Fit for Surgery – Effects of short-course multimodal individualized prehabilitation in high-risk frail colon cancer patients prior to surgery: A feasibility study

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Research

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Abstract

Background

Prehabilitation is a promising modality for improving patient-related outcomes after major surgery, however, very little research has been done for those who may need it the most; the elderly and the frail. The study aimed to investigate if high risk, frail patients with colorectal cancer and WHO performance status I and II could adhere to a short course multimodal prehabilitation intervention prior to surgery.

Methods

The study was conducted as a single-center, prospective one-arm feasibility study with limited-efficacy testing of eight patients. The intervention consisted of a physical training program tailored to the patients with both high-intensity interval training and resistance training three times a week, nutritional support with protein and vitamins, a consultation with a dietician, and medical optimization prior to surgery. The primary outcomes were the increase in maximum oxygen intake (VO_2 peak) during the intervention and per-protocol compliance and adherence. Secondary outcomes were: increase in body weight, increase in albumin, adverse events during the intervention, postoperative length of stay, and complications within 30 days after surgery.

Results

The mean age was 80 (range: 66-88). Seven completed the intervention. The mean increase in maximum oxygen intake (VO_2 peak) was 17 % (range: 0.6% - 28 %), with two patients being non-responders. All patients who had a pre-diagnostic weight loss increased their body weight with a mean of 2.5 kg (range: 1.3 – 4.0 kg). Adherence to high-intensity interval training was 87 %, whereas adherence to nutritional support was 57 %. The median postoperative length of stay was 3 days (range: 1-26).

Conclusions

This one-arm feasibility study indicates that multimodal prehabilitation including high-intensity interval training can be performed with high adherence to the program in patients with colorectal cancer and WHO performance status I and II.

Clinical trial registration

Clinicaltrials.gov: NCT04167436, Date of registration November 18 2019. Retrospectively registered.

Key Points

1. What uncertainties existed regarding the feasibility?;

A short course individualized multimodal prehabilitation prior to surgery with high-intensity interval training, resistance training, dietary and nutritional support, and medical optimization has not previously been described in high-risk frail colon cancer patients. Thus, it was not clear if the patients would be interested, could adhere, comply, or benefit from the interventions.

2. What are the key feasibility findings?:

Compliance and adherence to the high-intensity interval training were high. However, using 90% of the maximum heart rate as a monitor of intensity was problematic. Compliance with the nutritional supplements was low.

3. What are the implications of the feasibility findings for the design of the main study?

The high-intensity interval training should be monitored primarily by wattage, rather than the 90% of maximum heart rate. The nutritional supplements should be changed from an individualized dosage to a fixed amount in order to reduce the complexity of the interventions.

Background

Improved perioperative treatments, such as minimally invasive surgery, enhanced recovery after surgery, and early rehabilitation have dramatically reduced the overall early mortality for colorectal cancer patients in the last decades[1–3]. The primary beneficiary of these improvements has been the younger group and to a lesser extent the elderly, frail, and comorbid patients[4, 5]. These patients have a markedly increased risk of postoperative adverse events, mortality, complications, and would be expected to have the most to gain from additional efforts to improve the perioperative period.

One effort of improvement which may benefit the elderly and frail is prehabilitation[6] consisting of physical exercise, nutritional support, and medical optimization prior to surgery[7]. Recent meta-analyses have shown that prehabilitation may reduce the risk of postoperative complications and increase physical fitness after surgery[8, 9]. Several concurrent studies are investigating prehabilitation, but most studies and described pilot studies included primarily young and healthy individuals.

The current studies within the field of prehabilitation have not reported their interventions in sufficient detail for implementation and only one trial focusing on elderly and frail patients has been published[10]. Thus, we planned to conduct a feasibility study with limited-efficacy testing in patients with higher WHO performance status and colorectal cancer before a randomized trial, to ensure that the patients could benefit, perform and adhere to a protocolized individualized intervention and report the challenges within this population.

Methods

Design and setting

The study was conducted as a single-center, prospective feasibility study with eight patients undergoing multimodal prehabilitation prior to surgery for colorectal cancer. Patients were recruited from the Department of Surgery, Zealand University Hospital, Roskilde, Denmark between October 4th, 2018, and January the 14th 2019. The intervention was planned in three standardized individualized intervention components: Training intervention, Diet and Nutritional support, and medical optimization. All interventions were protocolled before the initiation of the study. A graphic description of the course of the intervention and testing can be seen in Fig. 1.

All patients received standard perioperative care, including a multi-disciplinary team conference, preoperative lung exercise education with positive expiratory pressure whistle, protein-enriched high-energy supplements 5 days prior to surgery, carbohydrate loading prior to surgery, and full enhanced recovery after surgery[11, 12]. Certified colorectal surgeons performed the surgeries.

Participants eligibility

All patients with WHO performance status I or II, with planned surgery for colon or rectal cancer, without neoadjuvant radio- or chemotherapy were eligible for the study. Patients were excluded if they were planned for abdominoperianal resection, serum creatinine > 250 mmol/L, not able to understand or write Danish, had severe cognitive deficit (Mini-Mental State Examination < 11[13]), not able to perform exercise, known metastatic disease, or withdrew consent.

The rationale for using WHO performance status as a screening tool

In Denmark, the government has introduced a cancer treatment guarantee, which means that patients are to undergo surgery within a maximum of 14 days from diagnosis to surgery. This study was approved to postpone the surgery for high-risk patients with potentially modifiable risk factors. Therefore, patients had to be assessed for eligibility shortly after referral to make sure that no patients had postponed surgery unless they were included in the study. For the majority of patients, WHO performance status has been rated at referral, and have good inter-observer reliability[14, 15] which made it the most optimal available tool for screening. We chose to include patients with WHO performance status I and II, but not III or IV since these patients rarely are planned for surgery and were expected not to be able to perform the planned training intervention.

Intervention

Training intervention

The training intervention consisted of High-Intensity Interval Training (HIIT) and resistance training in supervised individual training sessions of approximately one-hour duration 3 times a week for at least 4 weeks. The HIIT was performed on an exercise bike and consisted of 4 minutes warm-up, followed by 4 bouts of 2 minutes at an intensity > 90% of the participants' maximum heart. Between and after the bouts, low load intervals of a duration of 4 minutes was performed. Heart rate was continuously monitored by a chest-worn monitor (Polar A300®, Polar Electro, Finland). The threshold of 90% of the maximum heart rate was determined by a Cardiopulmonary Exercise Test (CPET) in each participant. The participant was able to adjust the load, with the physiotherapist encouraging the participant to obtain the > 90% of maximum heart rate during the bouts. After each bout and at the end of the HIIT training the participant was asked to rate self-exertion using the Borg RPE 6–20 scale[16]. After the HIIT session, resistance training was performed using machines (Technogym®, Italy) in the following order; chest press, lateral pulldown, and leg press. Three sets of 8–12 repetitions were performed in each machine. An 8-repetition maximum test (8-RM)[17] was used to calculate 1-RM. Resistance was set to progress throughout the intervention using the following model; week 1 (65% of 1-RM), week 2 (70% of 1-RM), week 3, 4, and 5 (75% of 1-RM). Beside HIIT and resistance training the patients were encouraged to perform light to medium aerobic exercise for at least 30 minutes a day at home. This was not supervised or registered.

Dietary and nutritional intervention

The nutritional intervention consisted of an addition of 0.4 g/kg bodyweight protein two times a day by TMP-90 Shake® (Friesland Campina, Netherlands) regardless of nutritional status or weight loss. One dose taken just after exercise or training, and one before sleep. In addition, a multivitamin tablet (Apovit Multi®, Apovit, Denmark) with 100% of the daily recommended dosage, and a D-vitamin with calcium tablet (38 µ + 400 Unikalk Mega®, Orkla Health A/S, Denmark) was taken daily. The dietary intervention consisted of an interview with a dietician within the first week after baseline testing. Estimation of current intake was done by a 24-hour food recall and daily dietary needs were conducted by estimation of base protein and total energy requirements by Harris-Benedict equation[18], with an added factor of 1.3–1.5, depending on the individual physical activity level. Patients were then advised how to change their diet to meet the excess demand for energy and protein, and if necessary instructed in using additional protein and energy drinks.

Medical optimization

The principal investigator performed medical optimization as part of the baseline testing and interview. Expanded routine blood work was performed including anemia parameters, hemoglobin A1c, cholesterol, vitamin status, minerals, white blood cell count, liver, and kidney parameters. If any unknown or poorly regulated disease was suspected, the patient was either referred to a specialist or adjusted in the medication, depending on the issue. Anemia needing correction was defined as ≤ 11.3 g/dL for both men and women, and patients were referred to intravenous administered Iron(III)isomaltoside (Monofer® Pharmacosmos A/S, Denmark) at the earliest convenience. Medical history was assessed and current medication was inspected for possible seponation or dose reduction. Patients with a high-risk intake of alcohol or smokers were encouraged to quit, and if interested referred to the in-hospital alcohol and tobacco cessation course.

The complete intervention described in protocols translated into English can be found in the supplementary material (Appendix 1–3). Full reporting of the training intervention in regards to Consensus on Exercise Reporting Template (CERT) guidelines[19] for reporting exercise interventions can be found in the supplementary material (Appendix 4).

Primary outcomes

The primary outcome was changes in maximum oxygen intake (VO_2 peak) between baseline and preoperative assessment by CPET. VO_2 peak was estimated at the maximum oxygen uptake/min/kg body weight. Previous studies on repeated CPET's have found a biological variation of VO_2 peak on 3.9% and an analytic variation of 2.2%[20]. Non-responders were defined as having an increase of less than 5% in VO_2 peak. Further, the time spent above 90% of maximum heart rate during HIIT was of primary interest as a measurement of per-protocol compliance. Total time spent above 90% of maximum heart rate during HIIT was measured for each training session and each bout. We considered complete training as a minimum of 4 minutes of training above > 90% of maximum heart rate and with a Borg's RPE > 16 and was used as goal of compliance. The percentage of completed training sessions was used as the measurement of adherence.

Secondary outcomes

Secondary outcomes were: change in maximum wattage during CPET, muscle strength, functional capacity, body weight, albumin, compliance with the dietary and nutritional intervention, adverse events during the intervention, postoperative length of stay, and complications within 30 days after surgery.

Other variables

Completion of the nutritional support was defined as $\geq 65\%$ of both protein and vitamin ingestion. Patients received a fixed amount of protein supplement at baseline and the day prior to surgery the residual supplement was measured and usage was calculated as a percentage of the required intake. WHO performance status and ASA score were estimated by the surgeon at the first visit in the outpatient visit. Charlson comorbidity score was calculated including tumor and age[21]. Frailty was determined by a least one positive criteria on Fried frailty [22, 23] or by a Geriatric-8 (G8) score < 14[24]. Discharge was managed through standardized discharge criteria. Recording of adverse events and postoperative complications were performed by an external assessor through medical records and graded by both the Clavien-Dindo classification[25] and the Comprehensive Complication Index[26]. Any readmission and Days at Home within 30 days after surgery (DAH-30)[27] was assessed through entries in medical records.

Testing

Testing was performed at baseline, the day prior to surgery, and four weeks after surgery. Testing included Cardiopulmonary Exercise Test (CPET) and five physical function tests: Handgrip strength, Isometric leg extension strength test[28], 6 minutes walk test, 30 sec. Sit to stand test[29], and 30 sec. stair climb test, in this exact order. The principal investigator performed all baseline testing. Pre- and postoperative testing (a day prior to surgery and four weeks after surgery) was performed by a physiotherapist specially trained to perform the testing procedures. CPET was performed on Jaeger® Vyntus® CPX (CareFusion, San Diego, US) by steep ramp until exhaustion, with an expected testing time of 8–12 minutes. Handgrip strength was measured using a hand dynamometer (Jamar Smart®, Patterson Medical, Saint Paul, Minnesota, US) with three measurements on each hand, starting with the left hand. Isometric leg extension strength test was performed with a Lafayette Manual Muscle Tester (model LIC.01165, Lafayette Instrument Company, Lafayette, IN US) with three measurements on each leg, starting with the left leg. 6-minutes walk test was performed in an undisturbed hallway on a 20 meters course. Sit to stand was performed as described by Jones et al[30]. Stair climb test was performed in an undisturbed stairwell with 10 steps of 17 cm's on each floor, with a maximum of twelve floors available. The number of steps achieved within 30 seconds was recorded. Test of strength for chest press, lateral pull-down, and leg press was conducted as an 8-RM test and a 1-RM calculated from Brzyckis formula[31]. Anthropometric measurements including skin

fold, circumference, weight, and height were performed together with Patient-Generated Subjective Global Assessment (PG-SGA)[32] which was used for nutritional screening. Frailty was assessed by both G8 score and Fried frailty[23] at baseline.

Statistics and reporting

No statistical analyses were performed. Reporting was conducted in adherence with the CONSORT statement for feasibility and pilot studies[33].

Results

Baseline characteristics and intervention

During the study period, nine patients were eligible and approached for inclusion. One patient declined to participate due to a scheduling conflict, leaving eight patients who agreed to participate, all diagnosed with colonic cancer at the time of inclusion. One patient later showed benign pathology, but was treated with the same oncological approach, and thus kept in the analysis. Patient characteristics at baseline can be seen in Table 1. Four men and four women were included with a mean age of 80 [range: 66–88]. Three had WHO performance status II, and five performance status I at inclusion. Six had involuntarily lost weight during the last six months. Six patients had a G8 score < 14, and seven had at least one positive criteria in Fried frailty. Four patients had a hemoglobin level ≤ 11.3 g/dL.

Table 1
Patient characteristics at baseline.

Patient	P1	P2	P3	P4	P5	P6	P7	P8
Age	66	86	86	78	88	80	78	79
Cancer	Colon	Colon	Colon	Colon	Colon	Colon	Colon	Colon
Gender	Female	Female	Female	Male	Male	Female	Male	Male
ASA	2	3	3	2	2	3	2	2
WHO PS	1	2	2	1	1	2	1	1
Charlson Comorbidity index	6	6	6	6	6	9	6	5
BMI (kg/m ²)	29.1	24.6	22.6	38.5	21.5	27.8	19.5	25.9
Smoking status	Previous smoker	Non-smoker	Non-smoker	Non-smoker	Previous smoker	Previous smoker	Active smoker	Previous smoker
Alcohol consumption	1 U/week	0 U/week	0 U/week	5 u/week	10 u/week	0 u/week	21 u/week	14 u/week
> 5 medications	-	-	+	+	-	+	+	-
% weight loss during the last 6 months	0%	2.8%	9.1%	0%	8.6%	2.6%	9.0%	3.4%
Primary Education	College level	Vocational trained	Vocational trained	Vocational trained	University	Primary education	College level	Vocational trained
T stage	3	2	2	2	3	2	4	2
N stage	2	0	0	0	0	0	1	1
G8 score	12	7	11	14.5	8	9	9	15
Fried frailty positive criteria	1	2	2	1	4	3	4	0
Hgb (g/dL)	8.06	10.8	12.25	13.05	12.57	11.28	9.83	11.44
Albumin (g/L)	35	38	38	36	34	30	32	33
CRP (mg/L)	6.7	< 2.9	< 2.9	< 2.9	6.3	17	2.9	23

ASA: American Society of Anesthesiologists classification. BMI: Body Mass Index. WHO PS: WHO performance status.

Seven patients completed the intervention, while one patient developed an abscess in the tumor needing hospitalization and percutaneous drainage which led to inability to complete the intervention. All seven patients, who completed the intervention, were tested preoperatively, but three patients were unable to perform the four-week postoperative testing due to complications. Four patients with anemia received intravenous iron with a single dose of Iron(III)isomaltoside. One patient developed previously unknown ECG changes on CPET, which was consulted with a cardiologist, but without the need for change in medication or further diagnostics. One patient was a current smoker but was not interested in smoking

cessation. The same patient had an alcohol intake above recommendations but reduced intake to zero without the need for further counseling.

Primary outcome: Change in functional capacity

The mean baseline VO_2 peak was 14 ml/min/kg [range: 8.8–17.6], with a mean maximum heart rate of 112 [range: 86–134]. The mean change in VO_2 peak between baseline and preoperative testing was 17% [range: 0.6–28%], with two patients being non-responders regarding the VO_2 peak, but both these patients increased in maximum wattage (9% and 14%) (Fig. 2). Description of changes in physical fitness is shown in Table 2.

Table 2
Changes between baseline testing and prior to surgery, and perioperative outcomes

Patient	P1	P2	P3	P4	P5	P6	P7
Intravenous iron	+	+	0	0	0	+	+
Percentage of protein ingested	99%	17.5%	72%	73%	58%	74%	21%
Change in physical capacity between baseline and prior to surgery							
VO ₂ at AT (ml/kg/min)	3.7 (39%)	0.6 (9%)	3.7 (40%)	1.7 (15%)	-4.2 (-33%)	1.7 (29%)	-1.8 (-18%)
Handgrip strength (kg)	12.8 (55%)	0.3 (1.4%)	-0.8 (-8%)	-6.7 (-19%)	-2.2 (-8.2)	0.5 (2%)	-13.5 (-34%)
6-MWT (m)	15.3 (3%)	6 (2%)	53 (19%)	20.3 (5%)	-15.2 (-6%)	50.6 (18%)	-77.3 (-19%)
STS (repetitions)	-1 (-9%)	0 (0%)	1 (11%)	0 (0%)	0 (0%)	1 (11%)	-1 (-9%)
Stair Climb Test (number of stairs)	2 (4%)	-4 (-13%)	1 (3%)	2 (6%)	5 (22%)	5 (36%)	-
Chest press* (kg)	6 (23%)	-	0 (0%)	11 (28%)	7 (100%)	2 (20%)	-4 (-24%)
Pull-down* (kg)	7 (24%)	9 (25%)	1 (5%)	1 (2%)	8 (25%)	2 (8%)	-7 (-26%)
Leg press* (kg)	58 (37%)	-11 (-18%)	2 (5%)	58 (38%)	14 (36%)	22 (34%)	-25 (-38%)
Change in blood work between baseline and prior to surgery							
Change in Hb	5.64 g/dL	0 g/dL	-0.64 g/dL	-0.64 g/dL	-0.48 g/dL	1.93 g/dL	0.16 g/dL
(g/dl)							
Change in albumin (g/L)	3 g/L	1 g/L	0 g/L	-2 g/L	2 g/L	8 g/L	-1 g/L

All measurements are given in absolute values between baseline and prior to surgery, with the change in percentage from baseline in parenthesis. *Indirect one-repetition maximum test calculated by Brzyckis formula.. **Highest complication graded by the Clavien-Dindo classification. Data from Patient 8 is not presented since postoperative testing was not conducted in this patient due to an abscess in the tumour needing hospitalization and percutaneous drainage. AT: *Anaerobic threshold*. DAH-30: *Days at Home within 30 days after surgery*. Hb: *Hemoglobin*. LOS: *Length Of Stay*. STS: *Sit to stand in 30 seconds*. VO₂: *Oxygen uptake*.

Patient	P1	P2	P3	P4	P5	P6	P7
Change in CRP (mg/L)	1.9 mg/L	0 mg/L	0 mg/L	0 mg/L	7.7 mg/L	0 mg/L	27.1 mg/L
Perioperative and postoperative outcomes							
Conversion of laparoscopy	-	-	-	+	-	-	-
LOS	2	3	1	4	2	26	6
Readmission	-	+	-	+	-	-	-
DAH-30	+	+	+	0	+	0	+
Stoma	-	+	-	-	-	+	-
Complication**	-	2	-	4a	-	4a	-
Day for full mobilization	1	1	0	2	1	?	3
Day for removal of urinary catheter	0	0	0	3	0	?	0
Day for starting oral nutrition	0	0	0	0	1	2	0
All measurements are given in absolute values between baseline and prior to surgery, with the change in percentage from baseline in parenthesis. *Indirect one-repetition maximum test calculated by Brzyckis formula. **Highest complication graded by the Clavien-Dindo classification. Data from Patient 8 is not presented since postoperative testing was not conducted in this patient due to an abscess in the tumour needing hospitalization and percutaneous drainage. AT: <i>Anaerobic threshold</i> . DAH-30: <i>Days at Home within 30 days after surgery</i> . Hb: <i>Hemoglobin</i> . LOS: <i>Length Of Stay</i> . STS: <i>Sit to stand in 30 seconds</i> . VO ₂ : <i>Oxygen uptake</i> .							

Primary outcome: Compliance and adherence

A total of 82 (87%) out of 94 possible training sessions were performed, but with great variability between patients (54–100%). The mean Borg's scale estimation for training sessions was 17 (range: 15-18.5). In three patients, we were not able to get an accurate heart rate either due to severe scoliosis (n = 1) or atrial fibrillation (n = 2). For the monitored training sessions, 87% met the goal of compliance of 4 min > 90% heart rate. For three patients we observed no drops in heart rate between bouts in the low load-interval phase, thus 40% of training sessions were performed with more than 8 minutes of > 90% in heart rate during the high interval bouts (Fig. 3a and 3b)

Secondary outcomes

Five patients had a weight loss the last six months before diagnosis, and all five increased their body weight, with a mean of 2.5 kg [range: 1.3-4 kg] during the intervention. None of the patients had weight loss during the intervention. Four patients reached the goal of the nutritional support of > 65% of ingested protein supplements. The main reason for not ingesting the protocolized protein intake was due to taste and texture, and one patient nausea and stomach aches. Two patients experienced a potential adverse event during the intervention, one had a urinary tract infection and one developed an abscess in the tumor. Three patients reported a reduction in pre-existing pain and one reduced need for pain medication.

Of the seven patients who completed the intervention, six had laparoscopic/robotic-assisted surgery, four of which had primary anastomosis. Conversion to laparotomy was performed in one patient, due to adherence of the tumor to the retroperitoneum. The mean surgical time was 195 minutes [range: 106– 324 minutes]. The median length of hospital stay was 3 days [range: 1–26]. Two patients were subsequently readmitted within 30 days of discharge. One for a urinary tract infection and one for fascia dehiscence from an open laparotomy incision. Three patients developed a postoperative complication (One Clavien-Dindo 2 [Comprehensive Complication Index: 20.9], and two Clavien-Dindo 4a [Comprehensive Complication Index: 42.9 and 69.8]).

Discussion

This feasibility study of prehabilitation demonstrated that frail high-risk patients undergoing major abdominal surgery generally were interested in prehabilitation, could adhere to the training, and increase their physical fitness within four weeks. The completion rate of HIIT was high and all patients with prediagnostic weight loss had an increase in body weight prior to surgery. However, the completion rate of nutritional support was low.

The increase in VO_2 peak is greater than previously described with HIIT in a healthy elderly population[34] but similar to what has been described in lung cancer patients[35, 36] and healthy colorectal cancer patients[37]. The elderly, frail, and vulnerable patients are absent from most prehabilitation studies[38] even though they have the most to gain from prehabilitation. In one of the only randomized controlled trials of prehabilitation in high-risk patients, Barberan-Garcia and colleagues[39] showed a significant reduction in postoperative complications (relative risk: 0.5; 95% CI, 0.3–0.8). However, the mean age was only 71.

The primary concern with the protocol was the use of heart rate to monitor the intensity of training. Several of the participants spent their complete training session above 90% of their maximum heart rate. From studies of HIIT in heart failure patients, heart rate seems to be a reliable monitor of intensity[40], but in our study population, we did not see the same cardiac adjustment of the load. Rather, the patients increased to their maximum heart rate rather rapidly and seemed to be capped there. Further, in three out of the seven patients, we were not able to reliably estimate their heart rate during the training sessions due to physical attributes mainly affecting the elderly population. One solution would be to use watt (SI unit: $\text{m}^2 \cdot \text{kg} \cdot \text{s}^{-3}$) as the monitor of load, but this requires further baseline testing either as CPET or as a steep ramp test before planning the individual training plan. This would be preferable in the many elderly with paroxysmal atrial fibrillation in which the heart rate does not decrease between high-intensity intervals. On the other hand, fixed wattage, as seen in Fig. 3b, doesn't take variability in physical performance between training sessions into account, which could potentially mean undertraining for some patients.

The main limitation of the study is the lack of a control group. There are both a placebo and a learning effect when conducting repeated measurements of physical function, this includes CPET and the measurement of VO_2max . It is not clear how much the increase in VO_2max is related to repeated testing in this population, and future studies of the increase in function should contain a control group. Another limitation is missing data, especially in postoperative testing. Only the patients without complications were tested 4 weeks after surgery with CPET, thus any conclusion on maintenance in physical function four weeks after surgery should be interpreted with caution. The testers of the preoperative and 4-week postoperative tests were not blinded to the first CPET test results or the progression during the training period since data was used to estimate the load used for testing. Further, different testers performed the baseline-, the preoperative, and 4-week postoperative tests which potentially could lead to a systematic difference. This could be solved by a separated blinded testing team and with each test for each patient performed by the same tester.

We did not have any follow-up or objective measurement of adherence to the dietician advice, besides the increase in body weight and serum albumin. The adherence to the protein supplements was low with only four out of seven reaching the aim of > 65% ingested. This was particularly prominent in patients with higher body weight, illustrating the limitation of a weight-based dosage. For example, one of the patients was prescribed more than 100-gram protein supplements a day. Furthermore, the weight-based dosage required weighing the supplements at home, rather than using a scoop which would be less cumbersome for the patients. This also showed the limitations of a multimodal individualized intervention in the outpatient setting. Each part of the prehabilitation intervention required a high degree of participation and resources from the participants, which we suspect that for some patients, surpassed their capacity. Thus, compliance varied significantly between participants especially in regards to the supplements. When planning future interventions this should be kept in mind and the complexity of the intervention should be reduced to a minimum.

A major strength was that training was supervised by the same team of physiotherapists and that all training was individually supervised and adapted. Further, the testing was standardized, performed in the same order for each participant, and each test. The high degree of adherence to enhanced recovery after surgery is another strength because the results of prehabilitation can then be treated as a therapeutic add-on to an optimal clinical setting. There were some potential adverse events and complications after surgery, as well as a very short length of hospital stay; however, further confirmatory trials are needed to ascertain these findings.

This one-arm feasibility study indicates that multimodal prehabilitation including HIIT, resistance training, protein supplementation, and medical optimization is feasible in elderly frail patients with colon cancer. Further research is necessary to make any clinical conclusions, especially randomized trials within elderly frail patients since they have the highest risk of not recovering after surgery and the most to gain from prehabilitation. Efforts should be made to develop and validate effective screening tools for high-risk patients who may benefit from prehabilitation efforts.

Patient and Public Involvement

Prior to initiation of the study a patient panel of 10 colorectal cancer patients were asked to evaluate the proposed intervention. Further, the patients included in the study were offered to participate in a semi-structured interview after completion of the intervention with two impartial representatives with the focus of evaluating the intervention and study design.

Abbreviations

ASA

American Society of Anesthesiologists

CERT

Consensus on Exercise Reporting Template

CPET

Cardiopulmonary Exercise Test

HIIT

High Intensity Interval Training

PG-SGA

Patient-Generated Subjective Global Assessment

VO₂peak

maximum oxygen uptake

WHO

World Health Organization

1-RM

One Repetition Maximum

8-RM

Eight Repetition Maximum

Declarations

Ethics and consent to participate

The study was approved by the Scientific Ethical Committee (SJ-607), the hospital Board of Directors, and the Data Protection Agency (REG-040-2017). All participants were informed that inclusion would mean postponing their surgery, conflicting with national guidelines. All participants gave oral and written consent prior to enrolment. The study is registered at clinicaltrials.gov (NCT04167436).

Consent for publication

The supplementary material contains pictures of a staff member showing the exercises. Written consent for publication of the pictures have been obtained from the individual.

Availability of data and materials

The technical appendix is presented in the supplementary material. Raw data is presented in the paper. A anonymised version of the datasets used during study are available from the corresponding author on a reasonable request.

Competing interest

The authors report no conflict of interest and are alone responsible for the content of the paper.

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Authors contribution

RDB, CJ, SOD, and IG conceived the idea and principle outlines for the study. RDB, CG, LBJ, and STS developed the study protocol and technical appendixes. RDB, CG, and LBJ collected the data. RDB did the analyses, all authors helped in the interpretation of the data. RDB wrote the manuscript, and all authors made critical revision of the manuscript of important content and approved it for publication.

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Figures

Figure 1

Outline of the course of testing and intervention. *All testing consisted of baseline questionnaires (G8 and fried frailty), nutritional screening (PG-SGA) and anthropometric measurement, blood work, Cardiopulmonary Exercise Test (CPET), Handgrip strength, Leg extension strength test, 6-minutes walk test, Sit to stand test (30 sec.) and stair climb test (30 sec.), In that exact chronological order. ** The intervention consisted of individual training three times a week with a minimum of 10 sessions. Nutritional counseling within the first week of inclusion (1.5 hour), 0.4 g/kg bodyweight protein supplement two times a day, and medical optimization. Medical optimization was performed on the same day of baseline testing. *** Discharge managed through standardized discharge criteria. Adherence to Enhanced Recovery After Surgery (ERAS) was recorded each day during admission.

Figure 2

Changes in VO₂ peak, Workload, and six minutes walk test at baseline, preoperative, and four weeks after surgery for each individual patient.

Figure 3

Examples of different issues within training sessions based on maximum heart rate. 3a: Examples of training sessions with continuous measurement of heart rate and Borg's RPE for three different patients. Horizontal lines represent the time within the interval spend above 90% of maximum heart rate (HR) within each interval. Patient 1 (red) represents the expected course of the HR during a training session. Patient two (blue) shows a training session where the HR did not decrease between high-intensity intervals. Patient three (orange) shows a patient with known paroxysmal atrial fibrillation, which is suspected to have atrial fibrillation during the training. HR was above 100% of the maximum HR completely during the session. HR during the last four minutes of training was not registered. 3b: Illustrative example of a high-intensity interval training bout of a frail patient with colonic cancer without an expected decrease in heart rate between high intensive interval bouts. Similar to patient two (blue) in figure 3a. The example was produced on Lode Corival rehab ergometer bike (Lode B.V., Groningen NL) on a patient not included in the feasibility study, in order to show the missing decrease in HR in correlation to intervals on a similar patient. Measure of Watt (Green line), Revolutions per minute (RPM (blue line)), Heart rate (Beats per minute, BPM (red line)), by time in minutes (x-axis). Oxygen saturation (SpO₂) was not measured. The resting pulse of 75, increased rapidly after the start of the bout, even on 30% of maximum wattage defined by CPET, and reached maximum pulse within the first minute of exercise. The pulse did not decrease in low-intensity phases. CPET: Cardiopulmonary Exercise Test. RPE: Borg's Rating of Perceived exertion (RPE) 6-20 scale.

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