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Original article

Evaluation of a multimodal personalized prehabilitation program in colon cancer patients undergoing surgery, focussing on changes in nutritional status, physical fitness and exploring clinical outcomes

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S U M M A R Y

Background & aims: Many hospitals implemented prehabilitation programs for colon cancer (CC), but only few studies evaluated prehabilitation in clinical practice. We evaluated the results of a prehabilitation program that was implemented as usual care in our hospital on changes in nutritional status and physical fitness, and by exploring clinical outcomes.
Methods: We conducted a prospective observational study to evaluate the prehabilitation program. The prehabilitation program that was implemented was as follows: at diagnosis (T0), patients were screened to assess whether they were physically unfit or fit: being unfit was defined as severe malnutrition (following the criteria of the Global Leadership Initiative on Malnutrition) and/or low cardiorespiratory fitness (VO_2max <18.2 ml/kg/min). Unfit patients were referred to a 4–6 weeks prehabilitation program supervised by a physiotherapist. Patients who were fit were referred to unsupervised (2 weeks) prehabilitation. Follow-up measurements were conducted 3 days before (T1) and 6 weeks after (T2) surgery. Nutritional status was assessed by fat free mass and protein intake. Physical fitness was evaluated through VO_2max, handgrip strength, 5 times-sit-to-stand test and maximal inspiratory pressure. Clinical outcomes were postoperative surgical and non-surgical complications, length of hospital stay and readmission, postoperative mortality and the Modified Iowa Level of Assistance Scale (mILAS).
Results: Between July 2022 and September 2023, 90 CC patients were screened for prehabilitation. Of those, 33% were unfit and referred to supervised prehabilitation. At diagnosis, 32% of supervised and 42% of unsupervised patients reached the minimally recommended daily protein intake. This changed to respectively 78% and 81% at T1. Between T0 and T1, improvements in physical fitness were most pronounced in the supervised group. Median length of hospital stay was 4 days (Q1-Q3: 3–7) in the supervised group and 3 days (Q1-Q3: 3–4) in the unsupervised group, while the mILAS score was similar. Complication rates, postoperative mortality and readmission rates appeared similar across groups.
Conclusions: Our findings suggest that improvements in nutritional status and physical fitness were most pronounced in the unfit patients. Supervised and unsupervised groups appeared to have similar complication rates after surgery, but these findings should be interpreted with caution given the small sample size.
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Abbreviations: 5TSTS, 5 Times Sit To Stand test; ASA, American Society of Anesthesiologists; CC, Colon Cancer; CRC, ColoRectal Cancer; ERAS, Enhanced Recovery After Surgery; EPF, Electronic Patient File; FFM, Fat Free Mass; GLIM, Global Leadership Initiative on Malnutrition; HGS, Handgrip Strength; LBM, Lean Body Mass; MIP, Maximal Inspiratory Pressure; mILAS, Modified Iowa Level of Assistance Scale; SF-BIA, Single-Frequency Bioelectrical Impedance Analysis; SRT, Steep Ramp Test.

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1. Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy globally with in 2022 an age-standardized incidence rate of 22 per 100,000 men and 15 per 100,000 women [1,2]. Surgical resection of the primary tumor is the cornerstone of curative treatment for CRC [3]. Approximately 30% of the patients experience complications following CRC surgery [4–7]. These complications can be severe, leading to worse overall survival rates, longer hospital stays, increased healthcare costs and lower quality of life [4,8].

The concept of prehabilitation is a coordinated, multidisciplinary approach to prepare patients for a planned surgery through a combination of interventions to improve overall health [9,10]. The overall goal of prehabilitation is to use the period between diagnosis and surgery to improve health status and minimize postoperative surgery-related functional decline and its consequences [11]. Prehabilitation for CRC patients is often multimodal as it focusses on the optimisation of physical fitness, nutritional status, psychological support, guidance on quitting smoking and alcohol, treatment of anaemia and management on co-morbidities and frailty [10].

There is an emerging body of evidence on the benefits of multimodal prehabilitation in CRC patients undergoing surgery [7,12–14]. Conclusions are predominantly based on findings from randomized controlled trials (RCTs), which showed decreased complication rates, improved functional recovery and reduced length of hospital stay [7,12–14]. Although RCTs are the golden standard for assessing the efficacy of an intervention, the generalizability to real-life clinical practice is complex as RCTs are usually performed in controlled conditions and often include a selected group of patients which can affect external validity [15,16]. Therefore observational studies in clinical settings are of added value as they reflect real-life clinical practice [15]. Optimisation of nutritional status and physical fitness are the backbone of current prehabilitation programs in clinical practice. Nevertheless, studies so far report limited information on how nutritional status and physical fitness change during and after prehabilitation [17,18]. Furthermore, there is an increasing interest in identifying patients who are at high risk of postoperative complications, to tailor interventions to those patients who are expected to gain the greatest advantage from prehabilitation [17,19].

The objective of this study was to evaluate a multimodal prehabilitation program for CRC patients undergoing surgery in a general hospital. Because clinical treatment of rectal caner differs from colon cancer (CC), which could influence the outcomes of prehabilitation, we report on the results of colon cancer patients in the current study. Specifically, the main aim is to describe the changes in nutritional status and physical fitness before and after surgery in unfit and fit CC patients following respectively supervised and unsupervised prehabilitation.Secondarily, exploratory, clinical outcomes were also assessed in both groups.

2. Materials & methods

2.1. Study setting and participants

We conducted a prospective observational study to evaluate a prehabilitation program in a general hospital in the Netherlands - Hospital Gelderse Vallei, Ede. The program is usual care in Hospital Gelderse Vallei since July 2022 and was designed based on the current scientific insights and guidelines [20–22] and adapted to the practical capabilities of the hospital. Multidisciplinary clinical consultation (surgeon, oncologist, gastroenterologist, radiologist, geriatrician, dietician, physiotherapist and specialized nurse) is organized for each patient at the moment of diagnosis. Besides the prehabilitation part of the XtraFit program, all patients received perioperative care according to the Enhanced Recovery After Surgery (ERAS) protocol for oncological colorectal surgery [20].

Between July 2022 and September 2023, 167 adult patients (age $\geq$18 y) suspected for CRC visited the XtraFit prehabilitation outpatient clinic. Of those, 60 patients were excluded because they had no CC, resulting in 107 patients who were diagnosed with CC. Subsequently 17 of the CC patients were excluded for the following reasons: no surgical treatment (Endoscopic mucosal resection (EMR), palliative care and best supportive care) and patients who received neoadjuvant chemotherapy. This because neoadjuvant therapy is administered during the prehabilitation period, which will potentially interfere with the outcomes of prehabilitation. This resulted in a total of 90 patients who were scheduled for elective surgical resection of primary CC and eligible for this evaluation study (Fig. 1). Since this study evaluated usual care, the local scientific research committee of the hospital approved the study and waived the need for approval by an Ethics Committee.

2.2. Set-up of the program

The backbone of the program consists of three moments of consultations with a certified and trained in-hospital dietician and with a physiotherapist (six consultations in total): at the time of diagnosis (T0), within three days before surgery (T1) and six weeks after surgery (T2), see Fig. 2 and Supplementary Table 1.

During those consultations, several measurements and assessments were conducted. An important step in the program is that patients are triaged into a supervised or into an unsupervised prehabilitation program at T0. This triage went as follows: at T0, patients with severe malnutrition and/or a low cardiorespiratory fitness were defined as being physically unfit and were referred to supervised prehabilitation; the rest of the patients was defined as physically fit and were referred to unsupervised prehabilitation. Severe malnutrition was defined according to the GLIM criteria as recommended by the ESPEN Guideline of Clinical Nutrition and Surgery [23]. This includes minimal one phenotypic criterium (percentage of non-volitional weight loss, low Body Mass Index (BMI) or reduced muscle mass) and minimal one etiologic criterium (reduced food intake, assimilation or disease burden, inflammatory/inflammation condition) [24]. Low cardiorespiratory fitness was defined as: a VO_2max <18.2 ml/kg/min using the Steep Ramp Test (SRT) according to the protocol of Bongers BC [25]. This threshold is based on previous literature showing that patients scheduled for elective colorectal surgery with a VO_2max <18,2 ml/kg/min were more likely to develop postoperative complications [26].

2.3. Supervised prehabilitation

The goal of supervised prehabilitation was to improve the patient's level of physical fitness and nutritional status. In Hospital Gelderse Vallei, patients usually have surgery within two weeks after diagnosis. For patients referred to supervised prehabilitation, surgery was postponed with minimal four and maximal six weeks to enable progress with personalized prehabilitation.

2.3.1. Nutritional advices – during the supervised prehabilitation program

At T0 personalized nutritional advice was provided by an in-hospital dietician. If indicated there was timely (every two to three weeks) follow up by phone consultations until surgery. The nutritional advice was based on the recommendations of the National dietetics prehabilitation guideline of the Netherlands [21].

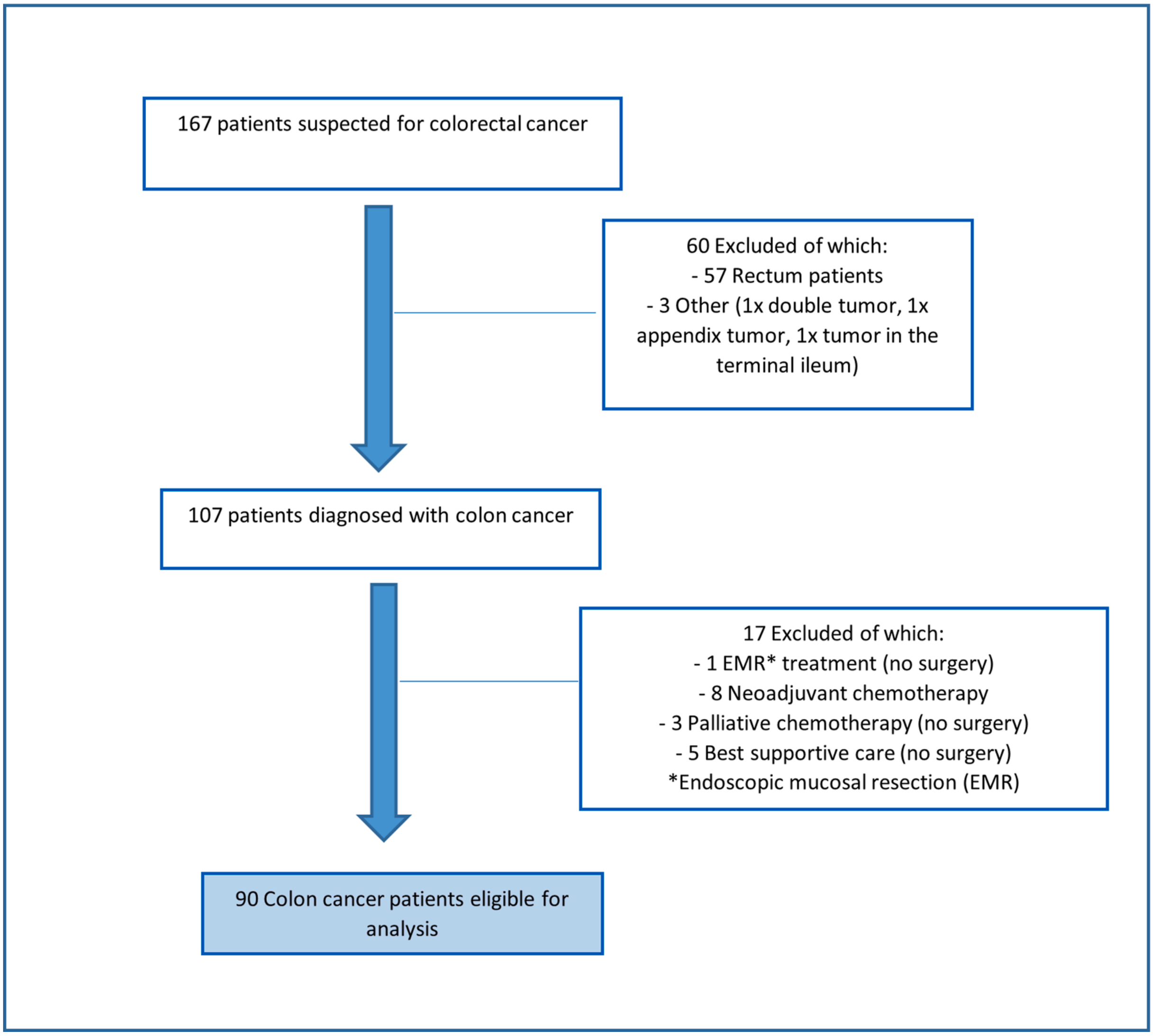

Fig. 1. Flow chart of number of colon cancer patients who were eligible for analysis.

Patients were encouraged to: I) optimize protein intake towards a total of 1.5–1.9 g/kg of FFM/day, II) Consume approximately four times a day a portion of 20–30 g of protein, where the last portion is 30 min before night' sleep to stimulate muscle protein synthesis, III) Consume 20–30 g of protein within 30–60 min after strength training, III) Optimize energy intake according to energy needs [27], IV) Use a vitamin D supplement when applicable according to guidelines of the Health Council of the Netherlands [28]. During the consultation at T0 these recommendations were translated into practical and personalised nutritional advices based on the food diary of the patient at diagnosis. Nutritional advices focussed on the consumption of proteins from habitual foods. The consultation aimed to provide education to increase knowledge and understanding of the role of nutrition (particularly protein) around surgery. The online protein calculator [29] tool of the hospital was available to support the practical application of the advices at home. General information about the role of proteins and examples of habitual products was provided via the digital E-care platform of the hospital or paper based. A medical protein-rich drink was only provided in case there was insufficient intake possible from habitual foods posing a risk on malnutrition.

2.3.2. Exercise therapy – during the supervised prehabilitation program

Patients with an indication for supervised prehabilitation were referred to a community-based certified oncological physiotherapist for a personalized exercise intervention. This intervention encompasses high intensity interval and strength training, at least 3 times a week during 4–6 weeks.

- The high intensity interval training according to the Wisløff protocol [30] was conducted on a bicycle, treadmill or rowing machine and has a duration of 28 min (4 intervals of 3-min moderate intensity, 4 min high intensity). The interval training aims to reach Borg levels 15–17 and > 85% of the maximum heart rate (measured during the SRT). Low-intensity training was a 30–60 min exercise, such as walking or cycling.
- Strength training consisted of two series, each including 6 exercises of 10 repetitions (leg press, chest press, biceps curl, lat pulldown, low row and the back trainer). The weight and resistance used in the program were individualized according to the calculated 1RM results at diagnosis (week 1: 65%, week 2: 70%, week 3: 65%, week 4: 70%). If the last 10 reps were not

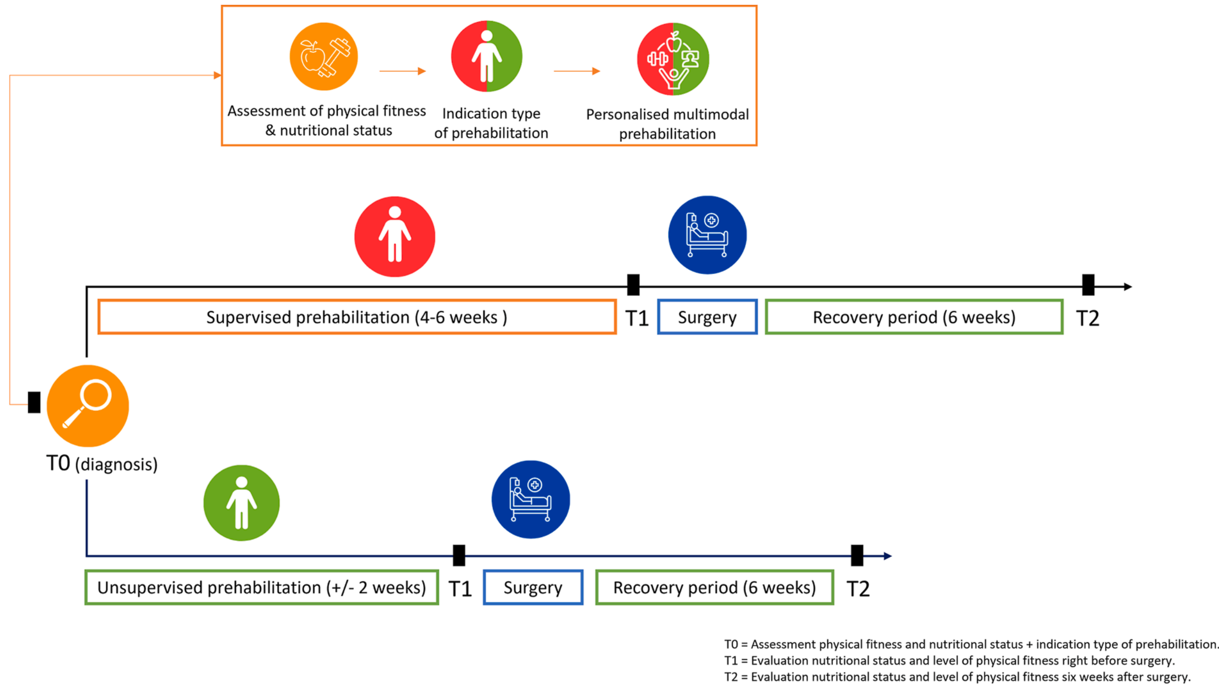

Fig. 2. Set-up of the personalized multimodal prehabiliation program, showing the triage to supervised or unsupervised prehabilitation at T0.

feasible, the weight or resistance was reduced by 5–10% in the subsequent workout; if an exercise was considered below Borg level 13, the resistance or weight was increased by 5–10% in the subsequent training.

- If inspiratory muscle training was indicated the patient received an inspiratory muscle training threshold device together with the advice to practice 30 inhalations on a daily basis, up to maximal 50% of the MIP. The training aims to reach Borg levels 13–15.

2.4. Unsupervised prehabilitation

Patients who were referred to unsupervised prehabilitation were directly scheduled for surgery after T0, which was on average after two weeks. The goal of unsupervised prehabilitation was to maintain nutritional status and the level of physical fitness between T0 and surgery.

2.4.1. Nutritional advices – during the unsupervised prehabilitation program

In the waiting time until surgery the patient applied the nutritional advices, provided by the dietician at T0. These advices were the same as for the supervised group.

2.4.2. Exercise therapy – during the unsupervised prehabilitation program

Regarding physical fitness, the patient received a personalized home-based training program. At T0, the physiotherapist explained this program and the patient was encouraged to apply this at home in an independent way. The personalized home based training program focused on:

- Aerobic fitness was targeted by 5 days a week hiking or bicycling (dependent on patients capabilities). This training aims to reach Borg levels 13–15.
- Muscle strength training was conducted by doing 4 exercises a day (repetitions dependent on patients capabilities), during 5 days a week. This training aims to reach Borg levels 13–15.
- If inspiratory muscle training was indicated the patient received an inspiratory muscle training threshold device together with the advice to practice 30 inhalations on a daily basis, up to maximal 50% of the MIP. The training aims to reach Borg levels 13–15.

Both the supervised and unsupervised program contained a smoking cessation intervention when needed. In addition, when needed, psychological support and hemoglobin optimization [22,31] in case of anemia [32], were part of standard clinical care and provided to both, the supervised and unsupervised programs. In case of frailty, assessed by the Geriatric 8 (G8) questionnaire [33], a geriatrician was involved.

2.5. Outcome measurements

Relevant baseline characteristics (age, sex, reason for colonoscopy, American Society of Anesthesiologists (ASA) classification, cancer stage, hemoglobin level and Charlson comorbidity index) were obtained from the electronic patient file (EPF). Information on consumption of alcoholic drinks and smoking status were collected from self-reported questionnaires at diagnosis. Information of the main outcome measurements, nutritional status and state of physical fitness, was conducted as follow:

Evaluation of nutritional status before and after surgery was assessed by a trained in-hospital dietitian involving measurements of: height in centimeters (cm) by a portable ruler (Seca 213, Benelux Seca Benelux, Naarden, The Netherlands) and body weight in kilograms (kg) using a digital scale (Seca 877, Seca Benelux, Naarden, The Netherlands) to calculate BMI in kg/m2. Fat free mass (FFM) was derived from Single-Frequency Bio-electrical Impedance Analysis (SF-BIA) with four electrodes (50 kHz, Bodystat 500, EuroMedix Leuven, Belgium) [34]. Protein intake was estimated from a 1-day food diary, if not available the single 24 h recall method was applied. These methods could be prone to day-to-day variability. However, theses methods are practical, efficient, and cost-effective for assessing dietary intake, with minimal burden on patients in clinical practice. During the consultations with the dietician, food diaries were checked for completeness and additional information on unclear items or amounts was obtained. Protein intake in grams was calculated by the dietitian using the calculator "Mijn Eetmeter" from The Netherlands Nutrition Centre (Nederlands Voedingscentrum) [35]. Evaluation of physical fitness before and after surgery was assessed by a trained in-hospital physiotherapist. It involved measurements of: cardiorespiratory fitness by using the SRT expressed by the VO_2max (ml/kg/min), handgrip strength (HGS) by a hand-held dynamometer (Hydraulic Jamar) [36] and the five times sit-to-stand test as described in reference (5TSTS) [37,38]. To determine the need for inspiratory muscle training in the prevention of pulmonary complications after surgery, maximal inspiratory pressure (MIP) was tested [39–41].

Data on the clinical outcomes: length of hospital stay and modified Iowa levels of assistance scale (mILAS), were collected from the EPF. The mILAS daily monitored in-hospital physical recovery after surgery. Herewith, the ability to perform five daily activities necessary for independent physical functioning is assessed. Higher scores indicate more assistance, whereas a score of 0 indicates a patient is functionally recovered and ready for discharge home from a physical therapy point of view [42,43]. In this study physical recovery during hospital stay assessed by mILAS was defined as the time in days needed to reach a mILAS score of zero. Data on postoperative complications were extracted from the Dutch ColoRectal Audit (DCRA) of the Dutch Institute for Clinical Auditing (DICA) encompassing: any postoperative complications (including surgical and non-surgical complications), surgical and non-surgical complications occurring within 90 days after surgery, readmission within 90 days after surgery and postoperative mortality. Non-surgical complications included pulmonary, cardiac, neurological, infectious or thromboembolic complications. Surgical complications were graded according to the Clavien-Dindo classification [44]. Herewith, mild surgical complications were defined as Clavien-Dindo 1 to 2, including wound infections opened at bedside, pharmacological treatments or blood transfusions. Severe surgical complications where equivalent to Clavien-Dindo classification 3 to 5, such as anastomotic leakage or mortality due to a surgical complication.

2.6. Data analysis

We focused on a descriptive analysis to generate insight in the characteristics of the supervised and unsupervised group and to describe changes in nutritional status and physical fitness during supervised and unsupervised program. The software program IBM® SPSS statistics version 25 was used to conduct the data analysis. Continuous data were tested for normality by visually inspecting Q-Q plots. Results are presented in medians and quartile 1 – quartile 3 (Q1-Q3) or means ± standard deviation or numbers and percentages (%). Missing data were reported, but not imputed.

3. Results

3.1. Patient characteristics

A total of 90 CC patients were eligible for analysis. Herewith, 33% (n = 30) of the included patients received an indication for supervised prehabilitation of whom 83% (n = 25) because of low cardiorespiratory fitness and 17% (n = 5) based on both low cardiorespiratory fitness and severe malnutrition, see Table 1. From the patients with an indication for supervised prehabilitation 26 out of 30 performed their physical exercise trainings under supervision of a community-based physiotherapist, 3 patients used the personalized home based training program and 1 patient refused any form of prehabilitation due to fear and uncertainty related to the postponement of surgery. The median (Q1-Q3) duration of the prehabilitation program was 17 (11–23) days for the unsupervised group and 38 (30–44) days for the supervised group. The median (Q1-Q3) age of patients in the supervised group (79 years; 74–81) was higher than in the unsupervised group (72 years; 63–78), Table 1. The percentage of women in the supervised group (67%; n = 20) was higher than in the unsupervised group (40%; n = 24). More patients in the supervised group had obesity (37%; n = 11) than in the unsupervised group (18%; n = 37). Also, more patients in the supervised group (73%; n = 22) had anemia compared to the unsupervised group (32%; n = 19). Regarding the pathological cancer stage, supervised patients had more often (50%; n = 15) a tumor in stage III, whereas unsupervised patients had more often (27%; n = 16) a tumor in stage II. More patients in the supervised group (50%; n = 15) had ASA classification III-IV compared to the unsupervised group (40%; n = 24). Lastly, the supervised group had less patients using alcohol compared to the unsupervised group. Smoking rates were similar across the groups.

3.2. Changes in nutritional status before and after surgery

At T0, FFM appeared higher in the unsupervised group (55.1 kg; Q1-Q3: 45.4–63.6) compared to the supervised group (49.1 kg; 44.1–57.8) (Fig. 3 and Supplementary Table 2). Between T0 and T1 FFM appeared stable in both groups. After surgery (T2), FFM in the supervised group showed an increasing (+4%) and in the unsupervised group a decreasing (−3%) trend compared to T0. The median protein intake at T0 in the supervised group was lower (1.2 g/kg FFM/day) compared to the unsupervised group (1.4 g/kg FFM/day). At T1, the median protein increased to 1.8 g/kg FFM/day in both groups. At T2, the median protein intake was 1.5 g/kg FFM/day in the supervised group and 1.6 g/kg FFM/day in the unsupervised group. At T0, 32% (n = 9) of the patients in the supervised- and 42% (n = 23) in the unsupervised group reached the minimal recommended daily protein amount of 1.5 g/kg FFM/day. The percentage of patients achieving the minimal recommended daily protein intake increased in the supervised group towards 81% (n = 17) and 78% (n = 29) in the unsupervised group at T1. Herewith, 17% (n = 5) and 3% (n = 3) in respectively the supervised- and unsupervised group used a medical protein-rich drink. At T2, 50% (n = 10) of the patients in the supervised- and 62% (n = 28) of the patients in the unsupervised group reached the minimal recommended daily protein amount. Missing data (20–30%) were mainly occurring at T1 and T2 (Supplementary Table 4).

3.3. Changes in physical fitness before and after surgery

At diagnosis (T0), VO_2max in the supervised group appeared lower (14.9 ml/kg/min; Q1-Q3: 13.3–18.0) than in the unsupervised group (23.8 ml/kg/min; 20.6–26.1) (Fig. 4 and Supplementary Table 3). Likewise, all other parameters of physical fitness appeared lower in the supervised group than in the unsupervised group at diagnosis. In the supervised group, VO_2max increased with 12% from T0 to T1, while it remained stable (+1%) in the unsupervised group. Six weeks after surgery (T2), the VO_2max in the supervised group is lower compared to T1, but higher than initial measured at T0. Overall, we observed improvement on all parameters of physical fitness in both groups from T0 to T2, but improvements were most pronounced in the supervised group,

Table 1
Details of why patients received an indication for supervised prehabilitation and patient characteristics at diagnosis.

	Unsupervised prehabilitation n = 60	Supervised prehabilitation n = 30
Indication for supervised prehabilitiation based on[a]		
Low cardiorespiratory fitness and severe undernutrition	N/A	5 (17%)
Only due to low cardiorespiratory fitness		25 (83%)
Only due to severe undernutrition		0 (0)
Execution of supervised prehabilitation[a]		
With a certified community based physiotherapist	N/A	26 (87%)
Application of the home based training program		3 (10%)
Other (refusal to participate)		1 (3%)
Age[b]	72 (63–78)	79 (74–81)
Sex[b]		
Men	36 (60%)	10 (33%)
Women	24 (40%)	20 (67%)
Referral to colonoscopy due to[a]		
Complaints	33 (55%)	24 (80%)
National colorectal cancer screening program	23 (38%)	3 (10%)
Surveillance	4 (7%)	3 (10%)
BMI classification[a]		
Healthy weight (≥18.5–<25 kg/m^2)	29 (49%)	8 (26%)
Overweight (≥25–<30 kg/m^2)	20 (33%)	11 (37%)
Obese (≥30 kg/m^2)	11 (18%)	11 (37%)
Height (cm)[c]	173 (9,8)	166 (7,4)
Cancer stage[a]		
I	21 (35%)	9 (30%)
II	16 (27%)	5 (17%)
III	21 (35%)	15 (50%)
IV	2 (3%)	1 (3%)
Anemia[a]**, number of patients with anemia**	19 (32%)	22 (73%)
Men [<8,0 mmol/L]	13 (36%)	8 (80%)
Women [<7.5 mmol/L]	6 (25%)	14 (70%)
ASA classification[a]		
I-II	36 (60%)	15 (50%)
III-IV	24 (40%)	15 (50%)
Charlson comorbidity index[b]	3 (2–4)	4 (3–5)
Alcohol consumption[a]		
Drinking alcohol	42 (70%)	16 (53%)
Not drinking alcohol	18 (30%)	14 (47%)
Smoking status[a]		
Non-smoker	32 (58%)	18 (60%)
Former-smoker	17 (31%)	8 (27%)
Current-smoker	6 (11%)	4 (13%)
Missing	5	0
Days between T0 and date of surgery[b]	17 (11–23)	38 (30–44)

[a] Presented as No., (%).
[b] Presented as median (Q1-Q3).
[c] Presented as mean (standard deviation).

see Fig. 4. Lastly, the MIP improved between T0 and T1 with +6% and +19% in respectively the unsupervised and supervised group. Missing data (20–30%) were mainly occurring at T1 and T2, see Supplementary Table 5.

3.4. Clinical outcomes

The median length of hospital stay in the supervised group was 4 (Q1-Q3: 3–7) days and 3 (3–4) days in the unsupervised group, see Table 2. The median number of days until the mILAS score is equal to zero was comparable between groups, namely 3 days (2–4) in both groups. Regarding any postoperative complications, it appeared that patients in the supervised group (20%; n = 6) face slightly more complications than the unsupervised group (15%; n = 9). Non-surgical complications occurred in only 3 patients in both groups. Surgical complication rates appeared similar in the supervised (13%; n = 4) and unsupervised group (13%; n = 8). Lastly, hospital readmissions and postoperative mortality rates were low and appeared similar across groups with respectively 5% (n = 3) and 2% (n = 1) in the unsupervised group and 3% (n = 1) and 3% (n = 1) in the supervised group.

4. Discussion

The aim of this study was to describe the changes in nutritional status and physical fitness before and after CC surgery in the supervised and unsupervised prehabilitation group and explore complication rates in both groups. The key findings of this study are as follow. First, one out of three patients was unfit at diagnosis and therefore received the indication for supervised prehabilitation. Second, during the preoperative phase protein intake improved in both groups while improvements in physical fitness were most pronounced in the supervised group. Third, postoperative protein intake improved in both groups compared to baseline, while physical fitness mainly improved in the supervised group. Last, clinical complication rates were low in both groups and appeared similar for the supervised and unsupervised group.

Before interpreting our findings we acknowledge several limitations. First, the exploratory nature on postoperative complications and the small sample size does not allow for strong conclusions as numbers are low in both groups. Second, we had substantial missing data in the follow up measurements, specifically for nutritional status and physical fitness right before surgery (T1) and 6 weeks after surgery (T2). This shows how

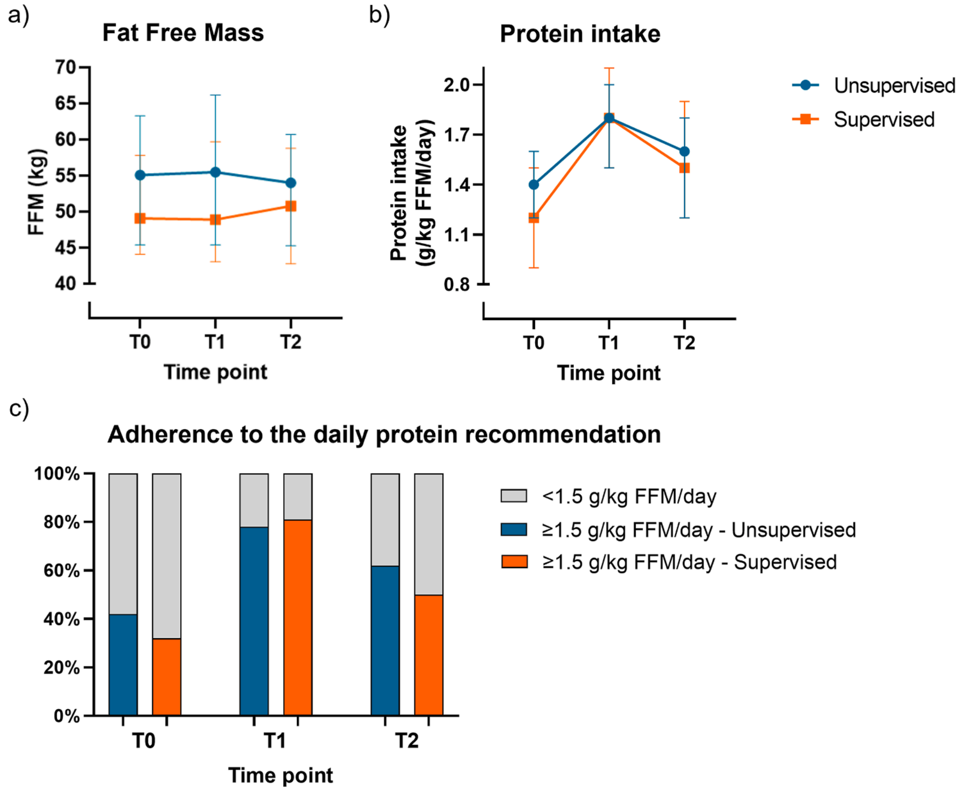

Fig. 3. Changes over time in a) fat-free mass, b) protein intake and c) percentage of patients adhering to daily protein recommendations. Figures a and b are medians and interquartile ranges. In all figures T0 is at diagnosis, T1 is day of surgery, T2 is six weeks after surgery.

challenging it is to gather complete data in real-life clinical practice. Third, in research settings, nutritional intake is commonly estimated using the mean values derived from a 3-day food diary. However, as this program is part of usual care, a 1-day food diary was utilized for reasons of feasibility. Last, regression to the mean may have impacted our findings; this is the tendency for a measurement that is very high or low upon first measurement to move toward the mean when measured again, due to random fluctuations rather than a systematic change [45]. In this study, the supervised group scored low on assessments of nutritional status and physical fitness at baseline. As a result of 'regression to the mean' those assessment may have moved to the mean in the sequential measurements.

Notwithstanding these limitations, this study has several important strengths and provides valuable insights in the real-life changes of nutritional status and physical fitness before and after CC surgery following multimodal personalized prehabilitation. The first strength lies in the real-life clinical care character of this study. Although RCTs are the gold standard for assessing the efficacy of an intervention, strict inclusion criteria and the low willingness of patients to participate, may result in selection bias and unrepresentative study populations [46]. In general, our supervised group appeared to have more female patients, with a higher BMI (≥30 kg/m2), who more often had a ASA 3 classification and more often cancer stage III or IV than patients typically included in RCTs [6,7,47]. This shows that our screening to triage patients to supervised prehabilitation worked to identify patients at higher risk of complications. Moreover, it also suggests that patients who are part of our supervised program represent a group of patients who are less prone to participate in RCTs; therefore observational real-life data better reflect daily clinical practices. This makes the findings of our study of added value to better understand for whom prehabilitation may be of interest [15]. An additional strength of this study is that this prehabilitation program is part of usual care for all CC patients undergoing surgery. This allows the evaluation of the composition of the program in real-life clinical practice. Notably, 87% of patients who were eligible for supervised prehabilitation accepted referral to a community-based oncological physiotherapist and completed their exercise therapy under supervision. These findings suggest that, beyond controlled research environments where participation is often motivated by intrinsic factors [16], the implementation and composition of prehabilitation within usual care play a crucial role in promoting successful engagement. The last strength is that we showed changes in nutritional status and physical fitness during and after prehabilitation. The current literature demonstrates limited information about the changes over time (before and after surgery) or provided only information on nutrition or physical fitness, but not on both.

4.1. Nutritional status

Several aspects of the nutritional component in our prehabilitation program are important to highlight. First, upon diagnosis only about 35% of all patients reached the minimally recommended daily protein intake of 1.5 g/kg FFM. This underlines the room for nutritional improvement on protein intake in both the supervised- and unsupervised group. After guidance from a dietitian in the program, around 80% of all patients reported a sufficient protein intake shortly before surgery. Those results suggest that face to face nutritional guidance by a dietician supported the majority of the CC patients in both groups to achieve their recommended daily protein needs within their usual diet and without the need for protein rich supplements. Six weeks after surgery around 55% had a protein intake of at least 1.5 g/kg FFM

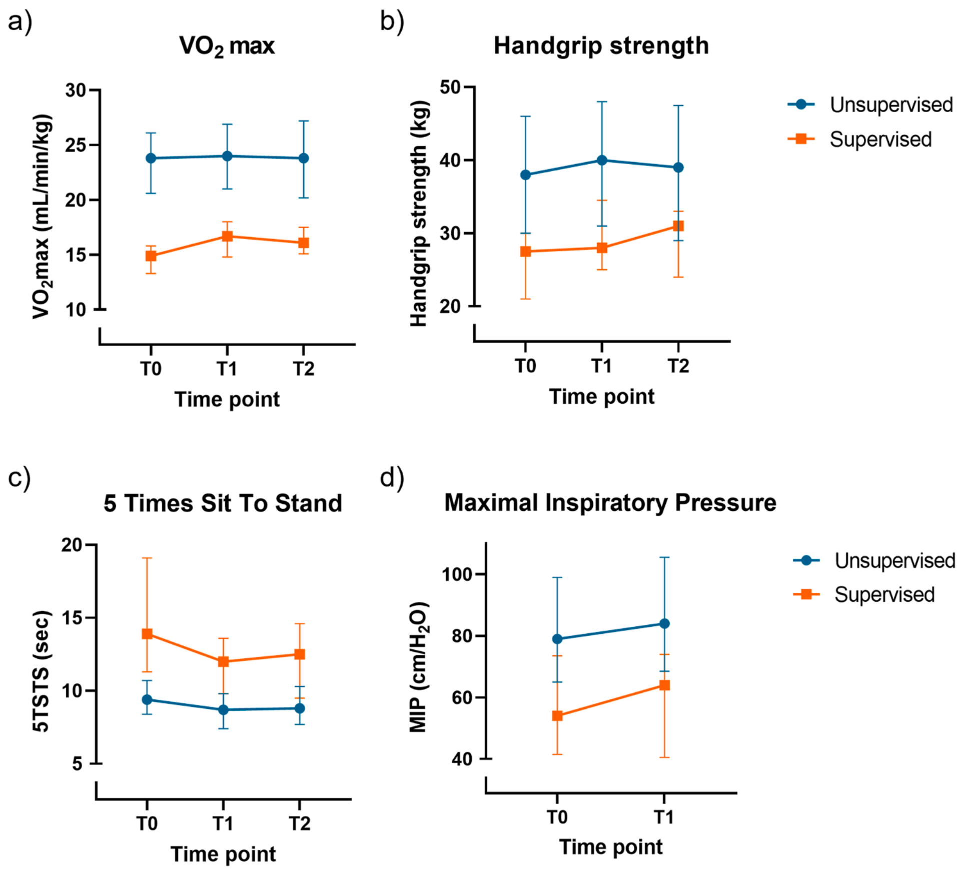

Fig. 4. Changes over time in a) VO2 max, b) Handgrip strength, c) 5 Times Sit to Stand test and d) Maximal Inspiratory Pressure. In all figures data are medians and inter-quartile ranges. T0 is at diagnosis, T1 is day of surgery, T2 is six weeks after surgery.

which is still above the levels measured at diagnosis. The nutritional goals at that time depend on the patient's stage of recovery, with continued emphasis on adequate protein intake if necessary, along with improving diet quality and promoting a healthy lifestyle to reduce the risk of recurrence. The observed improved protein intake may be attributed to the teachable moment, which is the moment patients face a cancer diagnosis which often motivates them to adopt healthier behaviors [17]. During the diagnostic day in our program, patients received both nutritional advice and exercise training, emphasizing education as a key tool for empowering and informing them. To maximize impact, we advocate a personalized approach through face-to-face consultations and tailored educational materials at the point of diagnosis.

The preservation of FFM during and after cancer treatment is important as low FFM is a poor prognostic factor among cancer patients and associated with adverse outcomes in CRC patients [48–50]. We showed that FFM was at least maintained in both groups during the prehabilitation period. After surgery FFM slightly decreased in the unsupervised group and increased in the supervised group compared to FFM at diagnosis. Similar results were described by a RCT were FFM was also measured with the BIA among CRC patients [51]. In that RCT, no significant changes in FFM, were observed in the control and intervention group during the prehabilitation period [51]. BIA is recommended to estimate fat free mass as part of nutritional assessment in clinical practice as it is non-invasive, portable, reliable and low in cost [24,52].

Table 2
Clinical outcomes and number of complications among patients following the unsupervised or supervised prehabilitation program.

	Total n = 90	Unsupervised prehabilitation n = 60	Supervised prehabilitation n = 30
Duration of hospital stay[a]	3 (3–5)	3 (3–4)	4 (3–7)
Days until mILAS is zero[a]	3 (2–4)	3 (2–4)	3 (2–5)
Patients with any postoperative complication[b,c]	15 (17%)	9 (15%)	6 (20%)
Patients with non-surgical complications[b]	6 (7%)	3 (5%)	3 (10%)
Patients with surgical complications[b]			
Mild (CDC 1–2)[d]	4 (4%)	3 (5%)	1 (3%)
Severe (CDC 3–5)[d]	8 (9%)	5 (8%)	3 (10%)
Hospital readmission[b]	4 (4%)	3 (5%)	1 (3%)
Postoperative mortality[b]	2 (2%)	1 (2%)	1 (3%)

[a] Presented as median (Q1-Q3).
[b] Presented as No., %.
[c] Within 90-days.
[d] Clavien Dindo Classification 3 or higher was classified as a severe complication.

Nevertheless, from the current literature the question arises whether BIA is sensitive enough to detect longitudinal changes in FFM [53]. This might be uncertain due to factors as hydration status, water distribution (intra-en extracellular), obesity and thus needs further research [53].

4.2. Physical fitness

We referred patients to supervised prehabilitation, based on thresholds of VO_2max <18,2 ml/kg/min and thresholds for severe malnutrition. The supervised patients were in general: older, more often female, had a higher BMI, suffered more often from anemia, had a higher tumor stage, lower FFM, and had a higher Charlson comorbidity index compared to unsupervised patients. These characteristics are in line with characteristics that have been associated with risk of complications following CRC surgery in literature [12,19,48,49,54–57]. At baseline, all parameters of physical fitness were lower in de supervised group compared to the unsupervised group, thus, our thresholds enabled us identify a group that would probably benefit most from prehabilitation. This is a unique aspect of our approach, as most other studies offered supervised prehabilitation to all patients. We observed that in both groups all parameters of physical fitness were better right before surgery than they were at baseline, but were most pronounced in the supervised group. This suggests that the set-up of the exercise therapy and prehabilitation duration suits the preoperative goals of both groups. The changes in physical fitness that we observed in our supervised group were comparable with findings from a study of community-based prehabilitation in older (70+years) and high risk patients (ASA 3–4) undergoing CRC surgery [54]. That publication showed that the outcomes of all functional tests (VO_2max, 1RM tests, 6MWT, SRT, 5TSTS) were significantly higher six weeks postoperative compared to baseline [54]. Furthermore, a systematic review and meta-analysis of RCT's evaluated the adherence and clinical effectiveness of home based prehabilitation. A systematic review and meta-analysis found that home-based prehabilitation may reduce postoperative complications (with low-certainty evidence) and improve preoperative functional capacity, hospital stay, and mental health outcomes, with good adherence. However, generalisability to real-world settings is limited due to tightly controlled conditions, high resource use per patient, and unclear distinctions between supervised and unsupervised home based prehabilitation programmes [58]. Regarding the execution of exercise interventions within prehabilitation programs, the literature describes a variety of settings ranging from supervised in-hospital (group)sessions, (digital) home train programs to involvement of a community based physiotherapist [54,59]. In our program, we worked with our regional oncological network of physiotherapists which enabled patients with an indication for supervised prehabilitation to execute their trainings in the proximity of their residence. In our program only one out of 30 patients refused the indication for prehabilitation, which suggests a high level of compliance. It is important that prehabilitation programs align with the preferences and abilities of patients, but also with the regional healthcare system of the hospital that is implementing the prehabilitation program.

4.3. Clinical characteristics

We had expected that the supervised prehabiltiation group would be more at risk of having complications from the start because of their lower VO_2max, level of malnutrition, higher rate of anemia, higher age, higher BMI, tumor stage and charlson comorbidity index [19,54]. However, although numbers are low, complication rates, postoperative mortality and readmission rates appear to be similar between the supervised and unsupervised group. The small sample size and observational nature of the study preclude us from drawing strong conclusions on the effect of supervised prehabilitation on clinical outcomes, but our study may point to a possible role of supervised prehabilitation in reducing complication rates. Furthermore, the absence of significant differences in postoperative complications should be interpreted in light of the exploratory nature of this outcome and the chosen complication classification. Also, while the use of the Clavien-Dindo classification allows for standardized reporting and comparability with other studies, it may be less sensitive to subtle or cumulative differences in postoperative morbidity, and, for future studies, alternative tools may be considered.

Moreover, from the patient perspective, a swift recovery to independent physical functioning after surgery is very important [59]. In the current study, both groups needed the same number of days to get to a level of independent physical functioning measured by the mILAS. Notably, the length of hospital stay in our study is one day longer in the supervised group than the unsupervised group. This underlines potential discrepancies between length of hospital stay and independent physical functioning as parameters of recovery. We can only speculate on why hospital stay was longer in the supervised group, however in literature, it is described that extended hospital stay despite being medically fit, appears more prevalent among older adults, likewise our supervised group was older than the unsupervised group [60]. Non-medical factors related to LOS are often due to organizational issues like information management and lack of external care facilities to support the complex needs of older adults [60]. The inclusion of the mILAS score as a clinical evaluation tool allows assessment beyond hospital duration and complication incidence, providing a more direct measure of functional recovery and readiness for discharge. The similar mILAS trajectories observed between groups suggest comparable levels of functional independence, despite differences in length of hospital stay.

5. Conclusion

Our findings indicate an improved nutritional status and physical fitness before and after surgery among CC patients who were not fit upon diagnosis and who therefore received our supervised prehabilitation program. Patients who were fit at diagnosis were able to at least preserve their nutritional status and physical fitness following our unsupervised prehabilitation program. We conclude that multimodal prehabilitation may support all patients undergoing CC surgery if personalized to their nutritional status, state of physical fitness and motivational goals.

Author contributions

Eva Valgaeren: Conceptualizing, Formal analysis and interpretation, Investigation, Methodology, Visualization, Resources, Writing – original draft. **Nynke Westra:** Conceptualizing, Investigation, Interpretation of data, Resources, Writing – review & editing. **Mirjam Holverda:** Conceptualizing, Investigation, Resources, Interpretation of data, Writing – review & editing. **Niels Klaassen-Dekker:** Writing - review & editing, Interpretation of data, Visualization. **Dieuwertje E. Kok:** Interpretation of data, Writing - review & editing. **Ellen Kampman:** Interpretation of data, Writing - review & editing. **Tjarda van Heek:** Conceptualizing, Methodology and interpretation, Resources, Supervision (supporting), Writing – review & editing. **Renate M. Winkels:** Conceptualizing, Methodology and interpretation, Supervision (lead), Writing – review & editing. All authors gave final approval to submit the work for publication and agree to be accountable for the quality of the work.

Data sharing statement

The nature and sensitivity of the data preclude full public sharing of data. However, data may be made available upon reasonable request by contacting the corresponding author.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to search for synonyms and writing more concisely to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2026.106700.

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