Prehabilitation *versus* Rehabilitation

A Randomized Control Trial in Patients Undergoing Colorectal Resection for Cancer

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ABSTRACT

Background: The preoperative period (prehabilitation) may represent a more appropriate time than the postoperative period to implement an intervention. The impact of prehabilitation on recovery of functional exercise capacity was thus studied in patients undergoing colorectal resection for cancer.

Methods: A parallel-arm single-blind superiority randomized controlled trial was conducted. Seventy-seven patients were randomized to receive either prehabilitation (n = 38) or rehabilitation (n = 39). Both groups received a home-based intervention of moderate aerobic and resistance exercises, nutritional counseling with protein supplementation, and relaxation exercises initiated either 4 weeks before surgery (prehabilitation) or immediately after surgery (rehabilitation), and continued for 8 weeks after surgery. Patients were managed with an enhanced recovery pathway. Primary outcome was functional exercise capacity measured using the validated 6-min walk test.

Results: Median duration of prehabilitation was 24.5 days. While awaiting surgery, functional walking capacity increased (≥20 m) in a higher proportion of the prehabilitation group compared with the rehabilitation group (53 *vs.* 15%, adjusted $P = 0.006$). Complication rates and duration of hospital stay were similar. The difference between baseline and 8-week 6-min walking test was significantly higher in the prehabilitation compared with the rehabilitation group (+23.7 m [SD, 54.8] *vs.* −21.8 m [SD, 80.7]; mean difference 45.4 m [95% CI, 13.9 to 77.0]). A higher proportion of the prehabilitation group were also recovered to or above baseline exercise capacity at 8 weeks compared with the rehabilitation group (84 *vs.* 62%, adjusted $P = 0.049$).

Conclusion: Meaningful changes in postoperative functional exercise capacity can be achieved with a prehabilitation program. **(Anesthesiology 2014; 121:937-47)**

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IN Canada, 1 in 13 men and 1 in 12 women will develop colorectal cancer during his or her lifetime, and surgical resection remains the primary treatment.[1] Despite advances in surgical technology, anesthesia and analgesia techniques, and improved perioperative care, complications after colorectal resection remain relatively high and thus represent a priority for quality improvement in general surgery.[2,3] Even in the absence of complications, the postsurgical period is associated with 20 to 40% reduction in physiological and functional capacity that, particularly in the elderly with comorbidities, may not return to preoperative function for several months, if at all.[4] Poor preoperative physical performance has been shown to increase the risk of mortality[5] and the number of postoperative complications[6] and prolong functional recovery.[7]

Efforts to improve recovery have traditionally focused on the postoperative period (rehabilitation). However, this may not be an opportune time to commence lifestyle changes as cancer patients may be fatigued, concerned about disturbing the healing process, or anxious as they await additional treatments for the underlying condition.[8,9] The preoperative period may in fact be a more salient time to intervene, as patients are generally in a better physical condition compared with the acute postoperative period, and may have a prolonged waiting period before surgery (in many healthcare systems). The process of enhancing an individual's functional capacity before scheduled surgery, aimed at improving the patient's tolerance to upcoming physiologic stress, has been coined *prehabilitation*.[10] An observational study suggested that, compared with a historical control, a 4-week

What We Already Know about This Topic

- Preoperative exercise, anxiety-reducing strategies, and protein supplementation may facilitate postoperative recovery
- In a randomized trial, the investigators thus tested the hypothesis that a month of prehabilitation improves postoperative exercise capacity

What This Article Tells Us That Is New

- Two months after surgery, prehabilitated patients were able to walk significantly further in 6 min

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preoperative trimodal intervention comprising moderate-intensity aerobic and resistance exercise, diet counseling with whey protein supplementation, and anxiety-reduction strategies was effective in improving preoperative functional walking capacity and accelerating postoperative recovery.[11] This study was, however, limited by lack of randomization, the use of a historical control, and absence of baseline measures for functional walking capacity.

To quantify the effect of prehabilitation on pre- and postoperative functional walking capacity, a parallel-arm single-blind superiority randomized controlled trial (RCT) was conducted to compare the impact of a trimodal program initiated 4 weeks before surgery (prehabilitation) to an identical program (rehabilitation) initiated after surgery and to be maintained, in both groups, for 8 weeks postoperatively. It was hypothesized that patients participating in the trimodal prehabilitation group would exhibit a clinically meaningful increase in functional walking capacity before surgery to a significantly greater extent than the rehabilitation group, and this preoperative improvement would translate into earlier recovery of functional exercise capacity after surgery.

Materials and Methods

Subjects

The study was approved by the Research Ethics Board of the McGill University Health Centre, Montreal, Quebec, Canada, and study procedures were carried out in accordance with ethical standards (ClinicalTrials.gov registration: NCT01356264). Patient enrollment was initiated in November 2011 and completed in March 2013 at a single university-affiliated tertiary center located in Montreal, Canada. Consecutive adult patients scheduled for curative resection of nonmetastatic colorectal cancer were approached at their initial office visit with their surgeon, and consent was obtained in eligible patients. Subjects were not eligible if they did not speak English or French or if they had premorbid conditions that contraindicated exercise.

Perioperative Care

Perioperative care was guided by a standardized multielement evidence-based comprehensive enhanced recovery after surgery pathway following the consensus review on best care for patients undergoing colorectal surgery.[12] A pilot study was conducted in 2008 by our multidisciplinary team on the feasibility of implementing the enhanced recovery after surgery pathway at our institution.[13] Thereafter, the enhanced recovery after surgery pathway was applied to all patients scheduled for elective colorectal resection.

Study Design

The study was designed as a single-blind parallel-arm superiority RCT. At the time of consent, subjects were instructed to complete a 3-day estimated food record of 2 week days and 1 weekend day. At the time of consumption, participants measured the quantity of all foods and beverages consumed using standard measuring cups and spoons and recorded methods of preparation. Approximately 4 weeks before each patient's scheduled operation, a medical examination was conducted and patients completed baseline questionnaires, as well as biochemical, functional, and anthropometric measurements. Upon completion of the baseline assessment, patients were randomly assigned on a 1:1 ratio by computer-generated random numbers to receive either the prehabilitation intervention or the rehabilitation intervention. No group stratifications were performed. Group allocation was concealed using sequentially numbered sealed envelopes. The scheduling of surgery was not affected by study group. To reduce the risk of bias, the person conducting the measurements was not aware of group allocation.

Patients in the prehabilitation group consulted with a kinesiologist, dietitian, and psychologist at the baseline visit and were instructed to begin the trimodal prehabilitation program at home immediately. Patients in the rehabilitation group participated in an identical consultation at a subsequent visit scheduled within 1 week of their surgery and were instructed to initiate the program at home after the operation. The rehabilitation group did not receive any intervention before surgery as they were promised an intervention to start soon after surgery. To facilitate adherence to the trimodal program, all patients received a standard instructional booklet, written in easily comprehensible language with pictures and figures, describing all elements of the program in detail. The booklet also contained a diary where the patients were asked to document all activities related to the program. All participants were visited after the operation, before hospital discharge, by the kinesiologist, nutritionist, and psychologist who reinforced the preoperative instructions. The postoperative program was carried out by all participants, regardless of group assignment, at home for 8 weeks.

To encourage and measure adherence, patients were contacted weekly by telephone and assessed with a standardized set of open-ended questions to uncover issues related to maintaining compliance to the frequency, intensity, or duration of exercise, the amount of whey protein ingested, and the use of the relaxation methods. Based on the information obtained through telephone and the patient diary, a percentage for compliance was tabulated for each element of the program and equally accounted for in the total compliance value calculated.

Exercise Intervention. A certified kinesiologist assessed and trained each participant following the guidelines of the American College of Sports Medicine.[14] The total-body exercise prescription consisted of up to 50 min of home-based, unsupervised exercise for at least 3 days per week, alternating between aerobic and resistance training. Aerobic exercise intensity was prescribed based on the rate of perceived exertion (Borg scale) from the 6-min walk test (6MWT). The Karvonen formula [(220 – age) – (resting heart rate × % intensity) + resting heart rate] was used to determine the heart rate to be maintained to achieve the desired, prescribed

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intensity. Aerobic exercise could include walking, jogging, swimming, or cycling at patient discretion. Each session included a 5-min warm-up, 20 min of aerobic exercise (starting at 40% of heart rate reserve), 20 min of resistance training (eight exercises targeting major muscle groups performed at an intensity of 8 to 12 repetitions maximum), and a 5-min cooldown. The participant demonstrated the exercises in the presence of the kinesiologist who provided corrective feedback as necessary. Progression of training intensity occurred when the participant could complete the aerobic exercise with mild exertion (Borg 12) and/or when the participant could complete 15 repetitions of a given resistance exercise. To complete the exercises at home, each participant was provided with a set of three resistance bands (light, moderate, and/or heavy resistance). Participants were also given a Borg scale and a heart rate monitor to facilitate compliance to the intensity of the aerobic exercise prescription (entered by the kinesiologist).

Nutrition Intervention. A registered dietitian assessed and provided individualized care to each patient based on the 3-day food diary completed at the time of enrollment. Macronutrient quantities (grams of carbohydrate, fat, and protein consumed) were estimated from each patient's food record with food exchange lists and composition tables. Macronutrient intake was evaluated based on *Dietary Reference Intake* values,[15] and food choices were compared to *Eating Well with Canada's Food Guide* recommendations.[16] Given that the primary goal of the trimodal intervention was to enhance functional capacity, protein was considered the macronutrient of greatest concern. Individual protein requirements were calculated as 1.2 g of protein per kilogram of body weight (adjusted body weight was used for obese patients), as per European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines for surgical patients.[17]

All patients were given a whey protein supplement to guarantee adequate daily protein intake (Immunocal®; Immunotec Inc., Vaudreuil, Quebec, Canada), at a quantity that matched the estimated dietary deficit. Patients were asked to consume the protein supplement within 1 h of their exercise regimen to capitalize on postexercise muscle protein synthesis.[18] Recipes to improve the palatability of the product were also provided. Nutritional care plans then focused on management of cancer-related symptoms (*e.g.*, diarrhea, constipation), blood glucose control if necessary, optimization of body composition (*i.e.*, weight loss/gain if necessary), and appropriate balance of food choices by providing practical suggestions based on actual intake.

Coping Strategies to Reduce Anxiety. All patients received up to a 60-min visit with a trained psychologist who provided techniques aimed at reducing anxiety, such as relaxation exercises based on imagery and visualization, together with breathing exercises. Each patient practiced these exercises with the psychologist and was then provided with a compact disc to perform these exercises at home two to three times per week. The psychologist also provided suggestions on how to enhance and reinforce patients' motivation to comply with the exercise and nutritional aspects of the intervention.

Outcomes and Measures

The primary outcome was functional walking capacity as measured by the 6MWT 8 weeks after surgery. The 6MWT, which has been validated in the colorectal surgical population,[19] evaluates the ability of an individual to maintain a moderate level of physical endurance. Moderate to strong correlations have been found between the 6MWT and maximum oxygen consumption values obtained with other methods of exercise testing.[20] The 6MWT was created to test exercise tolerance but is now used clinically and in research to test functional exercise capacity, defined as "the ability to undertake physically demanding activities of daily living."[21] Participants were instructed to walk back and forth a 15-m stretch of hallway for 6 min at pace that would make them tired by the end of the walk. The total distance covered in 6 min was recorded in meters. Participants were allowed to rest, although any time spent resting was accounted for in the total distance covered in 6 min. Standard motivational messages were given at each minute as per American Thoracic Society guidelines.[22] One practice walk was sufficient at baseline.[23] A change in 6MWT of 20 m was considered clinically meaningful as this is the estimated measurement error in community-dwelling elderly.[24] The 6MWT was conducted at baseline, before surgery, and at 4 and 8 weeks after surgery by an assessor blinded to group assignment.

Age- and sex-specific predicted distances were calculated using the following formula: predicted distance walked in 6 min (m) = 868 − (age × 2.9) − (female × 74.7), where age is in years, and the value "1" is assigned for females and 0 assigned to males.[25]

Secondary outcomes included self-reported physical activity, health-related quality of life, anxiety, and depression. All were assessed at baseline, before surgery, and at 4 and 8 weeks after surgery. Self-reported physical activity was measured by the Community Healthy Activities Model Program for Seniors questionnaire. Subjects estimate the number of total hours spent performing 41 listed activities of various intensities during the previous week. An estimate of weekly energy expenditure (kcal/kg per week) is determined by adding the energy cost of each of the activities performed (metabolic equivalents) over the week.[26] Evidence is available supporting its validity as a measure of recovery after elective abdominal surgery.[27]

The generic health-related quality of life questionnaire (the 36-Item Short Form Survey from the RAND Medical Outcomes Study [SF-36]) includes eight subscales: physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health; each subscale is scored on a 0 to 100 scale. Two summary scores can be derived, the physical component summary and mental component summary scores, each normalized to a mean

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of 50 and an SD of 10.[28] The SF-36 is commonly used in surgical populations, and evidence is available supporting its validity as a measure of perceived recovery of health.[29–31] The patients' psychological state was further assessed using the Hospital Anxiety and Depression Scale (HADS).[32] This questionnaire includes two subscales, anxiety and depression, each with seven items, scored from 0 to 3. A score greater than 8 on either subscale suggests the presence of a mood disorder.

Postoperative complication rates were graded by severity using the Dindo–Clavien classification, in which grade I complications require bedside management, grade II complications require pharmacologic treatment, grade III complications require surgical, endoscopic, or radiologic intervention, and grade IV complications require intensive care treatment.[33]

Statistical Analysis

Sample size calculations were based on a two-sample (repeated measures) comparison of mean changes at 8 weeks compared with baseline. Based on two previous studies performed by our group, we assumed that the average 8-week 6MWT in the rehabilitation group would be 25 +/– 66 m lower than baseline, compared with 35 +/– 68 m above baseline in prehabilitation group.[11,34] A sample size of 80 (40 per group) was required to detect these differences with a power of 80% and an alpha of 0.05.

Continuous data were compared using Student *t* test or Mann–Whitney U test, depending on the distribution of the data. Categorical variables were compared using chi-square or Fisher exact tests. All hypothesis tests were two sided. The primary outcome (6MWT at 8 weeks) was analyzed by calculating the mean difference compared with baseline. Changes in the primary (6MWT) and secondary (SF-36, HADS, Community Healthy Activities Model Program for Seniors) outcomes over time between the two groups were also analyzed using a random-coefficients model, using the treatment group and time as fixed effects, and patient identifier as a random effect, to account for the longitudinal nature of the data.

There were some missing data for several secondary outcomes. To minimize bias, missing data were handled with multiple imputations. In this procedure, missing items are estimated using the appropriate regression (truncated linear regression using the relevant lower and upper values for each measure) model from other observed data and repeated 10 times to generate ten different imputed datasets. Final uncertainty around point estimates incorporates the between (datasets) and within (variable) variances, according to Rubin's rules.[35] The impact of missingness on the results was examined by performing both multiple imputation and complete case analyses. Statistical significance was defined as *P* value less than 0.05. The *P* values for multiple comparisons of potentially correlated data were adjusted for multiplicity using the Tukey–Ciminera–Heyse multiple comparison procedure.[36] All analyses were performed with STATA 12 (Stata Corp., College Station, TX) or open-source R v2.13 statistical software.*

* The R Project for Statistical Computing. Available at: www.r-project.org. Accessed June 19, 2014.

Results

Subjects

A total of 106 patients were approached for consent, of which 89 patients were randomized (fig. 1). Twelve patients were excluded because either they did not undergo resection, underwent emergency surgery, were operated at a different hospital, withdrew consent, or were lost to follow-up. Therefore, a total of 77 patients were analyzed (38 in the prehabilitation group, and 39 in the rehabilitation group). The demographic, physiological, and nutritional characteristics of those patients who were randomized but excluded from the analysis for various reasons were similar to the population studied. Baseline patient and operative characteristics, as well as baseline measures, are reported in table 1.

The median duration between the baseline assessment and surgery was 24.5 days [interquartile range, 20 to 35] in the prehabilitation group and 20 days [interquartile range, 11 to 40] in the rehabilitation group ($P = 0.164$).

Outcomes

Functional Walking Capacity. All patients completed the 6MWT at every assessment. Mean baseline walking capacity was 421 m (SD, 120.0) in the prehabilitation group and 425 m (SD, 83.8) in the rehabilitation group (adjusted $P = 1.000$). The trajectories of mean walking capacity in both groups are shown in figure 2. The overall changes in 6MWT over time were different between the two groups (adjusted $P = 0.032$). Furthermore, there was a clinical and statistically significant difference in the mean change in walking capacity over the preoperative period and at 8 weeks after surgery (table 2).

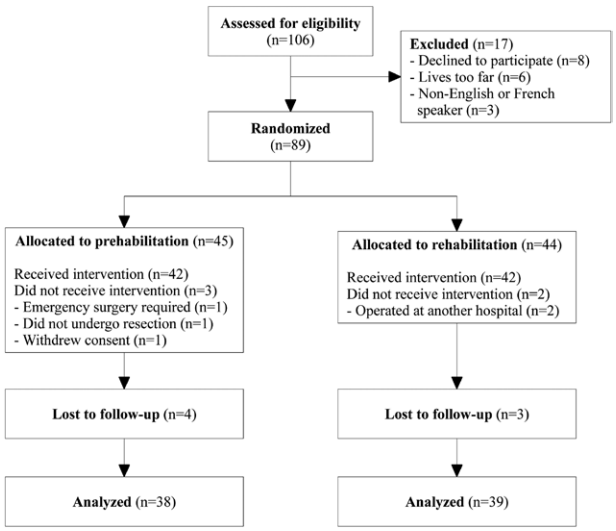

Fig. 1. CONSORT diagram for the trial.

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Preoperative Period. On average, patients in the prehabilitation period significantly improved while waiting for surgery by 25.2 m (SD, 50.2), while those in the rehabilitation group declined by 16.4 m (SD, 46.0); mean difference between the two groups was 41.7 meters (95% CI, 19.8 to 63.5).

Four Weeks after Surgery. At 4 weeks after surgery, almost 50% of patients in both groups remained more than 20 m below their baseline.

Eight Weeks after Surgery. At 8 weeks after surgery, patients in the prehabilitation group were on average above baseline, while those in the rehabilitation group remained below baseline (+23.4 m [SD, 54.8] *vs.* −21.8 m [SD, 80.7], adjusted $P = 0.010$); mean difference between the two groups 45.2 m (95% CI, 13.9 to 77.0)]. Again, a much higher proportion of patients in the prehabilitation group were either above or recovered to baseline walking capacity compared with the rehabilitation group (84 *vs.* 62%, adjusted $P = 0.049$).

Self-reported Physical Activity and Compliance to the Program. Missing data were present for at least one of the secondary outcomes in 22 patients (10 prehabilitation, 12 rehabilitation). There were no differences in the interpretation of the results of the multiply imputed or complete case analyses for SF-36 and HADS. However, for self-reported physical activity, the complete case analysis suggested a significant difference over time between the groups in favor of the prehabilitation group.

Self-reported Physical Activity. Self-reported physical activity and compliance to the program at each time point are shown in table 3. The change in self-reported physical activity was similar between groups.

Compliance to the Program. After surgery, compliance to the program was consistently higher in the prehabilitation group.

Perioperative Outcomes. There were no differences in the incidence of overall 30-day complications, complication severity, or emergency department visits and readmission, as well as no difference in median length of stay (table 4).

Self-reported Outcomes of SF-36 and HADS. Mean values for patient-reported health-related outcomes (SF-36 subscales, and anxiety and depression scores of the HADS) for both groups at each time point are shown in table 5. There

Table 1. Baseline Patient, Operative Characteristics, and Measurements

	Prehabilitation (n = 38)	Rehabilitation (n = 39)
Age, yr	65.7 (13.6)	66.0 (9.1)
Male sex	21 (55%)	27 (69%)
Body mass index, kg/m^2	26.9 (4.6)	28.5 (4.3)
ASA physical status		
I	4 (11%)	4 (10%)
II	24 (63%)	26 (67%)
III+	10 (26%)	9 (23%)
Comorbidities		
Ischemic heart disease	3 (7.5%)	2 (5%)
Hypertension	8 (21%)	12 (31%)
Diabetes	3 (7.5%)	5 (13%)
TNM cancer stage		
1–2	21 (55%)	26 (67%)
3	17 (45%)	13 (33%)
Neoadjuvant therapy	10 (26%)	8 (21%)
Adjuvant therapy within 8 weeks	14 (37%)	13 (33%)
Laparoscopic procedure	37 (97%)	35 (90%)
Type of resection		
Colon*	24 (53%)	23 (59%)
Rectum†	14 (37%)	16 (41%)
New stoma	13 (34%)	12 (31%)
6MWT (meters)	421 (120)	425 (84)
6MWT (% predicted)	65 (17)	65 (11)
Number of patients with 6MWT <400 m	13 (34%)	16 (41%)
Physical activity, kcal/kg per week [IQR]	25 [9–67]	34 [18–63]
Grip strength left hand, kg (SD)	29 (11)	32 (9)
Grip strength right hand, kg (SD)	30 (11)	34 (10)
Lean body mass, kg (SD)	52 (11)	56 (10)
Fat body mass, kg (SD)	31 (9)	31 (10)
Fat percentage, % of weight (SD)	37.0 (10)	35.5 (9)
Albumin, g/l (SD)	39 (5)	38 (7)

Data are presented as mean (SD), median [IQR], or n (%).

* Includes right and left hemicolectomy and sigmoid resection. † Includes anterior resection, low anterior resection, and abdominoperineal resection.

ASA = American Society of Anesthesiologists; IQR = interquartile range; TNM = tumor–node–metastasis; 6MWT = 6-min walk test.

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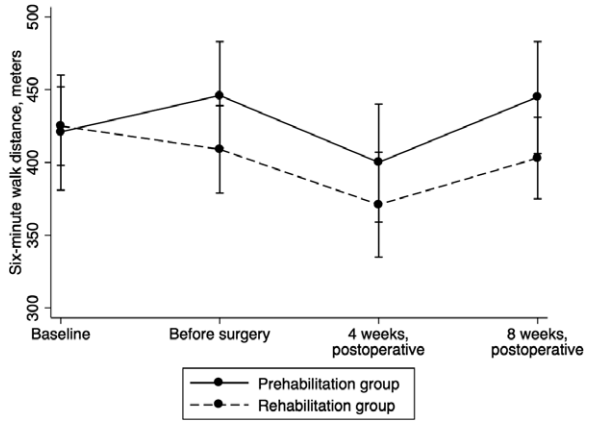

Fig. 2. Mean distance walked in 6 min at the four study time points for the prehabilitation and rehabilitation groups ($P = 0.016$). *Whiskers* represent 95% CIs.

were no differences over time between the two groups for any of the subscales of the SF-36 or HADS.

Discussion

Preparing patients for surgical resection of colorectal cancer with a preoperative trimodal program comprising home-based moderate aerobic and resistance exercises, nutritional counselling with whey protein supplementation, and anxiety-reduction strategies leads to a better functional walking capacity before and after colorectal surgery compared with starting the program postoperatively.

Preoperative conditioning, or prehabilitation, aims to improve preoperative functional and physiological capacity sufficiently to enable patients to withstand surgical stress and facilitate postoperative recovery.[10] In the present trial, the average 25.2-m increase in preoperative walking capacity achieved with trimodal prehabilitation offsets the average 21.8-m decline observed with rehabilitation in the first 4 weeks after surgery, thus providing a buffer and facilitating a faster return to baseline walking capacity. It is unclear which component of the trimodal intervention contributes most to recovery, or whether the increase in functional walking capacity is an effect of trimodal synergy. One review of 12 RCTs reported decreased length of hospital stay and fewer pulmonary complications after preoperative exercise in patients undergoing cardiac and abdominal surgery.[37] In contrast, a more recent systematic review of eight RCTs was unable to demonstrate that physical exercise alone provides physiological improvement and clinical benefit.[38] A previous RCT conducted by our group in patients undergoing colorectal surgery compared home-based programs of moderate *versus* intense exercise, and an unexpected result was found for the intense exercise group[34]: while waiting for surgery, functional walking capacity deteriorated in a third of patients assigned to the intense exercise program, with compliance at a mere 16%, thus indicating that the prescribed exercise regimen could not be maintained. Predictors of poor surgical outcome included deterioration while waiting for surgery, age over 75 yr, and high anxiety, thus supporting the need to better identify which factors, such as disease progression, catabolic state, poor compliance, and psychological stress, in addition to exercise, contribute to functional deterioration before surgery. The trimodal program thus evolved to combine moderate physical activity with nutritional counseling and whey protein supplementation together with coping strategies to address mental health and improve program compliance. In an observational, feasibility pilot study, patients enrolled in the new multimodal program, compared with historical controls, demonstrated significantly higher compliance and functional walking capacity throughout the perioperative period.[11] At a close analysis of the pilot study and the present investigation, it appears that while 40% of the pilot control group had recovered by 8 weeks without

Table 2. Changes in 6MWT over Time Compared to Baseline

	Prehabilitation (n = 38)	Rehabilitation (n = 39)	Adjusted *P* Value*
Presurgery			
Mean change in 6MWT during the preoperative period†, meters (SD)	+25.2 (50.2)	−16.4 (46.0)	<0.001
% of patients exhibiting clinically important changes during the preoperative period†			0.006
Deterioration‡	8 (21%)	14 (36%)	
No change§	10 (26%)	19 (49%)	
Improvement‖	20 (53%)	6 (15%)	
8 weeks after surgery			
Mean change in 6MWT at 8 weeks, meters (SD)	+23.4 (54.8)	−21.8 (80.7)	0.020
% of patients exhibiting clinically important changes at 8 weeks			0.022
Deterioration‡	6 (16%)	15 (38%)	
No change§	10 (26%)	14 (36%)	
Improvement‖	22 (58%)	10 (26%)	

* *P* value adjusted for multiple comparisons. † Time between baseline and immediate presurgery assessments. ‡ Greater than 20-m *decrease* compared with baseline. § Within 20 m of baseline. ‖ Greater than 20-m *increase* compared with baseline.
6MWT = 6-min walk test.

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Table 3. Self-reported Physical Activity and Total Trimodal Compliance at Each Time Point

	Prehabilitation (n = 38)	Rehabilitation (n = 39)	Adjusted *P* Value*
Baseline self-reported physical activity, kcal/kg per week (SD)	45.5 (49.8)	55.9 (68.4)	0.132
Self-reported physical activity before surgery, kcal/kg per week (SD)	81.2 (101.0)	61.7 (125.6)	
Self-reported physical activity 4 weeks after surgery, kcal/kg per week (SD)	46.4 (68.7)	32.8 (38.0)	
Self-reported physical activity 8 weeks after surgery, kcal/kg per week (SD)	47.7 (52.2)	35.7 (63.8)	
Compliance during preoperative period, % (SD)	78% (21)	N/A	
Compliance from surgery to 4 weeks, % (SD)	53 (30)	31 (26)	<0.001
Compliance from 4 to 8 weeks, % (SD)	53 (33)	40 (31)	0.117

Values are mean (SD), derived from multiple imputations.

* Denotes the *P* value from repeated-measures analysis that the changes over time in physical activity scores are different between the two groups, adjusted for multiple comparisons.

N/A = not applicable.

Table 4. Perioperative Outcomes

	Prehabilitation (n = 38)	Rehabilitation (n = 39)	*P* Value
Patients with at least one 30-day complication	12 (32%)	17 (44%)	0.277
Ileus	3 (8%)	6 (15%)	
Wound infection	3 (8%)	3 (8%)	
Anastomotic leak	2 (5%)	3 (8%)	
Abscess	1 (3%)	3 (8%)	
Pulmonary edema	1 (3%)	1 (3%)	
Urinary tract infection	1 (3%)	0	
GI bleeding	1 (3%)	0	
Intestinal ischemia	0	1 (3%)	
Grade of most severe complication			0.506
Grade I	5 (13%)	5 (13%)	
Grade II	3 (8%)	6 (15%)	
Grade III	4 (11%)	4 (10%)	
Grade IV	0	2 (5%)	
Primary hospitalization, days [IQR]	4 [3–5]	4 [3–7]	0.812
Total hospitalization*, days [IQR]	4 [3–6]	5 [3–9]	0.446
30-day emergency department visits	6 (16%)	9 (23%)	0.420
30-day readmission	6 (15%)	5 (13%)	0.780

* includes primary admission and any readmission.

GI = gastrointestinal; IQR = interquartile range.

any intervention, 62 and 84% of the rehabilitation group and prehabilitation group, respectively, returned to baseline levels, indicating that a clinically significant proportion of patients improve with this trimodal program.

In designing the present trial of the trimodal program, we addressed challenges encountered in the previous RCT, including the potential bias that ensues from not being able to blind patients to group assignment. For this reason, we chose not to opt for a sham intervention, but instead to provide all patients with a program which would be allocated either before or after surgery. This approach attracted patient participation, with a lower refusal rate than our previous trial. Furthermore, while a formal trimodal intervention may not be included as part of current practice after surgery, nutritional supplements and physical activity are increasingly encouraged in the context of enhanced recovery programs.[39–41] Therefore, we believe that the design was appropriate under the constraint of a clinical trial.

The interval of time from the diagnosis to surgery in the prehabilitation group was between 3 and 4 weeks and within the time recommended by the Canadian Oncological Society.[42] This time period was sufficient to produce an increase in functional walking capacity, with a mean difference in distance of approximately 40 m between the prehabilitation and the rehabilitation groups at each time point. Within the measurement error, which is estimated at 20 m, over 50% of subjects in the prehabilitation group improved by more than 20 m preoperatively, while in the rehabilitation group 36% decreased by more than 20 m. Eight patients (21%) in the prehabilitation group deteriorated before surgery, with

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Table 5. Patient-reported Measures of SF-36 Subscales and HADS

	Prehabilitation (n = 38)	Rehabilitation (n = 39)	Adjusted *P* Value*
SF-36 subscales			
Physical functioning†			0.468
Baseline	72.9 (27.4)	76.8 (22.1)	
Before surgery	73.5 (25.0)	72.6 (29.7)	
4 weeks	61.8 (31.6)	62.1 (30.5)	
8 weeks	74.3 (26.1)	72.3 (24.2)	
Role physical†			0.360
Baseline	52.9 (46.1)	53.0 (49.6)	
Before surgery	62.3 (44.3)	56.6 (50.4)	
4 weeks	24.2 (42.3)	15.8 (35.1)	
8 weeks	40.7 (45.6)	35.0 (44.6)	
Bodily pain†			0.623
Baseline	68.1 (27.7)	75.8 (24.6)	
Before surgery	74.7 (22.6)	73.6 (25.3)	
4 weeks	59.9 (30.7)	64.1 (28.2)	
8 weeks	74.2 (24.7)	73.2 (26.7)	
General health†			0.980
Baseline	62.0 (20.4)	63.5 (20.3)	
Before surgery	66.4 (22.8)	60.0 (25.8)	
4 weeks	66.0 (19.3)	64.9 (18.4)	
8 weeks	65.7 (22.9)	68.2 (19.5)	
Vitality†			0.597
Baseline	53.1 (19.9)	59.6 (21.6)	
Before surgery	60.3 (22.7)	59.2 (23.4)	
4 weeks	51.9 (25.4)	53.6 (23.6)	
8 weeks	61.0 (21.8)	62.6 (17.7)	
Social functioning†			0.656
Baseline	71.0 (25.8)	77.6 (21.2)	
Before surgery	72.3 (28.8)	75.4 (31.9)	
4 weeks	53.2 (30.4)	60.4 (26.5)	
8 weeks	75.6 (23.3)	72.4 (27.3)	
Role emotional†			0.672
Baseline	69.5 (44.8)	68.4 (38.8)	
Before surgery	62.8 (48.8)	53.4 (49.8)	
4 weeks	46.7 (53.9)	46.3 (48.5)	
8 weeks	69.4 (38.6))	52.9 (47.5)	
Mental health†			0.085
Baseline	67.8 (18.5)	72.7 (15.4)	
Before surgery	71.6 (21.5)	69.6 (24.8)	
4 weeks	70.6 (17.5)	70.6 (19.9)	
8 weeks	79.0 (16.1)	72.4 (20.9)	
HADS			
Anxiety‡			0.330
Baseline	6.9 (4.3)	6.8 (4.2)	
Before surgery	5.6 (3.9)	5.9 (4.7)	
4 weeks	4.9 (3.9)	5.4 (5.1)	
8 weeks	4.3 (3.4)	5.1 (4.7)	
Depression‡			0.999
Baseline	3.8 (4.6)	4.3 (4.0)	
Before surgery	3.2 (3.1)	3.6 (4.6)	
4 weeks	4.2 (3.3)	3.6 (4.1)	
8 weeks	3.2 (3.2)	3.7 (4.3)	

Data presented as mean (SD).

* Denotes the *P* value from repeated-measures analysis that the changes over time in subscale scores are different between the two groups, adjusted for multiple comparisons. † Range 0–100. Higher values represent better scores. ‡ Range 0–21. Higher values represent worse scores.

HADS = Hospital Anxiety and Depression Scale; SF-36 = the 36-Item Short Form Health Survey.

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a drop from a mean value of 500 m to 463 m. No specific reasons (tumor burden, low albumin, type of surgery, high HADS score) could be found, except that five of them had poor compliance to the trimodal program. One can also assume that, with an average baseline 6MWT of 500 m, well above the 60% predicted value of the prehabilitation group, there was not much room for further improvement. The magnitude of change in walking capacity in the prehabilitation group can be considered clinically relevant as it is above the range of the minimal clinically important difference for the 6MWT recently reported in the context of postoperative recovery.[43] This functional data is supported by a statistically significant increase in self-reported physical activity by the prehabilitation group during the 3 to 4 weeks before surgery, equivalent to an average of 10,000 kcal. However, the increased walking capacity and physical activity were not associated with improved health-related quality of life. Because the 6MWT only measures functional walking capacity, and not general health, this may not be unexpected. Six weeks after colorectal surgery, the correlation between the 6MWT and the physical subscales of the SF-36, while statistically significant, is only poor to moderate.[19] We did not specifically investigate the impact of prehabilitation on activities of daily living, return to employment, or leisure activities outside of what was queried in the Community Healthy Activities Model Program for Seniors questionnaire.

While there is no accepted standard definition, or standard measure, of postoperative recovery, measures of functional status and performance have been recommended.[27,44] The 6MWT, a test of functional exercise capacity, was chosen as the primary outcome because it integrates all components of physical activity including balance, speed, muscle force, and endurance. Evidence supports the 6MWT as a valid measure of recovery after colorectal surgery.[19] Advantages of the 6MWT as a measure of recovery include the lack of a ceiling effect and the fact that it is not affected by response shift, unlike self-reported symptoms or health-related quality of life. It does not require specialized equipment and can be administered even in a small place. As the error of the 6MWT has been estimated to be ±20 m,[24] the differences between the two groups over the prehabilitation period and at 8 weeks may be considered clinically important.

While physical activity was of primary importance, the additional roles of nutritional optimization and psychological motivation cannot be ruled out as essential contributors to the observed improvement in functional capacity, particularly in cancer patients.[45] Whey protein was chosen as the protein supplement because of its amino acid composition, including rich leucine content, which has been found to independently stimulate translation initiation of protein synthesis in skeletal muscle through activation of the mammalian target of rapamycin complex.[46] Whey protein supplementation has also been found to promote synthesis of intracellular antioxidant glutathione, attributed to its high cysteine content, and to attenuate proinflammatory cytokines in nonsurgical populations and thus may promote a protein-sparing effect after surgery.[47] The aim of the nutritional intervention was provision of protein and energy to guarantee available substrate for the anabolic window following exercise.[48] Similarly, the interaction with the psychologist aimed to teach the patients to take control of stressful occasions throughout the treatment and boost participation in the program.

There was no difference in clinical outcomes between the prehabilitation and rehabilitation groups. Patients were cared for within an enhanced recovery pathway with a very high use of laparoscopy, and length of stay was relatively low in both groups. Although this study was not powered to determine the impact of prehabilitation on clinical outcomes, we recently demonstrated that lower preoperative 6MWT was associated with an increased risk for cardiorespiratory complications.[49] These preliminary results are intended to serve as a proof of concept and need to be confirmed in a large randomized study, perhaps targeting prehabilitation efforts to patients with poorer baseline functional exercise capacity.

The results of this RCT have to be interpreted in view of several limitations. First, it is possible that patients randomized to the rehabilitation group could have sought out similar interventions on their own in the preoperative period. We did not ask patients in the rehabilitation group whether they changed their diet or sought out psychological support independently, but the majority of the rehabilitation group did not report any increase in physical activity in the preoperative period. At a close analysis of the Community Healthy Activities Model Program for Seniors questionnaire only six patients (15%) of this group reported vigorous physical activity in the preoperative period, which could explain the 41-m increase in 6MWT observed. Second, there was a moderate amount of missing data that had to be handled with multiple imputations, although all of the missing data were secondary outcomes. This was due to several reasons such as failure to answer all questions, the questionnaire was not returned, or unwillingness to fill the questionnaire. While multiple imputations may result in less bias than other methods of handling missing data,[50] and may be a valid method to handle as much as 30% missing data,[51] the potential for biased results is still present. Lastly, we did not measure immunologic changes over the study period. However, it is unclear whether any differences in immunologic parameters could have been detected at the time points selected for our study, as changes in immunologic indices are short-lived and their relationship to long-term outcomes is unclear.

Meaningful changes in functional exercise capacity can be achieved with prehabilitation in patients scheduled for elective colorectal surgery for cancer. The same multimodal intervention started after surgery did not produce similar functional benefits. There is a need to understand the mechanism for such functional improvement and the effectiveness of this intervention in the context of the continuum of cancer care.[9]

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Competing Interests

The authors declare no competing interests.

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