Multimodal prehabilitation in high-risk patients undergoing elective resection for colorectal cancer: A retrospective cohort study

Name	M. (Mayke) de Klerk
Student number	6118259
Course	Research Internship: Master Thesis
Status	Final
Lecturer	Dr. S.W.M. Weldam
Supervisor	Dr. E.G.G. Verdaasdonk, *Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands*
Professor	Prof. Dr. W.J.H.J. Meijerink, *Radboud University Medical Center, Nijmegen, the Netherlands*
Date	June 17, 2020
Master program	Clinical Health Sciences, Nursing Science University Medical Center Utrecht, Utrecht University
Number of words	3583
Number of words abstract	298
Number of words abstract Dutch	293
Reference style	Vancouver Superscript
Reporting guideline	STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)
Journal	Diseases of the Colon and Rectum

ABSTRACT

Title: Multimodal prehabilitation in high-risk patients undergoing elective resection for colorectal cancer: A retrospective cohort study.

Background: Colorectal cancer accounts for approximately 10% of cancer-related mortality worldwide and surgery is the only curative treatment. However, postoperative complications occur in up to 50% of all patients. The number and severity of complications are related to the patients' preoperative functional capacity and nutritional status. The window of time between the cancer diagnosis and elective surgery provides an opportunity to improve functional capacity and nutritional status. It may lead to a reduction of postoperative complications, this is called prehabilitation.

Aim: The aim of this study is to assess the impact of a four-week multimodal prehabilitation program on postoperative complications, prolonged length of hospital stay, unplanned readmissions, and mortality.

Method: Data was extracted from existing data and patients' electronic medical files. Univariate analysis was performed using Fisher's Exact and Mann-Whitney U test. Multivariate logistic regression analysis was performed afterwards.

Results: 351 patients were included in the study (n=275 non-prehabilitation, n=76 prehabilitation). The number of patients with postoperative complications differed significantly between groups (40% versus 26.3%, *p*=.032) in which prehabilitation was a protective factor (OR=0.5, 95% CI, 0.253-0.988, *p*=.046). Unplanned readmissions differed significantly (16.4% versus 5.3%, *p*=.014) in which prehabilitation was a protective factor (OR=0.313, 95% CI, 0.102-0.954, *p*=.041). Median hospital days of stay was significant 1 day shorter for the prehabilitation group (*p*=.004). Mortality and prolonged length of stay did not differ.

Conclusion: The multimodal prehabilitation program leads to a reduction of postoperative complications, fewer unplanned readmissions, and also shortens the median hospital stay compared with standard care in high-risk patients undergoing elective tumor resection.

Recommendations: Future research should focus on developing and organizing prehabilitation programs for other surgical indications. More insight is needed which patients most benefit from prehabilitation and how the programs can be more patient tailored.

Keywords: Prehabilitation, Colorectal Neoplasm [MeSH], Nutrition, Postoperative Complications [MeSH].

SAMENVATTING

Titel: Multimodale prehabilitatie voor hoog-risico patiënten die een electieve resectie voor colorectale kanker ondergaan: een retrospectieve cohort studie.

Achtergrond: Colorectale kanker is verantwoordelijk voor ongeveer 10% van de sterfte door kanker wereldwijd en een operatie is de enige curatieve behandeling. Echter ontstaan postoperatieve complicaties in 50% van alle patiënten. Het aantal en de ernst van de complicaties hangt samen met de preoperatieve fysieke capaciteit en voedingsstatus. Het tijdsvenster voor de operatie biedt een kans om deze patiëntfactoren te verbeteren. Dit kan leiden tot een verminderen van postoperatieve complicaties en een korter ziekenhuisverblijf. Dit wordt prehabilitatie genoemd.

Doel: Het doel van de studie is om de impact van het vierweekse multimodale prehabilitatie programma op postoperatieve complicaties, verlengd ziekenhuisverblijf, ongeplande heropnames en mortaliteit te toetsen.

Methode: De data is verzameld uit bestaande data en de elektronische medische patiëntendossiers. Univariate analyse werd uitgevoerd met de Fisher's Exact en Mann-Whitney U toets. Daaropvolgend werd een multivariate logistische regressie analyse uitgevoerd.

Resultaten: In totaal zijn er 351 patiënten in de studie geïncludeerd (n=271 niet-geprehabiliteerden, n=76 geprehabiliteerden). Het aantal patiënten met postoperatieve complicaties verschilde significant tussen de groepen (40% versus 26.3%, *p*=.032) waarin prehabilitatie een beschermende factor was (OR=0.500, 95% CI, 0.253-0.988, *p*=.046). Ongeplande heropnames verschilde significant (16.4% versus 5.3%, *p*=.014) waarbij prehabilitatie een beschermende factor was (OR=0.313, 95% CI, 0.102-0.954, *p*=.041). De mediane opnameduur in dagen was significant één dag korter voor de prehabilitatie groep (*p*=.004). Mortaliteit en een verlengd ziekenhuisverblijf verschilden niet tussen de twee groepen.

Conclusie: Prehabilitatie reduceert postoperatieve complicaties, ongeplande heropnames en de gemiddelde opnameduur in vergelijking met de standaard zorg bij hoog-risico patiënten met colorectale kanker.

Aanbevelingen: Toekomstig onderzoek moet gericht zijn op het ontwikkelen en organiseren van prehabilitatie programma's voor andere chirurgische indicaties. Meer inzicht is nodig in welke patiënten het meest profiteren van prehabilitatie en hoe de prehabilitatie programma's meer patiëntgericht kunnen zijn.

Trefwoorden: Prehabilitatie, Colorectale kanker, Voedingsstatus, Postoperatieve complicaties.

INTRODUCTION

Colorectal cancer (CRC) accounts for approximately 10% of cancer-related mortality worldwide and is the second most prevalent type of cancer[1–4]. There are many known risk factors for cancer, including excessive body weight, decreased physical activity, and age[5,6], as more than 50% of CRC patients are over 70 years old[7]. Surgery is the only curative treatment for CRC[5], however, postoperative complications such as ileus, hemorrhage, anastomotic breakdown, and various forms of infection occur in up to 50% of patients and are associated with up to a 40% reduction in physiological and functional capacity[3,8,9]. Higher complication rates are related to patient factors such as body mass index (BMI), adjuvant therapy, anaemia, tumor location, tumor stadium, and age[10–12]. It is estimated that older (aged 65 or older) and frail patients have a fourfold higher risk of developing postoperative complications[5,6,13].

Postoperative complications can lead to a prolonged length of hospital stay (LOS), unplanned readmissions, mortality, and therefore increased healthcare expenses[14–18]. The number and severity of postoperative complications are related to patients' preoperative functional capacity and nutritional status. Increased preoperative physical and nutritional status can enhance clinical outcomes and therefore reduce postoperative complications[19–22]. The window of time between the cancer diagnosis and elective surgery provides an opportunity to improve patients' functional capacity and nutritional status[23–26]. The study by Govaert[8] shows that there is a need to identify high-risk patients and to develop targeted quality improvement programs in order to prevent postoperative complications, such as a prehabilitation program[8].

Prehabilitation for cancer care is defined as "a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes several assessments (physical, metabolic, and psychological) that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient's health to reduce the incidence and the severity of current and future impairments"[27]. The literature shows that prehabilitation before the operation may lead to a reduction of postoperative complications in multiple specialties including cardiothoracic, orthopedic, and abdominal surgery[9,28–33]. Prehabilitation consists of endurance and resistance exercises, raising muscle mass and enhancing cardio-respiratory status[20,34]. However, the literature shows contradictory data concerning the composition of prehabilitation programs, as the duration of the exercise programs range from 2 to 8 weeks and some programs support only physical exercise[20,28,31]. One concern regarding training programs prolonged beyond 4 weeks is that they would negatively influence cancer outcomes. Nevertheless, the literature shows

that a prolonged treatment delay up to 6 weeks due to prehabilitation does not lead to poorer overall or cancer-free survival in CRC patients who underwent surgical treatment[22,35].

In 2018, a large, non-academic training hospital in the Netherlands commenced a pilot program prehabilitating CRC patients before major CRC surgery. A main reason was to reduce the incidence of postoperative complications, especially in patients with rectal cancer, which has a complication rate of up to 40% of all patients. Ten CRC patients participated in the pilot, underwent twelve supervised high-intensity training sessions in the hospital, and received personalized nutritional advice from a dietician. This pilot showed a 20% reduction in postoperative complications and that the prehabilitation program was feasible to perform. Since January 2019, the hospital consequently offers the possibility to participate in a multimodal prehabilitation program for all elective high-risk patients prior to major CRC surgery. Patients at high risk of postoperative complications are defined as patients with an American Society of Anesthesiologists (ASA) score of 3 or higher and/or are 65 years of age or older[36]. The prehabilitation program includes a four-week exercise training program guided by a physiotherapist, and patients also visit a dietician for personal nutritional guidance. Furthermore, measures are taken to reduce intoxications (smoke and alcohol cessation in the outpatient clinic), treat anaemia with iron supplementation, and reduce polypharmacy, which represent known risk factors for developing postoperative complications[10,37–41].

Previous research mostly involved randomized controlled trials or small cohort studies. To the researcher's knowledge, this is the first large cohort assessing the impact of a multimodal prehabilitation program on patient outcomes. Although the initial results of the prehabilitation program in this hospital showed positive results concerning patients' satisfaction and reduced postoperative complications, these results have not yet been evaluated on a larger cohort.

AIM

The primary objective of this study is to assess the impact of a four-week multimodal prehabilitation program on postoperative complications in high-risk patients undergoing resection for CRC during their in-hospital stay or within 90 days after discharge. The secondary objective is to assess the impact of the prehabilitation program on prolonged LOS and unplanned readmissions within 90 days after hospital discharge, and mortality in high-risk patients undergoing resection for CRC while in-hospital or within 90 days after discharge.

METHOD

Design

A single-center, retrospective, observational cohort study was performed at a large, non-academic training hospital in the southern part of the Netherlands. This design enabled assessing the exposure to the prehabilitation program since the patients were retrospectively identified at the beginning of the study and multiple measures occurred[42].

Population

Colorectal cancer patients who underwent major elective colorectal surgery between January 2017 and March 2020 were retrospectively identified from the obtained data. Non-prehabilitation patients were eligible if they were considered to be high risk for postoperative complications (defined by age $\geq$65 years and/or ASA $\geq$3) and had elective CRC surgery between January 2017 and December 2018. High-risk prehabilitation patients were eligible if they attended the four-week prehabilitation program followed by elective CRC surgery between January 2019 and March 2020. Prehabilitation patients who received high-intensity training elsewhere instead of training in the hospital were excluded. Patients with a minimally invasive anal excision were excluded since the surgical technique is not equal to other included surgical techniques. Regarding the retrospective design, the prehabilitation group had approximately 75 patients and the non-prehabilitation group 275 patients.

Prehabilitation program

High-risk patients undergoing elective CRC surgery were allowed to participate in the prehabilitation program which was part of usual care, however patients with illiteracy (inability to read and understand Dutch) could not participate. Patients began the prehabilitation program at least 4 weeks before the surgery. The four-week prehabilitation program included an exercise program, nutritional guidance, and treatment of intoxications, polypharmacy, and anaemia. The exercise program had two components: high-intensity training (three times per week supervised by a physiotherapist at the hospital) and low-intensity training (four times per week as independent home endurance training). Patients received tailored nutritional advice from a dietician to meet individual energy and protein needs combined with physical training, where the goal was to achieve a total protein intake of 1.9g per kilogram of lean body mass per day[43,44]. In addition, patients were advised to use 0.4g protein per kg within one hour of the high-intensity training and daily at bedtime to support muscle synthesis[45–49]. Patients were encouraged to cease smoking and/or using alcohol, and if desirable, they were referred to an institution for cessation support. Polypharmacy ($\geq$5 drugs/day)[40] was reduced through a preoperative geriatric consult and pre-operative anaemia (<6.8 mmol/L) was

treated using oral or intravenous iron supplementation. Except for the exercise program, non-prehabilitation patients received the same care as the prehabilitation patients following the enhanced recovery after surgery protocol and saw a dietician only if indicated.

Procedures

Due to the retrospective design, no recruiting or consent procedure has been conducted for this study. Eligible patients for the prehabilitation program were instead recruited in the outpatient clinic and could join the program on a voluntary basis. Patients were informed of the possibility of participating in the prehabilitation program during an outpatient clinic visit with the attending surgeon or nurse practitioner, who gave them written information about the program and afterwards asked about the decision to participate.

Data collection and measures

The data from January 2017 through December 2018 (CRC patients without prehabilitation) were compared with data from January 2019 through March 2020 (CRC patients with prehabilitation), which included data collected for standard care from the patients' electronic medical files and from the quality institute for oncological and palliative research and practice (in Dutch: Integraal Kankercentrum Nederland [IKNL]). The data were retrospectively extracted using two researchers (MDK and HVD) and collected in IBM SPSS Statistics 22 (Armork, New York, USA). Missing data and outliers were extracted and reviewed by consulting the patients' electronic medical files, which were checked in advance by the second researcher (HVD) and the epidemiologist involved in the study (LN). The final database was checked by the principle investigator (EV) and the epidemiologist (LN).

The baseline characteristics consisted of sex, age, BMI, ASA score, tumor location, tumor, node, metastasis classification, presence of comorbidities, anaemia, adjuvant therapies, and surgical technique. Comorbidities have been defined as stated in the IKNL database: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, connective tissue disease, gastrointestinal ulcer, liver disease, diabetes mellitus, hemiplegia, kidney disease, previous malignancies (except for skin cancer), and human immunodeficiency virus. The outcomes of postoperative complications, mortality, and unplanned re-admission were dichotomously measured 90 days following discharge. The outcome-prolonged LOS compared with standardized colorectal care path (5 days for colon cancer and 6 days for rectal cancer) was dichotomously measured.

Data analysis

The data were analyzed on an intention-to-treat basis using IBM SPSS Statistics 22 (Armork, New York, USA). Descriptive statistics of patient characteristics were gathered for all patients in n (%) or median (interquartile range [IQR]), and the distribution of the data was visually checked using histograms and Q-Q plots[50]. Using Fisher's Exact test[51] for categorical data, univariate analysis was performed to assess associations between the prehabilitation program and postoperative complications, prolonged LOS, unplanned readmissions, and mortality. Univariate analysis for non-normally distributed continuous variables was performed using the Mann-Whitney U test. In addition, the chi-squared test was used testing different types of postoperative medical (cardiovascular, respiratory, neurological, thromboembolic, infection other than respiratory or surgical, and other) and surgical (postoperative hemorrhage, anastomotic breakdown, ileus, abscess, fascia dehiscence, surgical site infection, bowel perforation, urethra leakage, and other) complications. Following the univariate analysis, multivariate logistic regression analyses were performed for significant differences to investigate predictors between the prehabilitation program and the study outcomes. The assumed predictors were included in the multivariate analysis based on the known risk factors for the study outcomes, where one variable per ten events was stated to prevent major problems in the analysis[52]. Odds ratios (ORs) and a 95% confidence interval (CI) were calculated, and a two-sided *p* value of <.05 was shown to be significant. The sample size was calculated using G*Power 3.1[53]. Using the number of patients in each group (approximately 75 for the prehabilitation and 275 for the non-prehabilitation), an α=.05, and a power=.80, a minimum difference between the proportions p^1=.25 and p^2=.1 could be investigated.

Ethical considerations

This study was submitted for approval to the Medical Research Committee Brabant (file number NW2020-11), who confirmed that the Medical Research Involving Human Subjects Act did not apply for this study. Because prehabilitation is part of usual care, this principle is enshrined in law in the Medical Treatment Agreement Act. The data were retrospectively collected applying the most recent version (version 7, October 2013) of the Declaration of Helsinki and the Guidelines for Good Clinical Practice[54]. Retrospective written informed consent was not required.

RESULTS

Baseline characteristics

A total of 625 patients were assessed in this study, as shown in Figure 1 (insert Figure 1). From the initial patient population, 274 patients failed to meet the inclusion criteria. Therefore, a total of 351 patients were included in the study, 22% (n=76) of which completed the prehabilitation program. The baseline characteristics of the prehabilitation and non-prehabilitation groups were similar, except for the prevalence of comorbidities (55% versus 71% for the non-prehabilitation group, *p*=.018). Outliers were checked, however none were removed since the outliers were valid values. The baseline characteristics of the prehabilitation and non-prehabilitation groups are shown in Table 1 (insert Table 1).

Prehabilitation program

The median duration of the prehabilitation program was 35 days (IQR 36; 18-54). The patients attended twelve high-intensity training sessions supervised by a physiotherapist at the hospital. One patient collapsed during the training, after which the cardiologist was consulted, and one patient discontinued the prehabilitation program due to tumor obstruction. Furthermore, one patient quit the program early due to logistical reasons, and one patient quit early due to physical discomfort after a fall that was not caused by the program. One patient quit early since the patient was physically too frail to participate in the program. Moreover, one patient was admitted to the hospital earlier than expected due to anaemia, despite the efforts of preoperative iron supplementation. The surgery was cancelled for three patients, which means that they quit the program.

Univariate analysis

The overall complication rate of all patients was 37% (130 of 351 patients). Among the prehabilitation patients, the postoperative complication rate was significantly lower (26.3% versus 40%, *p*=.032) but the incidence of one complication per patient occurred more often than in non-prehabilitation patients (13.2% versus 5.1%, *p*=.020). Prehabilitation patients had a significantly lower number of two or more postoperative complications per patient (13.2% versus 27.3%, *p*=.010) and significantly fewer postoperative medical complications (13.2% versus 26.5%, *p*=.015) than the non-prehabilitation patients. Moreover, the prehabilitation patients had a significantly lower median LOS in days (4 days versus 5 days, *p*=.004) and were less readmitted (13.2% versus 26.5%, *p*=.015) than the non-prehabilitation patients. A prolonged LOS compared with the number of planned hospital days in the standardized colorectal care and mortality occurred less often in the prehabilitation patients, but the

differences were not statistically significant. The postoperative outcomes for the prehabilitation and non-prehabilitation patients are shown in Table 2 (insert Table 2).

Multivariate logistic regression analyses

Multivariate logistic regression analyses were performed for the significant outcomes of postoperative complications and unplanned readmissions. The Hosmer-Lemeshow test proved that the model performance of multivariate logistic regression analysis was well calibrated[55] and eight variables were included as covariates based on known risk factors for postoperative complications after CRC surgery[13,56–59]. The multivariate logistic regression analysis showed that prehabilitation, corrected for seven covariates, was a protective predictor of postoperative complications (OR=0.5, 95% CI, 0.253-0.988, *p*=.046). Four covariates were shown to be significant: the presence of prolonged LOS compared with standardized colorectal care (OR=8.957, 95% CI, 5.223-15.360, *p*<.001), male gender (OR=1.744, 95% CI, 1.025-2.967, *p*=.040), rectal cancer (OR=2.488, 95% CI, 1.181-5.239, *p*=.016), and elderly patients (aged ≥65 years) (OR=1.057, 95% CI, 1.015-1.100, *p*=.008). The presence of comorbidities (*p*=.291), anaemia (*p*=.124), and adjuvant therapy (*p*=.874) were not significantly associated with postoperative complications.

Four variables were included as covariates based on known risk factors for unplanned readmissions following CRC surgery[60,61]. Multivariate logistic regression analysis showed that prehabilitation, corrected for three covariates, was a protective predictor of postoperative complications (OR=0.313, 95% CI, 0.102-0.954, *p*=.041). One covariate, the presence of a surgical complication (OR=11.422, 95% CI, 5.330-24.476, *p*<.001), was shown to be significant. The presence of a medical complication (*p*=.071) and prolonged LOS compared with standardized colorectal care (*p*=.066) were not significantly associated with unplanned readmissions. The multivariate logistic regression analysis is shown in Table 3 (insert Table 3).

DISCUSSION

This study aimed to assess the impact of a four-week, multimodal prehabilitation program on postoperative complications, prolonged LOS, unplanned readmissions, and mortality in high-risk patients undergoing elective resection for CRC. The principal finding is that prehabilitation significantly reduces postoperative complications, unplanned readmissions, and median length of hospital stay. This means that patients who attend the prehabilitation program are less likely to develop postoperative complications, be readmitted, and have a briefer hospital stay.

The results of this study showed a significant decrease of 13.7% of postoperative complications in the prehabilitation group. However, the impact of prehabilitation programs on postoperative outcomes in CRC patients greatly vary. Compared with existing literature, the study of Barberan[9] showed a significantly decreased number of postoperative complications (31% versus 62% in the control group, *p*=.001) and lower mean number of complications per patient for the prehabilitation group (*p*=.001), where prehabilitation was a protective factor (RR=0.5, 95% CI, 0.3-0.8). These findings are aligned with the present study, however the overall complication rate was 62% in the control group of Barberan's study[9] and 40% in the control group of the present study. This indicates that the overall complication rate was 22% higher in the study of Barberan[9], which may be because the present study consisted of a more homogenous group of patients. For instance, the study of Barberan[9] also included other surgical indications (e.g., pancreatic, gastric surgery) in the prehabilitation group and these types of surgeries are known to entail higher complication rates and longer lengths of hospital stay. This contributes to a higher overall complication rate and may explain the differences between the results of both studies.

Moreover, the study of Carli[62] described a contradictory result, namely that the prehabilitation program does not significantly decrease the number of postoperative complications (45.5% versus 45.5%; OR=0.9, 95% CI, 0.4-2.2, *p*=.90). However, in the present study, the prehabilitation patients were compared with patients receiving care as usual and the study of Carli[62] compared prehabilitation with rehabilitation in frail patients. It has been noticed that significant increases in lean body mass, functional capacity, and muscle strength often occur after 12 weeks in frail patients[63]. Therefore, an expanded training time above 4 weeks might be needed in order to physiological reserve preoperatively and reduce postoperative complications. The study of Carli[62] only included frail patients who participated in a four-week training program, which may have resulted in a lack of effect of the prehabilitation program and can therefore explain the contradictory results with the present study.

Furthermore, the present study found no significant different for mortality. However, mortality has been investigated in several studies and the found result is aligned with existing literature, as the studies of Barberan[9], Souwer[33], and Chia[64] found no significant differences in mortality. This may be explained by the fact that the overall mortality rates are low in CRC patients, as the age-standardized (world) mortality rate is 8.9% in both sexes[65], resulting in the overall low incidence of mortality in existing literature and the present study.

Regarding the outcome-prolonged LOS, the present study did not found a significant difference between the groups. Compared with existing literature, the study of Souwer[33] showed a significant difference between prolonged LOS and prehabilitation. Although these findings are not similar, the difference may be explained by the cut-off point. The study of Souwer[66] used a cut-off point of 14 days for a prolonged LOS, whereas the present study used a cut-off point of 5 and 6 days. The theory exists that a large amount of the data is around the used cut-off point, resulting in low differences between the groups and thus non-significant results in the present study.

A number of limitations exist within this study. The present study is a single-center study, which may limit the generalizability. However, to the researcher's knowledge, this is the first large cohort study assessing the impact of a multimodal prehabilitation program in high-risk CRC patients. The sample size of both group was sufficiently large with a post hoc power analysis of α=.05 and, effect size=.5 giving a power of .986, which means there was sufficient power to detect a valid association. This improved the generalizability of the results for CRC patients in need of colorectal surgery, which represents a strength of the present study. As a retrospective study, it is subjected to measurement errors. Attempts were made to minimize measurement errors by following a standardized data collection and data analysis protocol for all patients. Therefore, the data were gathered and systematically checked by two researchers, the principle investigator, and the epidemiologist. Moreover, selection bias may be present since patients in the prehabilitation group might have been more motivated than patients in the non-prehabilitation group since they could participate on a voluntary basis. This may have resulted in a higher tolerance or acceptability of the prehabilitation program. However, selection bias was minimized by establishing equal baseline characteristics using in- and exclusion criteria.

Furthermore, this study also has limitations regarding information bias inherent to using the retrospective database and it may not account for patient variables that were not recorded in the database of IKNL. For instance, no information was available regarding alcohol use or smoking status[37–39] and the database did not capture all possible known comorbidities, as only fourteen different types of comorbidities were recorded. In the present study, the univariate analysis shows that the presence of comorbidities in the prehabilitation group significantly differs. To prevent the impact of this difference, the presence of

comorbidities was considered as a possible confounder in the analysis. Moreover, due to the COVID-19 pandemic, fewer prehabilitation patients were included in this study since the prehabilitation program was temporarily halted.

This study provides valuable knowledge for all patients in need of colorectal surgical cancer treatment and whose potential postoperative complications play a major role. Based on the positive results of this multimodal prehabilitation program, it has clinical value for implementation in current practice in CRC patients undergoing elective surgery in the preoperative setting. Future research should focus on developing and organizing prehabilitation programs for other surgical indications. Furthermore, more insight is needed regarding which patients most benefit from prehabilitation and how the programs can be more patient tailored.

CONCLUSION

This study showed that the four-week, multimodal prehabilitation program leads to a reduction of postoperative complications, fewer unplanned readmissions, and also shortens the median length of hospital stay in high-risk CRC patients undergoing elective tumor resection. Multivariate logistic regression analyses showed that prehabilitation is a significantly protective predictor for postoperative complications and unplanned readmissions.

REFERENCE LIST

1. Kuipers EJ, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, et al. COLORECTAL CANCER. Nat Rev Dis Prim. 2013;1(15065):3-51.
2. Kuipers EJ, Rösch T, Bretthauer M. Colorectal cancer screening - Optimizing current strategies and new directions. Nat Rev Clin Oncol. 2013;10(3):130–42.
3. Van Rooijen S, Carli F, Dalton S, Thomas G, Bojesen R, Le Guen M, et al. Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: The first international randomized controlled trial for multimodal prehabilitation. BMC Cancer. 2019;19(1):1–11.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
5. Bruns ERJ, van den Heuvel B, Buskens CJ, van Duijvendijk P, Festen S, Wassenaar EB, et al. The effects of physical prehabilitation in elderly patients undergoing colorectal surgery: a systematic review. Color Dis. 2016;18(8):267–77.
6. McIsaac DI, Saunders C, Hladkowicz E, Bryson GL, Forster AJ, Gagne S, et al. PREHAB study: A protocol for a prospective randomised clinical trial of exercise therapy for people living with frailty having cancer surgery. BMJ Open. 2018;8(6):1–8.
7. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin. 2014;64(2):104–17.
8. Govaert JA, Fiocco M, Van Dijk WA, Scheffer AC, De Graaf EJR, Tollenaar RAEM, et al. Costs of complications after colorectal cancer surgery in the Netherlands: Building the business case for hospitals. Eur J Surg Oncol. 2015;41(8):1059–67.
9. Barberan-Garcia A, Ubré M, Roca J, Lacy AM, Burgos F, Risco R, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery : A Randomized Blinded Controlled Trial. Ann Surg. 2018;267(1):50–6.
10. Laso-Morales MJ, Jericó C, Gómez-Ramírez S, Castellví J, Viso L, Roig-Martínez I, et al. Preoperative management of colorectal cancer–induced iron deficiency anemia in clinical practice: data from a large observational cohort. Transfusion. 2017;57(12):3040–8.
11. Carli F, Zavorsky GS. Optimizing functional exercise capacity in the elderly surgical population. Curr Opin Clin Nutr Metab Care. 2005;8(1):23–32.
12. van Rooijen S, Carli F, Dalton SO, Johansen C, Dieleman J, Roumen R, et al. Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation. Acta Oncol. 2017;56(2):329–34.
13. Fagard K, Leonard S, Deschodt M, Devriendt E, Wolthuis A, Prenen H, et al. The

impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: A systematic review. J Geriatr Oncol. 2016;7(6):479–91.

14. Topp R, Ditmyer M, King K. The Effect of Bed Rest and Potential of Prehabilitation on Patients in the Intensive Care Unit. AACN Clin Issue. 2002;13(2):263–76.
15. do Nascimento Junior P, Módolo NSP, Andrade S, Guimarães MMF, Braz LG, El Dib R. Incentive spirometry for prevention of postoperative pulmonary complications in upper abdominal surgery. Cochrane Database Syst Rev. 2014;2014(2):1-45.
16. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Annals of Surgery. 2005;242(3):326–43.
17. Shah PM, Johnston L, Sarosiek B, Harrigan A, Friel CM, Thiele RH, et al. Reducing Readmissions While Shortening Length of Stay: The Positive Impact of an Enhanced Recovery Protocol in Colorectal Surgery. Dis Colon Rectum. 2017;60(2):219–27.
18. Zhuang C Le, Ye XZ, Zhang XD, Chen BC, Yu Z. Enhanced recovery after surgery programs versus traditional care for colorectal surgery: A metaanalysis of randomized controlled trials. Dis Colon Rectum. 2013;56(5):667–78.
19. Carli F, Charlebois P, Stein B, Feldman L, Zavorsky G, Kim DJ, et al. Randomized clinical trial of prehabilitation in colorectal surgery. Br J Surg. 2010;97(8):1187–97.
20. Piraux E, Caty G, Reychler G. Effects of preoperative combined aerobic and resistance exercise training in cancer patients undergoing tumour resection surgery: A systematic review of randomised trials. Surg Oncol. 2018;27(3):584–94.
21. Gillis C, Fenton TR, Sajobi TT, Minnella EM, Awasthi R, Loiselle SÈ, et al. Trimodal prehabilitation for colorectal surgery attenuates post-surgical losses in lean body mass: A pooled analysis of randomized controlled trials. Clin Nutr. 2019;38(3):1053–60.
22. Strous MTA, Janssen-Heijnen MLG, Vogelaar FJ. Impact of therapeutic delay in colorectal cancer on overall survival and cancer recurrence - is there a safe timeframe for prehabilitation? Eur J Surg Oncol. 2019;45(12):1–7.
23. Ven Fong Z, Chang DC, Lillemoe KD, Nipp RD, Tanabe KK, Qadan M. Contemporary Opportunity for Prehabilitation as Part of an Enhanced Recovery after Surgery Pathway in Colorectal Surgery. Clin Colon Rectal Surg. 2019;32(2):95–101.
24. Arthur HM, Daniels C, McKelvie R, Hirsh J, Rush B. Article Effect of a Preoperative Intervention on Preoperative and Postoperative Outcomes in Low-Risk Patients Awaiting Elective. Ann Intern Med. 2000;133(4):253–62.
25. Chen BP, Awasthi R, Sweet SN, Minnella EM, Bergdahl A, Santa Mina D, et al. Four-week prehabilitation program is sufficient to modify exercise behaviors and improve

preoperative functional walking capacity in patients with colorectal cancer. Support Care Cancer. 2017;25(1):33–40.

26. Silver JK, Baima J. Cancer prehabilitation: An opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes. Am J Phys Med Rehabil. 2013;92(8):715–27.
27. Carli F, Silver JK, Feldman LS, McKee A, Gilman S, Gillis C, et al. Surgical Prehabilitation in Patients with Cancer: State-of-the-Science and Recommendations for Future Research from a Panel of Subject Matter Experts. Phys Med Rehabil Clin N Am. 2017;28(1):49–64.
28. Gillis C, Buhler K, Bresee L, Carli F, Gramlich L, Culos-Reed N, et al. Effects of Nutritional Prehabilitation, With and Without Exercise, on Outcomes of Patients Who Undergo Colorectal Surgery: A Systematic Review and Meta-analysis. Gastroenterology. 2018;155(2):391-410.
29. Moran J, Guinan E, McCormick P, Larkin J, Mockler D, Hussey J, et al. The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: A systematic review and meta-analysis. Surg. 2016;160(5):1189–201.
30. Heger P, Probst P, Wiskemann J, Steindorf K, Diener MK, Mihaljevic AL. A Systematic Review and Meta-analysis of Physical Exercise Prehabilitation in Major Abdominal Surgery (PROSPERO 2017 CRD42017080366). J Gastrointest Surg. 2019:1-11.
31. Hijazi Y, Gondal U, Aziz O. A systematic review of prehabilitation programs in abdominal cancer surgery. Int J Surg. 2017;39:156–62.
32. Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, et al. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: A pilot study. Surg Endosc. 2013;27(4):1072–82.
33. Souwer ETD, Bastiaannet E, de Bruijn S, Breugom AJ, van den Bos F, Portielje JEA, et al. Comprehensive multidisciplinary care program for elderly colorectal cancer patients: "From prehabilitation to independence." Eur J Surg Oncol. 2018;44(12):1894–900.
34. Jones LW. Physical Activity and Cancer: Recent Results in Cancer Research. Phys Act Cancer. 2011;186:255–74.
35. Curtis NJ, West MA, Salib E, Ockrim J, Allison AS, Dalton R, et al. Time from colorectal cancer diagnosis to laparoscopic curative surgery—is there a safe window for prehabilitation? Int J Colorectal Dis. 2018;33(7):979–83.
36. Moreno RP, Pearse R, Rhodes A. American Society of Anesthesiologists Score: Still useful after 60 years? Results of the EuSOS Study. Rev Bras Ter Intensiva. 2015;27(2):105–12.
37. Thomsen T, Villebro N, Møller AM. Interventions for preoperative smoking cessation.

Cochrane Database Syst Rev. 2014;2014(3):2-16.
38. Sørensen LT, Jørgensen T, Kirkeby LT, Skovdal J, Vennits B, Wille-Jørgensen P. Smoking and alcohol abuse are major risk factors for anastomotic leakage in colorectal surgery. Br J Surg. 1999;86(7):927–31.
39. Grønkjær M, Eliasen M, Skov-Ettrup LS, Tolstrup JS, Christiansen AH, Mikkelsen SS, et al. Preoperative smoking status and postoperative complications: A systematic review and meta-analysis. Annals of Surgery. 2014;259(1):52–71.
40. Xue DD, Cheng Y, Wu M, Zhang Y. Comprehensive geriatric assessment prediction of postoperative complications in gastrointestinal cancer patients: A meta-analysis. Clin Interv Aging. 2018;13(1):723–36.
41. Bruns ERJ, Borstlap WA, van Duijvendijk P, van der Zaag-Loonen HJ, Buskens CJ, van Munster BC, et al. The Association of Preoperative Anemia and the Postoperative Course and Oncological Outcome in Patients Undergoing Rectal Cancer Surgery: A Multicenter Snapshot Study. Dis Colon Rectum. 2019;62(7):823–31.
42. Euser AM, Zoccali C, Jager KJ, Dekker FW. Cohort studies: Prospective versus retrospective. Clin Pract. 2009;113(3):214-217.
43. Velzeboer L, Huijboom M, Weijs P, Engberink M, Kruizenga H. Hoe berekenen we de eiwitbehoefte bij ondergewicht en overgewicht? Ned Tijdschr voor Voeding Diëtetiek. 2017;72(1):1–8.
44. Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: An approach for developing guidelines based on body mass index. Am J Clin Nutr. 2000;72(3):694–701.
45. Moore DR, Robinson MJ, Fry JL, Tang JE, Glover EI, Wilkinson SB, et al. Ingested protein dose response of muscle and albumin protein synthesis after resistance exercise in young men. Am J Clin Nutr. 2009;89(1):161–8.
46. Guimarães-Ferreira L, Cholewa JM, Naimo MA, Zhi XIA, Magagnin D, Dal Ponte de Sá RB, et al. Synergistic effects of resistance training and protein intake: Practical aspects. Nutrition. 2014; 30(1):1097–103.
47. Reidy PT, Walker DK, Dickinson JM, Gundermann DM, Drummond MJ, Timmerman KL, et al. Protein Blend Ingestion Following Resistance Exercise Promotes Human Muscle Protein Synthesis. J Nutr. 2013;143(4):410–6.
48. Yang Y, Breen L, Burd NA, Hector AJ, Churchward-Venne TA, Josse AR, et al. Resistance exercise enhances myofibrillar protein synthesis with graded intakes of whey protein in older men. Br J Nutr. 2012;108(10):1780–8.
49. Res PT, Groen B, Pennings B, Beelen M, Wallis GA, Gijsen AP, et al. Protein ingestion before sleep improves postexercise overnight recovery. Med Sci Sports Exerc. 2012;44(8):1560–9.

50. Schützenmeister A, Jensen U, Piepho HP. Checking normality and homoscedasticity in the general linear model using diagnostic plots. Commun Stat Simul Comput. 2012;41(2):141–54.
51. Connelly LM. Fisher's exact test. Medsurg Nurs. 2016;25(1):58-61.
52. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstem AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373–9.
53. Cunningham J, McCrum-Gardner E. Power, effect and sample size using GPower: practical issues for researchers and members of research ethics committees. Evid Based Midwifery. 2007;5(4):132–6.
54. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects [Internet]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ [cited 2019 Oct 16].
55. Nattino G, Pennell ML, Lemeshow S. Assessing the goodness of fit of logistic regression models in large samples: A modification of the Hosmer-Lemeshow test. Biometrics. 2020 [Accepted Article].
56. Etele ÉE, Sala D, Dénes M, Cozlea A, Darie R, Török Á. Elderly patients with colorectal cancer – A predisposed category for postoperative complications. Chir. 2019;114(3):331–42.
57. Ceretti AP, Maroni N, Longhi M, Giovenzana M, Santambrogio R, Barabino M, et al. Risk Factors for Prolonged Postoperative Ileus in Adult Patients Undergoing Elective Colorectal Surgery: An Observational Cohort Study. Rev Recent Clin Trials. 2018;13(4):295–304.
58. Zawadzki M, Krzystek-Korpacka M, Rzaca M, Czarnecki R, Obuszko Z, Sitarska M, et al. Risk factors in reoperations in colorectal surgery. Pol Prz Chir Polish J Surg. 2019;91(4):13–8.
59. Ishihara S, Matsuda K, Tanaka T, Tanaka J, Kiyomatsu T, Kawai K, et al. Patient factors predisposing to complications following laparoscopic surgery for colorectal cancers. Surg Laparosc Endosc Percutaneous Tech. 2015;25(2):168–72.
60. Almussallam B, Joyce M, Marcello PW, Roberts PL, Francone TD, Read TE, et al. What factors predict hospital readmission after colorectal surgery? Am Surg. 2016;82(5):433-8.
61. Damle RN, Alavi K. Risk factors for 30-d readmission after colorectal surgery: A systematic review. Journal of Surgical Research. 2015;200(1):200-7.
62. Carli F, Bousquet-Dion G, Awasthi R, Elsherbini N, Liberman S, Boutros M, et al. Effect of Multimodal Prehabilitation vs Postoperative Rehabilitation on 30-Day

Postoperative Complications for Frail Patients Undergoing Resection of Colorectal Cancer: A Randomized Clinical Trial. JAMA Surg. 2020;155(3):233–42.

63. Karelis A, Messier V, Suppère C, Briand P, Rabasa-Lhoret R. Effect of cysteine-rich whey protein (Immunocal®) supplementation in combination with resistance training on muscle strength and lean body mass in non-frail elderly subjects: A randomized, double-blind controlled study. J Nutr Heal Aging. 2015;19(5):531–6.
64. Chia CLK, Mantoo SK, Tan KY. "Start to finish trans-institutional transdisciplinary care": A novel approach improves colorectal surgical results in frail elderly patients. Color Dis. 2016;18(1):43–50.
65. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Gastroenteroloy Rev. 2019;14(2):89-103.
66. Souwer ETD, Bastiaannet E, de Bruijn S, Breugom AJ, van den Bos F, Portielje JEA, et al. Comprehensive multidisciplinary care program for elderly colorectal cancer patients: "From prehabilitation to independence." Eur J Surg Oncol. 2018;44(12):1894–900.

TABLES AND FIGURES

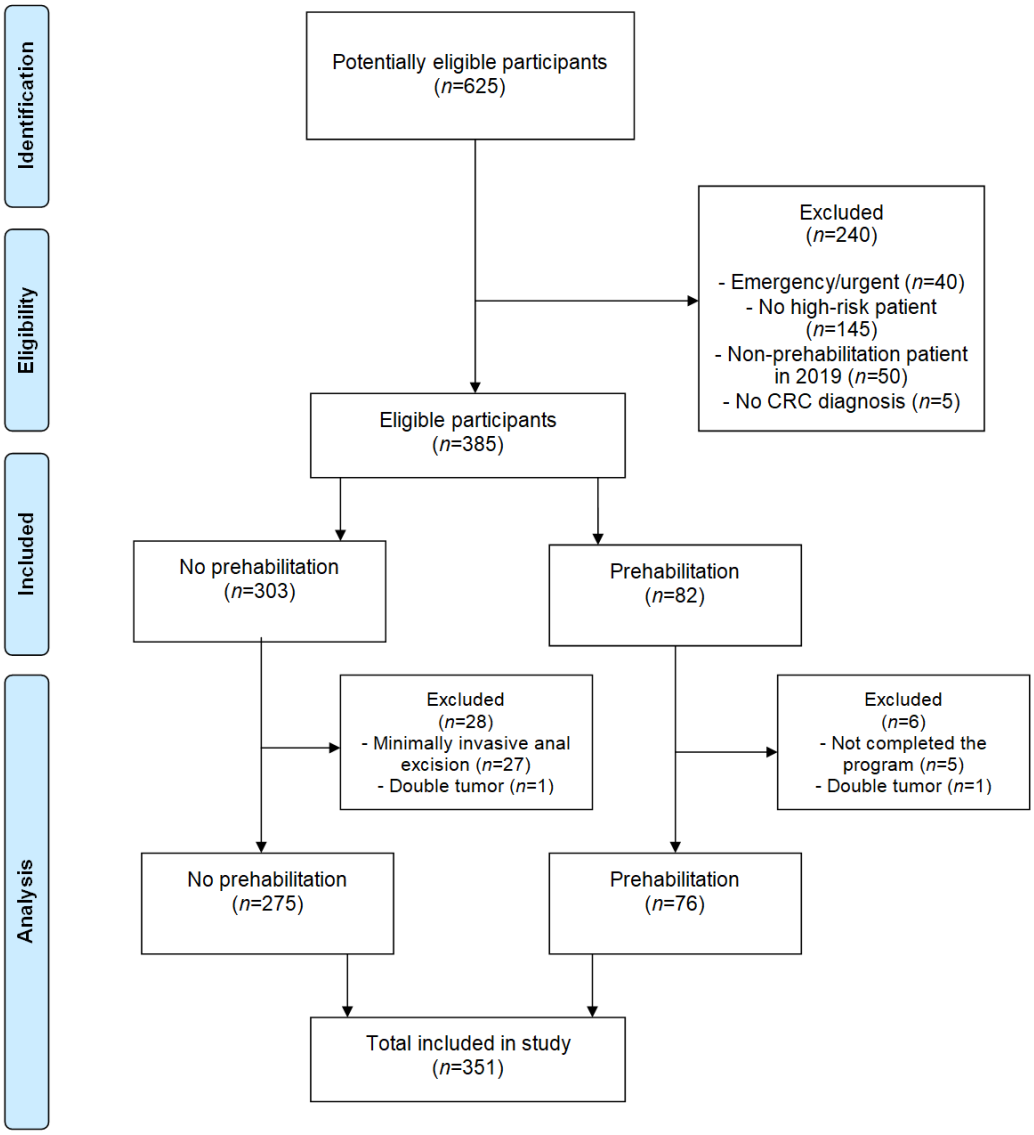

Figure 1 Flow diagram

Table 1 Baseline characteristics

	No prehabilitation n=275	Prehabilitation n=76	*P*-value	Total n=351
Characteristic				
Demographic data, n (%)				
Sex,				
Male	142 (52)	39 (51)	1.000	181 (52)
Age, years, median (IQR; min-max)	73.97 (8;39-91)	75.01 (9.2;61-85)	0.141[1]	74.07 (8.7;39-91)
Age ≥ 65 years	258 (94)	75 (99)	0.138	333 (95)
BMI, kg/m^2, median (IQR; min-max)	26.45 (6.2;17.31-53.41)	26.17 (5.4;18-54.01)	0.666[1]	26.42 (6.1;17.31-54.01)
Comorbidities	194 (71)	42 (55)	0.018	236 (67)
Oncologic data, n (%)				
Anaemia	76 (28)	25 (33)	0.392	101 (29)
Tumor location			0.774	
Colon	197 (72)	56 (74)		253 (72)
Rectum	78 (28)	20 (26)		98 (28)
TNM classification[2]			0.521	
I	71 (26)	20 (26)		92 (26)
II	105 (38)	24 (32)		129 (37)
III	86 (31)	29 (39)		115 (33)
IV	13 (5)	2 (3)		15 (4)
Adjuvant therapies[3]			0.214	
Radiotherapy	21 (26.9) (n=78)	2 (10) (n=20)		23 (23.5) (n=98)
Chemo radiation	15 (19.2) (n=78)	5 (25) (n=20)		20 (20.4) (n=98)
Surgical data, n (%)				
ASA index,			0.520	
I	12 (4)	2 (3)		14 (4)
II	135 (49)	40 (53)		175 (50)
III	110 (40)	32 (42)		142 (41)
IV	18 (7)	2 (3)		20 (6)
Surgical technique			1.000	
Laparoscopic	269 (98)	75 (99)		345 (98)
Open	6 (2)	1 (1)		7 (2)

IQR = Interquartile range; BMI = Body Mass Index; ASA = American Society of Anesthesiologists.[1]Mann-Whitney U test.
[2]TNM: Tumour, Node, Metastasis classification. Based on Union for International Cancer Control (UICC) 8th edition for colorectal cancer. [3]Adjuvant therapies only applies to patient with rectal cancer. In the Netherlands, patients with colon cancer do not receive adjuvant therapy.

Table 2 Univariate analysis for postoperative outcomes

	No prehabilitation n=275	Prehabilitation n=76	*P*-value
Outcome			
Hospital days of stay, median (IQR; min-max)	5 (3;2-42)	4 (4;2-27)	0.004[1]
Colon cancer, median (IQR; min-max)	5 (3;2-36) (n=197)	4 (4;2-27) (n=56)	0.020[1]
Rectal cancer, median (IQR; min-max)	6 (3;3-42) (n=78)	4.5 (4.5;3-20) (n=20)	0.093[1]
Prolonged length of stay[2], n (%)	115 (41.8)	25 (32.9)	0.186
Number of patients with postoperative complications, n (%)	110 (40)	20 (26.3)	0.032
Colon cancer	74 (37.6) (n=197)	13 (23.2) (n=56)	0.056
Rectal cancer	36 (46.2) (n=78)	7 (35) (n=20)	0.453
Number of complications per patient, n (%)			0.010
0	186 (67.6)	56 (73.7)	0.331
1	14 (5.1)	10 (13.2)	0.020
≥2	75 (27.3)	10 (13.2)	0.010
Type of complication[3]			
Medical, n (%)	73 (26.5)	10 (13.2)	0.015
Cardiovascular	21 (28.8)	5 (50)	1.000
Respiratory	16 (21.9)	1 (10)	0.316
Neurological	11 (15.1)	2 (20)	0.742
Thromboembolic	2 (2.7)	0	1.000
Infection other than respiratory or surgical	18 (24.7)	1 (10)	0.088
Other[4]	26 (35.6)	3 (3.9)	0.159
Surgical, n (%)	72 (26.2)	16 (21.1)	0.455
Postoperative hemorrhage	5 (6.9)	1 (6.3)	1.000
Anastomotic breakdown	14 (19.4)	2 (12.4)	0.538
Ileus	9 (12.5)	8 (50)	0.015
Abscess	10 (13.9)	5 (31.3)	0.332
Fascia dehiscence	1 (1.4)	0	1.000
Surgical site infection	8 (11.1)	4 (25)	0.299
Bowel perforation	1 (1.4)	0	1.000
Urethra leakage	0	0	1.000
Other	1 (1.4)	0	1.000
Surgical reintervention, n (%)	32 (11.6)	7 (9.2)	0.682
Complicated in-hospital stay[5], n (%)	44 (16)	10 (13.2)	0.595
Unplanned readmission <90 days after discharge, n (%)	45 (16.4)	4 (5.3)	0.014
In-hospital or <90 days after discharge mortality, n (%)	5 (1.8)	0	0.589

IQR = Interquartile range. [1]Mann-Whitney U test. [2]LOS compared with the standardized colorectal care of colon (5 days) or rectal (6 days) cancer surgery. [3]Number of different types of medical and surgical complications report up to over 100% of the total complication rate, since a patient can have more than one type of medical and/or surgical complication. [4]Renal dysfunction/failure, electrolytes disorders. [5]Defined as length of stay ≥14 days and/or surgical reintervention.

Table 3 Multivariate logistic regression analysis

	In-hospital or <90 days postoperative complications				***Unplanned readmission <90 days after discharge***	
Variable						
	Adjusted OR (95% CI), model A	***P*-value**	**Adjusted OR (95% CI), model B**	***P*-value**	**Adjusted OR (95% CI), model A**	***P*-value**
Nagelkerke R square	0.373		0.362		0.295	
Comorbidities		0.624		0.291		
No	Reference		Reference			
Yes	1.166 (0.632-2.151)		1.371 (0.763-2.466)			
Prehabilitation		0.043		0.046		0.041
No	Reference		Reference		Reference	
Yes	0.492 (0.248-0.978)		0.500 (0.253-0.988)		0.313 (0.102-0.954)	
Surgical complication						<0.001
No					Reference	
Yes					11.422 (5.330-24.476)	
Medical complication						0.071
No					Reference	
Yes					2.111 (0.939-4.742)	
Prolonged LOS[1]		<0.001		<0.001		0.066
No	Reference		Reference		Reference	
Yes	9.242 (5.348-15.971)		8.957 (5.223-15.360)		0.458 (0.199-1.051)	
Gender		0.028		0.040		
Female	Reference		Reference			
Male	1.828 (1.066-3.134)		1.744 (1.025-2.967)			
BMI, kg/m^2		0.283				
<18.5	Reference					
18.5-24.99	0.972 (0.128-7.358)	0.978				
25-35	1.023 (0.135-7.747)	0.983				
>35	1.921 (0.241-15.290)	0.538				
Tumor		0.012		0.016		
Colon	Reference		Reference			
Rectum	2.656 (1.234-5.715)		2.488 (1.181-5.239)			

Anaemia No Yes	 Reference 1.746 (0.932-3.271)	0.082	 Reference 1.625 (0.876-3.016)	0.124		
Adjuvant therapies No Yes	 Reference 1.101 (0.425-2.849)	0.843	 Reference 1.079 (0.421-2.761)	0.874		
Age, in years	1.064 (1.021-1.110)	0.003	1.057 (1.015-1.100)	0.008		

OR = Odds Ratio; CI = Confidence Interval; LOS = Length of stay; BMI = Body Mass Index. [1]LOS compared with the standardized colorectal care path of colon (five days) or rectal (six days) cancer surgery.