Making Patients Fit for Surgery

Introducing a Four Pillar Multimodal Prehabilitation Program in Colorectal Cancer

Stefanus J. van Rooijen, MD, PhD, Charlotte J.L. Molenaar, MD, Goof Schep, MD, PhD, Rianne H.M.A. van Lieshout, MSc, Sandra Beijer, PhD, Rosalie Dubbers, MSPT, Nicky Rademakers, MSPT, Nicole E. Papen-Botterhuis, Ir, PhD, Suzanne van Kempen, MD, Francesco Carli, MD, PhD, Rudi M.H. Roumen, MD, PhD, and Gerrit D. Slooter, MD, PhD

Background: Considering the relation between preoperative functional capacity and postoperative complications, enhancing patients' functional capacity before surgery with a prehabilitation program may facilitate faster recovery and improve quality of life. However, time before surgery is short, mandating a multimodal and high-intensity training approach. This study investigated feasibility and safety of a prehabilitation program for colorectal cancer.

Methods: Multimodal prehabilitation was offered to patients eligible for participation and they were assigned to an intervention or control group by program availability. The prehabilitation program consisted of the following four interventions: in-hospital high-intensity endurance and strength training, high-protein nutrition and supplements, smoking cessation, and psychological support. Program attendance, patient satisfaction, adverse events, and functional capacity were determined.

Results: Fifty patients participated in this study (prehabilitation 20, control 30). Program evaluation revealed a high (90%) attendance rate and high level of patient satisfaction. No adverse events occurred. Endurance and/or strength were improved. Eighty-six percent of patients with prehabilitation recovered to their baseline functional capacity 4 weeks postoperatively, 40% in the control group ($P < 0.01$).

Conclusions: Multimodal prehabilitation including high-intensity training for colorectal cancer patients is feasible, safe, and effective. A randomized controlled trial (NTR5947) was initiated to determine whether prehabilitation may lower morbidity and mortality rates in colorectal surgery.

Key Words: Prehabilitation, Colorectal Surgery, Multimodal, Functional Capacity, Enhanced Recovery After Surgery, Complications, Colorectal Cancer, Feasibility

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Colorectal cancer (CRC) is the second most prevalent type of cancer in the world, with more than 1.4 million cases and 700.000 deaths a year.[1] The most essential step in curative treatment is surgery. Although perioperative care improved greatly, postoperative morbidity and mortality rates still remain high.[2,3] Furthermore, major surgery is associated with a marked reduction in functional capacity, even in the absence of complications.[4,5] This is clinically reflected as delayed and impaired recovery, leading to a reduction in health-related quality of life (HRQoL).

The number of postoperative complications is correlated with patients' preoperative functional capacity, psychological well-being, and nutritional and smoking status.[6–12] Traditional approaches have targeted the intraoperative and postoperative period for rehabilitation and lifestyle changes. However, recent evidence shows that the preoperative period might be the optimal time-frame for intervention.[13–15] This approach, introduced as *prehabilitation*, is not yet implemented in daily clinical practice worldwide.

To date, trials with preoperative home-based training programs showed small effect sizes and had low compliance rates.[16,17] Moreover, moderate exercise programs have not yielded beneficial effects in a preoperative setting.[17] These findings may not be unexpected, because the preoperative training period is relatively short (maximum of 5 weeks).[18] In such a short time span, high-intensity training (HIT) attains a sufficient cardiopulmonary response for the improvement of postoperative outcome. Because of the load of this HIT,

From the Department of Surgical Oncology, Máxima MC, Veldhoven, The Netherlands (SJvR, CJLM, NEP-B, RMHR, GDS); Department of Sports Medicine, Máxima MC, Veldhoven, The Netherlands (GS); Department of Nutrition, Máxima MC, Veldhoven, The Netherlands (RHMAvL); Netherlands Comprehensive Cancer Organisation, Utrecht, The Netherlands (SB); Department of Physiotherapy, Máxima MC, Veldhoven, The Netherlands (RD, NR); Department of Psychology, Máxima MC, Veldhoven, The Netherlands (SvK); and Department of Anesthesiology, the Montréal General Hospital, McGill University, Montréal, Quebec, Canada (FC).

All correspondence should be addressed to: Stefanus J. van Rooijen, MD, PhD, Máxima MC, Department of Surgery, PO Box 7777, Veldhoven, The Netherlands.

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SJvR, GS, FC, RMHR, and GDS conceived the study. SJvR, CJLM, GS, RHMAvL, NEP-B, and GDS drafted the manuscript. SJvR, GS, RHMAvL, SB, NR, SvK, FC, RMHR, and GDS designed the study. SJvR, CJLM, GDS, RHMAvL, RD, NR, NEP-B, SvK, RMHR, and GDS are local investigators at the participating centers. The study is supervised and coordinated by SJvR, CJLM, GS, and GDS. SJvR and GDS were responsible for accurate execution of the study. All authors approved the final manuscript.

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thorough guidance of patients enhances feasibility and compliance to such a training program. Furthermore, evidence shows that prehabilitation should be multimodal including supervised high-intensity exercise training, adequate nutrition, smoking cessation, and psychological support for an optimal benefit.[19] In terms of nutrition, protein supplementation as an addition to training may lead to more effectiveness.[20–23] Psychological support and cessation of smoking may further enhance the effects of such a program.[24,25]

This pilot study was initiated to test the feasibility, safety, and effectiveness of a multimodal prehabilitation program intended to be studied in a randomized controlled trial (NTR5947).

METHODS

Subjects

This study was conducted between June 2016 and June 2017 at Máxima Medical Center (MC), Veldhoven, the Netherlands. Patients of at least 18 years old and scheduled for elective resection for CRC without neoadjuvant treatment were eligible for participation. Patients with metastatic disease, chronic renal failure, American Society of Anesthesiologists score 4 or 5, conditions interfering with the ability to perform the exercises such as paraplegia or orthopedic impairments, and patients unable to give informed consent were excluded.

Study Design

This nonrandomized prospective, hospital-based observational cohort study was approved by the Máxima MC Ethics Committee (NL54547.015.15). Patients were approached to participate when diagnosis was final and surgery was scheduled. After providing verbal and written consent, patients were assigned to the prehabilitation program or to the control group, which was dependent on program availability at time of inclusion (flow chart Fig. 1). The sample size was set to 30 in the control group and 20 in the intervention group based on previous studies.[17]

Both groups received perioperative care according to Enhanced Recovery After Surgery (ERAS) guidelines.[26] Patients were screened for anemia and optimized using iron injections (Ferinject) if needed (threshold >7 mmol/l or 12 mg/dl). A smoke cessation program of 4 weeks, which included intensive counseling (group and/or telephone sessions weekly) in combination with nicotine replacement therapy, was offered to all smokers. Both groups were assessed at standardized time points before and after surgery (Table 1). The multimodal prehabilitation program for the intervention group is described next.

Exercise Intervention

The prehabilitation group followed a 4-week program including 3 weekly hospital-based high-intensity endurance (interval) training, complemented with upper and lower body

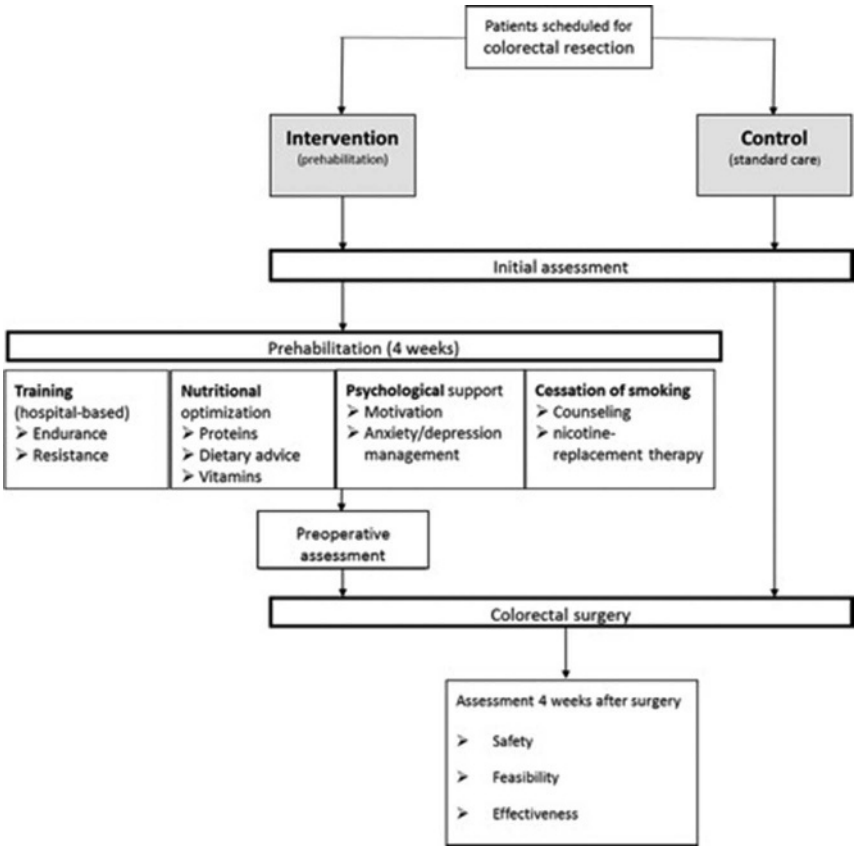

FIGURE 1. Flow diagram for 50 study participants undergoing elective colorectal surgery for cancer.

TABLE 1. Prehabilitation interventions. Assessments for both the intervention (prehabilitation) and control group before and after surgery

	Prehabilitation Pilot Study Scheme						
	Preoperative				Operation	Postoperative	
	−5	−4	−4 to −1	−1	0	4	52
Weeks	**Before Start**	**Baseline (t_0)**	**Multimodal Prehabilitation**	**Preoperative (t_1)**	**Surgery**	**30-day Follow-up (t_2)**	**1-yr Follow-up (t_3)**
Group (prehabilitation or control)	Both	Both	Prehabilitation	Prehabilitation	Both	Both	Both
Gastroenterologist	Inform patient Hemoglobin, iron	Iron injections when hemoglobin < 7 mmol/l	—	—	—	—	—
Case manager	Inclusion patient	G8 score Smoking cessation	Weekly phone calls	—	—	—	—
Sport physician	—	Informed consent VO_2max Anaerobic threshold Exercise electrocardiogram	—	—	—	—	—
Physiotherapist	—	6MWT Stair climb test Sit-to-stand test 1RM Activity questionnaire Fried Frailty Score	3 weekly: Endurance training Strength training (lateral pull down, step up, leg press, chest press and abdominal crunch)	6MWT Stair climb test Sit-to-stand test Activity questionnaire	—	6MWT Stair climb test Sit-to-stand test Activity questionnaire	—
Dietician	Food diary	Height, weight Weight loss %[a] Anthropometry Hand grip strength PG-SGA	Proteins[d] (Refit TMP 90 Shake) Vitamin D[c]	Food diary Height, weight Weight loss %[a] Anthropometry Hand grip strength PG-SGA	—	Height, weight Weight loss %[a] Hand grip strength PG-SGA	—
Psychologist	—	Intake Coping with anxiety	Coaching sessions if needed	—	—	—	—
Anesthesiologist	—	—	—	Preoperative screening[b]	ERAS[b]	ERAS[b]	—
Surgeon	—	—	—	ERAS[b]	ERAS[b]	ERAS[b]	—
Surgical resident	—	—	—	—	—	Outpatient data	—
Researcher	—	HRQoL GAD-7 PHQ-9	Half-hour instruction about the program	HRQoL GAD-7 PHQ-9	—	30-day morbidity and mortality HRQoL GAD-7 PHQ-9	HRQoL GAD-7 PHQ-9

[a]Weight loss in the past 3–6 months.

[b]Following Enhanced Recovery After Surgery (ERAS) guidelines.

[c]When indicated, as stated in the protocol, "50%" of RDA.

[d]1.5–1.8 g/kg per day to two shakes per day after training and before sleep performed on a stationary bicycle on moderate and high intensity.

6MWT, six-minute walk test; PG-SGA, Patient-Generated Subjective Global Assessment.

resistance training. Participants were also encouraged to walk or cycle for 60 minutes on the days between the supervised training sessions.

The endurance training was performed on a stationary bicycle with three blocks of moderate intensity and three blocks of high-intensity intervals. The training intensity was personalized using cardiopulmonary exercise testing data (electrocardiogram, VO_2max, heart frequency, anaerobic threshold (AT), and respiratory quotient).[27,28] The workload (watt) for the high-intensity block started at 65% of the maximum workload (at VO_2peak). This intensity results in a metabolic response in the range of 85–100% of VO_2peak (Borg scale 15–17) at the end of the high-intensity interval, which is considered an appropriate range for HIT. For recovery at moderate intensity, we chose a workload (watt) at 75% of VO_2 AT (or, if AT was not visible, 20% of VO_2peak). The workload was increased with 10% when Borg rating of perceived exertion scale was less than 13 and/or heart rate of less than 85% of the maximum heart rate and decreased with 10% when the exercise intensity in the first block could not be achieved in the last block.

Resistance training was performed in two series of ten repetitions per exercise (lateral pull down, step up, leg press, chest press, and abdominal crunch), targeting the major muscle groups. Resistance was based on baseline one-repetition measurement (1RM) of those exercises, starting at 65% of the 1RM in week 1, followed by 70% in week 2, and 75% in weeks 3 and 4.[29,30] If the patient was able to perform 15 repetitions in the last block, the dose was increased by 10% and or decreased by 10% if 10 repetitions could not be achieved.

Nutritional Intervention

The prehabilitation group received protein supplements (Refit TMP 90 Shake, Friesland Campina) twice a day during the program: (1) one portion within 1 hr after exercise and (2) one before bedtime (0.4 g/kg of body weight per serving). The participants completed a 3-day-food diary before the start and at the end of the program. Participants in the intervention group received a tailored dietary advice aiming at a total protein intake of 1.5–1.8 g/kg per day.[23,31,32] Vitamin D and multivitamins (50% of RDA) were provided daily during prehabilitation.[33–35]

Psychological Support

Preoperatively, patients in the intervention group were scheduled for a 90-min visit with a trained psychologist to address patients' anxiety level, to provide coping strategies, to teach relaxation techniques, and to discuss postoperative expectations. If desired, more sessions were offered during the 4 weeks of prehabilitation. When included in the intervention group, patients were individually informed by a researcher for half an hour for optimal understanding of the prehabilitation program. In addition, patients were phoned weekly by a specialized nurse to increase adherence to the program. During these contacts, coping mechanisms and psychological complaints were addressed, and training perseverance was further encouraged.

Outcomes

The primary outcomes were feasibility, determined as adherence to training sessions, and number of dropouts and safety, determined as occurrence of adverse events.[36,37] Dropouts as well as participants who finished the program received questionnaires developed by the researchers to assess the reason for dropout and program satisfaction respectively. The questionnaire was designed based on our patient experience and contained simple questions regarding program satisfaction, 1 = not satisfied, 5 = very satisfied, and questions with percentage of patients with the answer yes or no (Fig. 1).

A secondary outcome was functional capacity after prehabilitation and 4 weeks postoperatively, determined with the six-minute walk test (6MWT). During the 6MWT, the patient walked as far as possible along a 50-m stretch of corridor in 6 mins, according to the protocol.[38,39] An increase of 20 m was considered to be clinically relevant.[40–42]

Another secondary outcome was muscle strength as measured with 1RM, also determined after prehabilitation and 4 weeks postoperatively. Because determining 1RM directly (by lifting the maximum weight achievable for the patient) has been questioned because of a risk of serious muscular injury, we chose to define the 1RM by indirect measures using the Brzycki formula (1RM = weight × 36/(37 − repetitions)).[43,44]

Further information was extracted using screening methods and tests for functional capacity in both groups (cardiopulmonary exercise testing, hand grip strength test, stair climb test, and sit-to-stand test), physical activity level (modified Community Healthy Activities Model Program for Seniors[19]), nutritional status (Patient-Generated Subjective Global Assessment, skin fold measurements, anthropometry, body mass index and food diary), HRQoL (Short Form Health Survey-36, EORTC QLQ-C30, and EORTC QLQ-CR29), vulnerability of older patients (fried frailty score and G8 score), and depression and anxiety (Generalized Anxiety Disorder 7 [GAD-7] and Patient Health Questionnaire 9 [PHQ-9]). These questionnaires were captured to test complete logistics for the international randomized controlled trial (RCT) but were too few to perform proper analysis.

Follow-up included 4 weeks postoperatively (number and type of complications, reintervention, readmission, and mortality) and 1 yr after surgery (data to be analyzed) (Table 1).

Statistical Analysis

Data were analyzed on an intention-to-treat basis. The data on functional capacity and strength were described by means ± standard deviation for normally distributed data or medians (interquartile range [IQR]) for nonnormally distributed data per time point, and as individual absolute or proportional differences for patients in the intervention group.

Secondary outcomes were described as means ± SD for continuous normally distributed variables or median (IQR) for continuous nonnormally distributed variables. Categorical parameters were described as number plus percentage per time point. Statistical methods included t test and the Mann-Whitney U test for continuous parameters, distributed either normally or not normally, respectively, at a single postoperative time point.

A two-tailed $P < 0.05$ was considered statistically significant. Categorical and noncategorical data on feasibility were analyzed as qualitative measures. Statistical analysis was

performed using SPSS for Windows software (Version 22.0) and Graphpad Prism software for Windows.

RESULTS

Patient Characteristics

Patient characteristics are described in Table 2. Patients in the prehabilitation group had a lower average 6MWT (535 *vs.* 568, ns), VO_2peak (23 *vs.* 27, ns), and 1RM leg press (97 *vs.* 116, ns), suggesting a lower baseline functional capacity in the intervention group compared with controls. The number of anastomoses constructed, laparoscopy and conversion rate, duration of surgery, etc. were similar in both groups. In addition, postoperative complications, length of hospital stay, rates for mortality, reintervention, and readmission for both groups were similar to rates from hospital administration after standard care before the introduction of this prehabilitation program (Table 3). Most common postoperative complications included ileus, wound, and urine tract infections within 30 days

TABLE 2. Patient characteristics of 50 patients undergoing elective colorectal surgery for cancer

	Total Group	Prehab	Control
Patient Variables	***n* = 50**	***n* = 20**	***n* = 30**
Male sex, *n* (%)	27 (54)	10 (50)	17 (57)
Age, median (IQR)	71 (46–89)	75 (62–89)	71 (46–84)
Charlson Comorbidity Index,[a] median (IQR)	3 (2–7)	3 (2–7)	2 (2–7)
ASA score, *n* %			
0	—	—	—
I	5 (10)	2 (10)	3 (10)
II	39 (78)	15 (75)	24 (80)
III	6 (12)	3 (15)	3 (10)
BMI, media (IQR)	26 (18–35)	26 (18–29)	26 (19–45)
Anemia,[a,b] *n* (%)	10 (20)	6 (30)	4 (13)
Cigarette smoking,[c] *n* (%)	4 (8)	0	4 (14)
Pack years, median (IQR)	1 (0–15)	0 (0–19)	5 (0–15)
Disease stage,[d] *n* (%)			
0	1 (2)	0	1 (3)
I	16 (32)	6 (30)	10 (33)
II	13 (26)	8 (40)	5 (17)
III	19 (38)	6 (30)	13 (44)
IV	1 (2)	0	1 (3)
Mental status, median (IQR)			
PHQ-9	3 (1–6)	4 (2–10)	2 (1–4)
GAD-7	3 (1–8)	6 (3–13)	3 (0–7)
Functional capacity			
6MWT[e]	568 (518–598)	535 (498–586)	568 (521–605)
VO_2peak[e]	26 (20–28)	23 (18–26)	27 (24–30)
1RM leg press[e]	113 (89–133)	97 (81–130)	116 (93–157)
1RM chest press[e]	33 (26–47)	27 (18–35)	39 (31–61)
1RM lateral pull down[e]	36 (32–48)	33 (30–39)	44 (34–58)
Stoma,[f] *n* (%)	9 (18)	2 (10)	7 (23)
Colonic surgery, *n* (%)	37 (74)	18 (90)	19 (76)
Laparoscopic, *n* (%)	46 (92)	19 (95)	28 (93)
Conversion, *n* (%)	7 (15)	3 (16)	4 (16)
Anastomosis, *n* (%)	46 (92)	19 (95)	22 (88)
Duration of surgery, median (IQR), min	161 (82–354)	159 (82–268)	163 (83–315)

Prehabilitation intervention versus control group.

Medians with percentages or interquartile ranges (IQR) 25 and 75%.

[a]Comorbidity was defined using the Charlson Comorbidity Index.

[b]Hemoglobin level less than 7 mmol/l.

[c]Cigarette smoking at time of cancer diagnosis.

[d]Disease stage defined by the tumour nodes metastasis classification of malignant tumors.

[e]One-repetition maximum as measured 4 weeks preoperatively.

[f]Diverting stoma.

ASA, American Society of Anesthesiologists; BMI, body mass index.

TABLE 3. Postoperative characteristics of 50 patients undergoing elective colorectal surgery for cancer

Patient Outcomes	Total Group $n = 50$	Prehab $n = 20$	Control $n = 30$
CCI,[a] median (IQR)	6 (0–36)	7 (0–36)	5 (0–36)
Complications,[b] n (%)	11 (22)	5 (25)	7 (23)
Anastomotic leakage,[c] n (%)	2 (4)	0	2 (7)
Hospital stay,[d] median (IQR)	5 (2–41)	5 (3–16)	4 (2–41)
Reintervention,[e] n (%)	2 (4)	1 (5)	2 (7)
Readmission,[f] n (%)	1 (2)	0	1 (3)
Mortality[g]	0	0	0

Prehabilitation intervention group versus control group.

[a]Median comprehensive complication index.

[b]Number of patients with postoperative complications as defined by Clavien Dindo within 30 days after surgery.

[c]Colorectal anastomotic leakage as defined by the International Study Group of Rectal Cancer (ISREC) classification grade C.

[d]Median length of hospital stay in days.

[e]Reintervention during hospital stay.

[f]Readmission within 30 days after surgery.

[g]Mortality during hospital stay.

CCI, comprehensive complication index.

postoperatively. Eight (80%) of 10 patients with anemia were treated with preoperative iron injections of whom 4 (50%) responded with a hemoglobin level higher than 7 mmol/l.

Feasibility, Safety, and Program Satisfaction

No adverse events as a result of the study were reported. Three (15%) of 20 patients in the intervention group did not complete the program. One patient withdrew because she was a caregiver to her husband and did not have the time to finish the program; the two others could not complete the program because their surgery was rescheduled to an earlier moment (because of logistical challenges). Ninety percent ($n = 18$) of patients indicated that they felt less tired because of the program. Program evaluation revealed a high attendance rate at the training sessions: of the 17 (85%) patients who completed the program, 12 (71%) attended 90% or more of the 12 intended training sessions. The remaining 5 patients (29%) also attended more than 75% of training sessions, and overall, 88% of training sessions were completed by patients. A high level of patient satisfaction was reported (mean score of 4.6, 1 = not satisfied, 5 = very satisfied). Reasons for patients to join a prehabilitation program, factors related to program satisfaction, and major challenges in completing the program are given in Figure 2. Forty percent ($n = 8$) of the participants perceived no obstacles to the completion of the program as offered. When asked if they would follow the program again in retrospect, all patients confirmed, and all patients would recommend the program to family or friends.

Functional Capacity

Most patients ($n = 15$, 88%) in the prehabilitation group improved their functional capacity after 4 weeks of prehabilitation. Strength (1RM) increased for all 17 patients (mean increase of 17.5 kg). Sixty-four percent ($n = 11$) of the patients showed a clinically relevant (≥20 m) progression in 6MWT after prehabilitation (mean increase of 67 m).[14,17,45] There were 2 patients (12%) showing no progression in functional capacity. Both patients had a baseline 6MWT slightly above mean baseline functional capacity. Overall, more than half of patients in the intervention group progressed on all tests. All patients improved on at least three tests (of seven) for endurance and strength.

Four weeks after surgery, the mean functional capacity of patients in the intervention group increased compared with baseline, whereas the control group showed a decline in functional capacity (Fig. 3). A mean increase of 30.3 m compared with baseline is seen in the intervention group, and −16.3-m decrease in walking distance is seen in the control group. This suggests that patients recover above their baseline functional capacity after prehabilitation, whereas the control group shows a slight decline in condition ($P < 0.05$). We also observed that 86% ($n = 15$) of patients in the prehabilitation group recovered to baseline functional capacity within 4 weeks after surgery, versus only 40% ($n = 12$) in the control group ($P < 0.01$).

DISCUSSION

This study was initiated to assess the feasibility, safety, and effectiveness of a multimodal prehabilitation program for CRC patients undergoing elective surgery. We found that prehabilitation is feasible and safe, enables patients to improve their functional capacity preoperatively, and enhances recovery.

Feasibility, Safety, and Effectiveness

During this pilot series, we found that all patients who enrolled in the program attended at least 9 of 12 training sessions. The attendance was as high as 88% of the scheduled sessions. All scheduled visits to the dietitian and psychologist were attended. This sums up to a total of 17 in hospital appointments, which seemed not to be an obstacle for our patients. There were no adverse events because of the prehabilitation program. However, we learned that protein consumption just before sleep caused uncomforting and nausea in some patients. Therefore, we advised to take this dose at least 1 hr earlier. During the pilot, all patients had a session with a registered psychologist, but on evaluation, there was not much added value because fear for the operation and the cancer diagnosis overall was realistic and weekly counseling by the case manager (nurse specialist in colorectal care) would suffice. We now use validated questionnaires PHQ-9 and GAD-7 for screening to select individual patients for psychologist consultation. Weekly contact with the case managers warranted optimal patient information and patient involvement with a focus on persistent behavioral changes. None of the patients in the prehabilitation group were active smokers; however, all four smokers in the control group stopped preoperatively in our counseling program. Because of the high attendance and the lack of adverse events, the 4-pillar prehabilitation program proved to be feasible and safe.

All patients improved clinically in their physical performance after 4 weeks of training, because there was a mean increase of more than 30 m in the 6MWT.[42,46] Muscle strength was increased in all participants. Therefore, the program is effective in increasing functional capacity. Previous studies on

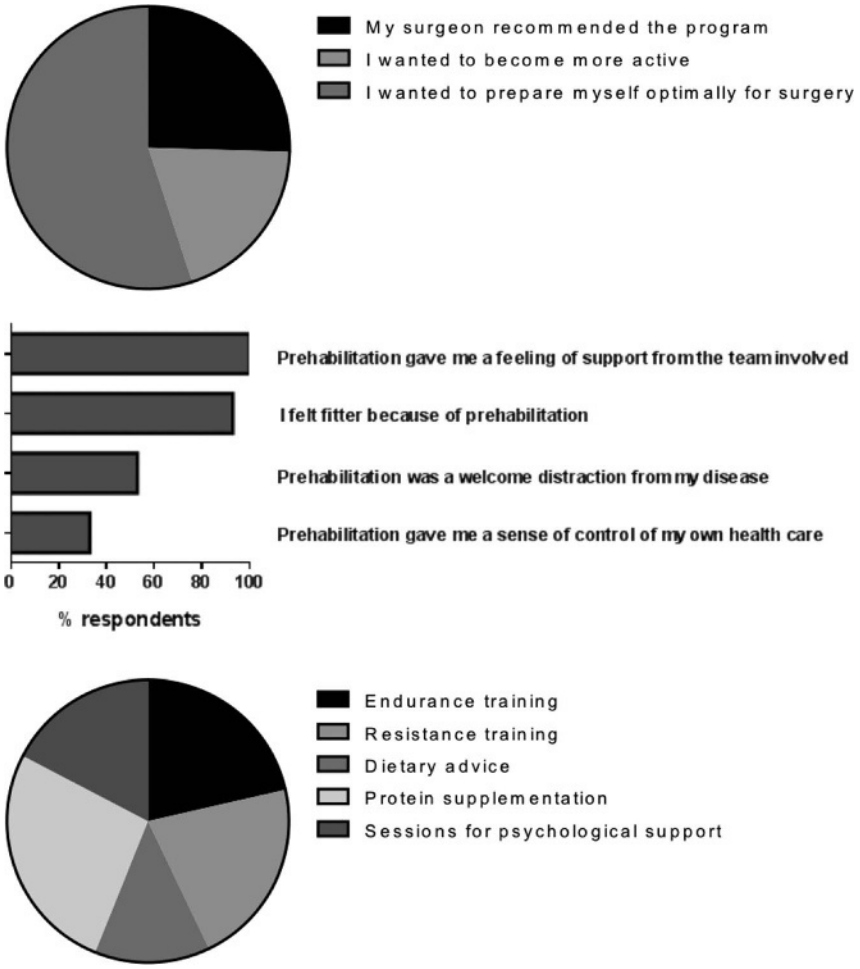

FIGURE 2. Program evaluation for all 20 patients in the prehabilitation intervention group undergoing surgery for CRC. A, Main reason for participating in the program. B, Which factors contributed to the usefulness of the program in your experience? C, Main challenge in completing the program.

prehabilitation describe that multimodal programs may be more effective.[25] Exercise, nutritional, psychological, and smoking cessation interventions seem most effective when combined and tailored to the individual patient. Earlier studies using lower-intensity and home-based programs resulted in only modest or no improvement in functional capacity.[17] We, therefore, opted for a supervised and personalized HIT.[47]

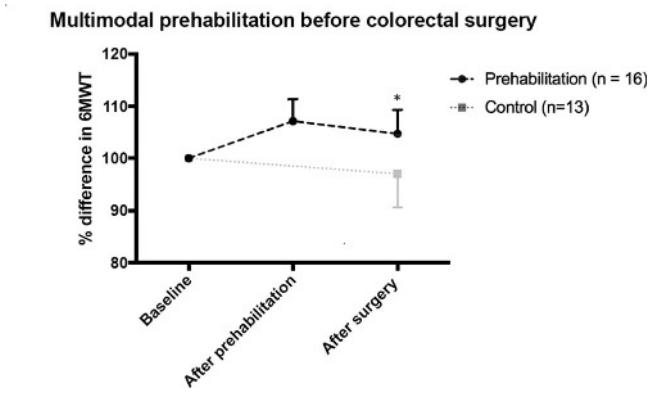

FIGURE 3. Patients undergoing a 4-week prehabilitation program before colorectal surgery showed progress after training and performed better postoperatively (analysis of variance, $P < 0.05$) on functional capacity (6MWT) compared with controls receiving standard care.

Four weeks after surgery, patients in the prehabilitation group had a mean functional capacity (6MWT) higher than at baseline. Their gain in functional capacity before surgery helped them recover. Patients in the control group did not have a second measurement before surgery. Four weeks after surgery, the mean functional capacity was below baseline. There is a statistically significant benefit for prehabilitation, although the study was not designed to prove this considering the nonrandomized fashion. However, on individual basis, there is a relevant difference because only 40% of the control group have reached baseline, whereas 86% of the prehabilitation group have reached baseline or performed better. Therefore, we state that the prehabilitation program could be effective in enhancing recovery. The increased recovery by prehabilitation will hopefully lead to less complications, a shorter hospital stay, a better quality of life, and a reduction in health care cost, which is to be proven in our international RCT.

Giving patients the opportunity to change their own behavior and have an effect on their own treatment was thought

to be extremely important. Because these patients felt actively engaged with their treatment, they were better informed, had more confidence in their treatment, and shared decision-making became standard practice.

Collaboration and Logistics

Although this prehabilitation program proved feasible, it could only succeed because of the collaboration of involved medical disciplines and hospital management. Most specialists tend to work in "silo's,"[48,49] but successful implementation of the program requires secure planning, coordination over disciplines, and flexible resources to facilitate all appointments for patients during prehabilitation. Regular meetings with representatives of all the disciplines allowed us to instigate and implement an appropriate framework for prehabilitation. Enthusiasm of patients was communicated to the whole research team and was an indispensable factor in further enhancing and sustaining commitment of involved health care practitioners.

The Dutch guidelines compel surgeons to operate within 5 weeks after diagnosis. To create the window of opportunity for prehabilitation, a speedy workup within 1 wk is mandatory. However, in many national and international laws, the "natural" waiting time for surgery allows for prehabilitation for a 4-wk period. In addition, "waiting time" targets for hospitals, which are publicly available, result in the expectation of patients that they will be operated within this period. Recent studies show that oncological outcome does not improve when colorectal patients are operated within these 5 weeks.[18] Moreover, the present study indicates that prehabilitation results in substantial benefits for patients in terms of improving functional capacity and this finding should be investigated on a larger scale. The planned RCT aims to show an association between increasing preoperative functional capacity using prehabilitation and better postoperative outcomes. Consequently, it may even be recommended to prolong the prehabilitation period further for individual patients.

Limitations

The aim of this study was to test feasibility of a multimodal prehabilitation program, and therefore, only 50 patients were included. Because of these small numbers and lack of randomization, limited conclusions can be drawn on the effects of the program. Especially for the analysis of postoperative outcomes on complications, quality of life and costs, a larger sample number is needed. A larger patient population may also facilitate analysis of responsiveness in different subgroups of patients. This study offered multimodal prehabilitation based on availability of the program. Because we wanted the patients to train in a group of approximately five patients, we had periods (blocks) to include for the control group and periods to include for the intervention. The design of the international RCT based on this pilot will rule out most bias.

Future Perspectives

Prehabilitation may be seen as a new era in healthcare focusing on prevention and lifestyle changes. The combination of current knowledge may allow us to improve care before any type of intensive treatment, such as surgery or chemoradiotherapy.[5,17,50,51] Prehabilitation improves patient education and gives patients a central role (patient empowerment). We hope to demonstrate enhanced recovery and facilitate the earlier start of adjuvant treatment. Potentially, there might be a higher compliance to adjuvant treatment and therefore benefit for oncological outcomes.[52]

The principal of future prehabilitation research and implementation includes support throughout the healthcare organization and the involvement of all relevant stakeholders (such as medical specialists, management, finance and health insurance companies), to allow patients to prepare optimally for any type of major treatment. New studies may evaluate community-based prehabilitation programs facilitating an accessible and individualized program to create definitive lifestyle changes for everyone.

CONCLUSIONS

This study demonstrated the feasibility, safety, and effectiveness of multimodal prehabilitation. The program consisted of HIT, optimal nutrition, smoking cessation, and psychological support for CRC patients. A randomized controlled trial (NTR5947) was initiated to determine whether prehabilitation may lower morbidity and mortality rates in colorectal surgery.

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REFERENCES

1. Torre LA, Bray F, Siegel RL, et al: Global Cancer Statistics, 2012. *CA Cancer J Clin* 2015;65:87–108
2. Kirchhoff P, Clavien P-A, Hahnloser D: Complications in colorectal surgery: risk factors and preventive strategies. *Patient Saf Surg* 2010;4:5
3. McDermott FD, Heeney A, Kelly ME, et al: Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. *Br J Surg* 2015;102:462–79
4. West MA, Parry MG, Lythgoe D, et al: Cardiopulmonary exercise testing for the prediction of morbidity risk after rectal cancer surgery. *Br J Surg* 2014;101:1166–72
5. West MA, Loughney L, Lythgoe D, et al: Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *Br J Anaesth* 2015;114:244–51
6. Schroeder D, Hill GL: Predicting postoperative fatigue: importance of preoperative factors. *World J Surg* 1993;17:226–31
7. Wilson RJ, Davies S, Yates D, et al: Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. *Br J Anaesth* 2010;105:297–303
8. Reilly DF, McNeely MJ, Doerner D, et al: Self-reported exercise tolerance and the risk of serious perioperative complications. *Arch Intern Med* 1999;159:2185–92
9. Girish M, Trayner E, Dammann O, et al: Symptom-limited stair climbing as a predictor of postoperative cardiopulmonary complications after high-risk surgery. *Chest* 2001;120:1147–51
10. Burden ST, Hill J, Shaffer JL, et al: Nutritional status of preoperative colorectal cancer patients. *J Hum Nutr Diet* 2010;23:402–7
11. Lawrence VA, Hazuda HP, Cornell JE, et al: Functional independence after major abdominal surgery in the elderly. *J Am Coll Surg* 2004;199:762–72
12. Sørensen LT, Jørgensen T, Kirkeby LT, et al: Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. *Br J Surg* 1999;86:927–31
13. Debes C, Aissou M, Beaussier M: Prehabilitation. Preparing patients for surgery to improve functional recovery and reduce postoperative morbidity. *Ann Fr Anesth Reanim* 2014;33:33–40

14. van Rooijen S, Carli F, Dalton SO, et al: Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation. *Acta Oncol* 2017;56:329–34
15. Mayo NE, Feldman L, Scott S, et al: Impact of preoperative change in physical function on postoperative recovery: argument supporting prehabilitation for colorectal surgery. *Surgery* 2011;150:505–14
16. Carli F, Scheede-Bergdahl C: Prehabilitation to enhance perioperative care. *Anesthesiol Clin* 2015;33:17–33
17. Carli F, Charlebois P, Stein B, et al: Randomized clinical trial of prehabilitation in colorectal surgery. *Br J Surg* 2010;97:1187–97
18. Yun YH, Kim YA, Min YH, et al: The influence of hospital volume and surgical treatment delay on long-term survival after cancer surgery. *Ann Oncol* 2012;23:2731–7
19. Minnella EM, Awasthi R, Gillis C, et al: Patients with poor baseline walking capacity are most likely to improve their functional status with multimodal prehabilitation. *Surgery* 2016;160:1070–9
20. Gillis C, Loiselle SE, Fiore JF Jr., et al: Prehabilitation with whey protein supplementation on perioperative functional exercise capacity in patients undergoing colorectal resection for cancer: a pilot double-blinded randomized placebo-controlled trial. *J Acad Nutr Diet* 2015;116:802–12
21. Cermak NM, Res PT, De Groot LC, et al: Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. *Am J Clin Nutr* 2012;96:1454–64
22. Wall BT, Cermak NM, van Loon LJ: Dietary protein considerations to support active aging. *Sports Med* 2014;44:S185–94
23. Morton RW, Murphy KT, McKellar SR, et al: A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. *Br J Sports Med* 2018;52:376–84
24. Thomsen T, Villebro N, Møller AM: Interventions for preoperative smoking cessation. *Cochrane Database Syst Rev* 2014;3:CD002294
25. Minnella EM, Bousquet-Dion G, Awasthi R, et al: Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience. *Acta Oncol (Madr)* 2017;56:295–300
26. Fearon KC, Ljungqvist O, Von Meyenfeldt M, et al: Enhanced recovery after surgery: A consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr* 2005;24:466–77
27. Weisman IM, Weisman IM, Marciniuk D, et al: ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167:211–77
28. Balady GJ, Arena R, Sietsema K, et al: Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010;122:191–225
29. Niewiadomski W, Laskowska D, Gąsiorowska A, et al: Determination and prediction of one repetition maximum (1RM): safety considerations. *J Hum Kinet* 2008;19:109–20
30. Horvat M, Ramsey V, Franklin C, et al: A method for predicting maximal strength in collegiate women athletes. *J Strength Cond Res* 2003;17:324–8
31. Deutz NE, Bauer JM, Barazzoni R, et al: Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. *Clin Nutr* 2014;33:929–36
32. Bauer J, Capra S, Ferguson M: Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. *Eur J Clin Nutr* 2002;56:779–85
33. Salles J, Chanet A, Giraudet C, et al: 1,25(OH)2-vitamin D3 enhances the stimulating effect of leucine and insulin on protein synthesis rate through Akt/PKB and mTOR mediated pathways in murine C2C12 skeletal myotubes. *Mol Nutr Food Res* 2013;57:2137–46
34. Mithal A, Bonjour JP, Boonen S, et al: Impact of nutrition on muscle mass, strength, and performance in older adults. *Osteoporos Int* 2013;24:1555–66
35. Gustafsson UO, Scott MJ, Schwenk W, et al: Enhanced Recovery After Surgery (ERAS) Society, for Perioperative Care; European Society for Clinical Nutrition and Metabolism (ESPEN); International Association for Surgical Metabolism and Nutrition (IASMEN): Guidelines for perioperative care in elective colonic surgery: Enhanced recovery after surgery (ERAS®) society recommendations. *World J Surg* 2013;37:259–84
36. Arain M, Campbell MJ, Cooper CL, et al: What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Med Res Methodol* 2010;10:67
37. Dronkers J, Lamberts H, Reutelingsperger I, et al: Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. *Clin Rehabil* 2010;24:614–22
38. Enright PL: The six-minute walk test. *Respir Care* 2003;48:783–5
39. Crapo RO, Casaburi R, Coates AL, et al: ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–7
40. Miyamoto S, Nagaya N, Satoh T, et al: Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. *Am J Respir Crit Care Med* 2000;161:487–92
41. Du Bois RM, Weycker D, Albera C, et al: Six-minute-walk test in idiopathic pulmonary fibrosis: test validation and minimal clinically important difference. *Am J Respir Crit Care Med* 2011;183:1231–7
42. Moriello C, Mayo NE, Feldman L, et al: Validating the six-minute walk test as a measure of recovery after elective colon resection surgery. *Arch Phys Med Rehabil* 2008;89:1083–9
43. Mayhew JL, Prinster JL, Ware JS, et al: Muscular endurance repetitions to predict bench press strength in men of different training levels. *J Sports Med Phys Fitness* 1995;35: 108–13
44. Braith RW, Graves JE, Leggett SH, et al: Effect of training on the relationship between maximal and submaximal strength. *Med Sci Sports Exerc* 1993;25:132–8
45. Slankamenac K, Nederlof N, Pessaux P, et al: The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. *Ann Surg* 2014;260:757–62
46. Bohannon RW, Crouch R: Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. *J Eval Clin Pract* 2017;23:377–81
47. Rognmo Ø, Hetland E, Helgerud J, et al: High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil* 2004;11:216–22
48. Ensor PS: The functional silo syndrome. *AME Target*, AME Study Group on Functional Organization; 1988:16
49. Pullin J: Organizational renewal- tearing down the functional silos. *AME Target*. AME Study Group on Functional Organization; 1989:4–14
50. van Rooijen SJ, Engelen MA, Scheede-Bergdahl C, et al: Systematic review of exercise training in colorectal cancer patients during treatment. *Scand J Med Sci Sport* 2018;28:360–70
51. van Eeghen EE, den Boer F, Bakker SD, et al: Outcome of rectal cancer after radiotherapy with a long or short waiting period before surgery, a descriptive clinical study. *J Gastrointest Oncol* 2016;7:321–5
52. Bos AC, van Erning FN, van Gestel YR, et al: Timing of adjuvant chemotherapy and its relation to survival among patients with stage III colon cancer. *Eur J Cancer* 2015;51:2553–61