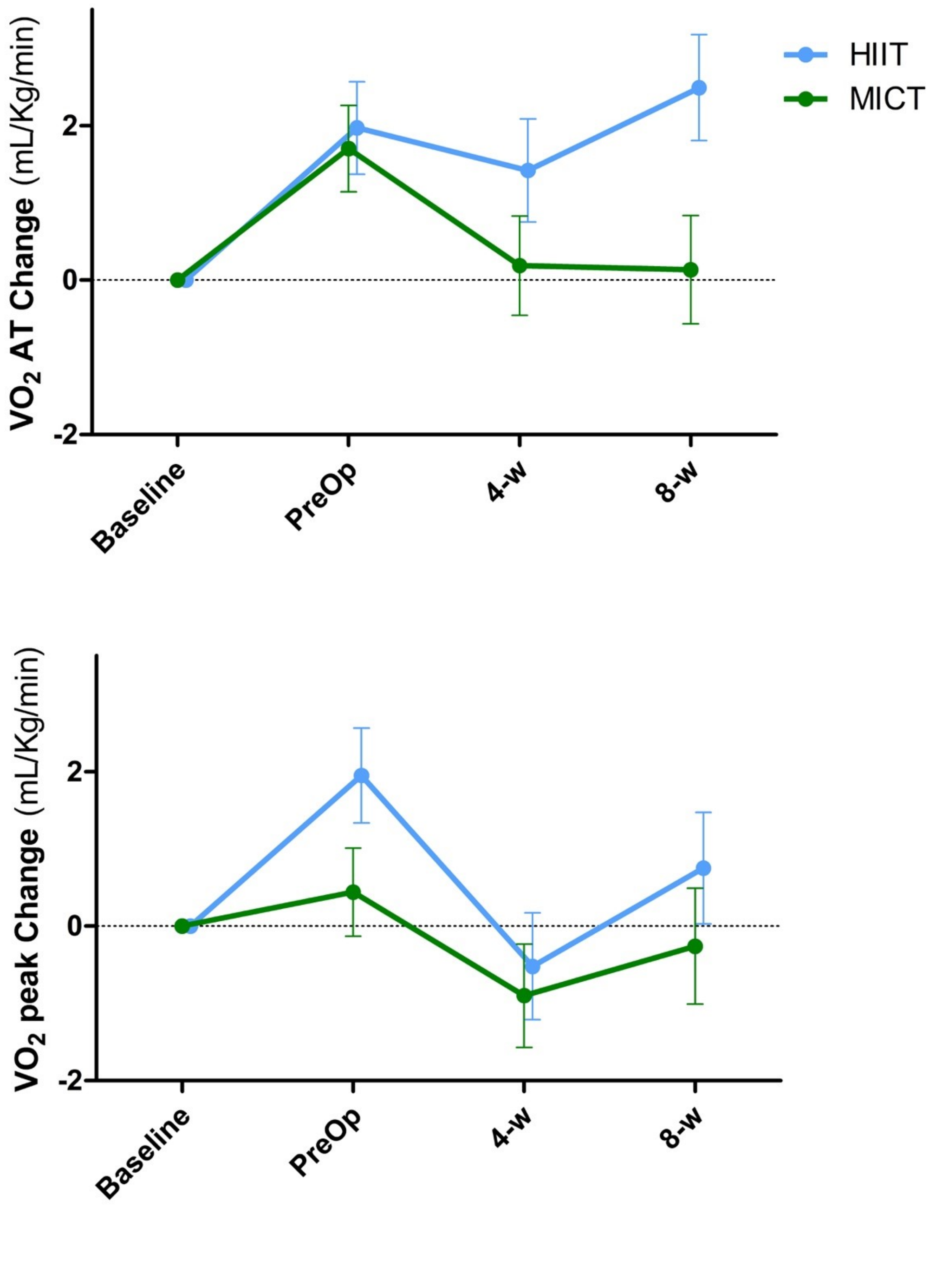
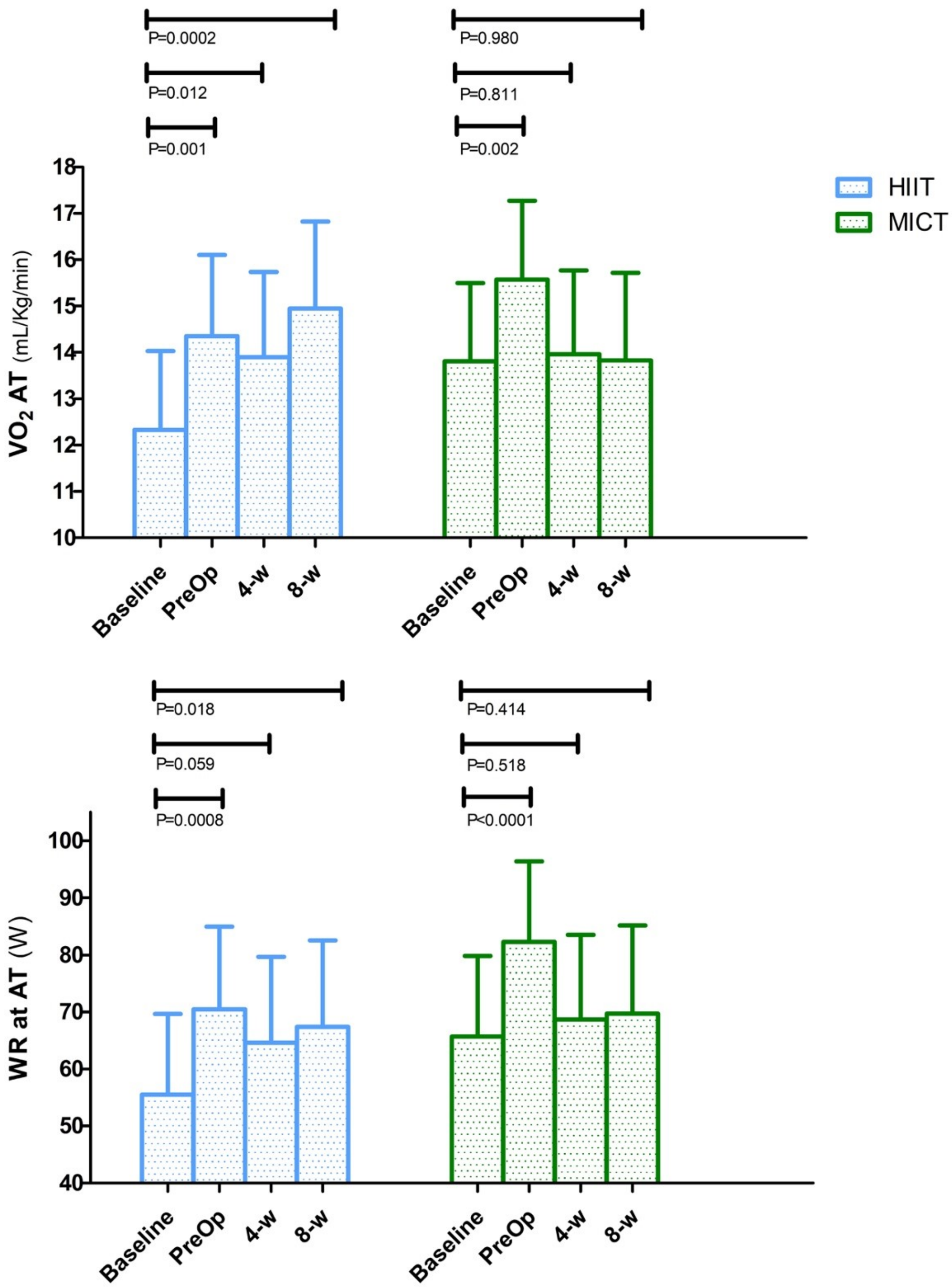


Figure 5.4. Within group analysis on absolute value of oxygen consumption ($\dot{V}O_2$) and work rate (WR) at the anaerobic threshold (AT). Details appear in Table 5.3.



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CHAPTER 6

GENERAL DISCUSSION

This doctoral thesis affords an original insight into the modulation of stress response to surgery and provides the methodological and conceptual knowledge to integrate prehabilitation into surgical cancer care.

Cancer is one of the most debilitating diseases worldwide.

Over 1.36 million new cases of bowel cancer are diagnosed annually, and more than 694,000 individuals die from the disease worldwide. For most solid cancers, radical surgery is first line treatment, ultimately associated with increased life expectancy. As a consequence of the continuous advances in cancer therapy, surgical volume is growing rapidly worldwide: in 2012, over 312 million operations were performed, which represents a 33.6% increase over eight years.[1] Nonetheless, major surgery carries impressive adverse consequences and, in elderly, is a leading cause of disability.[2,3] In older patients, an impactful functional impairment persists for months after surgery, affecting basic and instrumental activities of daily living such as housework, shopping, self-care and personal hygiene.[4] Historically, patient with cancer were recommended to rest and refrain from fatiguing activity after treatments, but this dogma has changed over the last decades.[5] Although exercise oncology has rapidly evolved over the last decades, efforts are primary focused on medical treatments, such as adjuvant and neoadjuvant chemotherapy and radiotherapy,[6] and rarely adopted in a structured, preventive perspective in conjunction with nutrition. To advance the scientific rationale and evidence in the field, my research work has focused on the urgent need to target physical, nutritional and psychological status as a main patient-centered outcome in oncologic surgical care. The study population in this thesis includes patients undergoing elective surgery for non-metastatic colorectal cancer.

Prehabilitation was designed as a preoperative intervention including exercise training, nutrition therapy and relaxation strategies to prevent functional decline after surgery. The main elements of strength and novelty of this approach that I contributed to develop and study, are i) the use of exercise and dietary prescription adopted as integrated preventive strategy; ii) the joint contribution of multiple health care providers in all program components, such as screening, assessment, design and prescription; iii) the use of multiple functional metrics to describe oncologic outcome, with a 2-month follow-up after surgery; iv) the target on a clinical high-risk population undergoing major surgery.

This thesis presents several original contributions. Prehabilitation safely improves physical fitness before surgery, measured by the walk test, retained for its accurate estimation of the capacity to perform daily living activities, and prevents the detrimental functional decline associated with surgery (Chapter 2). Patients with impaired functional status appear to be the target population for prehabilitation in term of functional response (Chapter 3). From a clinical perspective, this is of primary importance since improving physical functional before surgery is associated with a protective effect on severe complications after surgery (Chapter 4). These studies, integrated in a logic coherent progression, provide an innovative understanding of the modulation of stress response in high-risk population, where prehabilitation may break the vicious circle between low functional capacity and poor surgical outcome. Then, by exploring the perioperative profile of whole-body oxygen delivery and utilization, the comparison of different preoperative exercise intensities gives an insight into the modulation of the stress response to surgery (Chapter 5). Prehabilitation shows to induce multiple systems adaptations, thus reflecting a positive effect on overall respiratory, cardiovascular, and musculoskeletal systems. This benefit persists after surgery if a high-intensity interval training is included in the program.

Notably, caution should be exercised in interpreting the finding, as per limitations acknowledged in each chapter. From a methodological point of view, i) the retrospective nature of the first three studies calls for further trials to conclusively prove a causative relationship; ii) the single-center design may threaten external validity; iii) important loss in follow-up, especially after surgery, may limit study power to properly assess postoperative outcomes; iv) sample size calculation was based on functional measures, thus underpowered for outcomes such as length of stay and disease progression; and v) issues such as high level of required motivation, access, personnel availability, and financial cost may arise from this approach.

Exploring future directions, and trying to address the above-mentioned limitations, I trust both large multicenter trials (to test unexplored clinical outcomes), and smaller studies (to build a mechanistic understanding of the current data) will be needed. As explained, a causative relationship between prehabilitation and postoperative major complication is yet to be shown. This is the main outcome of a current international multicenter, prospective, randomized controlled trial that will include more than 700 patients undergoing colorectal surgery for cancer.[7] Beyond key data on surgical morbidity, this trial will deal with the main limitations of our previous studies, such as small sample size, lost in follow-up, and single-center design. Our research group at MUHC is playing a leading role in this project that relies on an extensive collaboration with groups in Denmark, France, Italy, Netherlands, and Spain.

Long term outcomes, such as disease progression and recurrence, are yet to be investigated. Since we recently reached an adequate follow-up time, we are currently conducting an analysis of our cohort jointly with the department of surgery at MUHC, aiming at exploring the effect of prehabilitation on 5-year disease-free and overall survival. Notably, giving the rapidly growing population of cancer survivors, prospective effect on overall survival is not limited to disease progression; the potential ability to counteract functional decline, treatment toxicity, weight gain, and metabolic dysfunction may reduce the risk of cardiovascular diseases, and secondary cancer.

Although chapter 5 demonstrates that prehabilitation induces significant perioperative change in whole-body O_2 uptake, it is unclear whether and to which extent this phenomenon results from a peripheral and/or central adaption, and through which cellular mechanisms such change occurs. Particularly relevant may be the complex interaction between mitochondria and autophagy, as this pathway plays a central role in muscle metabolism during stress response. To address this point, our research group is currently conducting a prospective trial, started in August 2018 (MUCH REB 2017-3157), to study perioperative mitochondrial dysfunction, autophagy inhibition, and muscle fiber differentiation in relation to prehabilitation. Furthermore, it is still unknown whether and how prehabilitation can modify tumor milieu and tumor cells metabolism.

Most patients suffering from cancer receive a battery of curative treatments. The implementation of prehabilitation along the entire cancer care is a current perspective of our group. Future studies would need to focus on the impact of prehabilitation and functional conditioning on dose-response curves of anti-cancer treatments, and its potential effects on treatments efficacy, toxicity, timing, and completion rates.

Conclusion

This doctoral thesis demonstrates the safety, tolerability, and efficacy of prehabilitation across the perioperative continuum of colorectal cancer surgery, with beneficial effect on important clinical and physiological outcomes, such as physical functioning and surgical morbidity. Given its ability to improve disease and treatment-related outcomes, my conviction is that prehabilitation should become a component of standard cancer care.

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