Improved Disease-Free Survival After Prehabilitation for Colorectal Cancer Surgery

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Objective: The objective of this study was to investigate the effect of prehabilitation on survival after colorectal cancer surgery.

Summary of Background Data: Preoperative multimodal exercise and nutritional programs (prehabilitation) improve functional capacity and recovery following colorectal surgery. Exercise may also affect cancer outcomes by mediating the systemic inflammatory response. The effect of prehabilitation on cancer outcomes is unknown.

Methods: Pooled data from 3 prehabilitation trials (2 randomized controlled trials, 1 cohort) in patients undergoing elective, biopsy-proven, primary non-metastatic colorectal cancer surgery from 2009 to 2014 within an enhanced recovery program were analyzed. Patients were grouped into +prehab or−prehab. The primary outcomes were 5-year disease-free (DFS) and overall survival (OS). DFS and OS were analyzed using Kaplan-Meier curves and multiple Cox regression.

Results: A total of 202 patients were included (+prehab 104, −prehab 98). Median prehabilitation duration was 29 days (interquartile range 20–40). Patient and tumor characteristics were well-balanced (33% stage III). Postoperative complications and time to adjuvant chemotherapy were similar. Mean duration of follow-up was 60.3 months (standard deviation 26.2). DFS was similar for the combined group of stage I–III patients ($P = 0.244$). For stage III patients, prehabilitation was associated with improved DFS (73.4% vs 50.9%, $P = 0.044$). There were no differences in OS ($P = 0.226$). Prehabilitation independently predicted improved DFS (hazard ratio 0.45; 95% confidence interval, 0.21–0.93), adjusting for stage and other confounders. Prehabilitation did not independently predict OS.

Conclusion: In this report, prehabilitation is associated with improved 5-year DFS in stage III colorectal cancer. This finding should be confirmed in future trials.

Keywords: cancer outcomes, colorectal cancer, colorectal surgery, disease-free survival, exercise, oncologic outcomes, overall survival, patient outcomes, prehabilitation, trimodal prehabilitation

(*Ann Surg* 2019;xx:xxx–xxx)

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Support: M.T. is supported by research scholarships from the Quebec Health Sciences Research Fund (FRQ-S) and the Canadian Institute for Health Research (CIHR).

The authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

ISSN: 0003-4932/16/XXXX-0001

DOI: 10.1097/SLA.0000000000003465

Despite advances in surgical techniques and implementation of enhanced recovery pathways, the incidence of postoperative complications following colorectal surgery remains high.[1] Functional capacity (physical and nutritional status as well as psychosocial factors) has been identified as a potentially modifiable risk factor for poor surgical outcomes.[2] Several studies have demonstrated an improvement in preoperative baseline functional capacity with targeted trimodal prehabilitation, which includes exercise, nutritional and psychological interventions.[3–6] Prehabilitation before surgery aims at improving patient physiological reserve to attenuate the risk of postoperative functional decline, and potentially decrease the incidence of postoperative complications and hasten recovery.[4,6–10]

Although early postoperative outcomes may be improved with prehabilitation, it is unknown whether this translates into better colorectal cancer outcomes.[4,5,8,9] There is some evidence that patients with lower baseline functional status have worse long-term oncologic outcomes.[11,12] Therefore, improvement of functional status through targeted prehabilitation may result in better cancer outcomes, either by influencing the timing of initiation and/or tolerability of adjuvant therapies, or through the effect of exercise, which may alter disease-free survival through a variety of biochemical and physiologic processes.[4,6,7,12–17] The long-term effects of trimodal prehabilitation on cancer outcomes have not yet been characterized. Therefore, the objective of this study is to investigate the effect of trimodal prehabilitation on long-term oncologic outcomes after elective colorectal cancer surgery.

METHODS

Study Population

A follow-up pooled analysis of 3 previous prospective studies conducted at a single high-volume specialist-referral center from July 2009 to August 2015 was performed.[4,6,7] These included 1 prospective pre- and postintervention cohort study[6] and 2 randomized controlled trials[4,7] investigating the effect of the implementation of a trimodal prehabilitation program on postoperative outcomes and recovery in colorectal cancer patients. Detailed methodology regarding patient enrolment, randomization, and group allocation has been previously reported.[4,6,7] In brief, adult patients undergoing colorectal surgery for nonmetastatic colorectal adenocarcinoma, including rectal tumors, were eligible to participate in those studies. Eligible patients were referred to the prehabilitation program by their treating surgeon. Subjects were excluded if they had metastatic disease at the time of diagnosis, if they were diagnosed with any medical condition precluding the safe use of physical activity, or if they were unable to understand English or French sufficiently to accurately complete the study questionnaires. The study protocol was approved by the local institutional review board.

In the present study, patients were further excluded if they underwent surgery for locally recurrent cancer, had in-situ disease on pathology specimen, unresectable primary tumors, or appendiceal

tumors. Patients with pulmonary nodules, liver lesions, or retroperitoneal lymphadenopathy noted on preoperative imaging with low initial suspicion for metastatic disease, but recognized to be malignant in the early postoperative period, were also excluded from this study and labeled as having metastatic disease at the time of surgery. None of the included patients were found to have an inherited colorectal cancer syndrome, such as Lynch syndrome and familial adenomatous polyposis.

Trimodal Prehabilitation

The trimodal prehabilitation program consisted of a combination of preoperative exercise, nutritional and psychosocial counseling. Patients randomized to the intervention group initially met with a kinesiologist, nutritionist, and trained psychologist for a global assessment. During this first visit, an individualized home exercise program (30 minutes of moderate aerobic activity 3–4 times per week with resistance training with[7] or without supervision[4,6]), nutritional counseling, whey protein isolate supplements, and anxiety-reduction techniques were provided to patients. Patients were instructed to follow their program until the day of their surgery. Duration of prehabilitation was mainly determined by the wait time until surgery and averaged 4 weeks in all studies. In 2 of the 3 included studies, control patients underwent a similar initial assessment preoperatively, but were instructed to follow their program in the postoperative period only (rehabilitation). Patients in the intervention and control groups were encouraged to continue their program for 8 weeks postoperatively. All 3 studies were conducted within a mature enhanced recovery program after colorectal surgery.[18]

Outcomes and Variable Definitions

Prospectively collected data from previous studies included baseline patient demographics (age, sex, body mass index, comorbidities classified using the American Society of Anesthesiologists score), prehabilitation program compliance, surgical procedure, length of stay, and perioperative outcomes [postoperative complications were measured using the Clavien-Dindo (CD) classification with severe complications defined as CD $\geq$3].[19] After obtaining institutional research ethics review board approval, tumor-related variables were retrospectively collected from electronic medical records and included tumor location, grade, lymphovascular invasion, perineural invasion, margin status, pathological TNM stage, lymph node harvest, and number of positive lymph nodes. Lymph node ratio was calculated from available data and dichotomized as $<$0.10 and $\geq$0.10.[20] Date of initiation of adjuvant systemic therapy was also recorded.

The primary outcomes of this study were 5-year disease-free (DFS) and overall survival (OS). Last date of contact and vital status at last contact were used to determine OS. Recurrence was determined from the review of all surveillance computed tomography scan and colonoscopy reports performed as per routine surveillance guideline schedule following curative resection of colorectal cancer.[21] DFS was defined as the time interval between surgery and the date of imaging/endoscopic test revealing the presence of metastatic disease or local recurrence. Secondary outcomes included receipt of adjuvant systemic therapy and time to initiation of systemic chemotherapy (oral or intravenous) from the day of surgery.

Statistical Analysis

Data are represented as n (%) for categorical variables and mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables. The prehabilitation and control groups were compared. Univariate analyses were performed using student *t* test to compare means and 2-sample Wilcoxon rank-sum (Mann-Whitney) test for medians of continuous variables. Two-sided Fisher exact and chi-square test were used for categorical variables. A subgroup analysis of stage III disease was performed to assess and compare chemotherapy-related outcomes between groups. Kaplan–Meier survival curves were generated to describe 5-year DFS and OS, and log-rank tests to compare the cumulative survival distributions. Multiple regression analyses were performed using Cox proportional hazard models to identify independent predictors of 5-year DFS and OS, adjusting for potential confounders. A multiple regression analysis using Cox proportional hazard model was completed for the subgroup of patients with stage III disease. A subgroup analysis was also performed for rectal cancer patients. All analyses were performed using STATA 12.1 (StataCorp, College Station, TX).

RESULTS

A total of 244 patients were reviewed, of which 202 were included. The prehabilitation group included 104 patients and the control group 98 (Fig. 1). A total of 42 patients were excluded and these were evenly distributed across studies. Baseline demographics, tumor and operative characteristics as well as perioperative outcomes were well balanced between groups (Tables 1 and 2). Mean age was 68.0 years (SD 11.0) and 26.7% of patients had ASA score$\geq$3. Seventy-five patients (37.7%) had rectal tumors and 66 (32.7%) stage III disease. Median prehabilitation duration was 29 days (IQR 20–40) and median compliance with trimodal prehabilitation program was 80% (IQR 50–100). For the rectal cancer patients, prehabilitation took place during the wait time after neoadjuvant therapy. Mean duration of follow-up was 60.3 months (SD 26.2). Receipt of adjuvant therapy and timing of initiation of systemic chemotherapy were similar between groups (Table 2).

On Kaplan-Meier survival analysis, 5-year cumulative OS and DFS did not significantly differ between patients who underwent prehabilitation and controls (96.4% vs 91.7% for OS and 85.3% vs 79.3% for DFS) (Figures 2A and 3). However, in the subgroup analysis of stage III disease, prehabilitation was associated with higher 5-year DFS compared to control group (73.4% vs 50.9%, log-rank $P = 0.045$) (Fig. 2B). Five-year DFS and OS were similar between groups in the subgroup analysis of rectal cancer patients (100% in the prehabilitation vs 94.5% in the control group for OS, log-rank test $P = 0.173$; 86.9% vs 79.9% for DFS, log-rank test $P = 0.366$) (Figure 4, supplemental, http://links.lww.com/SLA/B698).

Results of adjusted multiple Cox proportional hazard regression for DFS for all stages combined and for stage III disease are shown in Table 3. After adjusting for possible confounders, trimodal prehabilitation independently predicted improved DFS in all stages combined and in the subgroup of patients with stage III disease. In the OS models, prehabilitation was not significantly associated with the outcome. In addition, none of the covariates independently predicted OS as shown in Table 4. In the subgroup analysis of rectal cancer patients, prehabilitation independently predicted improved DFS (hazard ratio 0.22; 95% CI 0.05–0.91, $P = 0.036$) when confounders were adjusted for (Table 5, supplemental, http://links.lww.com/SLA/B698). Details regarding neoadjuvant therapy and wait times to surgery can be found in Table 6 (supplemental, http://links.lww.com/SLA/B698). Subgroup analyses of stage III disease and rectal cancer were not performed for OS owing to the lack of events (ie, death) (Fig. 3).

DISCUSSION

Trimodal prehabilitation is associated with an improvement in preoperative functional capacity and short-term postoperative recovery after major abdominal surgery, and may also decrease the incidence of postoperative complications.[3–6,8–10,22] Multiple recent

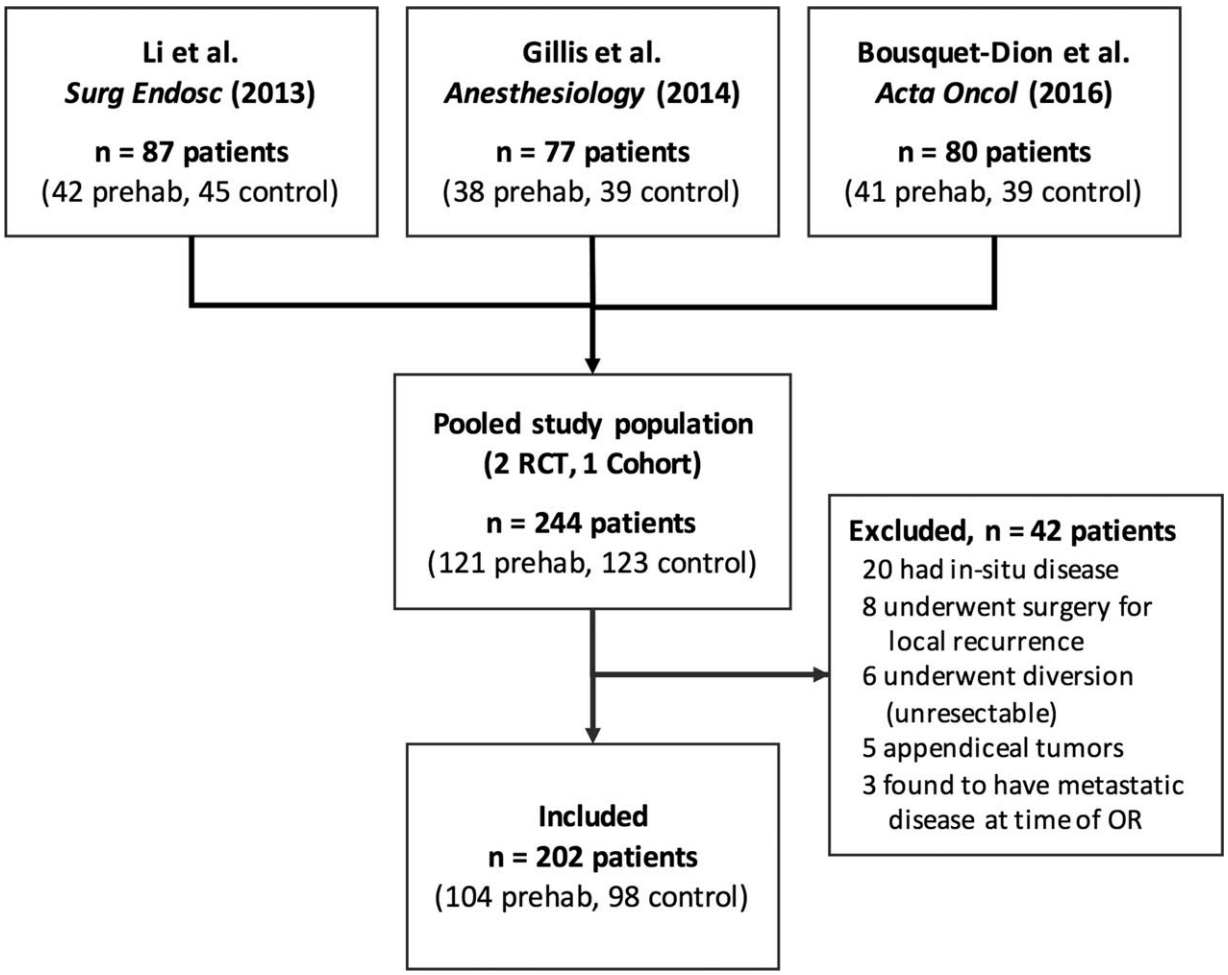

FIGURE 1. Flow chart of study population.

studies have also reported that exercise may alter DFS, but the long-term effects of trimodal prehabilitation on oncologic outcomes have, however, not yet been characterized.[13–17] The objective of this study was thus to investigate the effect of trimodal prehabilitation on survival after colorectal cancer surgery.

In the present study, prehabilitation was associated with an improved 5-year DFS in patients with stage III disease. A similar result was not observed when all stages were combined likely because of the low numbers of recurrences in stage I and II patients. In our multivariate analysis, prehabilitation was identified as an independent predictor of better DFS in all stages after adjusting for possible confounders. Although the literature is limited, our results compare to a recent study by West et al,[23] in which a greater proportion of subjects included in the prehabilitation group were found to have pathological tumor regression when compared to the control group. In addition, their study reported that exercise prehabilitation reversed the fall in functional capacity seen as a result of neoadjuvant therapy in patients with locally advanced rectal cancer.[23] Although we detected a statistically significant difference in 5-year DFS, we did not see any difference in 5-year OS. Our study may have been underpowered to detect a difference in OS owing to the small number of events and a type 2 error may have been introduced. However, it is very difficult to demonstrate statistically significant difference in OS in colorectal cancer studies given the high 5-year survival rate. In addition, DFS has been shown to be a good surrogate marker for OS.[24–28] Furthermore, since improvements in DFS were only identified in the subgroup analysis of stage III disease, concerns about multiple comparisons could be raised. However, the same effect was identified for the entire study group when confounders were adjusted for, which argues against multiple comparison problems.

Predictors of disease recurrence and adverse outcomes following curative surgical resection of colorectal cancer mainly include nonmodifiable tumor- and surgery-dependent characteristics.[21,29–35] It is estimated that 25% to 40% of colorectal cancer patients experience disease recurrence in the first 5 years following definitive surgical treatment, highlighting the clinical importance of this problem.[36,37] In our study, we identified a potentially risk-modifying intervention for long-term oncologic outcomes in patients undergoing curative-intent surgical resection of primary nonmetastatic colorectal cancer. The implementation of prehabilitation programs is feasible and may have other health benefits.[38,39] Nevertheless, there are concerns about the impact of delaying definitive surgical care to allow for adequate prehabilitation. However, a recent study by Curtis et al revealed that a delay of >12 weeks from diagnosis to resection did not impact OS.[40] This suggests that there is, in fact, a safe preoperative window for adequate prehabilitation without significantly affecting cancer outcomes as a result of disease progression.

TABLE 1. Baseline Characteristics and Perioperative Outcomes Data Presented as n (%) Unless Otherwise Specified

Variables	Prehab Group, n = 104	Control Group, n = 98	*P*
Mean age, y (SD)	68.8 (11.3)	67.1 (10.6)	0.278
Male sex	61 (58.7)	63 (64.3)	0.411
Mean body mass index (SD)	27.3 (4.4)	27.6 (4.8)	0.606
ASA			
1	11 (10.6	12 (12.2)	0.598
2	68 (65.4)	57 (58.2)	
3	25 (24.0)	28 (28.6)	
4	0	1 (1.0)	
Procedure*			
RHC	33 (31.7)	25 (25.5)	0.295
LHC	10 (9.6)	6 (6.1)	
AR/SR	21 (20.2)	26 (26.5)	
LAR	29 (27.9)	31 (31.6)	
Subtotal	0	3 (3.1)	
APR	10 (9.6)	5 (5.1)	
Transverse	1 (1.0)	2 (2.0)	
Surgical approach			
Open	8 (7.7)	5 (5.1)	0.603
Laparoscopic	91 (87.5)	90 (91.8)	
Converted to open	5 (4.8)	3 (3.1)	
Stoma creation	28 (26.9)	33 (33.7)	0.296
Median length of stay, days (IQR)	4 (3–6.5)	4 (3–6)	0.777
30-day complications	40 (38.5)	32 (32.7)	0.389
Superficial SSI	8 (7.7)	7 (7.1)	0.882
Deep SSI	4 (3.9)	6 (6.1)	0.528
Ileus	19 (18.3)	15 (15.3)	0.574
Cardiovascular	4 (3.9)	2 (2.0)	0.684
Respiratory	7 (6.7)	4 (4.1)	0.539
Severe 30-day complications (Clavien-Dindo ≥3)	6 (5.8)	5 (5.1)	0.835
30-day ER visits	17 (16.4)	15 (15.3)	0.840
30-day readmissions	10 (9.6)	12 (12.2)	0.549
30-day reoperation	1 (1.0)	2 (2.0)	0.612

SSI indicates surgical site infection.

*Procedure: RHC, right hemicolectomy; LHC, left hemicolectomy; AR/SR, anterior/sigmoid resection; LAR, low anterior resection; Subtotal, subtotal colectomy; APR, abdominoperineal resection; Transvers, transverse colectomy.

TABLE 2. Tumor Characteristics Data Presented as n (%) Unless Otherwise Specified

Variables	Prehab Group, n = 104	Control Group, n = 98	*P*
Tumor location			
Right-sided	34 (32.7)	27 (28.4)	0.766
Left-sided	31 (29.8)	32 (33.7)	
Rectal	39 (37.5)	36 (37.9)	
Neoadjuvant therapy	23 (59.0)	24 (66.7)	0.491
(y)pTNM			
0/1	36 (34.6)	37 (37.8)	0.910
2	32 (30.8)	31 (31.6)	
3	36 (34.6)	30 (30.6)	
(y)pT			
0/1	22 (21.2)	22 (22.5)	0.963
2	22 (21.2)	22 (22.5)	
3	52 (50.0)	47 (48.0)	
4	8 (7.7)	7 (7.1)	
(y)pN			
0	69 (66.4)	68 (69.4)	0.891
1	25 (24.0)	21 (21.4)	
2	10 (9.6)	9 (9.2)	
Total nodes, median (IQR)	19 (13–28)	19 (13–25)	0.989
Positive nodes, median (IQR)	0 (0–1)	0 (0–1)	0.565
Lymph node ratio ≥0.10	15 (48.4)	14 (56.0)	0.571
High-grade tumor	8 (7.7)	10 (10.3)	0.516
Lymphovascular invasion	38 (36.9)	35 (36.1)	0.905
Perineural invasion	35 (34.3)	28 (28.9)	0.409
Positive margins	4 (3.9)	3 (3.1)	1.000
Receipt of adjuvant chemotherapy	35 (33.7)	29 (29.6)	0.535
Timing of initiation of adjuvant chemotherapy in stage III	(n = 36)	(n = 30)	
None	6 (16.7)	3 (10.0)	0.537
≤56 days	24 (66.7)	19 (63.3)	
>56 days	6 (16.7)	8 (26.7)	
Mean follow-up duration, mo (SD)	59.2 (24.4)	63.0 (28)	0.179

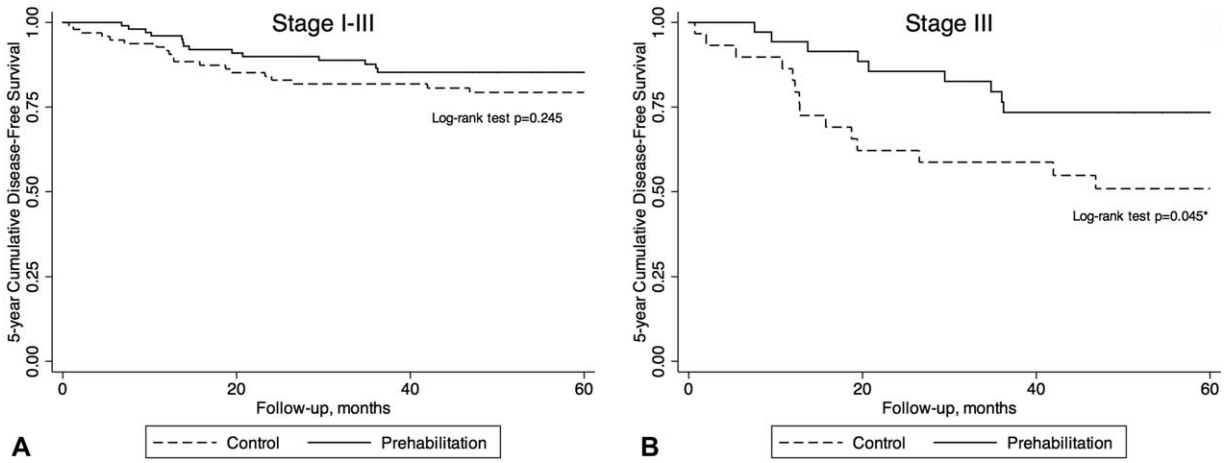

FIGURE 2. Kaplan-Meier survival curves of 5-year disease-free survival in patients undergoing prehabilitation vs control for (A) all stages and (B) stage III disease.

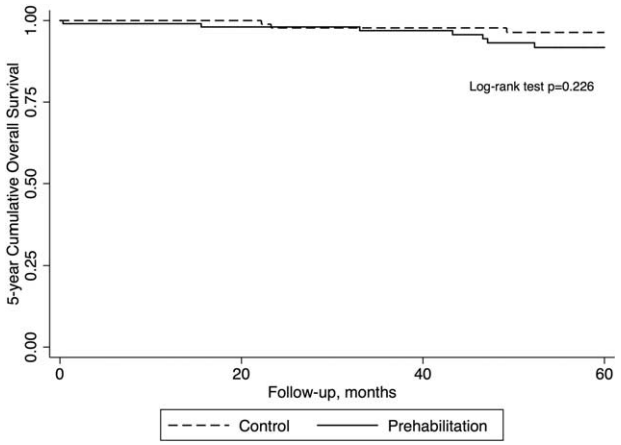

FIGURE 3. Kaplan-Meier survival curves of 5-year overall survival in patients undergoing prehabilitation vs control for all stages.

Several different mechanisms may potentially explain the results observed in our study. Exercise may alter disease-free survival through a variety of biochemical and physiologic processes.[13–17] Aerobic exercise may affect cancer outcomes by reducing excess visceral adipose tissue, an independent predictor of disease recurrence and mortality among colon cancer patients.[13,14] Furthermore, physical activity inhibits inflammatory cytokine production in adipose tissue, which has been associated with recurrence and mortality in individuals with colorectal cancer.[15] Evidence supports the presence of other independent anti-inflammatory effects of exercise beyond the reduction of visceral fat alone.[41] Circulatory shear flow induced by aerobic activity may also alter the viability, proliferation, and metastatic potential of circulating tumor cells.[17]

Although this evidence suggests a beneficial effect on survival with exercise, it is unclear whether prehabilitation results in long-term lifestyle changes that are significant enough to explain our results. In our study, data on levels of physical activity beyond 8 weeks postoperatively were not available and the long-term effects of prehabilitation on exercise pattern could not be assessed. However, patients who initiated the program in the preoperative period had a higher adherence immediately after surgery compared to those beginning the program postoperatively.[4] It is also unknown whether a dose–response relationship exists between the degree of compliance with prehabilitation programs and cancer outcomes. Furthermore, the additional roles of nutritional optimization and psychological counseling cannot be ruled out as essential contributors to the observed improvement in DFS.[42] Protein supplementation enhances muscle protein synthesis by providing adequate substrates for the anabolic effects of exercise resulting in increased lean body mass, muscle strength, and functional capacity.[43] Nevertheless, exercise, with nutritional optimization, is likely to play an important role in the recurrence rate decrease identified in the present study.

In addition, the improved preoperative baseline functional capacity achieved with prehabilitation may contribute to our results. Previous studies have reported that patients with a lower baseline functional status have poorer long-term oncologic outcomes, suggesting that an improvement in functional status may result in better survival.[11,12] Patients with higher functional capacity may have earlier initiation of adjuvant systemic therapy. However, prehabilitation was not associated with shorter time to initiation of adjuvant systemic therapy in our study. Other hypotheses include improved tolerance of systemic therapy as patients with higher functional capacity experience less clinically significant chemotherapy-related side-effects and complications that may affect cycle completion and dose reduction rate.[12] Improving preoperative baseline functional capacity may thus optimize chemotherapy regimen completion and survival.

Furthermore, prehabilitation may improve survival by decreasing the incidence of postoperative complications. The current body of literature, however, does not strongly support a decrease in postoperative morbidity with prehabilitation likely owing to the fact that most studies in colorectal cancer were underpowered to detect a significant difference.[8-10] In our study, prehabilitation did not reduce the incidence of postoperative complications. Nonetheless, postoperative complications have been associated with worse oncologic outcomes by delaying initiation of adjuvant therapy, and by mediating the systemic inflammatory response, an important predictor of adverse long-term prognosis.[15,44–53] Targeted prehabilitation may mediate a decrease in postoperative morbidity by increasing functional capacity and result in better oncologic outcomes by decreasing delays in initiation to adjuvant therapy.[44,45]

The findings of our study should be interpreted in light of several other limitations. First, the heterogeneity of prehabilitation programs in the 3 pooled studies may have affected our results. It is possible that the survival benefit seen with prehabilitation was greater in patients who participated in supervised exercise sessions compared to those who were randomized to the home-based regimen. However, the sample size did not allow for a subgroup analysis. In

TABLE 3. Multivariate Analysis of Disease-free Survival at All Stages and Stage III*

Variables	All Stages Hazard ratio (95% CI)	Stage III Hazard ratio (95% CI)
Age, per additional year	1.03 (1.00–1.07)	1.04 (0.99–1.08)
Male sex	1.23 (0.58–2.59)	1.16 (0.46–2.90)
ASA ≥3	0.65 (0.28–1.52)	0.46 (0.14–1.47)
Rectal surgery	0.78 (0.35–1.75)	1.01 (0.38–2.67)
Laparoscopy	0.43 (0.12–1.52)	0.36 (0.07–1.83)
Severe 30-day complications (Clavien-Dindo ≥3)	1.17 (0.15–9.24)	3.10 (0.34–28.19)
(y)pTNM stage		
1	Ref	—
2	4.61 (0.97–21.89)	—
3	32.33 (5.81–179.94)	—
Positive margins	3.99 (1.22–13.06)	3.71 (1.09–12.70)
Adjuvant chemotherapy	0.40 (0.13–1.24)	0.32 (0.09–1.14)
Prehabilitation	0.45 (0.21–0.93)	0.26 (0.10–0.68)

*All covariates included in the model are mentioned in the table.

TABLE 4. Multivariate analysis of Overall Survival for all Stages*

Variables	Hazard Ratio	95% Confidence Interval
Age	1.04	0.97–1.11
Male sex	1.10	0.31–3.93
ASA ≥3	0.65	0.13–3.11
Prehabilitation	1.99	0.50–8.02
Rectal cancer	0.38	0.08–1.86
Node-positive disease	1.37	0.16–11.88
Adjuvant chemotherapy	0.77	0.09–6.66

*All covariates included in the model are mentioned in the table.

addition, as controls also underwent a preoperative multidisciplinary assessment, they may have implemented lifestyle changes as a result of their awareness of the study (Hawthorne effect). This phenomenon may have resulted in exposure misclassification in the control group and reduced the effect size of the association identified in our study.

Furthermore, although validated frailty measurement tools or questionnaires were not used in patient selection in the initial studies, patients with lower baseline functional capacity seem to benefit the most from prehabilitation; a greater effect on long-term oncologic outcomes may be observed in this subgroup of frail patients.[54] However, in our study, data were not available to compare frailty indices between groups. Similarly, a subgroup analysis of frail patients could not be performed. Nevertheless, as our study population may have included healthy patients who are at low-risk of postoperative complications and functional decline, the beneficial effect of prehabilitation could simply reflect the beneficial properties of physical activity rather than the reduction in postoperative morbidity and improvement in functional recovery. Additionally, both colon and rectal cancer patients were included in this study and oncologic outcomes may differ between these two subgroups. In our study, we identified a possibly better DFS in prehabilitation patients with rectal cancer, but the effect did not demonstrate statistical significance, perhaps reflecting our small sample size. Lastly, in the present study, we conducted a post hoc analysis of 3 pooled trials. Initial power calculation and randomization were therefore not conducted to assess long-term outcomes, which may impact our results.

CONCLUSION

In this report, prehabilitation was not associated with improvement in OS, which may reflect the presence of type 2 error. However, despite the small sample size and heterogeneous study population, trimodal prehabilitation was associated with improved 5-year DFS in stage III colorectal cancer and independently predicted 5-year DFS for all stages on multiple regression analysis. This study may thus provide very preliminary evidence supporting the use of routine prehabilitation as an important adjunct in the treatment of primary nonmetastatic colorectal cancer, but should be confirmed in larger prospective trials. Future studies examining the cost implications of this intervention should be conducted to better assess prospects for scale-up, and optimize cancer care.

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DISCUSSANTS

J.W. Fleshman, Jr. (Dallas, TX):

Thank you, Dr. McLeod. As we all know, the American College of Surgeons is emphasizing strong for surgery in the pre-op evaluation phase of care for all surgical patients, and the impact of surgical outcomes is positive in that program thus far.

The authors have essentially reported a retrospective review of 202 patients from a single institution, which were treated with prehabilitation before laparoscopic surgical treatment of colorectal cancer in a setting of enhanced recovery after surgery. Prehabilitation included exercise, nutrition, and anxiety reduction for 4 weeks with no specific end point or goal. The rehab also continued for 8 weeks postoperatively in most cases. Improved surgical outcomes were reported previously. However, making the stretch to documenting the impact of prehabilitation on cancer outcomes may be a bridge too far, so to speak.

This is a very heterogenous group as determined by stage, operation, tumor site, and use of adjuvant therapy. No frailty or function scores were measured at baseline, and only 25% of the group was ASA–3 who might have benefited from prehabilitation.

The study is missing sample size and power calculation because of the retrospective nature of the study, and unfortunately the conclusion is based on a very small separate subset analysis performed on the 30% of the patient group with stage 3 disease who received chemotherapy adjuvantly, and then again for the 30% of the patient group with rectal cancer.

I would like to give a cautionary comment. No difference was found between the control and prehab groups based on surgical outcomes or OS and DFS, but a negative conclusion cannot be drawn because of the small sample size.

Also, subset analysis in the 66 patients with stage 3 cancer revealed improvement in DFS after prehabilitation. This subset analysis cannot be adequately powerful in such a small group, I am afraid. Adjusting for confounding factors in stage 3 colorectal cancer and all rectal cancer resulted in improved DFS in patients in the prehabilitation group.

The use of neoadjuvant therapy in rectal cancer has already been shown to improve DFS in rectal cancer patients. And I might add, neoadjuvant treatment was performed in 48 of 75 rectal cancer patients in this study.

I have 2 questions for the authors:

Could variation in wait times after neoadjuvant therapy for rectal cancer have impacted the prehabilitation outcomes?

Was the wait time extended and the prehabilitation extended to accommodate that wait time? How did the neoadjuvant therapy itself affect the prehabilitation compliance for those patients? Was it different from the colon cancer patients?

Number 2, rectal cancer adds complexity to the equation including diverting ostomy, neoadjuvant therapy, quality of life issues after reconstruction, and decreased survival compared to colon cancer. Would it not be better to analyze colon cancer separately? And having said that, what would be your recommendation for the ideal study to address your question?

Response From L. Lee:

Thank you, Dr Fleshman, for your comments. You are certainly right in that this is a retrospective study and certainly does have all the limitations inherent to essentially doing the secondary analysis of pretrials.

I will try to address some of your comments as you bring them up.

You are right in that none of these patients had any frailty indices that were assessed before surgery. The initial trials, especially the first one, was done as proof of contact, especially the very first prospective cohort that was done to demonstrate that this had some sort of effect, and our subsequent randomized trials were done to try to answer that question in a more scientifically rigorous manner.

The patient selection for these initial trials was, Are you willing to participate? A lot of this was secondary to whether you live close enough to come back for a lot of the interventions and the study questionnaires as well as the 6-minute walk test.

We are now doing another randomized trial looking specifically at frail patients, and these patients get the full frailty

assessment. This is currently ongoing, so hopefully we will be able to give you some answers to that relatively soon, but we are excited about the prehabilitation program. We strongly believe in it.

Just to go a little further on this, for the patients that we think would benefit from prehabilitation but do not necessarily fit into the trial inclusion criteria are referred anyway and undergo the program off protocol because we really strongly believe in this. And when you anecdotally talk to patients, and we have done certain other studies about the patient experience, they strongly believe in it as well and really feel that this has helped them quite a lot.

In terms of your power comment, I do not really have anything other than to say we are limited to the data that we have, as this was a secondary analysis of 3 trials. Again, the trial that we are currently undergoing as part of this multi-institutional international collaboration is powered appropriately for these outcomes, so again you are going to have to wait a little bit for the true answer to this question.

In terms of your 2 questions about rectal cancer, you are right. What seems as a relatively small minority of patients received neoadjuvant therapy in this cohort is unique to our center. We do a lot of trials regarding neoadjuvant therapy, and we try to not have too much study fatigue with patients. Also, a lot of the patients in the present study mostly had upper rectal cancers that do not necessarily require chemoradiotherapy. We also have many patients that are referred to having already completed neoadjuvant therapy at an outside institution and are referred to our center for definitive surgery. These patients are commonly seen 8, 12 weeks after completion of neoadjuvant therapy, and resection within 4 to 6 weeks, and this is when these patients get enrolled onto the prehabilitation program if they are eligible. So we do not alter the interval for surgery for the completion of the neoadjuvant therapy to surgery, or prehabilitation program, and this is true for colon cancer patients as well.

To answer your last question about whether we should be analyzing rectal cancer as well as colon cancer together, we were limited by sample size. As mentioned previously, we are now doing another trial in rectal cancer patients specifically trying to do prehabilitation during the entire 8- to 12-week interval of surgery to answer those questions because there are data right now suggesting that exercise during this time will increase the effectiveness of neoadjuvant therapy, and these patients may have higher rates of pathologic complete response.

Again, yes, this is basically a hypothesis-generating study to give some basis to the ongoing trials that we are part of. So it might take a little bit longer for us to have that data but, it is coming.

M. Zenilman (Brooklyn, NY):

Congratulations on leading the charge with prehabilitation. I have 3 simple questions.

First, in patients who did not get neoadjuvant therapy, did you have any pushback waiting 4 weeks for the cancer operation?

Second, as with anything else, sometimes we do not measure the right things. So I am not so sure when you are trying to do implement novel therapies, that 30 day morbidity and mortality are what is relevant. Activities of daily living are really more appropriate in frail and elderly patients who are at risk. Can they eat by themselves? Can they bathe themselves? Can they ambulate independently? This may be why we have really seen a lot of data showing that prehabilitation makes a difference.

Lastly, have you considered using any pharmacologic intervention? Some articles out there are showing rapamycin or the MTOR inhibitors can actually stop the senescence of cells in mice, and I haven't seen anybody try to use in humans.

Response From L. Lee:

Thank you, Dr Zenilman. Again, in terms of the wait time, our standard wait time in Canada is about 4 weeks from initial clinic visit to time of surgery. But this is a comment that constantly comes up when we talk about prehabilitation. Are we putting the patient at risk by waiting for surgery? There are increasing data to suggest that you can probably wait up to about 6 weeks from time of diagnosis to surgery without really any difference in long-term outcomes. We don't really have that much of a pushback in those cases.

As to your second question about the outcome measure, you are right in that for older patients, they do not necessarily think about long-term oncologic outcomes. Recovery may be a more important outcome for these patients.

We use the 6-minute walk test as the primary outcome measure for these prehabilitation trials, and we had a lot of pushback initially because there were people saying, What is this outcome measure? But we have shown that a higher 6-minute walk test is associated with higher functional status and capacity. So this is certainly a surrogate outcome. But activities of daily living itself are a bit messy as an outcome measure.

In terms of your third question about pharmacologic therapy, we have not really considered it. It is definitely an interesting point.

M. Stelzner (Los Angeles, CA):

I work at the veterans hospital, and we have it a little easier because we have geriatric centers in many places that we can ask, and they are willing to help us with these kinds of things.

I wonder when looking at your data, Dr Fleshman alluded to the issue of addressing the area of the patient population, and you said in the beginning the recruitment was very different 5 years later. What is your estimate as far as the heterogeneity in the intervention is concerned? Because what I see is that our geriatricians who are still new at this and are developing what they do with these patients over time, and as you are looking at the time period of 5 years, there may have well been developments in how the therapy or the intervention is structured, so this was not a very uniform thing that you would have with chemotherapy. Maybe that is part of the reason why you did not see as many benefits as you had probably anticipated.

Response From L. Lee:

Again, that brings up a very interesting thing. The very first prehabilitation trial that we did, which we did not include in this, we randomized our patients to very intense versus less intense exercise. We had very low compliance in the very intense exercise because patients simply were not able to do it. For example, rectal cancer patients would not do it because they could not sit on the bike. So we learned a lot of lessons from that initial trial.

Each one of these 3 trials built upon each other. Starting from the first trial, our prehabilitation program was already structured. In terms of the exercise program, for example, they met with a physical therapist who tailored exercise programs based on exertion, their heart rate, using a combination between light resistant exercises such as hip extensions as well as moderate aerobic activities. We let the patients decide if they wanted to walk, run, swim, bike, whatever they wanted to do. And then the subsequent trials built onto that to the

point where the last one tested whether supervised sessions could improve the beneficial effect.

We were not really able to analyze these separately because of the sample size issues.

Response From M. Stelzner (Los Angeles, CA):

Are you moving now to a more goal oriented system where you say some patients may take 3 weeks and others may take 6 weeks to get to the same increment of improvement?

Response From L. Lee:

Yes, definitely. Again, this is a little bit intuitive, but the worse you are, the more benefit you are able to see. For example, if a very fit patient was to be enrolled in a prehabilitation program, I probably would not have that much of a benefit compared to someone who was essentially bed-bound. Our latest trial demonstrated that prehabilitation patients were more likely to have increased their overall physical activity as well as intensity of exercise.