THE EFFECT OF PREHABILITATION ON SURGICAL COMPLICATIONS FOLLOWING COLON CANCER SURGERY – A PROSPECTIVE RANDOMIZED STUDY

Does Prehabilitation Improve Outcome in Colon Cancer Surgery – Study 1 (PRIO01)

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Research plan

Research project title

The effect of prehabilitation on surgical complications following colon surgery – a prospective randomized study

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Background

Cancer of the large bowel and rectum is the third most common kind of cancer in Sweden with 6500 new cases diagnosed each year. Cancer survival has improved over the past decades and approximately 65% of the patients live beyond 5 years of diagnosis. A great challenge of the surgical treatment is the high risk of complications that stem from the surgery. In academic literature, this is called postoperative complications. As many as 30% of the patients get at least one complication after elective surgery. In certain groups of patients, such as the sick and elderly, more than half of the patients suffer complications. These complications cause pain and suffering and they increase the risk of dying because of surgery. Furthermore, these complications come with prolonged hospital stay and increased costs [1, 2]. The complications include wound infections, pneumonia, urinary tract infection, deep venous thrombosis, pulmonary embolism, wound dehiscence, anastomotic leakage, sepsis, myocardial infarction, stroke and death. Different types of interventions aiming to improve the individual patient's physical and nutritive status before surgery have been given a lot of attention over the past years and more and more studies in this field are being published.

Prehabilitation encompasses all interventions that take place before a physiological event which aim to improve the outcome of this event. These interventions include physical training, psychological treatment and dietary improvements.

The conclusions that science has drawn so far regarding the effect of prehabilitation are not homogenous and it is still now known if preoperative interventions aiming to improve the physical and nutritional status of the patients actually reduces the risk of complications or affects the patient's well-being.

The effects of prehabilitation have been studied in the setting of elective abdominal surgery in a randomized controlled trial of patients 70 years or older and/or with a comorbidity corresponding to ASA III/IV. This study reported a 51% reduction in postoperative complications in the group that was given prehabilitation compared to the control group [3]. A systematic review has shown that prehabilitation of older patients before colorectal surgery improved the patients physical status but no statistically significant reduction of complications or hospital stay was seen. This review article concluded that there was a lack of scientific trials studying the effects of prehabilitation before colorectal surgery [4]. The included studies' quality was limited by small study populations, heterogenous control groups and poor patient compliance.

Another study demonstrated that physical and social function was improved by prehabilitation before colorectal surgery. However, only 71% of the patients completed the prehabilitation and only 56% of the patients completed follow-up [5]. These relatively low numbers constitute major scientific weaknesses. To sum up, the conclusions in the present scientific literature are contradictory regarding the effect prehabilitation has before surgery. Because of this, we aim to design and perform a randomized, prospective study with adequate sample size, intervention completion and follow-up to investigate of structured physical exercise and diet affects the outcome regarding complications and quality of life.

Scientific questions

Primary hypothesis

The primary hypothesis of this study is that prehabilitation with exercise and nutritional supplements will decreased morbidity, number of and severity of postoperative complications.

Secondary hypotheses

- Malnourished patients have a micronutrient deficiency to a greater extent than patients that are not malnourished.
- Micronutrient status can be improved with prehabilitation
- Prehabilitation increase the muscle mass
- Prehabilitation results in improved cardiopulmonary function measured with ergospirometry (V_{AT})
- Health-related quality of life according to SF-36 is improved with prehabilitation
- Fewer symptoms of depression and anxiety according to HADS (Hospital anxiety and depression scale) is observed with prehabilitation
- Immunonutrition and protein supplement combined with exercise will result in increased prealbumin and albumin in serum
- Frailty score is improved after prehabilitation
- Non-frail patients have fewer and less serious complications and shorter length of stay
- There is a correlation between frailty score and cardiopulmonary function measured with ergospirometry (V_{AT})
- Frailty index can be used to predict which patients that may benefit from prehabilitation
- Prehabilitation results in restored intestinal function earlier than for patients that go through standard care
- Prehabilitation results in shorter length of stay
- An increase in muscle mass reduce the risk of postoperative complications
- Prehabilitation is associated with fewer readmissions
- Prehabilitation is associated with reduced health care costs and social costs

Importance for health care and patient benefit

Today, the only available treatment that can cure colorectal cancer is surgery. This require that the patients general condition allows surgery and that the patient can get tumor free after the surgery. If preoperative intervention with exercise and diet can improve the patients physiological condition before operation, this might lead to a decrease of postoperative complications and a better quality of life. A reduction of the number and severity of complications will lead to shorter length of stay and fewer re-admissions which will result, not only in a reduction of healthcare costs but also less suffering for the specific individual.

Patients that initially are too weak to undergo surgery that go through a prehabilitation programme, might benefit to an extent that the decision not to operate may be altered.

Method

Abbreviated study design

The study will be conducted as a single-blinded randomized controlled trial. The trial will include patients with colon cancer scheduled for elective surgery at Helsingborg Hospital. Patients with a newly discovered tumor of the colon will, at the time of diagnosis, be informed of the finding and that a physician and a registered nurse from the surgical department at Helsingborg Hospital will contact them. Patients will receive oral and written information regarding participation in the study. In the first stage patients will only be informed that the study aims to reduce postoperative complications through diet and exercise. The reason for this is to avoid that patients by themselves initiate changes in diet or exercise routines which could pollute the study design [6]. The principal aim of the study is to evaluate if a standardized regimen combining diet and exercise results in fewer and less serious postoperative complications compared to conventional perioperative management consisting of a small dietician intervention if there is clinical suspicion of malnutrition and psychosocial support through contact nurse.

Preoperative evaluation

All included will undergo ergospirometry, frailty screening, blood sampling and evaluation of quality of life prior to surgery. All patients >=60 years of age who accept inclusion and are included in the study will undergo the aforementioned testing. As earlier studies have shown that patients with VAT<11 on ergospirometry have the greatest potential benefit of prehabilitation these patients with low cardiopulmonary function will be informed in writing and orally and asked to participate in the second part of the study. Patients who accept inclusion will be randomized to two groups; an intervention group and a control group. The intervention group will undergo preoperative exercise and special diet intervention. The control group will undergo conventional preoperative preparation. The study will adhere to the guidelines set forth in the “standardized course of care” by the Swedish Association of Local Authorities and Regions.

Patients who undergo ergospirometry but have a cardiopulmonary function above the threshold(i.e. VAT>11) will not be included in the study but will be followed as a

reference material(observational cohort). They will only participate in the first part of the study and undergo frailty assessment and evaluation of health-related quality of life and symptoms of depression and anxiety.

As a historical comparison we will map and categorize complications after colorectal surgery for the period 2009-2019. Patients will be identified from electronic databases(PASIS) and through ICD-codes which identify colorectal surgical procedures. Pertinent information will be gathered regarding:

A) Patient and disease characteristics(age, sex, present and past illness, current medication, cardiopulmonary function, ASA-classification, Time from diagnosis to surgery and routine labs)
B) The conducted procedure (surgeon, procedure length, blood loss, perioperative antibiotics, bowel preparation, laparoscopy or open procedure, vascular anatomy and technique of specimen removal)

Postoperative morbidity as defined by Clavien-Dindo and POMS (length of stay, vitals, time to return of normal bowel function, radiologic or physiologic diagnostic procedures undertaken, late complications and recurrence of cancer within 5 years after surgery).

Inclusion criteria

Part 1 of study

- Suspected colon cancer
- Age>=60 years

Part 2 of study
VAT<=11 at ergospirometri

Exclusion criteria

- Curative treatment intent not possible as assessed by the multi-disciplinary tumor board

Randomization procedure

Randomization will be conducted from opaque envelopes in blocks of 10 envelopes, a total of 180 envelopes.

Blinding procedure

To minimize the risk of subjectivity and undue influence of postoperative patient management due to group allocation (bias) the nursing staff and treating physicians will have no information regarding group allocation. This will apply to all members of the team involved in postoperative care including the physicians responsible for the study. The only people with knowledge of group allocation will be the contact and research nurses at the outpatient department. The contact and research nurses will not participate in the perioperative care of the study patients, which will prevent bias regarding the primary outcomes. The patients will be informed of the importance of not sharing information regarding group allocation with nursing staff and physicians. If it becomes necessary to reveal group allocation for medical reasons the research nurse will consult the same physician in all matters. This physician, who is also the principal investigator, will not take part in the surgical or perioperative care of the patient.

Interrim analysis

To enable evaluation of safety and, if necessary, minor changes to the study protocol an interim analysis will be conducted after inclusion of 15 patients in each group. The study will be prematurely terminated if there is a significant increase of serious complications(>Clavien-Dindo 3B) in the intervention group [7]. Minor changes to the study protocol may be made at this time if responsible researchers assess that they do not impair the ability of the study to answer the main hypothesis.

Statistical calculations

Power calculation

The study will be designed to identify a reduction in the prevalence of postoperative morbidity(as assessed by postoperative morbidity survey) on the fifth day from 50 % to 28 % with a beta-value of 0.8 and an alpha-value 0.05 based on calculations below.

The risk reduction is estimated from Dunne et al who showed that prehabilitation increased VAT by approximately 2 ml/kg/min which according to West et al decreases the odds of morbidity assessed by POMS by 40 % [8, 9]. Furthermore, immunonutrition has been shown to convey a 50 % reduction in the odds of postoperative infectious complications [10]. When these risk reductions are combined it is considered feasible that an intervention with diet and aerobic prehabilitation exercise will convey an absolute reduction in the risk of postoperative morbidity of 22 percentage points. I.e. a relative risk reduction of 44 %. For adequate statistical power 78 patients are needed in each group. We also factor in that up to 15 % of randomized patients might not be able to complete the study and therefore plan to include 90 patients in each group, in total 180 patients (Stata SE 13.1)

Statistical methods

Data will be stored deidentified in an electronic database that complies with the GDPR of the European Union and Swedish applicable laws. Analysis of parametric distribution will be conducted by Kologorov-Smirnov test. Statistical comparisons of group differences will be conducted by t-test for parametric variables, Kruskal-Wallis test for non-parametric variables and Fisher's exact test for categorical variables.

Quantitative analysis of risk factors for complications or impaired physiological function will be conducted by logistic regression for binary outcomes and linear regression for continuous outcomes respectively.

Definitions

Standard care in colon cancer

At the first visit to the surgical outpatient clinic, the patient fillis out a form that measures percieved health. This form encompasses physical, phsycological, social and existential aspects. The cancer contact nurse revies this with the patient to follow-up on any specific needs.

Patients who have lost weight, have deviating nutritional blood work or have problems eating recieve nutrition drinks and they are referred to the dietitian. If the patient wants, they are referred to a therapist of even a psychologist. The cancer contact nurse contacts the patients by phone, the week after this visit to provide phycological support and screen for other problems that might have been missed at the first visit. The purpose of this is to get the patient in as good shape as possible before surgery.

At the first visit, the patient gets a file with different brochures regarding things they can improve on their own before surgery (smoking- and alcolhol cessation) etc.

Ergospirometry

The anaerobic threshold occurs when the muscular metabolism goes from aerobic to anaerobic work and the pH stops dropping linearly and starts dropping exponentially, in relation to the muscular work load. This can be measured by invasive muscle-pH testing and a maximal exertion test. However, the Ventilatory Anaerobic Threshold (V_{AT}) can be estimated by a non-invasive, non-maximal exertion test. The patient stops biking upon perceived too big effort [11].

Previous studies have shown a strong correlation between low V_{AT} and high risk for postoperative complications, increased mortality and longer hospital stay [12]. In a study of prehabilitation before liver surgery, it was been shown that the exercise regime had good effect on cardio-pulmonary capacity, quality of life and was safe for old and frail patients to perform [8].

All included patients will go through an ergospirometri to establish V_{AT}. The test starts with 3 minutes of rest followed by 3 minutes of pedaling without resistance. Following this, the resistance is progressively increased until the study person stops pedaling by their own volition. The progressive increase of resistance occurs in steps of 10W-25W [11]. The test is followed by 5 minutes rest. Ventilation as gas exchange is measured by a breathing mask connected to a computer that calculates oxygen consumption (oxygen uptake) and carbon dioxide production. Pulse, 12-lead ECG, blood pressure and oxygen saturation of the blood is monitored during the entire session to guarantee the patient's safety. The protocol is described in detail by Dunne et al (2014) [13].

The ergospirometri will be performed at the department of clinical physiology it Helsingborg General Hospital. Patients who are randomized to an exercise intervention will perform this under supervision of a physical therapist in the hospital patient gym.

Frailty, comorbidity and disability

Frailty is a clinical syndrome including a decreased physiological reserve and a decreased ability to withstand physiological stressors. Frailty is often present in the multimorbid patient with disability, but is an independent clinical syndrome including, weightless, self-reported exhaustion, weakness, slow walking speed and low physical activity. Many instruments to screen for frailty has been developed, but there is lack of consensus in which instrument that is more advantageous to predict the risk for adverse effects after surgery.

The prevalence of frailty in patients that undergo colorectal cancer surgery has been shown to be 40% and frail patients have an increased risk of morbidity and mortality after surgery [14, 15]. The hypothesis is that prehabilitation can reduce the prevalence of frailty, reduce the risk of morbidity- and mortality that is associated with frailty and

that the preoperative use of a frailty index can be used to predict the risk of complications in patients with VAT<11 that are planned for colorectal surgery.

- Frailty will be assessed using:
  - Frailty Phenotype,
  - Edmonton frail scale
  - RAI-score (Risk-analysis-index)
  -
- Disability will be assessed using:
  - ADL
  - IADL

Comorbidity will be assessed using the Charlson comorbidity index.

Sarcopenia

Sarcopenia, (low muscle mass), has a prevalence of up to 40% in colorectal cancer patients. It is associated with an increased risk of postoperative complications [16]. Fat free mass will be measured with bioelectrical impedance to examine if prehabilitation affects the muscle mass.

Health-related quality of life

It has been shown that colorectal cancer surgery reduces quality of life [17]. Our hypothesis is that prehabilitation eliminate or at least decrease the reduction in health-related quality of life after surgery.

Health-related quality of life is reduced after planned colorectal surgery. The SF-36 (short-form 36 Health Survey) is a generic self-reported health-related quality of life questionnaire that is available in a Swedish validated and reliability-tested version [18]. The SF-36 questionnaire consists of 35 individual questions divided into eight subscales that represent eight domains of health. The scores on items pertaining to the same dimension are then aggregated to generate a score for each of the eight domains of health (physical functioning, role physical, pain, social functioning, role emotional, vitality, mental health, and general health perception). The numerical answers are then recorded according to a pre-specified algorithm to yield scores ranging for 0 to 100 for each domain. It takes 8 minutes to answer the questions [10].

It's been shown that scores on six of eight domains deteriorated after colorectal cancer surgery and improved to baseline thereafter. Scores on all subscales but mental health and general health perception were significantly lower than baseline at 1 month postoperatively and at 2 months, the score for role physical remained significantly below baseline [17].
No studies on the potential effect of prehabilitation on health-related quality of life in colorectal cancer surgery exist. In this study, The SF-36 will be used to measure health-related quality of life in all the included patients before randomization, before operation, 30 days postoperatively, 3 and 6 months postoperatively, and 1,3 and 5 years postoperatively.

Symptoms of depression and anxiety

Approximately 30% of patients with cancer are affected with symptoms of anxiety and depression [19]. Prehabilitation has been shown to reduce these symptoms in patients suffering from colon cancer [20]. Previous studies that have shown a reduction of these symptoms have had psychological support as a part of the prehabilitation program. Our hypothesis is that prehabilitation in this study will result in reduced anxiety and depression even though the patients won't receive professional psychological support, other than the support provided in the standard care program, which include counselling if necessary.

HAD (hospital anxiety and depression scale) is a questionnaire used to measure symptoms of depression and anxiety in an in- or outpatient setting. HAD has been tested in older populations and seem to have a good accordance compared to other questionnaires [21, 22]. It takes 3-5 minutes to complete the test. An advantage with this form compared to other questionnaires is that it covers not only symptoms of depression but also symptoms of anxiety.

Immunonutrients

Immunonutrition can be defined as intake of a diet rich in glutamin, arginin and Omega-3 fatty acids during a period of 5-7 days prior to operation. A metanalysis of 14 randomized controlled studies in patients that underwent colorectal surgery showed that immunonutrition significantly reduced the frequency of complications [10]. It is however unclear if immunonutrition combined with exercise and protein supplement further can reduce the frequency of complications.

Macronutrients

Our hypothesis is that protein supplement combined with exercise can improve patients physical level of function and reduce the risk of postoperative complications. Older individuals are particularly dependent of an adequate intake of protein (20-30grams per meal) to maintain a normal muscle protein synthesis [23]. European Society of Clinical Nutrition and Metabolism recommend a protein intake of 2 grams per kilo per day for patients with cancer. The intake of protein in patients with acute or chronic kidney failure should be limited to 1 gram per kilo per day.
A low albumin (<35g/L) has been shown to be a better marker to predict postoperative morbidity than weight loss and BMI in patients with colorectal cancer [24]. Even though albumin is a useful marker to predict surgical complications, it is a flawed marker to indicate malnutrition. Prealbumin (transthyretin) might be a favorable marker since the half-life is shorter than for albumin (2-3 days). This may be more useful for detecting acute changes in nutritional status to the recognition of rapid nutritional changes [25].

Protein supplement as a part of a prehabilitation intervention has previously been examined in a study randomizing patients to structured prehabilitation before surgery or structured rehabilitation after surgery [20]. The study showed that prehabilitation resulted in better physical level of functioning, but no difference in number and severity of complications were observed. Protein supplement with no other interventions have shown to improve the walking capacity compared to placebo in patients who will have surgery for colorectal cancer [26].

Micronutrients

A number of micronutrients (Zink, Iron, Copper, Calcium, Selenium, Vitamins A, C and D, folate, cobalamin) are essential to adequate muscle protein synthesis, postoperative wound healing and adequate immune response after surgery. It is therefore theoretically possible that these substances can affect the results of prehabilitation and also reduce the risk of postoperative complications. Several studies have shown a correlation between protein intake, micronutrient reserves, muscle strength and frailty [27]. Up to 30% of patients with colorectal cancer have shown suffer from malnutrition [24]. It is not known if or to what extent these malnourished individuals also suffer from a micronutrient deficiency. Furthermore, there are no studies that have explored if micronutrient deficiency can affect the result of prehabilitation or increase the risk for postoperative complications.

PETH

PETH (Phosphatedylethanol) is a validated laboratory method to quantify alcohol intake with 100% specificity. Alcohol intake has proven to increase the risk of surgical and affects cardiac function, immune defense and hemostasis [28]. To avoid confounding, it is necessary to quantify the patients' alcohol.

Blood analysis

A broad spectrum of blood analyses will be performed. Patients will be samples before the CT (sampling 1), preoperatively (sampling 2) and postoperatively (sampling 3).

If there are pathological samples at sampling 3, patients will be followed by the surgical outpatient clinic in Helsingborg of cared for by primary care.

Laboratory analysis will be performed by the department of clinical chemistry at Helsingborg General Hospital. Included patients will have the same patient insurance as all patients cared for by Region Skåne.

Samplings 1, 2, och 3:

- S-Cu
- S-Ceruloplasmine
- S-Selenium
- S-Ascorbic acid
- P-Cobolamin
- P-Folate
- P-Homocystein
- S-Mettylmalonate
- Zink
- P-albumine
- P-α2-makroglobuline
- S-Fe
- S-Ferritin
- S-Hepcidin
- S-sTfR
- S-TIBC
- MCH
- MCV
- Calcidiol(25(OH)D)
- S-Ca
- S-Ca^{2+}
- S-PTH
- S-Retinol
- P-Mg
- Omega-3
- SuPAR
- Peth

Detailed description of the second part of the study

Intervention cohort

Patients who accept participation and have $V_{AT}<11$ will be randomized to either the control group or the intervention group.

Exercise

Based on the subject's cardiopulmonary function (VAT), an interval training program will be designed. The training will be conducted 4 times a week (Monday, Tuesday, Thursday and Friday). Patients will be included and begin interval training as soon as a legit referral of a suspected colon cancer is present at the Surgical Department at Helsingborg Hospital. If the patients meet the listed criteria for inclusion in the study the patients will be enrolled in the training program and trained until 3 days prior to surgery. The reason for this is purely practical in order to allow the patient to rest at least one day before cycle test 2 and one day further before surgery. The training is done on an ergometer and takes a total of about 60 minutes at a time where 15 minutes is warm up, 30 minutes is interval training of 60-90% of VAT and 15 minutes is cool down. The training is performed in accordance with Dunne et al (2016) [8]. The training will be performed in a room at the hospital. It will, when possible, be performed in groups and will be led by a physical therapist. Patients will be offered free transport to and from the hospital as well as lunch in connection with the training.

Diet

• Assessment of the study dietician regardless of clinical nutritional status.
o diet anamnesis; "48-recall", i.e. complete review of the intake of food in the last 48 hours.
o Length, weight, weight change, body composition
o Albumin, Prealbumin (S-Transthyretin - TTR), C-Reactive Protein
• Target caloric intake is set to 30-35 kcal / kg / day and for protein is set to 2g / kg / day
• Supplementation with nutritional drink Fresubin Protein Energy Drink, 2-3 pcs daily on dietary suspicion of insufficient protein energy intake. If additional protein is needed, Fresubin protein powder is given.
• Supplementation with dietary supplements in the absence of micronutrients in blood sampling 1 according to appendix 1.
• Immunonutrition from 7 days preoperatively with Nestlé Oral Impact 3x300ml

Control Group

Patients randomized to this group will follow pre and postoperative standard routines for elective abdominal cancer surgery at Helsingborg Hospital. This means, among other things, psychosocial support via contact nurse and curator if needed. Dietician on clinical suspicion of nutritional problems and mobilization with the help of paramedical staff in the postoperative department.

Operation

All included patients will be operated according to standard and generally accepted colorectal cancer surgical techniques. The procedure is performed by consultant surgeons specially trained for colon cancer surgery. The operation will either be performed as minimal invasive surgery with or without robot or conventional open surgery. Regardless of the surgical method, the procedure is done according to a standard procedure, which involves dissecting the intestine in embryological planes ensuing best oncological outcome for each patient. This technique removes the cancer with a good margin, which has been shown to lead to fewer relapses and better survival for the patient.

The staff and the surgeon are only aware that the patient is included in the study.

Evaluation of complications

Postoperative Morbidity Survey (POMS) is an instrument developed to identify complicated postoperative procedures that result in extended care time. POMS assess the incidence of morbidity in 8 domains (Renal, Cardiovascular, Pulmonary, Infectious, Neurological, Hematological, Gastrointestinal, Wound Related and Pain) regardless of etiology. POMS can be used both retrospectively and prospectively and has low interindividual variance [29, 30].

Clavien-Dindo is a scale developed to classify the severity of a complication based on which therapeutic consequence is needed. According to Clavien-Dindo, complications are graded on a five-degree scale from complications that did not require active treatment to fatal complications [7]. Together, POMS and Clavien-Dindo provides a picture of the incidence of complications as well as the severity.

Follow-up

The follow-up will be done with registration of post-operative complications, time to restored bowel function on a daily basis and total days of admission will be registered. After 30 days post operatively the chart will be checked again for further postoperative complications, re-admission. The patient will also perform SF-36 and HAD on day 30 postoperatively.

Thereafter SF-36 and HAD as well as studies of the patient chart will be carried out after 3 and 6 months, and after 1, 3 years and 5 years postoperatively.

Patients excluded before randomization will be followed up as mentioned above until day 30 post operatively.

Health economics

Health economics is a discipline that analyzes health and medical care from an economics perspective. As the resources of society are limited and the demand for care is increasing, methods are needed to be able to make priorities in the healthcare sector. Our hypothesis is that preoperative intervention with exercise and diet improves the patient's physiological conditions before surgery, which can lead to reduced postoperative complications and improved quality of life and thus lower costs for healthcare and society at large.

Some studies have shown that the mean cost for a complication is around SEK 120.000, which corresponds to a doubling of the cost of care for these patients. And in these studies one-third of the investigated unit's budget was used to fund the management of complications [31, 32].
Within the tenets of this study, we intend to calculate costs for hospital care and for society at large, and in what way these are affected by post-operative complications. Our hypothesis is that prehabilitation reduces the costs of secondary postoperative complications.

References

1. North RCC. Colorectal Cancer Annual Report. 2017
2. North RCC. National Program for Colorectal Cancer Care. 2016
3. 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;267:50-56.
4. Bruns ER, 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. Colorectal Dis. 2016;18:O267-77.
5. Mayo NE, Feldman L, Scott S, Zavorsky G, Kim DJ, Charlebois P et al. Impact of preoperative change in physical function on postoperative recovery: argument supporting prehabilitation for colorectal surgery. Surgery. 2011;150:505-514.
6. Berkel AEM, Bongers BC, van Kamp MS, Kotte H, Weltevreden P, de Jongh FHC et al. The effects of prehabilitation versus usual care to reduce postoperative complications in high-risk patients with colorectal cancer or dysplasia scheduled for elective colorectal resection: study protocol of a randomized controlled trial. BMC Gastroenterol. 2018;18:29.
7. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-213.
8. Dunne DF, Jack S, Jones RP, Jones L, Lythgoe DT, Malik HZ et al. Randomized clinical trial of prehabilitation before planned liver resection. Br J Surg. 2016;103:504-512.
9. West MA, Lythgoe D, Barben CP, Noble L, Kemp GJ, Jack S et al. Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery: a prospective blinded observational study. Br J Anaesth. 2014;112:665-671.
10. Cerantola Y, Hübner M, Grass F, Demartines N, Schäfer M. Immunonutrition in gastrointestinal surgery. Br J Surg. 2011;98:37-48.
11. Wasserman K. Principles of Exercise Testing and Interpretation. Lippincott Williams & Wilkins; 2005
12. Wilson RJ, Davies S, Yates D, Redman J, Stone M. Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. Br J Anaesth. 2010;105:297-303.
13. Dunne DF, Jones RP, Lythgoe DT, Pilkington FJ, Palmer DH, Malik HZ et al. Cardiopulmonary exercise testing before liver surgery. J Surg Oncol. 2014;110:439-444.
14. Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010;210:901-908.
15. 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;7:479-491.
16. Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. Br J Cancer. 2012;107:931-936.

17. Antonescu I, Carli F, Mayo NE, Feldman LS. Validation of the SF-36 as a measure of postoperative recovery after colorectal surgery. Surg Endosc. 2014;28:3168-3178.
18. Sullivan M, Karlsson J, Ware JE. The Swedish SF-36 Health Survey--I. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. Soc Sci Med. 1995;41:1349-1358.
19. Brintzenhofe-Szoc KM, Levin TT, Li Y, Kissane DW, Zabora JR. Mixed anxiety/depression symptoms in a large cancer cohort: prevalence by cancer type. Psychosomatics. 2009;50:383-391.
20. Gillis C, Li C, Lee L, Awasthi R, Augustin B, Gamsa A et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. Anesthesiology. 2014;121:937-947.
21. Djukanovic I, Carlsson J, Årestedt K. Is the Hospital Anxiety and Depression Scale (HADS) a valid measure in a general population 65-80 years old? A psychometric evaluation study. Health Qual Life Outcomes. 2017;15:193.
22. Lisspers J, Nygren A, Söderman E. Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample. Acta Psychiatr Scand. 1997;96:281-286.
23. Breen L, Phillips SM. Skeletal muscle protein metabolism in the elderly: Interventions to counteract the 'anabolic resistance' of ageing. Nutr Metab (Lond). 2011;8:68.
24. Hu WH, Cajas-Monson LC, Eisenstein S, Parry L, Cosman B, Ramamoorthy S. Preoperative malnutrition assessments as predictors of postoperative mortality and morbidity in colorectal cancer: an analysis of ACS-NSQIP. Nutr J. 2015;14:91.
25. Truong A, Hanna MH, Moghadamyeghaneh Z, Stamos MJ. Implications of preoperative hypoalbuminemia in colorectal surgery. World J Gastrointest Surg. 2016;8:353-362.
26. Gillis C, Loiselle SE, Fiore JF, Awasthi R, Wykes L, Liberman AS et al. Prehabilitation with Whey Protein Supplementation on Perioperative Functional Exercise Capacity in Patients Undergoing Colorectal Resection for Cancer: A Pilot Double-Blinded Randomized Placebo-Controlled Trial. J Acad Nutr Diet. 2016;116:802-812.
27. Yannakoulia M, Ntanasi E, Anastasiou CA, Scarmeas N. Frailty and nutrition: From epidemiological and clinical evidence to potential mechanisms. Metabolism. 2017;68:64-76.
28. Tønnesen H, Nielsen PR, Lauritzen JB, Møller AM. Smoking and alcohol intervention before surgery: evidence for best practice. Br J Anaesth. 2009;102:297-306.
29. Patel AB, Reyes A, Ackland GL. Non-inferiority of retrospective data collection for assessing perioperative morbidity. PeerJ. 2015;3:e1466.
30. Grocott MP, Browne JP, Van der Meulen J, Matejowsky C, Mutch M, Hamilton MA et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. J Clin Epidemiol. 2007;60:919-928.
31. Zoucas E, Lydrup ML. Hospital costs associated with surgical morbidity after elective colorectal procedures: a retrospective observational cohort study in 530 patients. Patient Saf Surg. 2014;8:2.
32. Govaert JA, Fiocco M, van Dijk WA, Scheffer AC, de Graaf EJ, Tollenaar RA et al. Costs of complications after colorectal cancer surgery in the Netherlands: Building the business case for hospitals. Eur J Surg Oncol. 2015;41:1059-1067.