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

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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 $\geq$19 meters) or not (6MWD change $<$19 meters). The primary outcome measure was 30-d 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 $\geq$19 m preoperatively, and 99 (55.3%) did not. Subjects whose FC increased had lower CCI (0 [0–8.7] versus 8.7 [0–22.6], $p = .022$). Furthermore, they were less likely to have a severe complication (adjusted OR 0.28 (95% CI 0.11–0.74), $p = .010$), and to have an ED visit.

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

Abbreviation: 6MWD: 6-min walk distance; 6MWT: 6-min walk test; CCI: Comprehensive Complication Index; CHAMPS: Community Healthy Activities Model Program for Seniors questionnaire; CI: confidence interval; FC: functional capacity; GEE: generalized estimating equation; IQR: interquartile ranges; MCID: minimal clinically important difference

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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-discipinary 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

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yet to be shown. This represents the 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.

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 counseling, 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 min, 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 d 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 <19 m versus ≥ 19 m). 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 the 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.

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, $n = 6$).

Table 1. Patient characteristics.

	Preoperative 6MWD change		
	<19 m $n = 99$	≥19 m $n = 80$	p
Age (years)	67.8 (65.7–69.9)	68.0 (65.2–70.7)	.861
>75 years old, *n* (%)	27 (27)	25 (31)	.621
Male, *n* (%)	60 (61)	53 (66)	.553
BMI (kg/m^2)	28.2 (27.3–29.1)	27.3 (26.3–28.3)	.353
Obesity (BMI ≥ 30), *n* (%)	32 (32)	28 (35)	.751
Hemoglobin (g/dL)	13.3 (12.2–14.5)	13.6 (12.3–14.8)	.942
Albumin (g/L)	40 (38–41)	41 (37–42)	.304
Current smoker, *n* (%)	7 (7)	5 (6)	1.0
Medically treated diabetes, *n* (%)	20 (20)	14 (18)	.704
Neoadjuvant chemotherapy, *n* (%)	15 (15)	14 (18)	.688
Previous abdominal surgery, *n* (%)	56 (56)	43 (54)	1.0
ASA score, *n* (%)			.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)	.105
CR-POSSUM physiologic score	9 (8–10)	9 (7–10)	.494
CR-POSSUM operative severity	8 (7–11)	7 (7–11)	.673
Tumor TNM stage			.582
0–I	35 (35)	29 (36)	
II	25 (25)	27 (34)	
III	33 (33)	22 (27)	
IV	6 (6)	2 (3)	
Baseline 6MWD (m)	443 (424–462)	416 (391–440)	.077
Physical activity (kcal/kg per week)	23.3 (10.5–53.5)	24.3 (10.0–53.0)	.824

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

Baseline characteristics are shown in Table 1. Eighty subjects (45%) increased their 6MWD by ≥19 m before surgery (group ≥19 m), whereas 99 participants (55%) did not (group <19 m). There were no significant differences between the two groups in demographic, clinical characteristics, or self-reported baseline physical activity. Nonetheless, subjects in the ≥19 m group were likely to have a lower walking capacity at baseline (6MWD, 416 (391–440) m versus 443 (424–462) m, $p = .077$).

Of our cohort, 111 subjects (62%) had prehabilitation and 68 (38%) were assigned to the control group. In the preoperative period, compliance with 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-d complication severity was lower in the ≥19 m group compared with the <19 m group (CCI 0 [0–8.7] versus 8.7 [0–22.6], $p = .022$) (Table 3). The proportion of patients with severe complications was lower in the ≥19 m group than the <19 m group (25/99 (25%) versus 8/80 (10%), $p = .011$).

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), $p = .011$).

Secondary outcomes

Patients in the >19 m group had less hospital visits after discharge (10 (13%) versus 25 (25%), $p = .038$). There were no significant differences in the duration of hospital stay, numbers of readmissions, and in types of complications (Table 5). No patients died during this period.

Table 2. Operative characteristics.

	Preoperative 6MWD change		
	<19 m $n = 99$	≥19 m $n = 80$	p
Procedure performed			.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)	.538
Laparoscopic surgical approach	75 (76)	70 (88)	.056
New stoma formation	25 (25)	19 (24)	.863
Duration of surgery (minutes), median [IQR]	190 [135–253]	186 [130–245]	.281
Blood loss (mL), median [IQR]	150 [100–300]	150 [100–300]	.554
Clinically significant intraoperative complications	5 (5)	6 (8)	.542

Values are number (%) otherwise noted. IQR: interquartile range.
aLaparoscopic interventions converted into open were not considered in this category.

Table 3. Postoperative outcomes.

	Preoperative 6MWD change		
	<19 m $n = 99$	≥19 m $n = 80$	p
30-d comprehensive complication index, median [IQR]	8.7 (0–22.6)	0 (0–8.7)	.022
Participants with at least 1 complication within 30 d	50 (50)	30 (38)	.097
Length of primary hospital stay (days), median [IQR]	4 (3–6)	3 (3–5)	.236
30-d ED visit	25 (25)	10 (13)	.038
30-d hospital readmissions	14 (14)	5 (6)	.142

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

Table 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	.007	0.29	0.11–0.75	.011
Age, 75+ years old	1.00	0.97–1.03	.878	1.00	0.96–1.05	.772
Gender, male	2.12	0.89–5.02	.088	2.56	0.99–6.63	.053
BMI ≥ 30	0.98	0.90–1.07	.739	0.96	0.87–1.07	.463
ASA ≥ 3	2.27	1.02–5.01	.042	1.92	0.77–4.78	.162
Cancer stage						
1	0.87	0.23–3.18	.828	0.78	0.18–3.36	.745
2	0.81	0.26–2.61	.735	0.76	0.20–2.91	.689
3	1.12	0.37–2.39	.834	0.91	0.25–3.31	.893
4	2.70	0.50–14.52	.247	2.43	0.32–18.5	.389
Laparoscopic surgery	0.46	0.19–1.08	.074	0.91	0.32–2.57	.857
Rectal surgery	2.01	0.91–4.33	.071	2.27	0.92–5.59	.531

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

Table 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 (%). 6MWD: 6-minute walk distance.

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 physiopathological 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 an 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 m [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, non-randomized 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.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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