COLORECTAL CANCER SURGERY

clinical improvements introducing prehabilitation

SJ van Rooijen

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CLINICAL IMPROVEMENTS
INTRODUCING PREHABILITATION

STEFANUS JOHANNES VAN ROOIJEN

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Aan mijn dierbare grootouders
To my dearest grandparents

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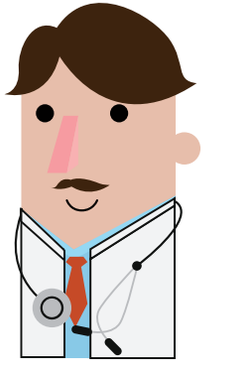
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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THESIS



INTRODUCTION

Colorectal cancer

Colorectal cancer (CRC) is the second most prevalent type of cancer in the world, with over 1.4 million cases and 700.000 deaths annually.[1] The only curative step in the treatment stratagem is surgery. Although perioperative care has improved greatly due to improvements in patient selection, anesthetic and analgesic approaches combined with minimally invasive operating techniques and enhanced recovery after surgery programs (ERAS), postoperative morbidity and mortality rates are still high.[2–4]

Postoperative complication rates are reported up to 35% and are directly related to higher mortality rates, decreased functional capacity, lower health related quality of life (HRQoL) and an increased expenditure on healthcare.[5] The most feared complication after colorectal surgery is colorectal anastomotic leakage (CAL). Although many attempts have been made to prevent its occurrence, incidence rates remain rather stable. For instance, a 5.8% CAL rate after colon resection versus a 9.4% rate after rectum resection was reported by the Dutch Surgical Colorectal Audit. Worldwide, these rates vary between 1.5 and 21%.[3,6,7] CAL is associated with a 40% mortality rate,[8,9] decreased disease-specific survival and increased cancer recurrence rates.[10–14] Even in the absence of complications, only 40% of individuals who undergo major colorectal surgery return to their baseline functional capacity as measured by VO2 peak delaying and impairing postoperative recovery.[15]

A suboptimal outcome after colorectal surgery creates ample room for improvement. However, which colorectal domains allow for a change?

Focus of research in colorectal surgery

Research focusing on three separate phases associated with colorectal surgery may be identified (figure 1). Elements of the preoperative period includes patient selection, risk stratification, shared decision making and optimal preparation. Intraoperative research focuses on optimizing anesthetic and surgical techniques. Research on postoperative recovery includes early complication detection, optimizing health related quality of life (HRQoL) and the enhanced recovery after surgery program (ERAS). Along with clinical research, many experimental studies have been performed to understand the process of anastomotic healing and to identify markers to predict CAL. The focus of this thesis however is related to clinical aspects of CAL, its prediction and preoperative patient optimization.

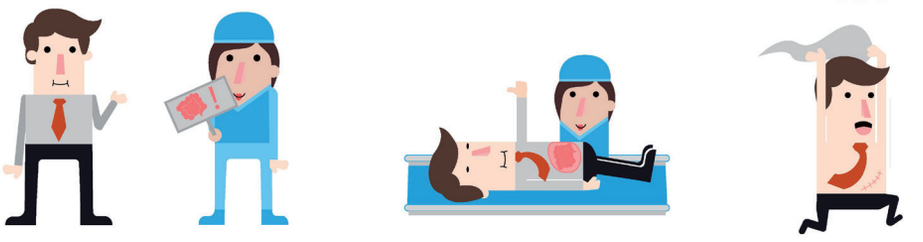


Figure 1. Phases of surgery: Preoperative, intraoperative and postoperative.

Preoperative factors

Governmental regulations and national guidelines dictate that the waiting period for Dutch colorectal cancer patients should not exceed five weeks. Interestingly, this phase varies internationally between several days up to 6 weeks. A somewhat longer preoperative period allows for a 'window of opportunity' to optimally prepare patients. One aspect of optimal preparation includes identification of modifiable risk factors and, if present, tailored adjustment.

Risk scores

Many of the known risk factors, i.e. age and sex, are non-modifiable. Some of these are included in the so called colon leakage score (CLS) that was developed to define the risk of CAL.[16] The CLS is a list of factors derived from a systematic search that can be consulted prior to colorectal surgery. Unfortunately, it was just validated in one hospital and is restricted to left-sided colorectal resections. The prognostic colorectal leakage index (PROCOLE) was developed for the prediction of CAL of an individual. Validation was only performed in a small cohort.[17]

Both CLS and the PROCOLE scores only incorporate intraoperative parameters, precluding its use for preoperative counseling. In contrast, a score using preoperative parameters is possibly a more useful tool during preoperative counseling. In the absence of a method properly predicting operative risks during the preoperative phase, preoperative optimization that is tailored to the individual patients will remain a challenge.

Preoperative risk modification possible

A variety of risk factors that may be modified prior to surgery have been reported. Malnutrition, poor functional capacity, cigarette smoking, anemia and increased state of anxiety were all identified.[18–21] Prehabilitation programs are being developed to optimize these risk factors. The introduction of such a multimodal prehabilitation program is a logical step for improving the patient's preoperative condition. This promising approach was thought to decrease CAL rates, as many risk factors are related to patients' lifestyle.[21–23] From a physiological point of view and based on limited practical experience from small trials, it seems feasible to achieve clinically relevant effects with such a prehabilitation program during the four weeks' period between cancer diagnosis and surgery. However, feasibility of a multimodal program and its possible benefits on postoperative outcome have not been identified so far.

Uniform definitions are required

Generally accepted definitions of the nature of risk factors, complications and specifics of programs such as prehabilitation are crucial for the interpretation of success rates. Although some definitions on these issues were proposed,[24,25] no uniform definition exists for both prehabilitation and CAL in the clinical setting.[26] As a consequence, comparing study results and translating current knowledge into the clinical decision-making process is hazardous.

Several surveys aimed to reach consensus regarding the definition of CAL although most were restricted to a single country.[27] However, it must be appreciated that variation in leakage rates of Western and Asian research groups is large. For instance, CAL rates in Asian publications are substantially lower.[13,28–31] Such differences are possibly explained by variations in operation technique, tumor location and patient characteristics. However, little attention was paid to potential differences in the CAL definition and the available methods of diagnosis.[32,33]

Although CAL is defined by some as a defect in the bowel wall at the anastomotic site leading to communication of intra- and extra luminal compartments,[34] this definition does not translate well into the clinical situation. Therefore, many authors proposed new definitions or diagnostic criteria of both clinical and radiological features,25 and on the impact of a leak on the treatment plan. However, since the pathophysiology of anastomotic leakage is multifactorial, the manifestation of a clinical leak can be rather variable.[32] Furthermore, due to the increased use of (routine) diagnostics such as CT or contrast enema, 'radiological' leaks not influencing patient management are diagnosed quite often.[35] These issues hinder comparison of study results and weaken the reliability of further analyses. A mismatch between these different CAL rates in turn hampers the construction of evidence-based guidelines on patient management and surgical technique.

Intraoperative factors

Many intraoperative surgical risk factors for postoperative morbidity and mortality, and especially CAL, formed the subject of various research projects. For instance, the role of laparoscopy or of stapled anastomosis in right colonic resections, or the role of a diverting stoma in rectum resections likely influenced CAL rates.[36,37] However, the exact role of these findings is still under debate.

Non-surgical factors including anesthesiological techniques probably also contribute to the risk of CAL and other severe postoperative complications.[38] Recently, a multidisciplinary approach for surgical complication prevention is gaining interest. Following the introduction of basic principles such as perioperative antibiotic prophylaxis, omitting hair removal before surgery, maintaining perioperative normothermia and facilitating discipline in the operating room, surgical wound infection rates were reduced and possibly also CAL rates.[39] These observations warrant a close(r) collaboration between surgical and anesthesiological teams and supports the concept of a multimodal modifiable risk factors approach. Although other intraoperative variables such as operation time, blood loss and blood transfusion requirements have been widely accepted as risk factors, other intraoperative – and thus potentially modifiable and anesthesiological – risk factors are yet to be discovered.[38]

For instance, fluorescence-guided surgery may lower rates of CAL. Although no randomized controlled trials were hitherto published, indocyanine green fluorescence (ICG-FA) is a potential promising method for assessing perfusion at the site intended for anastomosis.[40] More research is needed to relate ICG-FA to a potential reduction of CAL. ICG-FA may also serve as a novel method to identify peritoneal metastasis and small lymph nodes.[41] The introduction of ICG-FA altered the original surgical plan in up to 29% of patients.[42]

Postoperative factors

The goal of the postoperative phase is to recover optimally prior to hospital discharge and to reach baseline (preoperative) functional status, needed to perform activities of daily living (ADL) independently, ideally within a few weeks. An optimal functional status may support patients to resume their lives as soon as possible, or to withstand additional treatments such as chemotherapy or surgery for metastasis. A Netherlands Cancer Registry (NCR) study showed that a late start of chemotherapy negatively influenced survival rates, possibly as a result of an impaired functional capacity.[43] A total of 11.000 stage 3 CRC patients (2008-2013) were analyzed, and a portion of 4.899 patients who were not treated with chemotherapy demonstrated a meagre 39% five-year survival rate. Conversely, five-year survival rate increased to 54% if chemotherapy started >12 weeks postoperatively, and to 76% if started within 6 weeks after operation. It is thought that an improved functional capacity may facilitate an earlier adjuvant chemotherapy start and finalization thus increasing survival. Interestingly, an optimal functional status is also closely correlated to the HRQoL in this patient population. [44,45] After the introduction of the ERAS program, hospital stay was limited to an average 3-4 days whereas recovery to baseline functional capacity was quicker.[46–49] Currently, almost 20 years after its first introduction, adherence to the different components of the ERAS program is unfortunately wearing off, thereby limiting its effect.[50] A revival of the ERAS protocol by adding the latest evidence and by improving and monitoring adherence may again enhance outcomes in colorectal surgery.

ERAS was not able to facilitate earlier detection of major complications such as CAL, which to date remains a major challenge. CAL due to technical failure will possibly probably occur within the first few days after surgery. CAL due to other reasons will become evident within 3-6 days post-surgery. A recent publication of the Dutch Snapshot Research group revealed a surprisingly higher incidence of 'late' anastomotic leakage than was previously expected (CAL >30 days: 20%, <30 days: 13.4%).[51] Consequences of CAL such as peritonitis and sepsis might be limited if treated promptly. Several studies trying to identify CAL at the earliest stage have met with limited success.[52–58] Imaging using radiological techniques has a disappointingly low sensitivity and a high rate of false negative conclusions.[35] An improved evidence-based algorithm is required for early detection of CAL.

AIMS OF THESIS

To optimize the perioperative stratagem in colorectal care.

Part I (Chapter 2, 3 and 4)

1. To identify relevant perioperative and modifiable risk factors of CAL in order to develop a clinical improvement program.
2. To determine the level of consensus on the definition of CAL among Dutch and Chinese colorectal surgeons.
3. To gain insight in the use of different components of definitions of CAL used in the literature, which will serve as the basis of a future Delphi-based proposal for a novel and widely accepted definition of CAL.

Part II (Chapter 5, 6 and 7)

1. To identify modifiable preoperative risk factors of CAL.
2. To investigate whether multimodal prehabilitation is valuable for improving patients' preoperative status.
3. To identify modifiable intraoperative risk factors of CAL allowing for recommendations aimed at improving the quality of care for colorectal patients.
4. To prospectively validate a previously developed risk assessment score termed colon leakage score (CLS).

Part III (Chapter 8 and 9)

1. To evaluate the existing literature on effectiveness of a (multimodal) prehabilitation program versus no prehabilitation (current care) for cancer patients undergoing colorectal surgery.
2. To investigate feasibility and safety of a multimodal prehabilitation program for colorectal cancer patients.

Part IV (Chapter 10, 11 and 12)

1. To determine the impact of multimodal prehabilitation on the patients' functional capacity and postoperative complications.
2. To elucidate the potential of exercise in patient optimization during (neo)adjuvant chemoradiation therapy.
3. To assess the current screening methods, evidence based content, implementation models and outcome measurements of prehabilitation.

OUTLINE OF THESIS

This present thesis covers 4 areas in colorectal cancer surgery including risk factors and the definition of colorectal anastomotic leakage, modifiable risk factors and risk assessment, the introduction of prehabilitation and future perspectives of prehabilitation.

Part I - Anastomotic leakage: risk factors and definitions

Identification of colorectal patients who are at risk for severe complications such as CAL is exceedingly important. In Chapter 2, matched analysis of colorectal patients with and without CAL was performed. Several perioperative modifiable risk factors were identified and integrated in a 12-month improvement program.

As clear consensus on definitions regarding CAL and specific complications in the global literature is lacking, a consensus assessment among Dutch and Chinese colorectal surgeons was initiated. Moreover, a systematic literature review on the definition of CAL was executed (Chapter 3 and 4). The review identified a lack of worldwide accepted definitions of both colon and rectal anastomotic leakage whereas consensus on CAL among Dutch and Chinese colorectal surgeons was absent.

Part II - Modifiable risk factors and risk assessment in colorectal surgery

Many risk factors of complications after colorectal surgery have been identified but most are not modifiable. Two studies were aimed at identifying modifiable preoperative (Chapter 5) and intraoperative (Chapter 6) risk factors. The risk of developing severe complications is related to the number of preoperatively modifiable risk factors. Surgeons and anesthesiologists should act together to challenge all potential perioperative risk factors.

The colon leakage score as an independent tool for preoperative CAL risk assessment was tested in our own hospital population (Chapter 7). The CLS was not predictive for CAL, neither for determining a clinically relevant cut off value to guide the decision making process nor for constructing a diverting stoma.

Part III - Improving colorectal outcome with prehabilitation

The preoperative phase of colorectal care may require optimization. A Cochrane review was initiated that was aimed at studying aspects of prehabilitation as a tool for enhancing patients' preoperative status thereby improving surgical outcome (Chapter 8). Limited studies on prehabilitation were found, although the concept seemed promising. The potential benefit of multimodal prehabilitation for colorectal patients was validated in a pilot study (Chapter 9). This 4-week program proved feasible, significantly increased patient satisfaction, improved functional capacity and facilitated faster recovery.

Part IV - Future perspectives of prehabilitation

An (inter)national collaboration may stimulate the development of a multimodal value-based healthcare approach in colorectal patients. In Chapter 10 the first multimodal prehabilitation program is described that is currently tested in an international randomized controlled trial (NTR5947).

Future initiatives on prehabilitation may focus on patients with the poorest functional status. Therefore, the possibilities of prehabilitation during (neo)adjuvant therapy was investigated in rectal cancer patients (Chapter 11). Exercise therapy may be beneficial for colorectal cancer patients during adjuvant treatment. However, the possible advantages of training during neoadjuvant treatment shall still be explored by prehabilitation trials.

Sharing expertise and protocols will optimize care for colorectal patients. In Chapter 12, a FIT4Surgery model (Facts, Integration and Tools) that is able to facilitate these changes for current prehabilitation initiatives in the Netherlands and abroad was introduced. Facts describes the need for triage and the evidence on different component that are considered essential in multimodal prehabilitation. 'Integration' presents outcomes of patients' questionnaires to assess the motivation of both patients and specialists, and 'Tools' describes the available outcome measures that may be used.

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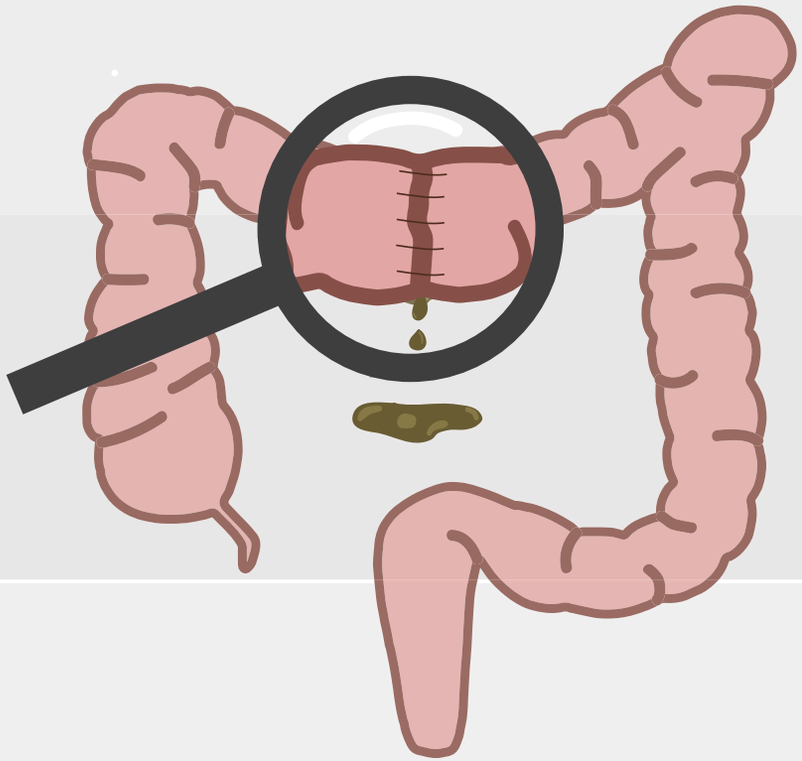
PART I

ANASTOMOTIC LEAKAGE: RISK CLASSIFICATION AND DEFINITIONS

Chapter 2 Perioperative modifiable risk factors for colorectal anastomotic leakage.
Submitted.

Chapter 3 Definition of colorectal anastomotic leakage: a consensus survey among Dutch and Chinese colorectal surgeons.
World J Gastroenterol 2017; 23 (33): 6172-6180.

Chapter 4 Use of colorectal anastomotic leakage definitions in literature: results of a systematic review.
Submitted.



CHAPTER 2

PERIOPERATIVE MODIFIABLE RISK FACTORS FOR COLORECTAL ANASTOMOTIC LEAKAGE

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Submitted.



ABSTRACT

Background

Colorectal surgery is still facing major complications, in up to 35% of patients. Colorectal anastomotic leakage (CAL) is the most feared outcome, with a reported incidence of 1.5-23%. This study was initiated to identify perioperative and potentially modifiable risk factors for CAL.

Methods

A retrospective matched patient cohort undergoing colorectal surgery with primary anastomosis was identified (2012-2014). Perioperative risk factors were analyzed (univariate analysis, odds ratio (OR) with 95%CI) and compared between patients with and without CAL (CAL+/CAL-). Multivariate logistic regression analysis was done to explore the combined effect of significant individual risk factors.

Results

Forty CAL+ patients were matched with 141 CAL- patients. Significant and (modifiable) risk factors for CAL were: BMI<20 or 30+, presence of comorbidity, presence of an epidural, antibiotics given in time, the amount of fluids administered, blood loss and blood transfusions given. A trend was seen for the number of pack years (>15). The length of hospital stay, complication and mortality rate, and comprehensive complication index, were significantly higher in patients with CAL. Expenditures increased on average € 26.375, - in case of CAL.

Conclusion

This study identified preoperative and intraoperative and potentially modifiable risk factors of CAL. Based on these findings, an improvement program will be developed and initiated in a Dutch teaching hospital.

Key words: colorectal anastomotic leakage, surgery, modifiable, perioperative, risk factors.

Introduction

Although surgery is the best option for cure of over 1.4 million colorectal cancer patients worldwide this treatment still faces major complications, in up to 35% of patients 1. Although in the last decades the perioperative care improved importantly (due to proper patient selection, minimally invasive operating techniques, the type of anastomosis, construction of a deviating stoma, improved anesthetic and analgesic approaches, and the introduction of the enhanced recovery after surgery [ERAS] program) 2–5, the postoperative morbidity and mortality rate remains high 6,7.

Colorectal anastomotic leakage (CAL) is the most feared complication7,8. CAL is directly associated with increased mortality (up to 40%) 9,10, decreased disease-specific survival, a lower health related quality of life (HRQoL), and an increased rate of cancer recurrence and health expenditure 7,8,11–17. Many attempts have been made to prevent the occurrence of CAL, however, the incidence remains stable and high (between 1.5 and 21% worldwide) 7,8. Since surgery is the cornerstone in treatment, serious attention to lower the number of CAL is still warranted.

Many (non)-modifiable risk factors related to CAL have been identified. To reduce the number of CAL improvements in all phases (preoperative, intraoperative and postoperative) of care are required. Moreover, it is logical to focus on modifiable risk factors to improve the status of the individual patient before surgery 18.

In the present study we compared patients with CAL with matched controls regarding various perioperative risk factors. The specific aim was to identify relevant preoperative and intraoperative modifiable risk factors for CAL. The outcome of this study might than be useful to subsequently develop an improvement program with the aim to lower the morbidity and mortality rate in colorectal surgery in a Dutch teaching hospital.

Methods

Patient data

Data of a cohort of patients undergoing elective colorectal surgery with primary anastomosis in Máxima Medical Center (MMC) between January, 2012 and December 2014, were analyzed. MMC is a 550-bed community and teaching hospital situated in the southern part of The Netherlands serving a population of approximately 200.000 inhabitants. In MMC, laparoscopic surgery is the standard operative technique for colon and rectum abnormalities. For colon surgery no bowel preparation was used. In rectal surgery bowel preparation was used without selective decontamination. Open surgery was performed in case of previous major abdominal surgery, or tumor growth into nearby organs (T4 tumors). In MMC, colorectal surgery is only done by certified gastrointestinal surgeons dedicated to this type of operations since 2006. For the present analysis we applied a retrospective matched case control design using data from electronic patient records.

Cases and controls

Cases were cohort patients with colorectal anastomotic leakage following elective colorectal surgery for benign or malign disease treated between 2012 (January) and 2014 (December). Although there is no uniform worldwide definition available for colon and rectal anastomotic leakage 19, we adhered to the gradation system as proposed by the International Study group of Rectal Cancer (ISREC) 20,21. All patients with CAL were first identified from treatment codes and were classified as grade C leakage (defined as leakage requiring relaparotomy). Patients whose leak was only detected on radiological examination and was not clinically relevant were not considered to have CAL. A CT scan with contrast enema was in the majority of cases used to detect CAL, unless clinical deterioration of the patient required immediate reoperation by decision of a dedicated colorectal surgeon. Routine contrast enema or radiodiagnostics were not performed after surgery.

Controls were cohort patients undergoing elective colorectal anastomotic surgery who did not develop CAL during the same study period. To each case we matched up to 4 random controls with the same age (range with a maximum of 10 years), sex, and type of surgery (right sided or left sided colorectal surgery). Where insufficient controls were available we relaxed the matching on operation side and if necessary further relaxed the matching on sex.

Data collection

Preoperative data accrual including characteristics such as age, sex, malignant disease (yes/no), TNM classification of malignant tumors, body mass index (BMI), malnutrition (SNAQ), diabetes mellitus (DM), comorbidity, American society of anesthesiologists (ASA) physical status classification, cigarette smoking, alcohol use, anemia, corticosteroid use and the use of neoadjuvant therapy (yes/no) were retrieved from electronic patient files and intraoperative registration data. Intraoperative data assessment included type of surgery, emergency surgery, laparoscopic or open surgery, conversion, administration and time of antibiotics, temperature, use of an epidural, total fluids administered, urine production, blood loss, blood transfusion, type of anastomosis (side to side, end to end, side to end), stapled or hand-sewn anastomosis, construction of a (diverting) stoma, and duration of surgery. These data were retrieved from electronic surgical and anesthesiological sources and operative notes. Postoperative characteristics as C-reactive protein at postoperative day 1, 3 and 5, colorectal anastomotic leakage, other postoperative complications as scored by Clavien Dindo 22, the comprehensive complication index (CCI) 23, length of hospital stay, and in hospital mortality were also tabulated.

Additionally to this primary outcome, we calculated the CCI for all patients. The CCI is a combined outcome measure reflecting morbidity and mortality. A CCI score above or equal to 20 is associated with clinically relevant morbidity 23,24.

Besides patient data, financial data was collected by the financial and control department of the hospital. Only in-hospital costs were considered for analysis. In hospital was defined as the day of hospital admission until the day of discharge including a 30 day follow up. Total expenditures included costs related to treatment at the nursing ward, intensive care stay, medium care stay, laboratory tests, outclinic visits, (radio)diagnostics, operating theatre, allowance medical specialists, and additional materials used for treatment.

Definitions

The patients' nutritional status was carefully determined by calculating the short nutritional assessment questionnaire (SNAQ) score. A SNAQ score higher than or equal to 3 was considered malnutrition. BMI was classified into two categories to address underweight, normal weight, and obesity: lower than 20 or higher or equal to 30, versus between 20 and 30. Comorbidity was defined as any previous (chronic) disease. Cigarette smoking (yes/no) was defined as patients who previously and/or currently smoked cigarettes or cigars, and was also expressed in number of pack years (number of years smoked with one pack of cigarettes a day). Alcohol use was categorized as more or less than three units daily. Anemia was defined as a preoperative hemoglobin level of 6 mmol/L or lower. Steroids were scored as the present use of corticosteroids excluding exhalers. Neoadjuvant chemoradiation therapy (yes or no). Colorectal surgery included right sided hemicolectomy, transversum resection, left sided hemicolectomy, sigmoid resection or low anterior rectal resection.

Statistical analysis

All analyses were done in SPSS version 22 (IBM IBM Corp., Armonk, NY, USA) and statistical significance was accepted at a two-sided p-value <0.05. The influence of preoperative and intraoperative characteristics as potential risk factors for CAL was expressed as odds ratios (OR) with 95% confidence intervals (95%CI) as calculated by conditional logistic regression analysis. This was done by using the Cox-regression functionality of SPSS including a time variable fixed at 1, the case indicator (i.e. CAL) as the event, the risk factor as the covariate and the case-control set indicator as the stratum. First, we estimated crude ORs for each potential risk factor by univariate analysis. Subsequently we performed a multivariate analysis to explore the combined effect of individual risk factors. In this analysis we included all variables that were associated with CAL in univariate analysis at a p-value of <0.05. In an additional multivariate analysis, we excluded variables that had a p-value >0.1 in the previous multivariate analysis.
To explore the effect of relaxation of matching criteria, we performed a sensitivity analysis limiting the study population to cases and controls that fulfilled the matching criteria.

We compared outcome parameters for patients with and without CAL. For the consequences of CAL we compared outcome parameters using the Mann Whitney-U test for continuous parameters and the Chi-square test for categorical parameters.

Results

181 patients were retrospectively analyzed. Forty CAL patients were found during the selected study period and were than matched with 141 patients without CAL. There were more male than female patients (60%), and 70% of patients were operated on laparoscopically. Patient characteristics were similar in both groups (table 1).

Significant and potentially modifiable preoperative risk factors for CAL were: BMI <20 or 30+ (OR 2.6; 95%CI 1.2-5.6), and the presence of any comorbidity (OR 3.1; 95%CI 1.3-7.1) (table 2). Neoadjuvant therapy in rectal surgery patients reduced the risk for CAL (OR 0.04; 95%CI 0.05-0.3). A significant trend was seen for the number of pack years (OR 2.1; 95%CI 0.9-4.8). Intraoperative modifiable risk factors were correct timing of administration of antibiotics within the limits of 15-60 minutes prior to incision (OR 0.3; 95%CI 0.1-0.8), the use of an epidural (OR 3.2; 95%CI 1.5-6.8), amount of fluids administered (OR 1.5; 95%CI 1.1-2.1), blood loss (OR 1.1; 95%CI 1-1.2) and blood transfusion (OR 10.5; 95%CI 2.8-38) (table 3). Neoadjuvant therapy and administration of antibiotics in time increased both the OR for severe complications in both univariate and multivariate analysis and thus appeared to be significant and independent variables (table 4).

The length of hospital stay, comprehensive complication index, complication rate and mortality rate were significantly higher for patients with CAL (table 5). 47% (CAL+ 100%, CAL- 40%, p<0.01) of the patients showed one or more postoperative complications (excluding CAL) as measured on the Clavien Dindo scale. The expenditures increased with a total of 26.375, - euro's (3 to 4-fold increase) when a patient suffered from CAL.

Discussion

Anastomotic leakage remains the most feared outcome after colorectal surgery. This study revealed several potentially modifiable risk factors of CAL, both preoperatively and intraoperatively. By challenging these modifiable risk factors, this may result in improved postoperative outcome and patient satisfaction, and may significantly reduce the health expenditures.

Colorectal anastomotic leakage remains a challenge. A new approach is required to lower its incidence. Since there are many risk factors known to be related to CAL, we may need a combined effort to target all these risk factors. We therefore specifically focused on risk factors that are potentially modifiable in the perioperative care setting. By the present analysis we observed some of them. Preoperatively, patients' BMI and comorbidity may be further examined to deliberate a change in patients' nutritional status or in the considered treatment. Neoadjuvant therapy in rectal surgery patients appeared to be not a negative factor for occurrence of CAL in this study. Prospective trials also suggest that neoadjuvant therapy does not influence CAL rates 25–29. Although smoking behavior, the number of pack years, ASA grade, diabetes mellitus, anemia and the use of corticosteroids have not shown significant relation to CAL in the present study, based on previous literature we may still conclude the importance to change these potential and modifiable risk factors 7,8,11,30,31.

Intraoperatively, the use of epidural anesthesia, amount of fluids administered, blood loss, and blood transfusion were observed to be risk factors for CAL. Also correct timing of administration of antibiotics appeared to increase the risk of CAL, while it is suggested to administer within the limit of 15-60 minutes prior to incision. Surprisingly, the conversion rate, emergency surgery, body temperature, and operation time did not reveal a significant increase in risk for CAL. This is contradictory to data of previous studies 11. Emergency surgery, conversion rate and operating time were all related to a poorer patient's status and difficulties during surgery 11,32–37. Normothermia is also recommended since its direct relationship to surgical side infections 38,39.

Postoperatively, early diagnosis of CAL might significantly reduce its clinical consequences in terms of morbidity and mortality. Unfortunately, clinical examination using the DULK score and performing a CT scan have been shown insufficient as early predictors of CAL 40,41. This study showed an increase in CRP levels and a significant difference in complication rate and CCI score for patients with CAL. Although baseline levels of CRP and leukocytes substantially rise due to surgical stress and abdominal infection, they are – unfortunately - neither specific for CAL.

There have been many improvements in perioperative care the last years. The introduction and full compliance to ERAS showed tremendous results in the postoperative outcome and recovery of patients 4,5,43–45. This improvement has been mainly due to the multimodal approach, facilitating a change in the total care plan of the patient. By adding latest evidence to this ERAS program, with a greater focus on the preoperative phase and its modifiable risk factors, we may again be able to reach a significant change in care for patients undergoing colorectal surgery 11,18,46. Moreover, we may be able to further reduce the expenditures, since in this study we found a 3 to 4-fold increase when a patient suffered from CAL.

Although this study included a relatively large number of CAL patients, it remains a retrospective and matched cohort study. Further research should focus on much larger cohorts, preferably in a multicenter and prospective setting. We therefore initiated a prospective multicenter cohort study: the LEAK CHECK, conducted by the Dutch Taskforce Anastomotic Leakage in over 20 hospitals in several countries 11. In this way we may be able to further specify the preoperative and intraoperative risk factors that are potentially modifiable.

This present study was initiated as part of a three-year program to give insight in a specific study population of patients undergoing colorectal surgery in a teaching hospital. Based on this patient data, a program was initiated to improve colorectal care. This twelve month improvement program included the following items: a protocol to improve the hemoglobin level preoperatively if lower than 7 mmol/l 18,30,47, improved temperature regulation 38,39, optimization of compliance to the ERAS program 44,48, optimal perioperative nutrition and fluid management 11,49, introduction of a smoke cessation program 50, enhanced postoperative mobilization 49, introduction of chewing gum and coffee on the ward 51–54, introduction of prehabilitation 18,55, and improved discharge logistics, and patient information. Currently, the results of the improvement program are being analyzed and compared to the data of this study that may serve as a historical control setting for our department.

Conclusion

This study identified preoperative and intraoperative potentially modifiable risk factors of CAL: BMI<20 or 30+, presence of comorbidity, presence of an epidural, antibiotics given in time, the amount of fluids administered, blood loss and blood transfusions given. Based on these findings, an improvement program will be developed and initiated in a Dutch teaching hospital.

Table 1. Various patient and treatment characteristics and anastomotic leakage in patients undergoing colorectal surgery with primary anastomosis.

	No CAL n = 141	CAL n = 40	OR (95%CI)
Age in years (range)	65 (25-90)	66 (19-87)	0.997 (0.95-1.04)
Male sex (%)	84 (60)	23 (58)	1.6 (0.41-6.2)
Benign disease[-] (%)	19 (14)	12 (30)	3.1 (1.2-7.7)*
TNM (%)^			
0	0	0	-
I	31 (21)	10 (32)	Reference
II	0	0	-
III	56 (40)	10 (25)	0.5 (0.2-1.5)
IV	36 (26)	7 (18)	0.1 (0-0.9)
Location[&] (%)			0.2 (0.1-0.7)*
Colon	102 (72)	37 (93)	
Rectum	39 (28)	3 (8)	
Laparoscopy[+] (%)	98 (70)	26 (65)	0.8 (0.4-1.8)

Legend 1. Median values with range or percentage. *Significant parameters (p<0.05). -Surgery for benign disease including inflammatory bowel disease (IBD), diverticulitis; ^TNM classification of malignant tumors; &rectum versus colon surgery; +laparoscopy versus open surgery.

Table 2. Preoperative modifiable risk factors for colorectal anastomotic leakage.

	No CAL n = 141 (%)	CAL n = 40 (%)	OR (95%CI)
BMI (%)[=] <20 or 30+ kg/m^2	23 (16)	14 (35)	2.6 (1.2-5.6)*
Malnutrition[0] (%)	34 (25)	8 (20)	0.74 (0.31-1.8)
Diabetes Mellitus^ (%)	14 (10)	4 (10)	1.06 (0.33-3.38)
Comorbidity[#]	69 (49)	29 (73)	3.1 (1.3-7.1)*
ASA grade[$]			1.4 (0.7-2.7)
I	31 (24)	8 (20)	Reference
II	85 (65)	26 (65)	1.3 (0.5-3.4)
III	14 (11)	5 (13)	1.4 (0.4-5.8)
IV	0	1 (3)	-
Cigarette smoking	37 (31)	8 (20)	1.4 (0.7-2.8)
Pack years >15[!]	25 (21)	14 (35)	2.1 (0.9-4.8)
Alcohol use**	7 (6)	0	-
Anemia***	29 (21)	11 (28)	1.4 (0.6-3.2)
Corticosteroids******	7 (5)	1 (3)	0.5 (0.06-4.1)
Neoadjuvant therapy[-]	57 (40)	1 (3)	0.04 (0.05-0.3)*

Legend 2. Median values with standard deviation (SD) or percentage. *Significant parameters (p<0.05). =BMI = Body Mass Index kg/m2; 0Malnutrition defined as SNAQ >= 3; ^type II diabetes mellitus (DM); #comorbidity as any previous (chronic) disease; $ASA = American Society of Anesthesiologists score; !number of years smoked with one pack of cigarettes a day; **alcohol use of more than three units a day; ***anemia hemoglobin level <6mmol/L; ****present use of oral corticosteroids excluding exhalers; -neoadjuvant therapy including chemoradiation, rectal surgery patients only.

Table 3. Intraoperative modifiable risk factors for colorectal anastomotic leakage.

	No CAL n = 141	CAL n = 40	OR (95%CI)
Emergency surgery (%)	11 (8)	3 (8)	1.1 (0.3-3.9)
Conversion[--] (%)	24 (17)	12 (30)	2.3 (0.996-5.2)
Antibiotics not in time (%)**	88 (62)	6 (15)	0.05 (0.01-0.2)*
Temperature <36°C[#] (%)	80 (57)	22 (55)	1 (0.5-2)
Epidural presence yes (%)	62 (44)	29 (73)	3.2 (1.5-6.8)*
Fluids administered* (range)**	2.5 (0.5-7)	2.9 (1-6.1)	1.5 (1.1-2.1)*
Urine production** mean (range)**	3 (0-17)	2 (0.3-8.5)	0.9 (0.8-1.1)
Blood loss[-] mean (range)	220 (0-2085)	441 (0-3000)	1.1 (1-1.2)*
Blood transfusion^ (%)	4 (3)	10 (25)	10.5 (2.8-38)*
Stoma[&] (%)	17 (12)	6 (15)	1.3 (0.5-3.8)
Stapled anastomosis[=] (%)	97 (69)	24 (60)	0.6 (0.3-1.4)
Surgery duration[)] (range)	145 (72-324)	147 (75-271)	1 (0.99-1.01)

Legend 3. Median values with (interquartile) range (25 and 75%) or percentage. *Significant parameters (p<0.05). --Laparoscopy converted to open surgery; **antibiotics administered within 15-60 minutes prior to start incision; #temperature lower than 36 degrees at the start of surgery; ***fluids administered in liters including NaCl, ringer's lactate, and glucose salt; ****urine production during surgery in L; -blood loss in ml; ^blood transfusion as administration of one or more packed cells containing 300ml of blood; &diverting ileostomy; =stapled anastomosis yes or no;)duration of surgery in minutes.

Table 4. Uni- and multivariate analyses of preoperative and intraoperative modifiable risk factors of colorectal anastomotic leakage.

	Crude OR (95%CI)[&]	Adjusted OR (95%CI)[&&]
Benign disease[)]	3.1 (1.2-7.7)*	0.3 (0.04-3.3)
Colon versus rectum	0.2 (0.1-0.7)*	0.4 (0.1-2.3)
BMI[=] <20 or 30+ kg/m^2	2.6 (1.2-5.6)*	3.3 (0.6-18)
Comorbidity[#]	3.1 (1.3-7.1)*	2.3 (0.4-12.5)
Pack years >15[!]	2.1 (0.9-4.8)	1 (0.2-5)
Neoadjuvant therapy[-]	0.04 (0.05-0.3)*	0.03 (0.001-0.7)*
Epidural presence yes	3.2 (1.5-6.8)*	2.1 (0.5-9)
Antibiotics not in time[$]	0.05 (0.01-0.2)*	0.02 (0.001-0.4)*
Fluids administered* **	1.5 (1.1-2.1)*	1.7 (0.7-4.3)
Blood loss[-]	1.1 (1-1.2)*	0.9 (0.7-1.2)
Blood transfusion^	10.5 (2.8-38)*	15.6 (0.5-519)

Legend 4. *Significant parameters (p<0.05). &Calculated by using univariate logistic regression analysis. &&Multiple logistic regression including all statistical significant variables from the univariate analysis.)Surgery for benign disease including inflammatory bowel disease (IBD), diverticulitis; =BMI = Body Mass Index kg/m2; #comorbidity as any previous (chronic) disease; !number of years smoked (>15) with one pack of cigarettes a day; -neoadjuvant therapy including chemoradiation, rectal surgery patients only; $antibiotics not administered within 15-60 minutes prior to start incision; ***fluids administered in liters including NaCl, ringer's lactate, and glucose salt; -blood loss in ml; ^blood transfusion as administration of one or more packed cells containing 300ml of blood.

Table 5. Postoperative recovery and various parameters of patients undergoing colorectal surgery with primary anastomosis.

	No CAL	CAL	P-value
	n = 141	n = 40	
CRP* (IQR)			
POD 1	65 (42-101)	92 (62-139)	<0.05
POD 3	136 (89-226)	244 (163-339)	<0.05
POD 5	131 (69-193)	210 (125-388)	<0.01
Complications^ (%)	56 (40)	40 (100)	<0.01
CCI[#] (range)	10.9 (18.1)	60.7 (21.5)	<0.01
Length of hospital stay[-] (range)	6 (5-11)	24 (13-43)	<0.01
Mortality (%)**	1 (1)	7 (18)	<0.01

Legend 5. Median values with (interquartile) range (25 and 75%) or percentage. Continuous parameters are compared using the Mann Whitney-U test. Categorical parameters are compared using the Chi-square test. *C-reactive protein (CRP) measured on postoperative day (POD) one, three and five; ^including any postoperative complications as measured by Clavien Dindo excluding CAL; #Comprehensive complication index (CCI) mean values with standard deviation; -length of hospital stay in days; **in hospital mortality.

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CHAPTER 3

DEFINITION OF COLORECTAL ANASTOMOTIC LEAKAGE: A CONSENSUS SURVEY AMONG DUTCH AND CHINESE COLORECTAL SURGEONS

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ABSTRACT

Aim

To determine the level of consensus on the definition of colorectal anastomotic leakage (CAL) among Dutch and Chinese colorectal surgeons.

Methods

Dutch and Chinese colorectal surgeons were asked to partake in an online questionnaire. Consensus in the online questionnaire was defined as > 80% agreement between respondents on various statements regarding a general definition of CAL, and regarding clinical and radiological diagnosis of the complication.

Results

Fifty-nine Dutch and 202 Chinese dedicated colorectal surgeons participated in the online survey. Consensus was found on only one of the proposed elements of a general definition of CAL in both countries: 'extravasation of contrast medium after rectal enema on CT scan'. Another two were found relevant according to Dutch surgeons: 'necrosis of the anastomosis found during reoperation', and 'a radiological collection with percutaneous drainage'. No consensus was found for all other proposed elements that may be included in a general definition.

Conclusion

There is no universally accepted definition of CAL in the Netherlands and China. Diagnosis of CAL based on clinical manifestations remains a point of discussion in both countries. Dutch surgeons are more likely to report 'subclinical' leaks as CAL, which partly explains the higher reported Dutch CAL rates.

Keywords: Colorectal anastomotic leakage, colorectal surgery, definition, complication.

Core tip: The present international online survey proves the inconsistent views as to what is considered colorectal anastomotic leakage among surgeons in the Netherlands and China, and shows large differences between the countries. This is in line with the current literature, since there is no uniformly accepted definition worldwide. We therefore propose to perform a systematic literature review to identify the available definitions. The final stage would be to perform a Delphi analysis within a representative panel of colorectal surgeons to develop a widely accepted definition of colorectal anastomotic leakage.

Introduction

Colorectal anastomotic leakage (CAL) remains gastrointestinal surgeons' most feared complication, despite important improvements in perioperative care and the development of novel surgical techniques. It is associated with high rates of morbidity and mortality[1,2], poor quality of life[3], and increased healthcare costs[4,5]. Since CAL influences the direct postoperative course and has recently been proven to impact oncological outcome as well[6-8], it is frequently used as an outcome measure in clinical studies. However, the CAL rates vary considerably in the international literature from 1.5% to 23%[9,10]. Large variations in leakage rates have been reported between studies published by Western and Asian research groups, in which the reported incidence of CAL in Asian publications is substantially lower[5,11-14]. Such differences can be partly explained by the variations of operation technique, tumor location, and patient characteristics[15,16]. However, little attention has been paid to potential differences in the CAL definition and the available methods of diagnosis.

Although CAL is sometimes defined as "a defect in the bowel wall at the anastomotic site, leading to communication of intra- and extraluminal compartments"[17], this definition translates rather difficult to the clinical situation. Therefore, many authors formulate new definitions or diagnostic criteria in their studies, which usually include clinical and radiological features[18], and the impact of a leak on the treatment plan. However, since the pathophysiology of anastomotic leakage is multifactorial, the manifestation of a clinical leak can be rather variable[15]. Furthermore, due to the increased use of (routine) diagnostics such as CT or contrast enema, "radiological" leaks that do not eventually influence patient management are diagnosed more often. These factors complicate comparison of study results, and weaken the reliability of further analyses. This in turn hampers the construction of evidence-based guidelines on patient management and surgical technique.

Clearly, there is a need for a generally accepted and practical definition for CAL and its diagnostic criteria to serve as a template for future research on CAL and the clinical decision-making process[19]. Several surveys have been performed to reach consensus regarding the definition of CAL, however, most of them were restricted to a single country[19]. We hypothesized that the aforementioned reported differences in incidence rates between Asian and Western countries can partly be explained by differences in the definitions and diagnostic methods used. The aim of this study was therefore to determine the level of consensus regarding different aspects of a general definition of CAL within and between populations of Chinese and Dutch colorectal surgeons, who can be considered good representatives of the East and West, respectively.

Materials and methods

An online survey was performed among colorectal surgeons from the Netherlands and China. In the Netherlands, the survey was constructed and run through an online database using SurveyMonkeyTM (Palo Alto, CA, USA). Colorectal surgeons in the Netherlands were identified from the contacts section of the colorectal subdivision of the Dutch Society of Gastro Intestinal Surgery (NVGIC): the Taskforce Coloproctology (WCP). Within this subdivision, 141 senior and junior colorectal surgeons were identified. Respondents were invited to partake in the online survey by email. Dutch surgeons completed the questionnaire between May and June 2015.

In China, the survey was conducted on the platform provided by DXY (www.dxy.cn), which is the largest medical website in China with more than one million registered medical users. An invitation was sent to all the registered colorectal surgeons to invite them to participate in a five-minute survey. Due to a relatively large number of registered users, the survey was designed to be terminated when 200 replies were received. Surgeons from Hong Kong, Macao, and Taiwan were not invited in this survey, because of the application of different medical systems in those areas. A demographic chart of the regions represented by the respondents can be observed in Figure 1.

The survey was divided into three major categories with questions addressing the general definition, and the clinical and radiological diagnosis of CAL. It was partly adapted from a previous study of Adams et al[20] and was initially constructed in English, and then translated to Dutch and Chinese by surgeons fluent in both English and Dutch and English and Chinese for the Dutch and Chinese versions, respectively, and checked for interpretation bias. Details of the English questionnaire are shown in Table 1 (See supplementary data for Dutch and Chinese versions).

Category I mainly focused on the agreement of general definitions used in the international literature[20]. Surgeons were asked to state whether ten different clinical situations should or should not be included in a general definition. Category II focused on clinical manifestations and their predictive value for CAL. A 10-point grading scale ranging from 1 (not predictive at all) to 10 (very predictive) was used to assess the agreement of the respondents' views on the clinical parameters. The parameters used were partially adapted from the Dutch Leakage Score (DULK)[11]. Category III consisted of four questions regarding the use of radiological examination and the influence of this diagnostic method on patient care. This third category was also partially adapted from Adams et al[20]. The last general question focused on surgeons' views regarding the cause of very early anastomotic leakage.

Definitions

Very early anastomotic leakage was defined as leakage occurring within the first 3 d post-surgery. Postoperative ileus was defined as an interval of more than 4 d from surgery until passage of flatus or stool and the tolerance of an oral diet[21]. Blind loop was defined as a bypassed loop of bowel after the construction of an end-to-end or end-to-side bowel anastomosis.

Statistical analysis

Basic descriptive statistics were used to summarize data for the online survey. Consensus was defined as > 80% agreement between respondents on various statements, as described by Duncan et al[22]. If less than 80% of respondents deemed the statements important, it was stated that no consensus was reached. Graphical depictions of information were used where appropriate to facilitate data interpretation. Chi square test or Mann-Whitney test were applied with proper indications. A P-value smaller than 0.05 was considered to indicate statistical significance.

Results

Of the 141 colorectal Dutch surgeons who were invited to partake in the online survey, 62 respondents accepted the invitation, and 59 completed the survey, resulting in a 42% response rate and 95% survey completion. In total, 100% of 201 questionnaires received from Chinese surgeons were completed. A demographic chart of the regions represented by the respondents can be observed in Figure 1, as it shows that this survey covers 96.8% (30/31, Hong Kong, Macao, Taiwan not included) of provinces and areas of China.

Consensus was found on only one clinical situation proposed as an element of a general definition in both countries: ‘extravasation of contrast on enema’ (Figure 2), and in the Netherlands on two additional elements: radiological collection for which percutaneous drainage was needed (50/59 respondents, 85%) and necrosis of the anastomosis visible upon reintervention (51/59 respondents, 86%). For all other items on the available general definitions, clinical and radiological diagnosis of CAL, no consensus was found. Scores were significantly different between China and the Netherlands for the following elements: radiological collection treated conservatively (21% vs w respectively, $P = 0.010$), necrosis of the blind loop on reintervention (41% vs 69%, respectively, $P \leq 0.001$), and air surrounding the anastomosis on CT scan (65% vs 44%, respectively, $P = 0.004$).

Grades given for the clinical parameters are shown in Figure 3 for both China and the Netherlands. Clinical deterioration, increased C-reactive protein (CRP), tachypnea, and tachycardia were seen as being most contributory for the clinical suspicion of CAL in the Netherlands, and were given a weighed score of 7.83, 7.45 7.13 and 7.13, respectively (Table 2). In China, clinical deterioration and abdominal pain other than wound pain were deemed most attributable for the suspicion of anastomotic leakage in the direct postoperative period, with scores of 6.67 and 6.61, respectively. Increased plasma concentration of CRP received the lowest score of all parameters in China (4.35), while in the Netherlands this was deemed more sensitive (7.45, $P < 0.001$). Upon categorization of the grades for the value of clinical parameters into different categories of the numeric scale: disagree (0-3), neutral (4-6) and agree (7-10), most surgeons from both countries (45%-59% of surgeons for each parameter) remained neutral towards the added value of specific clinical parameters during the postoperative course.

The data on radiodiagnostics are shown in Table 3. The majority of Chinese and Dutch surgeons perform radiodiagnostics upon clinical suspicion of a leak. The distribution of the answers over the different classifications, however, was significantly different between the two nationalities (Chi square test, $P = 0.020$). Expected false-negative rates for CT scans were equal for surgeons in both countries. A significantly larger portion of the Chinese

colorectal surgeons (25.4% vs 13.6%, P ≤ 0.001) would consider performing a reoperation for the suspicion of CAL without performing radiological diagnostics. The distribution of the scores differed significantly between countries as to in how many cases a reoperation is considered without previous radiodiagnostics (Chi square test, P = 0.002).

Concerning the question about early CAL, 90.6% of the Chinese surgeons agreed that the cause of such should be considered a technical failure, whilst only 70.4% of the Dutch colorectal surgeons agreed to this statement (P ≤ 0.001).

Discussion

Despite extensive research in the field of CAL, no international consensus regarding a practical definition exists, which limits the transparency and comparison of study outcomes. Several definitions of CAL have been proposed during the last decade[18,23], but review of the literature shows that newly published papers fail to adopt these definitions[24]. Instead, authors seem to prefer to use their own definitions or no definition at all[24]. It could be postulated that these previously proposed definitions were not yet implemented in clinical practice and (retrospective) research because of limited awareness of the existence of such a definition and/or lack of support from a large expert group.

Reports from Asian studies show CAL rates that are substantially lower than those reported by Western research groups[25]. This could partially be explained by demographic differences that exist in patient population, availability and use of diagnostic tools, or how perioperative care is structured. Another explanation could be that Chinese surgeons only report a leak as such in case a reintervention is required.

On the other hand, despite the lower prevalence of obesity in Asian countries, rates of type II diabetes mellitus and metabolic syndrome are relatively high due to ethnic and genetic factors. Indeed, Asians account for 60% of diabetes mellitus cases worldwide[26], which is considered an important risk factor for CAL[27,28]. Furthermore, the most common location of colorectal tumors in the Asian population is the left hemicolon[16,29], compared to the Western population, in which the predominant side is the right[29,30]. The literature shows a significantly higher CAL risk for surgeries on colorectal tumors located in the left hemicolon[31]. These regional differences therefore fail to completely explain the variation in reported CAL rates. It is very likely that important regional differences exist as to what is considered an anastomotic leak, i.e., Asian surgeons may report a leak mostly when a reintervention is required, while the Western surgeons may report latent leaks. In order to gain more insight into these differences in views, the present survey was conducted both in China and in the Netherlands, countries that are considered to be representative for their continent.

In the first part of the survey, surgeons were asked whether different statements including clinical and radiological signs and interventions regarding CAL should be considered anastomotic leakage. Of ten statements, only one was deemed as CAL by more than 80% of respondents in both countries: ‘Extravasation of contrast after rectal enema visible on CT scan’. This is generally considered a radiological hallmark sign for anastomotic leakage after left-sided colorectal surgery and should naturally be included in a general definition. Moreover, other important and evident CAL signs including “Radiological collection around the anastomosis treated

with percutaneous drainage" and "Necrosis of the anastomosis seen at reoperation" received more than 80% positive responses in the Netherlands, however, not in China, and thus were not considered as consent according to the predetermined criteria. Despite this, the majority of the Chinese surgeons also agreed on these items and their answers did not differ significantly from those of their Dutch colleagues. In conclusion, it seems that for the evident signs of CAL, the majority of surgeons from both countries have quite similar views.

"Radiological collection treated conservatively" was only considered to be CAL in 21% of the Chinese surgeons (versus 39% in the Netherlands), which is almost a consensus of NOT including this statement in a general definition of CAL. On the contrary, it is at least remarkable that in current grading systems, a radiological collection can be considered anastomotic leakage. As such this is reported as a grade A CAL according to the International Study group of Rectal Cancer (ISREC)[18] and grade I-II CAL according the Clavien-Dindo Scale.

Despite the fact that only a minority of Dutch surgeons consider conservatively treated radiological collections as CAL, these numbers are higher than those among the Chinese. These differences in views regarding the subclinical signs of CAL may eventually lead to a significantly higher reported CAL rate in the Dutch studies than the Chinese ones. However, considering the fact that more than 30%[32] of the CAL do not require invasive intervention, the treatment provided by surgeons from both countries may eventually be similar, i.e., leading to a similar intervention rate for the complication. To rule out the reporting difference in this regard, one solution is to report complications with a Clavien-Dindo score higher than IIIa, which actually is also commonly accepted and applied in recent studies.

The second part of the survey focused mainly on clinical markers and parameters for CAL. Early clinical diagnosis of CAL remains a challenge for surgeons worldwide. Many clinical symptoms and biomarkers have been suggested as early signs of CAL[33-36]. However, previous studies of these parameters have shown that almost none of these parameters yield sufficient diagnostic accuracy to allow for a confirmative diagnosis[37]. This explains our findings that most surgeons do not base their diagnosis of CAL on these parameters, which results in a relatively low score of their contribution to the suspicion of CAL. Surgeons from both countries deemed 'deterioration of clinical condition' as an important symptom of CAL, which further accentuates the complexity of CAL diagnosis based on its clinical manifestations. We believe the surgeons' opinions indeed reflect the unsatisfactory status of CAL diagnosis, which stresses the need for further research in this field[38]. However, important differences exist between the two countries. Although surgeons from both countries agreed about the predictive value of higher temperature, abdominal pain other than wound pain, and increased leukocyte count, more than half of the clinical parameters scored significantly lower in China than in the Netherlands. Although these abnormal clinical manifestations are indeed very common after gastrointestinal surgery[39], it seems that they are considered less suggestive by the Chinese surgeons.

The third part of the survey focused on radiological tools used in the diagnosis of CAL. Based on the present data, the majority of the surgeons in both countries would perform radiological examination on patients in whom CAL was suspected (these numbers are slightly higher in the Netherlands), and more than half of the treatment plans would be changed after the imaging. In this regard, although differences have been found in the views of Chinese and Dutch surgeons regarding the definition of CAL, the treatment they provide is similar. However, our data also show that surgeons from both countries do not blindly rely on the results from radiodiagnostics. Instead, they state that in approximately 30% of the cases in which CAL is suspected, CAL is eventually diagnosed in spite of a negative radiological report. This correlates with previously reported false negative rates of CT scans[40]. Experience with inaccurate CT scan reports may be a reason for surgeons to consider reoperation without affirmative CT results, which according to the data, occurs in about 25% of cases.

Further research and education may facilitate the achievement of international consensus. However, definition without considerations of the practical issues in different regions is unlikely to gain sufficient popularity. In 2010, the ISREC proposed a graded system for the diagnosis and treatment of CAL[18]. Grade A CAL refers to anastomotic leakage for which no active therapeutic intervention is required. It seems that this grade correlates with the second statement "Radiological collection surrounding the anastomosis treated conservatively" that is not classified as CAL according to the majority of both Dutch and Chinese surgeons. This discrepancy between an established definition and the views of colorectal surgeons could partly explain why the ISREC definition has not been adopted in practice and science. In accordance with that, our survey clearly demonstrates how different practices may influence surgeons' opinion.

For example, in the Netherlands the Enhanced Recovery After Surgery (ERAS) program has been widely adopted for years, and recommends no abdominal drainage after surgery. In China, on the contrary, ERAS is less commonly implemented, and an intra-abdominal drain is often left in situ for longer period after surgery. Moreover, CT imaging is less commonly used for radiodiagnostics of CAL, and laboratory analysis by means of CRP is not yet implemented in routine practice in many rural areas. This could explain why increased CRP was deemed least contributory in the diagnostic process in the present survey. These points, though small, significantly influenced

the results, and would certainly influence the applicability of a proposed CAL definition.

To embed a successful definition in clinical practice, research on CAL would greatly benefit from establishing a uniform definition and recording in national databases. We will therefore continue to perform an extensive and systematic literature review. The results from that review and the consensus assessment described in this paper will lead to an international Delphi analysis that will allow us to reach consensus on a new definition proposal that will be supported by a large panel of experts. We sincerely welcome others to participate in this further research, in order to formulate a new definition based on joint experience and opinions.

The most important limitations of the study are the following. The content of questionnaires is always susceptible to researcher imposition and there may be a level of subjectivity in the answers given. Furthermore, the relatively low numbers of respondents from both countries would have a negative influence of the generalizability of study results. Finally, the original questionnaire was constructed in English and translated into Dutch and Chinese, which could introduce bias and weaken the validity of comparisons between the countries. Finally, as some of the clinical parameters used in the questionnaire were derived from the DULK-score, which was constructed and validated in the Netherlands, it is plausible that the Dutch participants scored similarly on these items because they were familiar with the content of the DULK-score, or because they have been (in)directly involved in the construction of the scoring system. However, the use of the DULK-score has not remained limited to the Netherlands, and it is unknown whether the subset of Dutch surgeons familiar with the DULK-score is higher than the number of Chinese surgeons who use this score routinely, and whether this difference is large enough to alter the data significantly.

In conclusion, no international consensus of a practical definition of CAL is yet available, which limits the transparency and comparison of published results. The present international online survey proves the inconsistent views as to what is considered CAL among surgeons in the Netherlands and China, and shows large differences between countries. Dutch surgeons are more likely to report 'subclinical' leaks as CAL, which partly explains the higher reported Dutch CAL rates. Surgeons from both countries rely on radiological diagnostics and laboratory parameters in the decision-making process, but are well aware of the limitations of these diagnostic aids. A Delphi analysis within a representative panel of colorectal surgeons is desired to develop a widely accepted definition of CAL.

Acknowledgements

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Comments

Background

Colorectal anastomotic leakage (CAL) is the most feared complication after colorectal surgery. No international consensus exists regarding a general definition of CAL.

Research frontiers

Over the past decades, thousands of articles on CAL have been published. Unfortunately, a uniform and accepted worldwide definition of CAL is not available. This limits the transparency and comparison of study results and usefulness in clinical practice.

Innovations and breakthroughs

An international survey has been performed to identify the differences in reported definitions of CAL and to evaluate the opinions of expert leaders in both a Western and Eastern country.

Applications

The present international online survey proves the inconsistent views as to what is considered CAL among surgeons in the Netherlands and China, and shows large differences between the countries. This is in line with the current literature, since there is no uniform accepted definition worldwide. We therefore propose to perform a systematic literature review to identify the available definitions. The final stage is to perform a Delphi analysis within a representative panel of colorectal surgeons to develop a widely accepted definition of CAL.

Terminology

CAL is the major complication after colorectal surgery with a stable incidence (1.5%-23%). It is associated with high rates of morbidity and

mortality, poor quality of life, and increased health expenditure. Since CAL influences the direct postoperative course and has recently been proven to impact oncological outcome as well, it is frequently used as an outcome measure in clinical studies.

Peer-review

In this study, the authors have presented a thorough and critical analysis of the availability of a definition of CAL and the opinions of both Dutch and Chinese surgeons regarding this definition.

Figure 1. Demographic chart of the Chinese regions this survey covers.

The gray scale reflects the number of participants in each region, varying from 21 from Zhejiang to 1 from Hainan. Correlating with the number of colorectal surgeons in each region, more surgeons from the east regions participated in this survey. Tibet and Ningxia had no participants, which also corresponds to the fact that the number of surgeons is very limited compared to the east provinces. Due to the application of different medical systems, doctors from Hong Kong, Macao, and Taiwan were not invited in this survey.

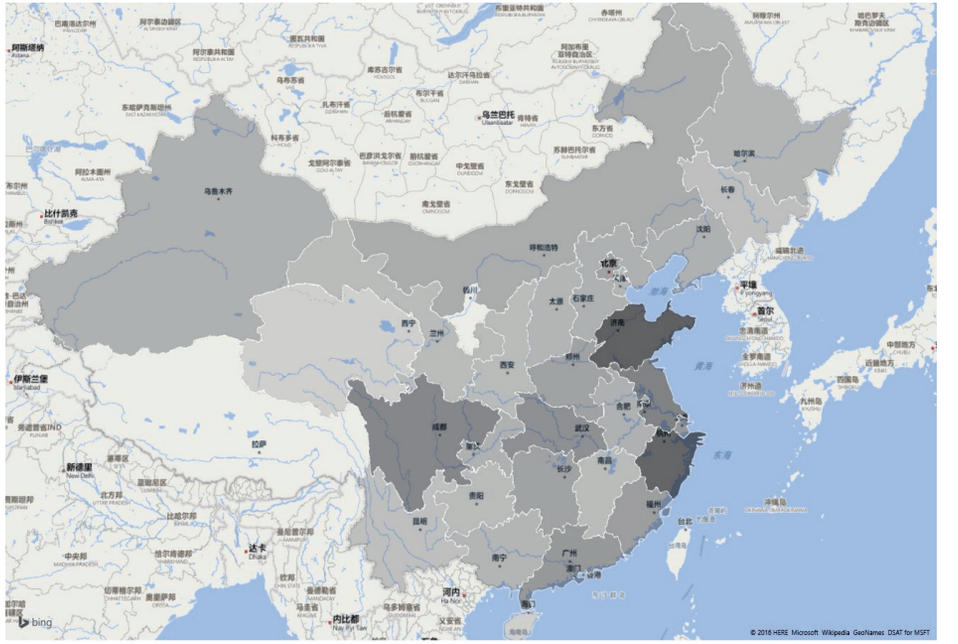


Figure 2. Percentage of respondents in agreement to general definitions of colorectal anastomotic leakage in the Netherlands (white bars) and China (dark grey bars). The dotted line indicates the 80% consensus threshold for the different statements. An asterisk indicates a significant (P < 0.05) difference between percentages of agreement of Dutch and Chinese surgeons.

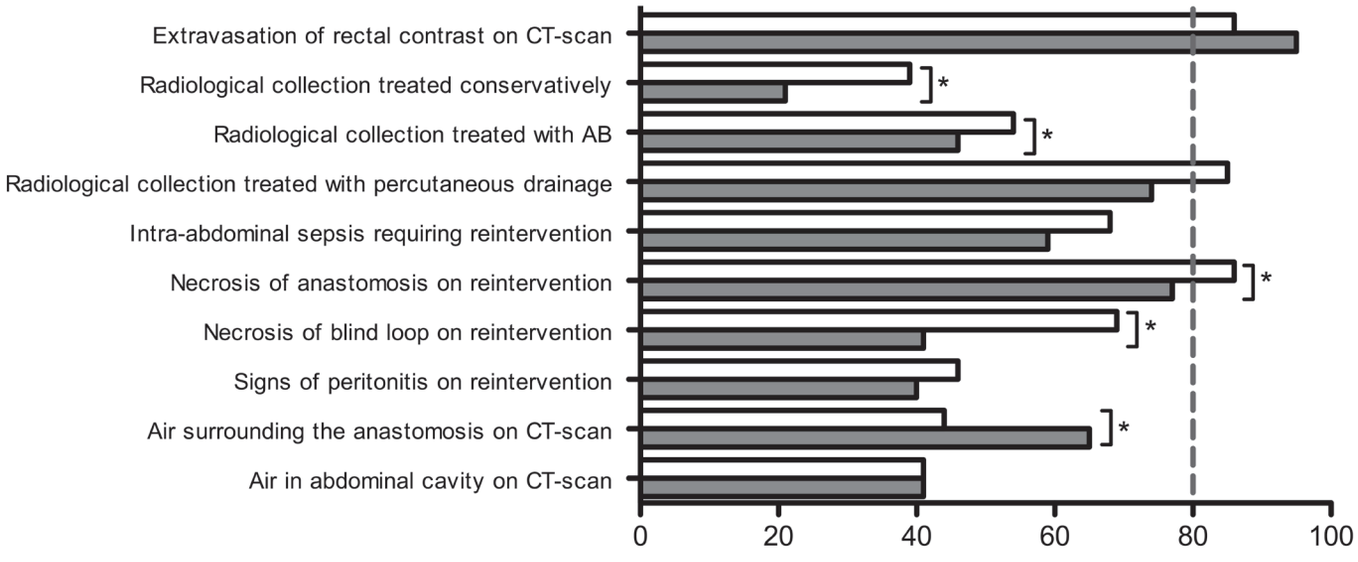


Figure 3. Distribution of categorized scores for the value clinical parameters in the direct postoperative phase. Comparison between the Netherlands (A) and China (B). Scores are divided into three categories: numeric scales ranging from 0-3 are depicted in grey (disagree), 4-6 depicted in black (neutral), and numeric scales ranging from 7-10 (agree) in white.

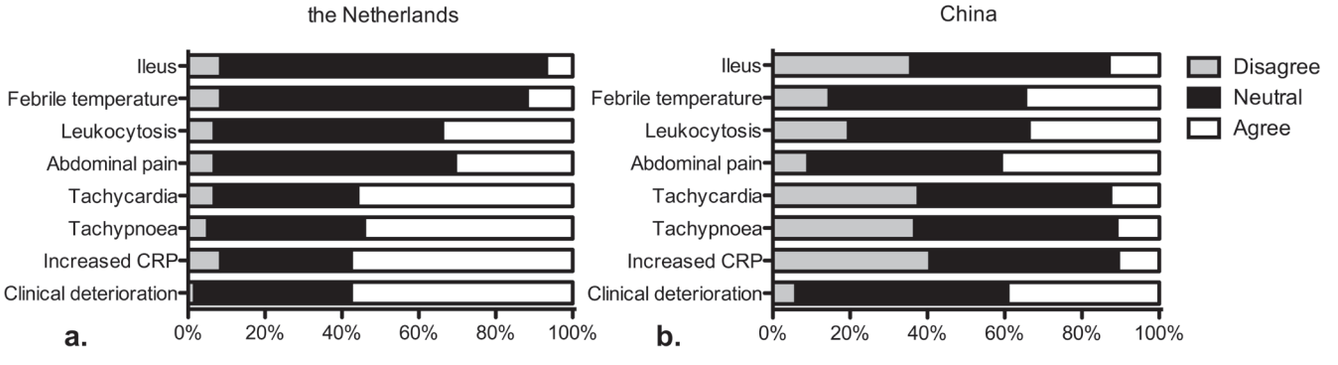


Table 1. English questionnaire on definition of colorectal anastomotic leakage.

General definition

Do we have to consider the following findings as anastomotic leakage?	Yes	No
1 Extravasation of contrast after rectal enema on a CT scan		
2 Radiological collection around the anastomosis and no treatment		
3 Radiological collection around the anastomosis treated with antibiotics		
4 Radiological collection around the anastomosis treated with percutaneous drainage		
5 Abdominal sepsis and reoperation needed		
6 Necrosis of the anastomosis seen at reoperation		
7 Necrosis of the blind loop seen at reoperation		
8 Signs of peritonitis during reoperation		
9 Air bubbles around the anastomosis seen on a CT scan		
10 Free intra-abdominal air seen on a CT scan		

Clinical diagnosis

In what extent do the following clinical parameters contribute to the suspicion of colorectal anastomotic leakage? Please note the relevance on a numeric scale of 0-10:

1	Increased C-reactive protein
2	Increased leukocytes
3	Tachycardia
4	Increased respiratory rate
5	(Sub-) febrile temperature
6	Postoperative ileus (>4 d)
7	Deterioration in clinical condition
8	Abdominal pain, other than wound pain

Radiological diagnosis

Answer the following questions using percentages
(0% = never, 100% = always)

1	In how many percent of patients with clinical suspicion of anastomotic leakage do you perform radiodiagnostics?
2	In how many percent of patients with clinical suspicion of anastomotic leakage do radiodiagnostics change your treatment policy?
3	In how many cases did the CT scan report no anastomotic leakage while there finally was an anastomotic leakage.
4	In how many percent of cases do you consider a reoperation without previous radiodiagnostics?

Early anastomotic leakage

In your opinion, is 'very early (<3 d) anastomotic leakage the result of technical failure?

1	Yes
2	No

Table 2. Sensitivity scores of clinical parameters for the suspicion of anastomotic leakage in the direct postoperative period in China and The Netherlands.

	China	The Netherlands	P-value
Clinical parameter	**Score ± SD**	**Score ± SD**	
Increased CRP*	4.35 ± 2.466	7.45 ± 1.871	<0.001
Leukocytosis	5.96 ± 2.596	6.53 ± 1.824	0.095
Tachycardia	4.55 ± 2.411	7.13 ± 1.937	<0.001
Tachypnea	4.46 ± 2.244	7.13 ± 1.937	<0.001
Febrile temperature	6.23 ± 2.281	5.86 ± 1.963	0.207
Postoperative ileus	4.47 ± 2.363	5.76 ± 1.679	<0.001
Clinical deterioration	6.67 ± 2.033	7.83 ± 1.205	<0.001
Abdominal pain	6.61 ± 2.247	6.74 ± 1.835	0.659

*CRP: C-Reactive Protein.

Table 3. Surgeons' opinion regarding the value of radiodiagnostics in the diagnosis of colorectal anastomotic leakage.

	China (%)	The Netherlands (%)	*P*-value
In how many percent of patients with clinical suspicion of anastomotic leakage do you perform radiodiagnostics?			
Responders, *n* (%)	202 (100)	55 (93)	
0%-20%	3.0	0	
21%-40%	6.4	0	
41%-60%	6.9	1.8	
61%-80%	24.3	16.4	
81%-100%	59.4	81.8	
Average	83.3	91.5	0.285
In how many percent of patients with clinical suspicion of anastomotic leakage do radiodiagnostics change your treatment policy?			
Responders, *n* (%)	202 (100)	54 (91.5)	
0%-20%	10.9	13.0	
21%-40%	9.9	5.6	
41%-60%	27.7	44.4	
61%-80%	30.2	25.9	
81%-100%	26.7	11.1	
Average	63.6	55.9	0.028
In how many cases did the CT scan report no anastomotic leakage while there finally was an anastomotic leakage?			
Responders, *n* (%)	202 (100)	52 (88.1)	
0%-20%	40.6	51.9	
21%-40%	29.2	28.8	
41%-60%	25.2	15.4	
61%-80%	4.0	1.9	
81%-100%	1.0	1.9	
Average	31.8	28.7	0.221

In how many percent of cases do you consider a reoperation without previous radiodiagnostics?			
Responders, *n* (%)	202 (100)	53 (89.8)	
0%-20%	58.4	84.9	
21%-40%	18.8	13.2	
41%-60%	17.3	0	
61%-80%	4.5	0	
81%-100%	1.0	1.9	
Average	25.4	13.6	< 0.001

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CHAPTER 4

USE OF COLORECTAL ANASTOMOTIC LEAKAGE DEFINITIONS IN LITERATURE: RESULTS OF A SYSTEMATIC REVIEW AND RECOMMENDATIONS FOR FUTURE REPORTING

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ABSTRACT

Background

Anastomotic leakage is the most feared complication following colorectal surgery, but a common definition is still lacking. This complicates comparison of study outcomes and quality of care between hospitals. The aim of this study was to gain insight in the use of different definitions in the literature.

Methods

A systematic literature search was performed in different biomedical databases, and a total of 361 manuscripts containing a definition on colorectal anastomotic leakage (CAL) were used for further analyses. Definitions were clustered based on the description of clinical and radiological signs and the consequences of a leak, forming a total of 11 categories.

Results

A vast number (73,9%) of papers published on this subject did not include a definition of CAL. Leakage rates vary strongly between rectal and colon anastomoses (7,48 and 5,32%, respectively) and with the type of definition used. Nineteen percent of authors used a grading system to illustrate the severity of the anastomotic leaks. Reporting of data regarding the operative procedure and the postoperative period varied substantially between studies.

Conclusion

The present review shows a lack of a commonly used definition of colorectal anastomotic leakage. This systematic review provides inisght in the different components of definitions that might serve as the basis of a Delphi-based proposal for a novel definition. The authors believe that implementation of a graded system with treatment recommendations will enhance unifromity of patient care and may lead to decreased treatment delay.

Introduction

Colorectal anastomotic leakage (CAL) remains the most feared complication after colorectal surgery with a reported incidence of 1.5-23%[1, 2]. CAL substantially adds to the morbidity and mortality rates and thereby decreases patients' health-related quality of life (HRQoL)[3-7]. Compared to a normal postoperative course, the high number of reoperations and the associated increased length of hospital stay lead to a fivefold increase in expenditures on health care[8]. Furthermore, evidence arises from recent literature that CAL impacts the oncological prognosis, leading to an increased local recurrence and a decreased disease-specific survival[9, 10]. Despite the large number of experimental and clinical studies conducted on this subject, and although CAL is commonly used as an outcome measure in these reports, no consistent definition of CAL is applied in literature[11].

General definitions such as 'a defect of the intestinal wall at the anastomotic site leading to a communication between the intra and extra luminal compartments'[12] or 'the leak of luminal content from a surgical joining between 2 hollow viscera'[13] can be applied in case the leak is evident. However, this definition is more difficult to apply when a patient presents with atypical symptoms, which is often the case[14]. Due to the lack of a generally accepted definition of CAL, reported leakage rates vary significantly, which complicates comparison of study outcomes and comparison of quality of care in individual institutions. The use of (inter)national registration systems could potentially yield very large patient populations for database studies, and would therefore positively influence the impact of the presented results. However, the application of these registration systems for scientific research is also limited because of the aforementioned issues. Reinke et al. evaluated the ability of two different registration systems, an administrative and a clinical registry, to identify anastomotic leaks, and found that both types of databases had acceptable specificity but poor sensitivity for diagnosis of CAL[15]. There is an obvious need for an internationally accepted definition for both colon and rectal anastomotic leakage that will serve as a template for future research and to improve clinical decision-making.

Several definitions have been proposed in the past decades[11, 16]. However, none of the suggested definitions functions as leading in current literature. We believe that this lack of acceptance is mainly due to the lack of an expert panel supporting the construction of these definitions. Our research team performed a consensus assessment among Dutch and Chinese colorectal surgeons and concluded there was no national or international consensus on what should comprise a general definition of CAL[17]. The aim of the present systematic review is therefore to gain insight in the use of different components of definitions used in the literature, which will serve as the basis of a future Delphi-based proposal for a novel and widely accepted definition of CAL.

Materials & Methods

An extensive systematic literature search in the biomedical databases of Medline and Embase was performed in January 2016 in accordance with the guidelines as presented in the PRISMA statement. All retrospective and prospective papers discussing colorectal surgery with the construction of an anastomosis, published between January 1990 and January 2016, in which anastomotic leakage was a primary or secondary outcome measure, were reviewed for the presence of a definition of CAL and/or details of clinical or radiological assessment. No restrictions were placed on the type of surgery or the indication of surgical resection (i.e., malignant or benign disease). The following papers were excluded from review: reviews, meta-analyses, articles discussing upper GI-surgery and animal studies. The search included normal search terms and MeSH-terms on anastomosis: colorectal anastomotic leak, anastomotic leakage, dehiscence, and anastomotic failure. Definitions that were found were assessed for the presence of clinical and radiological diagnostic methods, grading systems and the clinical usability of the definition. The definitions were clustered based on the description of clinical and radiological signs and the consequences of a leak (i.e. whether radiological or surgical intervention was required) as part of the definition, forming a total of 11 categories (table 1). Two researchers (AJ and SvR) conducted the selection process, and a third researcher (VS) was consulted in case of disagreement on the inclusion or exclusion of papers. A complete list of the included papers in this review can be found in the supplementary data (see table 1, supplementary data). A two-sample test for proportions was used to calculate the difference in CAL rates between colon and rectal anastomoses.

Results

A total of 2938 abstracts and 1382 full-text articles were reviewed for the presence of a definition of colorectal anastomotic leakage and/or a description of clinical and radiological signs used for the diagnosis of CAL. 1021 papers were excluded from analysis as they did not contain a definition of CAL. 361 papers met the inclusion criteria and were further used for data analysis. A total of 344 papers were used for the calculation of reported incidence rates, after the exclusion of papers using the same study population, protocol papers and manuscripts using matched cohorts. See figure 1 for the flow diagram of the inclusion process. Figure 2 renders all included peer reviewed papers published between 1990 and 2015 on colorectal anastomotic leakage with and without the description of a definition. It shows that although CAL was the primary outcome in these studies, a vast number of publications did not include a definition for CAL. A total of 30 randomized controlled trials, 165 prospective studies and 152 retrospective studies were included. The following data were extracted from the included articles: study type, surgical procedure or intervention, definition of CAL, reported leakage rates for colon and/or rectal anastomoses, median days postoperative of diagnosis of CAL, means of assessment of anastomotic integrity during surgery, number and percentages of deviating ostomies, and finally the description of clinical symptoms associated with CAL (e.g. fever, abdominal pain, leukocytosis). In order to clarify the differences between the identified definitions, they were then subclassified into 11 categories, based on combinations of the presence or absence of several components of the definition: clinical symptoms, radiological signs and/or findings during reintervention. The categories listed in table 1 can be appreciated to increase in completeness, varying from, category 1, which consists of reports that only include clinical symptoms in their definition of CAL, to category 8, which includes all possible aspects of a presentation of CAL. The papers included in category 9 only deemed the CAL that was observed during reoperation to be proven, papers referring to the ISREC classification were clustered in category 10, whereas category 11 contains definitions that did not fit any of the aforementioned descriptions. See table 1 for examples of the categorized definitions and the mean reported incidence rates of CAL associated with their classification. It can clearly be appreciated that these leakage rates vary strongly with the type of definition used for the diagnosis of CAL (leakage rates for rectal anastomoses varying between 2,4 and 12,3% for categories 9 and 11, respectively, and colonic leakage rates between 4,4 and 6,6% for categories 1 and 4, respectively).

Signs and symptoms

A total of 238 papers (65,9%) reported clinical signs and symptoms associated with colorectal anastomotic leakage, either as part of the formulated definition, or in the description of the method of diagnosis. The most commonly described clinical signs and symptoms were as follows: purulent or fecal discharge from drain, peritonitis, fever, purulent discharge from the rectum and abdominal pain (table 2).

Grading systems

A small proportion of authors (69 out of 361 papers, 19%) explicitly stated the use of a grading system when formulating a definition (table 3). The authors of 15 papers referred to the International Study group of REctal Cancer (ISREC)-classification [38-44, 36, 45-49], whereas 11 authors used the Clavien Dindo classification[22, 33, 50-58]. The grading systems used in literature were further clarified in table 3, and mainly divided the clinical cases based on clinical presentation, means of diagnosis or the resulting management of the complication.

Colon versus rectum

A comparison was made between leakage rates of rectal versus colon anastomoses, which showed that the rectal anastomoses were at significantly higher risk of developing a leak (7,48% vs. 5,32%, Odds Ratio: 0,71 (95%CI: 0,693 – 0,736), Z = -21,72, p-value = <0.001). Only papers providing separate numbers for colonic and/or rectal anastomotic leakage were taken into account for this analysis (n=84 for colonic CAL, n=223 for rectal CAL). Comparison of the reported rates of CAL in both anatomical regions further showed that the incidence rates have remained stable over the past decades (fig. 3).

Uniformity in data reporting

Information that had been taken into account in this review also included specific information regarding the operative procedure and the period directly following surgery. The median time to diagnosis of CAL was only sparsely described in the investigated papers: a total of 56 papers (15,5%) reported a mean or median interval to CAL diagnosis, ranging from 3,5 to 43 days. Furthermore, standard testing of the integrity of the primary

anastomosis was underreported in most papers: only 71 authors (20%) reported data on standard intraoperative testing with e.g. insufflated air or water, contrast enema, donut assessment, palpation of the anastomosis or flexible sigmoidoscopy. The information regarding the construction of a deviating ostomy was described much better in the included papers: a total of 241 papers (66,8%) reported on the number of cases in which a deviating ostomy was created during the index surgery, however, hardly any papers reported whether these consisted of colostomies or ileostomies.

Discussion

The present literature review shows that there is no commonly used definition of both colon and rectal anastomotic leakage available. The numbers of papers published on this subject have increased tremendously over the past years. Surprisingly, our study showed that more than half of these papers do not report on what is considered CAL, despite the fact that CAL was their primary outcome measure. Another important finding of this study was the large variety of definitions used, which also impacted reported CAL rates between categorized definitions. This systematic review provides insight in the different components of definitions used that might serve as the basis of a future Delphi-based proposal for a novel definition that will be used by clinicians and researchers worldwide.

Several definitions of CAL have been proposed in the past, ranging from a theoretical to an extensive clinical description, and definitions including grading systems to differentiate between stages of clinical severity and their impact on treatment [97, 98]. The Dutch Surgical Colorectal Audit, a registration database for colorectal surgery patients, described CAL as a leakage of bowel content or abscess formation near the anastomosis for which a relaparotomy and/or radiologic drainage was conducted[99]. Descriptions in all reviewed papers are in some way similar and mostly describe the general entity of CAL. However, as the clinical presentation of this specific complication can differ significantly with regards to severity, such a general definition of CAL is limited in its clinical usability and comparison of data.

The international study group of rectal cancer (ISREC) introduced a grading system in which the clinical impact of rectal anastomotic leakage is included[97, 100, 101]. Grade A severity indicates no change in patient management, whereas grade B requires active therapeutic interventions but is manageable without relaparotomy. Grade C leakage has the largest clinical impact and requires relaparotomy. The most commonly used other grading systems in this systematic review based their severity grading either on clinical presentation, means of diagnosis or the resulting management of the complication. Grading the severity of CAL is of importance as it may give an indication of the required intervention, prognosis and consequences for the individual patient. A confined anastomotic leak with mild clinical symptoms may be treated conservatively or with oral antibiotics alone, while an abscess surrounding the anastomosis may be drained radiologically. Although the ISREC definition and grading system is rather complete and has been used by a number of authors, it has not yet been fully implemented in daily clinical practice and research. Some authors believe that by the use of this definition, no distinction can be made between anastomotic leakage and a presacral abscess, which is not necessarily an indication for a leak, as

it could be formed due to peroperative spill or an infected hematoma[42, 102]. The fact that others did indeed classify presacral abscess formation as indicative for a leak[103, 104], clearly shows that several issues need to be resolved in order to come to complete agreement regarding a new definition for CAL.

We may even discuss whether CAL is the right description and outcome of this puzzle, as (microscopic) 'leaks' will by definition be present in every newly constructed anastomosis. Therefore, it would be more appropriate to focus on the period of intestinal healing directly following surgery instead. An impaired healing process may result in clinical consequences such as a prolonged hospital stay, administration of antibiotics, radiological drainage of an abscess, a reoperation including a prolonged hospital stay or even intensive care stay, and in worst case scenario long lasting sepsis with substantial additional consequences for the patient (e.g. significant duration of hospitalization, delayed return to functional capacity and work or additional treatment [chemotherapy/surgery for metastasis], and/or decreased health related quality of life), or even death. We may consider to address and modify all risk factors that are potentially related to the healing process. These modifiable risk factors may be patient related and present preoperatively[105], or may be part of the intraoperative approach such as vascularization, technique of anastomosis construction, blood loss and use of inotropes[106-108]. We may consider impaired healing as part of a future definition but should also include the effects that these outcomes have on our patients. From the patient's point of view, prolonged hospital stay or even a re-intervention could be seen as being more important than the burden of living with a temporary or permanent stoma. For another patient, however, the struggles of such a stoma might not outweigh the substantial risk and clinical consequences of developing CAL. We find it remarkable that in all the reviewed papers the presence or absence of any ostomy was not considered as a major issue in the definition or grading of CAL.

Before we are able to formulate a definition for colorectal anastomotic leakage that will be accepted by both clinicians and research groups worldwide, several issues need to be addressed. First, the terminology of a leak varies widely as shown in this review (See table 1). This makes interpretation of study outcomes rather difficult. In this respect we would prefer to speak of impaired gut healing. Secondly, timing of CAL occurrence has also been described as part of the definition. This present study shows that there is a wide range within the postoperative course to diagnose CAL. It is unclear whether the duration of follow-up taken into account in the different papers has had a significant influence on this range, as a considerable number of CAL cases are diagnosed after the direct postoperative period of 30 days[109, 76]. In fact, when also taking into account cases of CAL that are diagnosed after discharge and/or more than 30 days after low anterior resection,

incidence rates show an up to 40% increase [109, 110, 76]. Interestingly, some studies found that the construction of a deviating ostomy reduced the numbers of early anastomotic leak. This was, however, not the case for the late anastomotic leaks suggesting that in the presence of a temporary ostomy CAL diagnosis is delayed[110, 109]. Some authors may consider early and late anastomotic leakage as separate entities, and may therefore underreport late anastomotic leaks as such[111]. It was indeed shown that the clinical course differs considerably between early and late CAL. with early CAL requiring more often a relaparotomy and the construction of a permanent ileostomy. Finally, preoperative radiotherapy increases the risk of late, but not early CAL [76, 112, 111].

Furthermore, colon and rectal anastomotic leakage may be seen and described as separate entities. Reasons to consider rectal and colonic anastomotic leakage as two separate problems include the different reported incidence rates, which were again confirmed by the results of this review, the different anatomy, surgical techniques and microbial composition[113]. However, the studies included in this review that reported separate incidence rates for rectal and colon anastomoses did not specify what was considered rectum and colon. This is interesting, as specialists involved in the care of the colorectal patient such as radiologists, surgeons and pathologists, define the rectosigmoid junction differently. In radiology, the rectosigmoid junction is somewhat arbitrarily defined as 15 cm above the anal verge, or, in some cases, 15 cm above the dentate line. As surgeons and pathologist can directly view the anatomical landmarks, the rectosigmoid junction is determined differently: where the teniae coli coalesce to form a continuous outer longitudinal muscle layer[114]. In contrast to rectal anastomotic leakage, an exact definition of colonic anastomotic leakage is only sporadically found in literature [100, 115]. It is highly recommended that these aforementioned issues are resolved in collaboration with an expert panel prior to the construction of a novel definition.

Besides the development of uniform definitions for complications, uniform reporting of data has also gained attention over the past years, with the CONSORT Statement for RCT's being one of the first to provide guidance about what should be reported in a research article[116]. Several other guidelines have been developed since, a trend that is welcomed and supported by a number of organizations such as the Council of Science Editors and the International Committee of Medical Journal Editors[117, 118]. Based on the findings (and the lack thereof) regarding the reporting of data in this extensive literature review, the authors believe the research field of colorectal anastomotic leakage would greatly benefit from increased guidance on the reporting of data. We strongly feel that both uniformity in the use of a CAL definition as well as equality in the reported information would positively influence comparability of study data and would allow

for the reliable interpretation of meta-analyses. In collaboration with an expert working group, the Dutch Taskforce for Anastomotic Leakage, a set of guidelines has been drafted to address this issue. The authors therefore recommend that newly published papers in this field adhere to the standard reporting of the following 11 points: type of surgery and height of anastomosis, standard testing of integrity of anastomosis both during and after surgery (prior to temporary stoma reversal), construction of deviating ostomies and type of ostomy (primary and secondary), median interval of CAL diagnosis from day of surgery, diagnostic tools used to establish diagnosis of CAL, clinical symptoms associated with the diagnosis of CAL, separate leakage numbers for colon and rectal anastomoses, the use of a grading system and associated treatment plan. A checklist describing these 11 points in more detail can be found in the supplementary data (table 4).

The need for an all-embracing definition of colorectal anastomotic leakage continues to exist, so that comparability of study results and understanding between all members of the medical team increases. The authors strongly believe that implementation of a graded system with treatment recommendations for the different severity grades will enhance uniformity of patient care and may lead to decreased delay in treatment[119, 120].

The results of this paper and those of a consensus assessment among surgeons in the Netherlands and China[17] will be used to initiate a Delphi round, that will eventually lead to the formulation of a uniform definition of CAL supported by a large panel of experts.

Figure 1. PRISMA flow diagram of selection process.

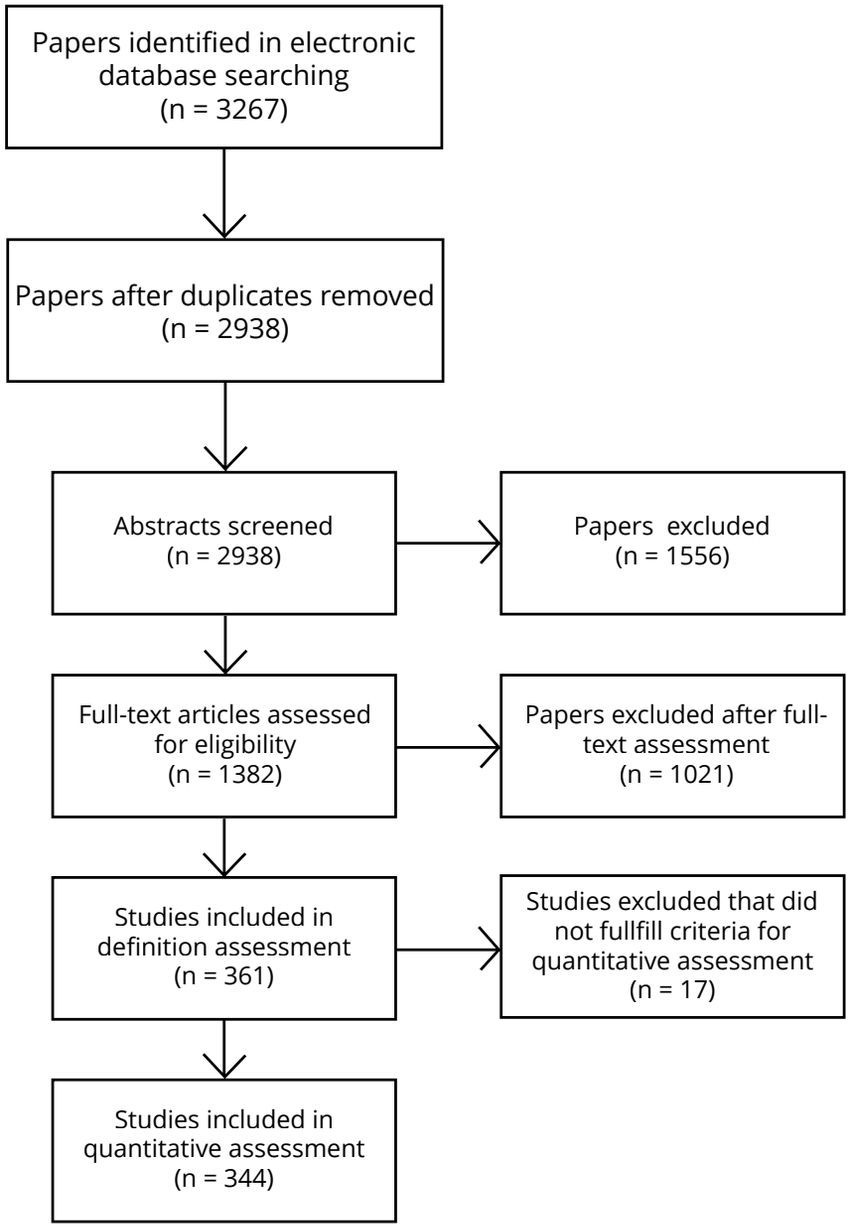


Figure 2. Peer reviewed papers published on colorectal anastomotic leakage with (n=361) and without (n=1021) the description of a definition from 1990 to 2015.

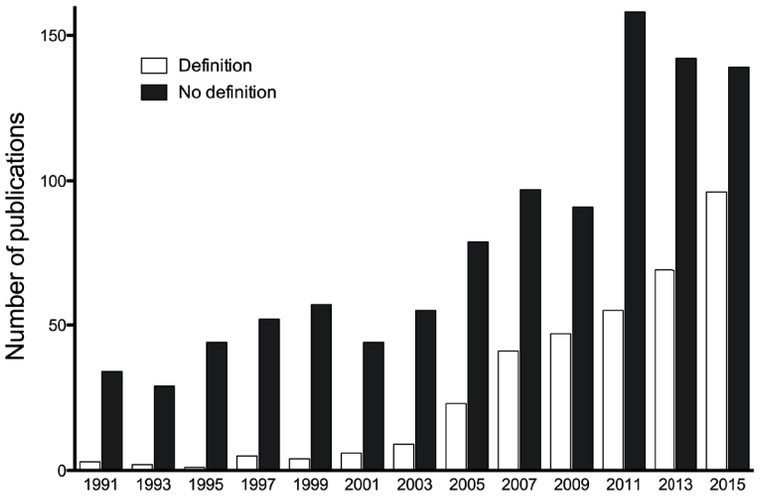


Figure 3. Reported mean incidence rates for colon and rectal anastomotic leakage over the past 25 years.

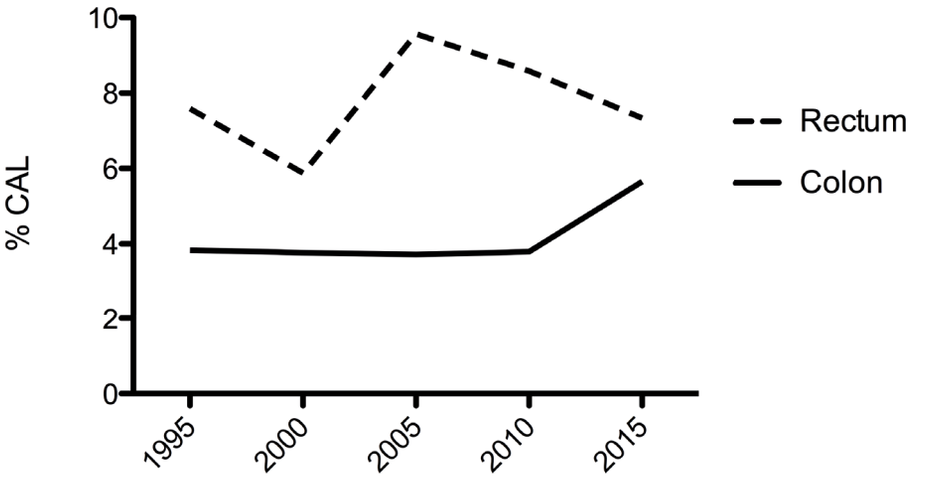


Table 1. Classification of definitions of colorectal anastomotic leakage (CAL); examples and % CAL per classification.

Classification (n) papers	Descriptions	% CAL mean (range)
1. Clinical diagnosis (n=23)	The definition of anastomotic leakage was clinical and included: peritonitis caused by leakage, discharge of feces from the abdominal drain, rectovaginal fistula, leakage from all staple lines, pelvic abscess without radiologically proven leakage mechanism. [18] Anastomotic leakage was defined clinically by peritonitis resulting from the leakage, with signs of acute abdomen, anal bleeding, or suspicious quality of drainage. [19]	C= 4.4 (0 – 7.6%) R= 8.1 (2.3 – 33)
2. Imaging diagnosis (n=11)	Colorectal anastomotic leakage was defined as a radiographically confirmed extravasation of contrast at the anastomosis. [20] An anastomotic leak was verified either by a radiographic enema performed with computed tomography (CT) scan (standard for the inpatient setting), X-ray, or by endoscopy. [21]	C=N.A. R=6.4 (5.7 – 12.5)
3. Requiring reintervention (n=34)	Anastomotic leakage was further defined, in line with recent proposals, as a defect of the intestinal wall at the site of the anastomosis requiring surgical or radiological intervention.[22] Anastomotic leak was defined as minor leak requiring percutaneous intervention or major leak requiring laparotomy.[23]	C=5.4 (0.7 – 7.1) R=6.6 (1.2 – 17.6)
4. Theoretical (n=20)	Anastomotic leakage defined as a defect in the intestinal wall at the anastomotic site, which led to a linkage between intra- and extraluminal compartments. [24] Anastomotic leakage was defined as the leak of luminal content from a surgical join between two hollow viscera.[25]	C=6.6 (2.3 -10) R=8.2 (0 – 21.6)
5. Clinical suspicion confirmed by imaging and/or reoperation (n=71)	Anastomotic leakage was suspected due to fecal discharge from wound or drain, fever, pelvic abscess, local peritonitis, discharge of pus per anus, a CT scan was performed to confirm diagnosis.[26] Anastomotic leakage was defined as the presence of clinical symptoms such as fever or septicemia combined with the occurrence of pelvic abscess, presence of rectal pus discharge, formation of a rectovaginal fistula, or presence of peritonitis within 30 days after surgery, leading to a clinical and/or radiological examination or repeat surgery to confirm the diagnosis. [27]	C=6.1 (1.8 – 13.2) R=10.1 (0.6 – 30.4)
6. Clinical and imaging diagnosis (n=96)	To define anastomotic leak both the clinical signs, symptoms (signs of localized or generalized peritonitis, fecal discharge from the wound and/or drain) and radiologic investigations are used.[28] The definition of anastomotic leakage included any clinical or radiologic evidence of anastomotic dehiscence (such as discharge of intestinal content through a drain), regardless of whether reoperation or any other intervention was required. Additional tests such as chest and abdominal computed tomography were performed to assess leakage-related complications.[29]	C=5.6 (2.3 – 7.0) R=8.2 (1.5 – 22.5)
7. Imaging diagnosis or at reoperation (n=24)	A leak was defined as a breakdown of a colonic anastomosis associated with an intra-abdominal collection identified either by contrast radiographs or by the surgeon at the time of a subsequent operation.[30] In case of imaging, leakage was considered to be present when free air or contrast was visible around the anastomosis. In case of relaparotomy, leakage was considered to be present when a dehiscent anastomosis was visualized. [31]	C=4.6 (0 -21) R=9.0 (5.2 – 21.1)
8. Clinical and/or imaging and/or at reoperation (n=64)	Anastomotic leakage was defined by at least one of the following criteria: 1) an anastomotic defect noted on physical examination, 2) an anastomotic defect confirmed in the operating room, 3) an anastomotic defect seen on proctoscopy, 4) radiologic evidence of a leak consisting of either a defect in the anastomosis and an adjacent fluid collection, or stranding or the extravasation of rectal contrast into the extraluminal space, or 5) clinical evidence of a leak such as feculent output from a pelvic drain.[32] Clinical leak was defined as an anastomotic dehiscence verified by any of the following: imaging [computed tomography (CT) or barium enema], change in drainage material, operative intervention showing drainage, endoscopic evidence of anastomotic dehiscence, or signs of sepsis.[33]	C=5.4 (1.7 – 20.3) R=8.7 (2.2 – 28.5)
9. Diagnosis only at reoperation (n=3)	Anastomotic leakage was defined as the presence of bowel content leaking from a defect in the anastomosis, identified at repeat operation.[34] Patients with operatively confirmed anastomotic leak.[35]	C=N.A. R=2.4 (2.4- 2.4)
10. ISREC (n=8)	Leakages were classified into three groups: A) CAL requiring no active therapeutic intervention B) AL requiring active therapeutic intervention but manageable without re-laparotomy C) CAL requiring re-laparotomy. Patients presented symptoms and signs of leakage such as sepsis, fever, elevated white cell count and C-reactive protein, perineal or pelvic pain, localized or generalized peritonitis and discharge of blood or puss per rectum. CAL was diagnosed by computed tomography (CT) with intravenous contrast. [36]	C=N.A. R=7.8 (5.6 – 17.7)
11. Other (n=7)	Anastomotic leaks were categorized as either major clinical leaks with signs of generalized peritonitis requiring emergency abdominal reoperation or minor leaks diagnosed on clinical signs, generally confirmed radiologically, and managed expectantly without abdominal reoperation. [37]	C=N.A. R=12.3 (7.5–13.9)

C = Colon, R = Rectum, N.A. = Not applicable

** % leakage calculated with pooled means from all papers included in specific category. The range of the reported incidence of the different articles included in a specific category is given.*

Table 2: Symptoms associated with colorectal anastomotic leakage as reported in definition or means of diagnosis.

Symptom	Reported in papers: n (%)
Peritonitis	115 (48.3)
Discharge from drain	115 (48.3)
Fever	97 (40.8)
Discharge from rectum	68 (28.6)
Rectovaginal fistula	68 (28.6)
Abdominal pain	66 (27.7)
Dehiscence identified upon palpation	59 (24.8)
Leukocytosis	55 (23.1)
Sepsis	43 (18.1)
Tachycardia	26 (10.9)
Tachypnea	19 (8.0)
Discharge from wound	18 (7.6)
Increased C-reactive protein (CRP)	14 (5.9)
Ileus	13 (5.5)

Table 3: Use of various grading systems for the severity of colorectal anastomotic leakage.

Reference	Grading terms	Description
Midura et al. 2015[23] **Snijders et al. 2015**[59] **Garcia et al. 2013**[60]	Minor / Mild	Can be treated conservatively or by radiologic intervention
Van 't Sant et al. 2012[61] **Frye et al. 2009**[37] **O'Grady et al. 2007**[62] **Oguz et al. 2007**[63] **Fa-Si-Oen et al. 2005**[64] **Raveenthiran et al. 2004**[65] **Eckmann et al. 2004**[66] **Kanellos et al. 2004** [67, 68] **Marusch et al. 2002**[69] **Galandiuk et al. 1991** [70] **Tuson et al. 1990**[71]	Major / Severe	Requires surgical reintervention
Vermeer et al. 2014 [42]	Presacral abscess	Abscess on the anterior side of the of the sacrum without extravasation of enteral contrast on CT-scan or signs of generalized peritonitis due to CAL
	Anastomotic leakage	Extravasation of enteral contrast on CT- scan, the presence of a PA in combination with a defect in the anastomosis on palpation or the presence of fecal peritonitis when performing a laparotomy.
Hua et al. 2014[72] **Walker et al. 2004**[73]	Minor / Local	Can be treated conservatively or by radiologic intervention
	Major / General	Requires surgical reintervention
	No clinical / Radiological	Diagnosed radiologically, without clinical symptoms
Ashraf et al. 2013[74]	i peritoneal	Requires laparotomy, washout and formation of stoma
	ii contained pelvic	Managed with EUA with pelvic washout, with or without VAC endosponge therapy
	iii localized perianastomotic	Managed conservatively by percutaneous radiological drainage and/or antibiotics
Shiomi et al. 2015 [38] **Yun et al. 2015**[39] **Dauser et al. 2014**[40] **Placer et al. 2014**[41] **Reilly et al. 2014**[48] **Kawada et al. 2014**[49] **Krarup et al. 2014**[75] **Vermeer et al. 2014** [42] **Boesen et al. 2013** [43] **Kulu et al. 2013** [44] **Morks et al. 2013** [76] **Nerup et al. 2013** [36] **Saber et al. 2013**[47] **Bakker et al. 2012** [45] **Penninckx et al. 2012** [46]	ISREC: Grade A	No change in patients' management
	Grade B	Requires active therapeutic intervention but is manageable without re-laparotomy
	Grade C	Requires re-laparotomy.
Garcia-Granero et al. 2013[60] **Asoglu et al. 2013**[51]	Minor	Conservative medical treatment, Clavien-Dindo grades I and II
	Major	Need of reoperation or percutaneous radiological drainage, Clavien-Dindo grades III to V
Mongin et al. 2014[77] **Ogilvie et al. 2012**[78] **Piessen et al. 2012**[58] **Fong et al. 2011**[79]	Symptomatic / Clinical	The presence of peritonitis, fever, or when gas, pus, or feces were discharged from the abdominal drain or from the vagina.
Lim et al. 2006[80] **Millan et al. 2006** [81] **Rudinskaite et al. 2005**[82] **Bell et al. 2003**[10] **Dehni et al. 1998**[83] **Petersen et al. 1998**[84] **Moore et al. 1996**[85] **Bokey et al. 1995**[86] **Bugiantella et al. 2014**[87] **Leroy et al. 2004**[88] **Brown et al. 2001**[89] **Merad et al. 1998**[90] **Akyol et al. 1992**[91]	Asymptomatic / Radiological / Occult	Considered if CAL was assessed on the systematic CT scan with contrast enema performed before diverting stoma reversal, without any relevant clinical symptom
Hellan et al. 2015[33] **Richards et al. 2015**[22] **Yamaguchi et al. 2015**[50] **Asoglu et al. 2013**[51] **Nakajima et al. 2013**[53] **Nakajima et al. 2012**[52] **Gorissen et al. 2012**[54] **Lagoutte et al. 2012**[55] **Manceau et al. 2012** [56] **Piessen et al. 2012**[58] **Park et al. 2011**[57]	Clavien Dindo Classification	Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions
		Grade II: requiring pharmacological treatment
		Grade III: Requiring surgical, endoscopic or radiological intervention
		Grade IV: life-threathening complication
		Grade V: Death of a patient
Platell et al. 2005[92]	i	No treatment
	ii	Antibiotics
	iii	Drainage
	iv	Reoperation
Killingback et al. 2002[93]	Clinical grade I	Requiring reoperation
	Clinical grade II	Not requiring reoperation
	Subclinical grade III	No clinical consequences
Ogilvie et al. 2012[78]	Small	5 mm or less
	Medium	6-19 mm
	Large	20 mm or larger
Smith et al. 2007[94]	Intraoperative	Visualization of methylene blue dye outside of the colon (in the operative field)
	Postoperative	Defined clinically as a constellation of fever, abdominal pain/peritonitis, and leukocytosis, radiographically, or by the institution of treatment indicating that the patient had a leak (such as the creation of a diverting ostomy)
Lim et al. 2015[95]	Type I	Generalized peritonitis
	Type II	Localized peritonitis with or without abscess
	Fistula or chronic sinus	Any type of fistula-associated leakage or chronic sinus formation
Caulfield et al. 2013[96]	Gross	defined as a disruption of the anastomosis identified at reoperation or extravasation of contrast medium at the anastomotic site on an imaging study, irrespective of the presence of symptoms.
	Occult	An abscess or free pelvic fluid collection without extravasation of contrast medium was considered an occult anastomotic leak

Table 4: Items suggested by the Taskforce Colorectal Anastomotic Leakage to be considered in standard reporting.

Item	Report
Construction of anastomosis	
- **Type of surgery**	- Colon/rectum
- **Height of anastomosis**	- In cm from the anal verge
- **Stoma construction**	- Primary/secondary
	- Deviating ileostomy/deviating colostomy/end ileostomy/end colostomy
- **Test of integrity during surgery**	- Air leak test/…
Clinical symptoms	
- **DULK score**	- Yes/no, if yes score: …
- **Leukocytosis**	- > $10x10^9$/l
- **Sepsis**	- Yes/no
- **Tachycardia**	- > 100/minute
- **Tachypnea**	- > 20/minute
- **Increased C-reactive protein**	- > 250
- **Discharge from wound**	- Yes/no
- **Abdominal pain (other than wound pain)**	- Yes/no
- **Fever**	- > 38 degrees Celsius
- **Discharge from drain**	- Yes/no
- **Discharge from rectum**	- Yes/no
- **Rectovaginal fistula**	- Yes/no
- **Ileus**	- No stool > 4 days postoperatively
Diagnosis	
- **Moment of diagnosis**	- Median interval in days from surgery
- **Diagnostic tools**	- CT/X-thorax/laboratory/…
- **Dehiscence identified upon palpation**	- Yes/no
- **Radiological diagnosis**	- No leakage, infiltration anastomosis, abscess around anastomosis, free abdominal air, free fluids abdomen
Outcome	
- **Hospital stay**	- Number of days until discharge
- **Prolonged hospital stay**	- > 5 days
- **Intensive care stay**	- Yes/no
- **Treatment**	- Conservative, ileus treatment, antibiotics, percutanal drainage, reoperation with extra suture and deviating stoma, reoperation with reconstruction new anastomosis and deviating stoma, reoperation with end stoma
- **Delayed functional recovery**	- Yes/no
- **Delayed start of additional therapy (chemo/surgery for metastasis)**	- Yes/no
- **Delayed return to work**	- Yes/no

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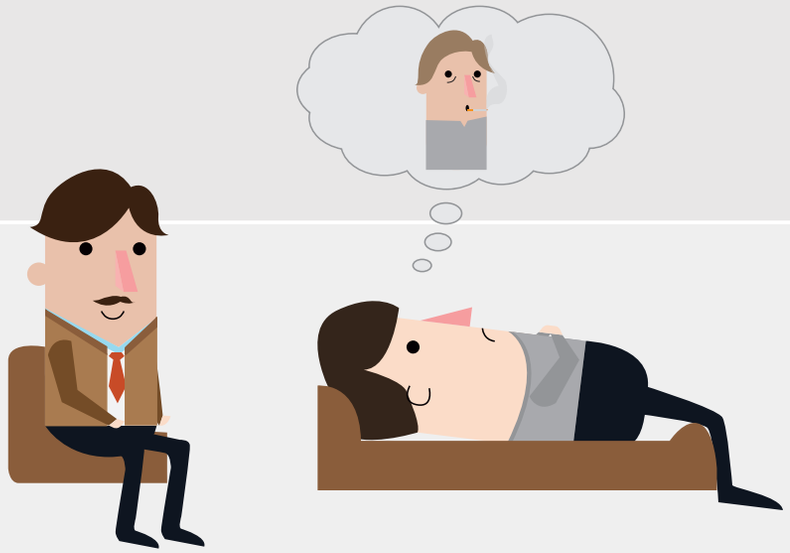
PART II

MODIFIABLE RISK FACTORS AND RISK ASSESSMENT IN COLORECTAL SURGERY

Chapter 5 Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation.
Acta Oncol. 2017 Feb; 56 (2): 329-334.

Chapter 6 Intraoperative modifiable risk factors of colorectal anastomotic leakage: why surgeons and anesthesiologists should act together.
International Journal of Surgery. (36); 2016.

Chapter 7 Can anastomotic leakage in left sided colorectal surgery be predicted?
Submitted.



CHAPTER 5

PREOPERATIVE MODIFIABLE RISK FACTORS IN COLORECTAL SURGERY: AN OBSERVATIONAL COHORT STUDY IDENTIFYING THE POSSIBLE VALUE OF PREHABILITATION.

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ABSTRACT

Background

Colorectal cancer (CRC) is the second most prevalent type of cancer in the world. Surgery is the most common therapeutic intervention, and associated with a 20% to 40% reduction in physiological and functional capacity. Postoperative complications occur in up to 50% of patients resulting in higher mortality rates, increased cancer progression, and greater hospital costs. The number and severity of complications is closely related to patients' preoperative performance status. The aim of this study was to identify the most important preoperative modifiable risk factors, that could be part of a multimodal prehabilitation program.

Methods

Prospectively collected data of a consecutive series of Dutch colorectal cancer patients undergoing colorectal surgery were analyzed. Modifiable risk factors were correlated to the Comprehensive Complication Index (CCI) and compared within two groups: none or mild complications (CCI=0 or CCI<20), and severe complications (CCI>=20). Multivariate logistic regression analysis was done to explore the combined effect of individual risk factors.

Results

In this 139 patient cohort, risk factors related to severe postoperative complications (CCI >=20) are ASA score III (OR 4.4, 95% CI 1.04-18.6), and hemoglobin level <7mmol/L (OR 3.3, 95% CI 1.3-8.2). Number of pack years smoking, malnutrition, alcohol consumption, neoadjuvant therapy, higher age, and male sex, were also seen more frequently in the severe complication group. Number of risk factors was predictive for an increased CCI score >=20 (OR 5.2, 95% CI 1.8-15). Patients with CCI >=20 had a significantly longer hospital stay (16 vs 6 days, p<0.001).

Conclusion

This study revealed that the risk of getting severe complications increases with the number of risk factors present preoperatively. Several preoperative patient related risk factors are modifiable. Multimodal prehabilitation may improve patients' preoperative status and should be investigated in a multicenter randomized controlled trial. With an international consortium (Copenhagen, Montréal, Paris, Eindhoven) we initiated a randomized controlled trial (NTR5947).

Key words: Prehabilitation, colorectal surgery, Comprehensive Complication Index, colorectal cancer, functional capacity, Enhanced Recovery After Surgery, anastomotic leakage, complications.

Introduction

Colorectal cancer (CRC) is the second most prevalent type of cancer worldwide with over 800.000 new patients diagnosed yearly. The only way to cure this condition is by surgical removal of the tumor. Unfortunately, postoperative complications occur in up to 50% of patients and lead to a higher mortality rate, increased hospital costs and a lower Health Related Quality of Life (HRQoL). , Even in the absence of complications, major surgery is associated with a 20% to 40% reduction in physiological and functional capacity, which can be measured by energy expenditure, endurance time, workload and heart rate during maximum exercise. In patients that need adjuvant chemotherapy an optimal functional capacity is mandatory and complications will often lead to a delayed start or cancellation of treatment.

Efforts to improve the recovery process have primarily focused on the intraoperative (eg, minimally invasive surgery, afferent neural blockade) and post-operative period (eg, "fast track" early nutrition and mobilization).1, The latter protocols have been designed to facilitate the return of functional activities and accelerate convalescence known as rehabilitation. However, the post-operative period may not be the best time to ask surgical patients to make significant changes in their lifestyle, as patients are tired and concerned about perturbing the healing process as well as being depressed and anxious as they await additional treatments for their underlying condition. The preoperative period may in fact be a better time to intervene in the factors that contribute to recovery. This may alleviate some of the emotional distress surrounding the anticipation of surgery and the recovery process.

Although some have used education to prepare patients for procedures, little has been developed to systematically improve patients' preoperative status. Many of the patient related risk factors (eg anemia, diabetes mellitus, cigarette smoking) for postoperative complications have already been identified and might be modifiable prior to surgery to improve postoperative outcome measures (eg length of hospital stay, complication index, HRQoL).1 Poor physical performance capacity increases the risk of complications after major non-cardiac surgery and prolongs recovery after abdominal surgery. The role of nutritional status and psychological well-being in surgical recovery may also not be underestimated and might be improved accordingly. , Standard consultation of a dietician and psychologist may enhance patients' preoperative status by improving their oral intake, offering nutritional supplements (i.e. multi vitamins, proteins) and strategies to cope with anxiety. The nutritional status of patients affected by colorectal cancer is directly influenced by the presence of cancer, and by other factors such as age, (neo)adjuvant cancer therapy and stage of the disease. It is as well documented that patients awaiting major surgery experience anxiety concerning their upcoming operation, its outcome, and their course of healing and recovery.

All current evidence demonstrates there is a necessity - and opportunity - to enhance patients' preoperative functional status to improve postoperative outcome. Prehabilitation might offer the solution to preoperatively optimize patients' performance status to withstand intensive treatments as surgery. , Unfortunately, only small trials evaluated the impact of prehabilitation prior to colorectal surgery.

Currently, based on the literature, it is not exactly known how preoperative modifiable risk factors are distributed among colorectal cancer patients. This information would support any intervention in order to optimize patients' preoperative status. Therefore, the general aim of this study was to identify modifiable preoperative risk factors in colorectal patients and to investigate whether multimodal prehabilitation could be valuable to improve the preoperative status. For this purpose, we employed a prospective observational cohort study.

Methods

A consecutive series of Dutch colorectal cancer patients undergoing surgery with primary anastomosis collected from May 2015 until June 2016 in Máxima Medical Center (MMC) were analyzed. The MMC is a 543-bed community and teaching hospital situated in the southern part of The Netherlands serving a population of approximately 200.000 inhabitants.

Pre- peri- and postoperative data were extracted from the electronic patient files and perioperative registration data. Relevant patient related risk factors that might be optimized prior to surgery to lower the risk of peri- and postoperative complications were identified by screening the literature: body mass index (BMI), ASA grade III, diabetes mellitus (DM), current smoking and pack years >15, alcohol use >3 units per day, hemoglobin below 7 mmol/L, Short Nutritional Assessment Questionnaire (SNAQ) score >3, neoadjuvant chemo or radiotherapy, and oral corticosteroid use. These factors were prospectively recorded by integrating the required information in the routine patient registration system.

Outcome

The primary outcome for this study was the Comprehensive Complication Index score (CCI). The CCI is a combined outcome measure of morbidity and mortality, and summarizes the postoperative wellbeing of the patient concerning complications based on the Clavien-Dindo classification. As a CCI score above 20 was depicted as clinical relevant morbidity, we used this cut-off point to dichotomize the data into a less severe and severe group. In addition, baseline characteristics were described separately for patients without any complications and mild complications (mild (CCI 0-<20)), and patients with severe complications or death (severe (CCI>=20)).

Statistical analysis

Baseline characteristics were compared between different categories of CCI (mild and severe) using the Pearson Chi-square test for categorical variables, the unpaired t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables.

The influence of preoperative characteristics on the risk of severe post-operative complications was expressed as odds ratios (OR) with 95% confidence intervals (95%CI) as calculated by univariate logistic regression analysis. Multivariate logistic regression analysis was done to explore the combined effect of individual risk factors. We included all variables that were associated with severe post-operative complications in univariate analysis at a p-value of <0.05 into the multivariate model.

To explore the effect of burden of risk factors on risk of severe complications, we included the number of risk factors in each patient as an independent covariate into the logistic regression analysis. All analyses were done in SPSS version 22 (IBM IBM Corp., Armonk, NY, USA) and statistical significance was accepted at a two-sided p-value <0.05.

Results

During the inclusion period 139 patients were prospectively analyzed. Patient characteristics are described in table 1. The mean comprehensive complication index score (CCI) was 8.7 (SD 14.5) (median 0, interquartile range 0-20.9), and 35% of the patients showed one or more postoperative complications as measured with the Clavien Dindo scale. On the other hand, 65% of the patients had no complication at all (CCI = 0).

Baseline characteristics were described according to two categories of CCI including no complications and mild complications (CCI=0 and <20) and severe complications (CCI>=20) (Table 1). In the severe complications group, compared to the none-to-mild complications group, patients were on average older and more were male patients. A significant proportion of patients had an ASA score higher than III (p=0.03) and a hemoglobin level lower than 7 (p<0.01). Further, a SNAQ score higher than 3, high use of alcohol, and long term-smoking were reported more frequently in the severe complication group. The length of hospital stay was significantly higher in the severe complication group (16 vs. 6 days, p<0.01). With increasing number of risk factors a higher proportion of patients had severe complications (Figure 1).

A multiple logistic regression analysis was performed for all statistical significant variables within the univariate analysis. In the univariate analysis patients with BMI <20 or 30+ had a lower OR (0.3, 95% CI 0.1-0.95) for severe complications but this was not observed in the multivariate analysis (OR 0.3, 95% CI 0.1-1.1) (Table 2). Both ASA grade III (OR 4.4, 95% CI 1.04-18.6) and hemoglobin level <7 (OR 3.3, 95% CI 1.3-8.2) increased the OR for severe complications in univariate and multivariate analysis. The OR for severe complications strongly increases with the number of risk factors present preoperatively with an OR of 5.2 (95% CI 1.8-15) among patients with more than one risk factor. This is depicted in table 2.

Discussion

This prospectively collected consecutive case series of colorectal cancer patients confirms the existence and distribution of potentially modifiable preoperative risk factors that are associated with postoperative complications as measured by the CCI score. We depicted a CCI score above 20 as clinically relevant morbidity.16,17 For scores below 20, patients have not encountered any major events such as colorectal anastomotic leakage, prolonged ileus, neither a reoperation. This cut off value is supported by the significantly increased length of hospital stay of the severe complication group. Factors like poor nutritional status, ASA score III, cigarette smoking, anemia (Hb<7 mmol/L), alcohol consumption >3 U/d, neoadjuvant therapy, DM, male sex, and higher age, have been all shown to be independent risk factors for complications in colorectal surgery.1,2,13,14,15 In the present study sample ASA score III and hemoglobin level <7 mmol/L were found statistically significant risk factors whereas other factors were not statistically significantly associated with severe complications.

About 25-40% of all patients are undernourished on admission to the hospital as in our cohort this was observed with our finding of 14%. Moreover, malnutrition is further deepened during hospitalization and has been recognized as an independent risk factor of perioperative morbidity and severe postoperative complications. Remarkably, in the present study population either underweight or obese patients actually had less severe complications. This might be explained by the small study population and the striking low number of patients with low hemoglobin levels within those specific BMI groups. Despite this, malnutrition in general bears a significant association with postoperative mortality and cardiopulmonary complications after surgery. Nutritional support is therefore still recommended, even in well-nourished patients.18

The on average poor lifestyle (including physical inactivity, obesity, dietary pattern, smoking and alcohol consumption behavior) of colorectal cancer patients, combined with the disease activity and change in metabolism results in a high rate of complications. Cigarette smoking and substantial alcohol consumption are well-known risk factors for postoperative complications.15 Smoking has a transient effect on the tissue microenvironment and a prolonged effect on inflammatory and reparative cell functions leading to delayed healing and complications. A period of 4 to 8 weeks smoking cessation prior to surgery has already been shown to significantly reduce postoperative complications and morbidity. With about one fifth of all patients as current smokers and alcohol consumers, a smoking and alcohol cessation program should be considered.

Next, our finding of low hemoglobin levels being associated with severe complications in colorectal cancer patients is in line with numerous

other studies, and indicate that more focus should be put on presurgical management of anemia. Patients should be screened preoperatively (at least 4 weeks before surgery) to identify insufficient hemoglobin levels (< 7mmol/l). In case of iron insufficiency, optimization of hemoglobin levels using iron injections is preferable. Additionally, hyperglycemia is regarded as a predictor of complications of any type in colorectal surgical procedures. In the present study cohort we were not able to investigate the glucose level in all of our patients. It might be of value to track patient's glucose level preoperatively since Diabetes Mellitus (DM), hyperglycemia, and a high preoperative HbA1c are all independent risk factors of the worst complication in colorectal surgery: colorectal anastomotic leakage (CAL). Although DM may not be a modifiable risk factor in itself, the glucose level could be monitored and stabilized, and perioperative hyperglycemia could be prevented. Even in non-DM patients, perioperative hyperglycemia sustains a significantly higher risk of postoperative adverse events.

As seen in the present case series, the chance of severe complications rises with the addition of each risk factor. This indicates that a multimodal program could be favorable to tackle as many modifiable risk factors as possible in the individual (high) risk patient. Next to these factors, we also found a trend that with increasing clinical stage more patients had a CCI score higher than 20. Although our sample size is modest and thus results must be interpreted with caution, the factors identified as associated with complications do indicate the potential for improving patients preoperative status. The addition of a multimodal prehabilitation program may enhance patients' preoperative performance status, might help them to recover faster and be less dependent on healthcare support during and after treatment.11,12 Since certain patients will undergo neoadjuvant treatment, it might be interesting to prehabilitate during this. Unfortunately, no evidence exists of prehabilitation programs or exercise training during neoadjuvant treatment, and therefore no suggestions can be given.

The first and largest randomized controlled trial on surgical prehabilitation, compared two exercise regimens (intense exercise on a stationary bike vs walking and deep breathing) for several weeks before colorectal surgery.11 The primary outcome was functional walking capacity measured by the six-minute walk test (6MWT) between 5 to 9 weeks postoperatively. Subgroup analysis identified that patients whose functional exercise capacity improved preoperatively, regardless of the exercise technique used, recovered well in the postoperative period. However, those patients who further deteriorated in the preoperative phase despite the exercise regimen were at greater risk for prolonged recovery after surgery. Poor preoperative physical function (fatigue, malnutrition and physical performance) and presence of anxiety and depression were also significant confounding predictors of prolonged recovery.10,11 These results suggest that exercise training alone, although it can improve the functional exercise capacity, is not sufficient to attenuate the surgical stress response in all patients. Therefore, to our opinion it is important to address factors that promote the beneficial adaptations to training like nutrition and coping behavior.

To improve both exercise capacity and nutritional state it is necessary that dietary intake is well balanced against the energy use during exercise. High intensity training combined with supplemental whey proteins within one hour after training is recommended to achieve the ultimate improvement in functional capacity in a short time span of 4 weeks.9,12 Nutritional supplementation 4 weeks before and after surgery has been shown to enhance preoperative functional walking capacity and recovery in patients undergoing colorectal resection for cancer.12 Not only the nutritional status of patients should be optimal, but also the hemoglobin level. An improved hemoglobin level, combined with training, may lead to substantially better effects preoperatively, and will lower the chance for severe complications as seen in this present cohort.

Since the number and severity of complications appears to be closely related to patients' preoperative status, we believe the medical community has the responsibility to develop and test a multimodal intervention program targeting those problems. Current standard preoperative and postoperative clinical care do not routinely include special nutrition, exercise, smoking cessation and psychological support before surgery. Interventions used in studies on these parameters all have been proven to have a clinical relevant effect on the reduction of postoperative complications.12 Although much of this is known, remarkably, it is not routine practice to implement this knowledge in daily clinical practice. If all these interventions are orchestrated in an innovative multimodal prehabilitation program, to our opinion it should be feasible to design a very effective intervention that might beneficially influence the outcome of this patient group. Since we do not know the exact content and effects of a multimodal program, we first have to design such a study. Secondly, we have to test the proposed multimodal intervention program in a randomized trial. And finally, if successful, we will implement that program in daily clinical practice worldwide.

Conclusion

This prospectively collected cohort study of 139 CRC patients revealed that potentially modifiable patient factors were prevalent and that the risk of severe postoperative complications increases with the number of risk factors present preoperatively. Multimodal prehabilitation may improve patients' preoperative status which may be associated with improved outcomes of the operation, recovery and adherence to further cancer treatment and rehabilitation. In order to obtain sufficient statistical power a multicenter randomized controlled trial should be performed. Such a study would be the first to systematically combine existing knowledge from a variety of different medical specialties and basic scientists into a prehabilitation protocol for CRC patients, focusing on modifiable preoperative risk factors, and improvement of functional capacity to lower the postoperative complication rate. With an international consortium (Copenhagen, Montréal, Paris, Eindhoven) such a randomized controlled trial (NTR5947) has been initiated.

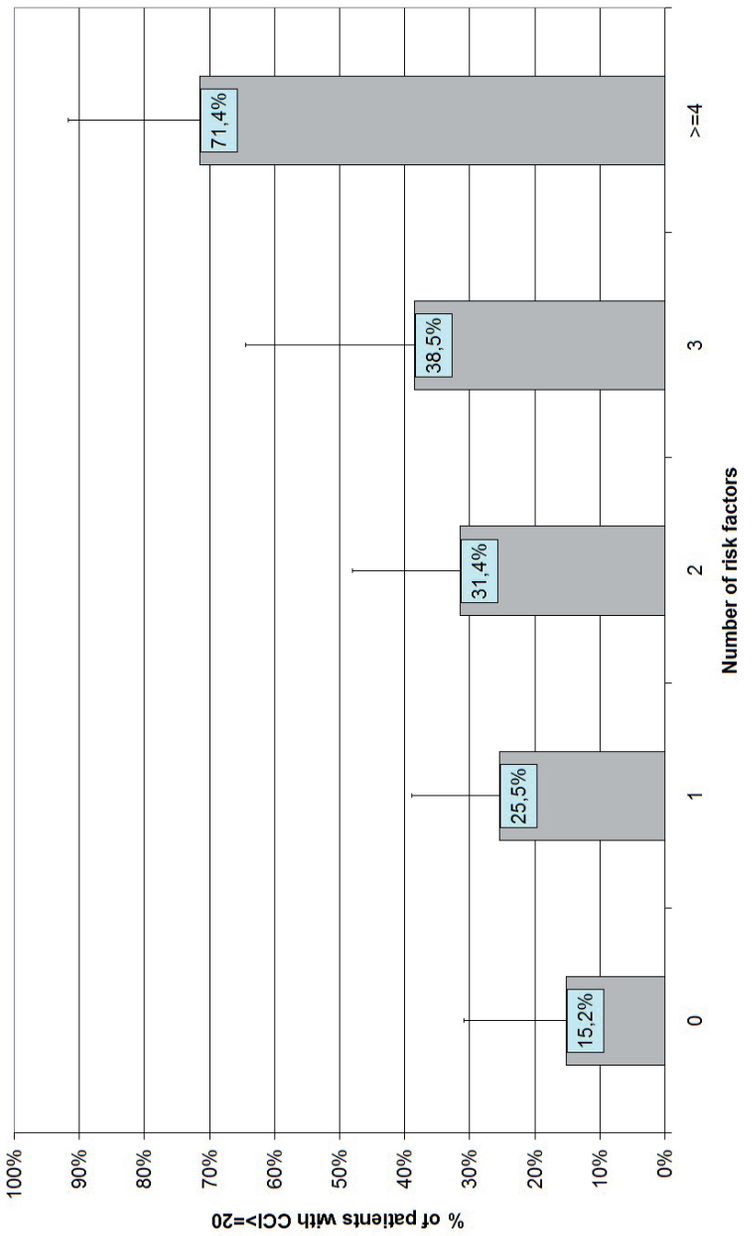


Figure 1. Percentage of colorectal cancer patients with severe postoperative complications (CCI score >= 20), related to the number of preoperative risk factors (ASA III, Body Mass Index (BMI) <20/>30, Pack Years (PY) >15, alcohol (AH) >3 units/day, Hemoglobin level (Hb) <7 mmol/L, Short Nutritional Assessment Questionnaire (SNAQ) >3, neoadjuvant therapy). Y-bars indicate upper 95% confidence limits. Percentages are displayed within the bars.

Table 1. Baseline characteristics according to severity of complications as indicated by the Comprehensive Complication Index (CCI) in a consecutive sample of 139 colorectal cancer patients, the Netherlands 2015-2016.

	Total group	None or mild CCI=0 and <20	Severe CCI>=20	P-value**
	N = 139	n = 100	n = 39	
Age in years	69 (39-91)	68 (39-88)	72 (53-91)	0.086
Male sex	57%	53%	76%	0.146
Body mass index (kg/m2)	25.1 (18-44)	26.1 (18-39)	25.6 (19-44)	0.511
BMI <20 or BMI>=30	22%	27%	10%	0.103
DM	12%	11%	13%	0.763
ASA grade				0.025
I	22%	26%	13%	
II	66%	66%	64%	
III	12%	8%	23%	
Current smoking	17%	16%	18%	0.781
Ever smoked	56%	54%	62%	0.421
Pack years	7 (0-70)	5 (0-70)	15 (0-60)	0.156
Alcohol use >3 Units/day	16%	13%	23%	0.144
Hemoglobin <7 mmol/L	19%	12%	62%	<0.001
SNAQ >= 3	14%	12%	18%	0.359
Corticosteroids (present use, excluding inhalers)	3%	3%	3%	0.890
Neoadjuvant therapy	12%	11%	15%	0.478
Risk factors*				
0	24%	38%	15%	0.127
1	37%	39%	36%	0.045
>1	39%	23%	49%	0.011
Length of hospital stay	7 (5-11)	6 (5-7)	16 (11-25)	<0.001

Legend 1. Medians plus range and number plus column percentages (%) are presented for continuous and categorical variables, respectively. Univariate analysis was performed for all preoperative potential risk factors. *Risk factors are body mass index (BMI), ASA grade III, diabetes mellitus (DM), current smoking, number of pack years, alcohol use >3 units per day, hemoglobin below 7 mmol/L, Short Nutritional Assessment Questionnaire (SNAQ) score >3, neoadjuvant chemo or radiotherapy, and oral corticosteroid use; ** none or mild versus severe complication group. A p-value <0.05 was considered statistically significant

Table 2. Uni- and multivariate analyses of preoperative risk factors of severe postoperative complications (CCI>=20) in a consecutive sample of 139 colorectal cancer patients, the Netherlands 2015-2016.

	None or mild vs severe CCI<20 v.s. CCI>=20	None or mild vs severe CCI<20 v.s. CCI>=20
	Crude OR (95%CI)*	Adjusted OR (95%CI)**
Age (years)	1.0 (0.99 -1.1)	-
Male	1.8 (0.8-3.8)	-
Body mass index (kg/m2) BMI <20 or BMI>=30	0.3 (0.1-0.95)	0.3 (0.1-1.1)
Diabetes Mellitus	1.2 (0.4-3.7)	-
ASA grade (compared to ASA I)		
II	2.0 (0.7-5.7)	1.7 (0.6-5.0)
III	5.8 (1.5-22.6)	4.4 (1.04-18.6)
Current smoking	1.1 (0.4-3.1)	-
Pack years >15	2.0 (0.9-4.1)	-
Alcohol use >3 Units/day	2.0 (0.8-5.2)	-
Hemoglobin <7 mmol/L	4.6 (1.9-11.1)	3.3 (1.3-8.2)
SNAQ >= 3	1.6 (0.6-4.4)	-
Corticosteroids (present use, excluding inhalers)	0.9 (0.1-8.4)	-
Neoadjuvant therapy	1.5 (0.5-4.3)	-
Number of risk factors (compared to 0)* **		
1	2.3 (0.8-6.5)	-
>1	5.2 (1.8-15)	-

Legend 2. *Calculated by using univariate logistic regression analysis. **Multiple logistic regression including all statistical significant variables from the univariate analysis. ***We did not include this variable into the multivariate analysis because it is constructed out of these variables.

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CHAPTER 6

INTRAOPERATIVE MODIFIABLE RISK FACTORS COLORECTAL ANASTOMOTIC LEAKAGE. WHY SURGEONS AND ANESTHESIOLOGISTS SHOULD ACT TOGETHER.

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ABSTRACT

Background

Colorectal anastomotic leakage (CAL) is a major surgical complication in intestinal surgery. Despite many optimizations in patient care, the incidence of CAL is stable (3-19%).1 Previous research mainly focused on determining patient and surgery related risk factors. Intraoperative non-surgery related risk factors for anastomotic healing also contribute to surgical outcome. This review offers an overview of potential modifiable risk factors that may play a role during the operation.

Methods

Two independent literature searches were performed using EMBASE, Pubmed and Cochrane databases. Both clinical and experimental studies published in English from 1985 to August 2015 were included. The main outcome measure was the risk of anastomotic leakage and other postoperative complications during colorectal surgery. Determined risk factors of CAL were stated as strong evidence (level I and II high quality studies), and potential risk factors as either moderate evidence (experimental studies level III), or weak evidence (level IV or V studies).

Results

The final analysis included 117 articles. Independent factors of CAL are diabetes mellitus, hyperglycemia and a high HbA1c, anemia, blood loss, blood transfusions, prolonged operating time, intraoperative events and contamination and a lack of antibiotics. Unequivocal are data on blood pressure, the use of inotropes/ vasopressors, oxygen suppletion, type of analgesia and goal directed fluid therapy. No studies could be found identifying the impact of body core temperature or mean arterial pressure on CAL. Subjective factors such as the surgeons' own assessment of local perfusion and visibility of the operating field have not been the subject of relevant studies for occurrence in patients with CAL.

Conclusion

Both surgery related and non-surgery related risk factors that can be modified must be identified to improve colorectal care. Surgeons and anesthesiologists should cooperate on these items in their continuous effort to reduce the number of CAL. A registration study determining individual intraoperative risk factors of CAL is currently performed as a multicenter cohort study in the Netherlands.

Keywords: Anastomotic leakage, colorectal, surgery, CAL, intraoperative, modifiable, risk factor, anesthesiology

Highlights

1. There are many intraoperative risk factors of CAL which are modifiable by improvements in perioperative care.
2. Many studies performed, however data not always univocal.
3. Multicenter registration study is necessary to determine the exact contribution of each intraoperative factor in development of CAL.
4. Temperature <36 degrees Celsius, perioperative anemia, intraoperative blood loss and transfusion, duration of surgery, intraoperative events and contamination are all modifiable risk factors of CAL.
5. Even in non-diabetes patients perioperative hyperglycemia increases the risk of CAL.

Introduction

Despite extensive research, the incidence of colorectal anastomotic leakage (CAL) has not decreased (3-19%) over the past decades.1–3 Research on CAL may focus on the preoperative, intraoperative and postoperative phase.

Research on the preoperative period mainly determines patient and surgery related risk factors of CAL. Many of these factors, i.e. age and sex, are non-modifiable. Some are included in the Colon Leakage Score (CLS) that was developed to define the proportion of CAL-risk.4 The CLS is a list of factors derived from a systematic search that can mainly be consulted prior to colorectal surgery. In addition, prehabilitation programs are being developed to optimize the patient's preoperative condition and nutrition. This promising approach will likely contribute to decrease CAL as many risk factors are related to the patients' lifestyle.5–8

Many intraoperative surgical risk factors of CAL were subject of research projects. For instance, the role of laparoscopy or stapled anastomosis in right colonic resections was determined. Also the role of a defunctioning stoma for reduction of CAL after rectum resections was proposed.9,10 However, the importance of many of these findings is still under debate. Non-surgical factors influencing the patients' condition during surgery including anesthesiological techniques might also have a large contribution to the risk of CAL. Recently, a multidisciplinary approach to prevent surgical complications is gaining interest. A combination of interventions was found to reduce the superficial surgical wound infection rate and possibly also CAL.11 This observation warrants a close(r) collaboration of surgical and anesthesiological teams. Although other intraoperative variables such as operation time, blood loss and blood transfusion requirements have been widely accepted as risk factors, other intraoperative potentially modifiable risk factors are to be discovered yet.

The postoperative status of the patient is closely monitored to detect CAL as early as possible.12 To date, many studies have been performed, and the Enhanced Recovery After Surgery program (ERAS) has been introduced to improve surgical outcome.13 CAL due to a technical failure will most probably occur within the first few days after surgery. CAL due to other reasons will become evident within 3-6 days post surgery. Consequences of CAL such as peritonitis and intra-abdominal sepsis might be limited if treated promptly. Several studies trying to identify CAL at the earliest stage have met with limited success.12,14–19 Imaging using radiological techniques has a disappointingly low sensitivity. An evidence-based algorithm is required for early detection of CAL.

Some modifiable risk factors possibly influencing the perioperative period such as medication (i.e. corticosteroids and non-steroidal anti-inflammatory drugs), poor nutritional status (i.e. body composition, albumin level) and other lifestyle related factors were not included in this review since these factors are considered as an integrated part of prehabilitation. The present review therefore systematically identified existing and modifiable intraoperative risk factors of CAL allowing for recommendations aimed at improving the quality of care for colorectal patients. Collaboration between surgeons and anesthesiologists on improving these items may be the key in the continuous effort to reduce the number of CAL.

Material and methods

A complete search was conducted on August 20th , 2015 using the PubMed version of MEDLINE, the OvidSP version of Embase and the Cochrane library (January 1970 to August 2015). Articles were restricted to the English language. Reference lists were checked for additional studies. Both clinical and experimental studies were included. The main outcome measure was the risk of anastomotic leakage and other postoperative complications during colorectal surgery. Letters and papers omitting CAL as outcome were excluded. Determined risk factors of CAL were stated as strong evidence (level I and II high quality studies), and potential risk factors as either moderate evidence (experimental studies level III), or weak evidence (level IV or V studies).20

2.1 Search strategy

Two searches were performed separately by two independent researchers (SJ van Rooijen, D Huisman) with support from the clinical library of Máxima Medical Center (MMC) and VU Medical Center (VUmc). The search headings 'anastomotic leakage' and 'colorectal surgery' were used in combination with predefined keywords as established by colorectal surgeons of MMC and VUmc (hyperglycemia, glucose level, temperature, anemia, blood loss, tissue oxygen tension, inotropes, vasopressors, blood pressure, mean arterial pressure, hypotension, fluid administration, goal directed therapy, blood transfusion, antibiotics, analgesia, epidural, operation duration, intraoperative events, conversion, contamination and surgical experience; Figure 1). If disagreement existed between the two researchers, a third author (F Daams) aimed at reaching consensus.

Results

The existing evidence regarding intraoperative modifiable parameters was classified into 3 categories, the general status of the patient, tissue perfusion and a surgery related section (table 1).

3.1 General patient status and CAL

Hyperglycemia

Eight studies (human / experimental / retrospective / Cochrane review and 2 recent multicenter RCT's) showed a negative influence of a high preoperative HbA1C on the onset of CAL.19–26 In general, hyperglycemia is regarded as a predictor of complications of any type in colorectal surgical procedures.27 Diabetes mellitus, hyperglycemia and a high preoperative HbA1c are all independent risk factors of CAL.28–35 Risk rates depend on level of hyperglycemia and starts at levels of >140mg/dL with odds ratio's varying from 1.2-4.3. An observational study concluded a higher risk on adverse events due to intraoperative hyperglycemia (>180mg/dL) in non diabetic versus diabetic patients (OR 5.1).36 However, other observational studies found that non diabetic patients sustained a significantly higher risk of postoperative adverse events compared to diabetic patients, probably as a result of perioperative hyperglycemia.21–26

Temperature

Body core temperature below 36 °C beyond 60 minutes induces vasoconstriction and is associated with increased surgical site infection (SSI) rates.32,37 Unfortunately, no studies indicating the relation of body temperature and CAL were identified. One animal study showed multidirectional changes in perioperative temperature on early stage tissue regeneration after small bowel resection.38

3.2 Tissue perfusion and CAL

Blood loss and anemia

Intra-operative blood loss is an important predictor of CAL.39–41 Even blood loss > 100ml is significantly associated with an increased risk of CAL.4,42 A ≥50 percent drop or hemoglobin levels <7 g/dL (4.4 mmol/l) following gastrointestinal surgery are predictive of adverse events.43 A case control study of the Swedish Rectal Cancer registry concluded that severe bleeding was associated with a 1.45 odds ratio of CAL44, whereas other studies discovered even a higher 3.1-3.32 odds ratio if blood loss was >200ml.45,46 Severe blood loss causes hypovolemia, tissue hypoxia, and subsequent impaired anastomotic healing.47,48 As laparoscopic surgery for rectal cancer is associated with attenuated blood loss, this technique appeared beneficial compared to an open approach.49–52

Anemia is a risk factor for postoperative myocardial infarction and a potent risk factor for CAL.39,53–56 Serum hemoglobin <9.4 g/dL (5.9 mmol/l) in the preoperative setting predicted anastomotic leaks.35,57 One other study demonstrated that perioperative anemia <8g/dl (5mmol/l) was associated with increased postoperative complications and mortality.58

Tissue oxygenation

A cohort study found that low tissue oxygen tension was an important deficit leading to wound dehiscence and CAL after colorectal surgery.59 Three RCT's demonstrated that perioperative supplemented 80% FiO2 during surgery as well as 6 hours postoperatively reduced anastomotic dehiscence.59–61 Anastomotic leakage was significantly higher in patients with an indexed oxygen delivery of <400 ml/min/m(2).62 Animal studies reported that tissue oxygen tension was increased by supplemental oxygen37 and that hyperbaric oxygen enhanced colonic anastomotic healing and anastomotic tissue strength.63 However, in general, there are deleterious effects described after perioperative high oxygen fractions.64

Vasopressors / Inotropes

Literature on the use of vasopressors or inotropes during or after surgery is unequivocal. Two retrospective cohort studies found that the administration of these substances was an independent risk factor for the onset of CAL in 137 and 22 CAL patients, respectively.39,65 However, small, experimental and retrospective studies demonstrated opposite results.65,66 Besides, types of vasopressors and inotropes were not always clearly specified.39

Blood pressure

A preoperative >90mmHg diastolic blood pressure was associated with a higher risk on CAL as reported in one retrospective study.67 Preoperative poorly controlled hypertension has a known association with perioperative bradycardia, tachycardia, and hypertension.68 The duration of severe intraoperative hypotension (51 versus 37 minutes, P = 0.049) was also identified as a risk factor of CAL.39,67 The relation of mean arterial pressure levels (MAP) and CAL has not been described in the literature.

Fluid management

Suboptimal peroperative fluid management might result in CAL and has been shown a risk factor of postoperative complications such as myocardial infarction.53 Over the years, the necessity of preventing perioperative hypovolemia and – vice versa - fluid overload to prevent perioperative complications became clear.69,70 Although this consideration primarily led to definition of a liberal or restrictive fluid management, subsequently an individualized perioperative goal-directed fluid management strategy was advised.71 Aims are to preserve cardiac function and perfusion of vital organs during surgery.72 Some studies showed reductions in perioperative morbidity and/or mortality using such a goal directed fluid management, especially in high risk abdominal surgical patients.72–76 Other studies, however, did not demonstrate such differences.76–78 Despite these controversial results, goal directed therapy (GDT) is considered in ERAS guidelines as beneficial in selected, high risk, cases.79,80 Benefits of GDT in a high risk abdominal surgical population were reflected in improved postoperative outcome and lower complication rates including surgical site infection according to the NSQIP definition.73 A moderate grade recommendation of a near-zero fluid balance in low risk patients and low risk surgery (and therefore by definition not in abdominal surgery) was advised.80 Earlier studies of GDT including one RCT showed marked improvements in morbidity and shortened length of hospital stay (LOS)81,82 while three other RCT's and retrospective studies did not show any benefits of GDT or amount of infused fluid.69,77,78,83,84

Blood transfusion

The requirement of multiple blood transfusions is an independent risk factor of CAL.85 Four retrospective studies, two prospective studies and a systematic search suggested an association with intraoperative blood transfusion and CAL.46,85–90 A systematic review also linked intra-operative transfusions and a blood loss >100 mL with increased CAL rates.89

3.3 Surgery related issues and CAL

Antibiotics

The combination of intravenous and oral antibiotics decreased the risk of surgical site infections. However, a consequent change in risk of CAL was not observed yet.91–96 Antibiotic administration between 15-60 minutes before the incision was found to limit the risk of postoperative wound infections.97

Analgesia

A retrospective study suggested that the institution of epidural anesthesia did not have with an effect on CAL but may nevertheless be recommended to shorten LOS.88 Two systematic reviews and the Swedish rectal cancer registry data reporting on 1474, 4000 and 39.345 patients, respectively demonstrated that epidural analgesia did neither increase CAL rates nor appeared beneficial regarding postoperative outcome.44,98–101 An experimental dog study showed that epidural analgesia promoted anastomotic healing.102 Moreover, three retrospective studies found that patients receiving epidural analgesia demonstrated the lowest CAL rate.103 In contrast, a meta-analysis of 12 small randomized controlled trials suggested that epidurals increase the CAL rate.104 In conclusion, epidural analgesia or multimodal approach is advised in ERAS guidelines and in general -but not specifically focused on CAL- for open surgery. In contrast, no advise is provided on the use of epidural analgesia in laparoscopic procedures.80

Duration of surgery

Prolonged surgery is correlated with higher intra- and postoperative complications. Moreover, an 1.53-9.9 odds ratio of developing CAL was reported.105–108 A national retrospective cohort including 13.648 patients also concluded that operation time was associated with an increased chance of anastomotic leaks.109 On the other hand, morbidity and mortality rates were not increased when prolonged laparoscopy operations was compared to open surgery.110

Intraoperative events

Intraoperative adverse events such as bleeding complications or iatrogenic injury to solid organs were found to significantly increase the risk of developing CAL.111 Conversion during colorectal surgery also augmented postoperative morbidity and mortality although the risk of CAL was not affected.112–115

Contamination

Several RCT's, meta-analysis, systematic reviews and cohort studies have found that mechanical bowel preparation (MBP) does not influence a risk of colonic anastomotic leakage.116–126 One RCT and one review revealed that rectal cancer surgery without MBP was associated with a higher postoperative complication rate.127,128 A combination of MBP and oral antibiotics preparations may decrease morbidity.129 Moreover, if MBP is combined with oral antibiotics, CAL is reduced by nearly half, as shown in a retrospective review including 8442 patients.130 Surgery performed in emergency settings without preoperative preparation has an increased risk for anastomotic dehiscence.131

Intraoperative contamination or dirty wounds are independent risk factors of anastomotic leakages as demonstrated by a prospective multicenter cohort study.42 Two retrospective studies and a prospective surveillance also identified intraoperative contamination as a surgery-related risk factor.85,107,132

Surgical experience

The surgeon's operative experience has a clear influence on the development of CAL as was recognized in several studies.46,133,134 A prospective study of 2363 patients also stipulated the importance of the individual surgeon as an independent risk factor of CAL.135 In contrast, 19 non-randomized observational studies including 14.344 colorectal resections did not identify any differences in CAL between experts and expert supervised trainees.136 Another observational study revealed that surgical skills, preoperative factors and patient characteristics all equally contributed to the risk of CAL.137

Discussion

This literature review provides existing evidence of intraoperative modifiable risk factors of CAL. The exact role of a number of individual intraoperative risk factors of CAL have not always been clearly specified in the past. There is strong evidence to suggest that a large number of intraoperative non-surgical parameters significantly increase the risk of CAL including hyperglycemia, anemia, mistimed or no (suitable) administration of antibiotics, a minimal 100 cc blood loss, blood transfusion, intraoperative events and more than 2 hours of surgery. As a consequence, it is highly important to optimize patients' preoperative status as well as intraoperative status. It is therefore advised to boost hemoglobin levels if lower than 8g/dl (5mmol/l),138,139 to administer antibiotics between 15 and 60 minutes prior to skin incision,97,140–143 and to restrict blood loss, intraoperative events and duration of surgery.111

Blood glucose levels require intraoperative monitoring whereas hyperglycemia must be corrected preoperatively aiming at a 4.4 to 6.1 mmol/l level. 32,36,140,144–147 A simple finger glucose meter allows for monitoring of diabetic as well as non diabetic patients during the operation. Even the latter category, once hyperglycemic, has a higher risk of postoperative complications and CAL. Iron supplements preoperatively might be the most successful in increasing the hemoglobin concentration, but there is still no major clinical trial to support this finding for patients undergoing colorectal surgery.148,149 Another option, although more invasive, is to preoperatively supply erythropoietin (EPO). Since one third of patients with a colorectal carcinoma who are candidate for surgery are anemic preoperatively, it is even more important to optimize the hemoglobin level.150 Accurate administration of intravenous antibiotics prior to surgery has not been directly linked to an decreased risk of CAL, although it lowers postoperative wound infections. However, some studies concluded that the combination of selective digestive decontamination (SDD) and mechanical bowel preparation might lower the risk of CAL. Unfortunately this is not based on the highest levels of evidence and therefore cannot be recommended as standard practice. Operating time and intraoperative adverse events can be limited if the preoperative work up is optimal including the right diagnostics, to have experienced surgeons and operating team, to facilitate optimal surgical conditions, to perform laparoscopic surgery if feasible to limit blood loss and blood transfusions150 and to limit operations to high volume centers.151–155

Considering potential risk factors of CAL, from the present review data on the influence of body core temperature,156 the role of MAP, blood pressure, inotropes / vasopressors, fluid management, tissue oxygenation and epidural analgesia appeared underexplored. All these factors are

anesthesia related potential modifiable risk factors.

Due to heterogeneous methods for intraoperative temperature monitoring combined with surgical setting related difficulties to increase core temperature accurately, it is hard to determine the exact relevance and implications on CAL. Despite the unknown relation of temperature on CAL, a body core temperature of at least 36 degrees is recommended for several reasons (i.e. patient comfort, coagulation, postoperative recovery) and might be achieved with optimal prewarming which starts preoperatively.157–160

Perfusion and other hemodynamic parameters of anesthesia perioperatively are mostly modifiable and will possibly be related to the development of CAL. Splanchnic vasoconstriction and subsequent deterioration of microcirculation results in anastomotic hypoxia. Therefore it is recommended to accurately maintain a level of MAP at least greater than 60, since it is considered generally sufficient for providing adequate perfusion pressures to vital organs.161

However, we found no direct relation between MAP and CAL. For example, the exact influence of blood pressure on CAL in light of preoperatively poorly regulated blood pressure - possibly resulting in disrupted auto regulation and hypoperfusion due to relative intraoperative hypotension for the new set point – needs to be determined. As well the exact role of auto regulatory blood pressure mechanisms in the pre-existent hypertensic patient in a perioperative setting on risk on CAL needs to be elucidated. Further, the beneficial or harmful effects of using inotropes / vasopressors to optimize blood flow and perfusion pressures and any potential relation towards CAL should be assessed. Beneficial effects might be related to optimizing cardiac output. Harmful effects might be a result of splanchnic vasoconstriction, deterioration of microcirculation resulting in tissue hypoxia. However, until now the underlying mechanism remains unclear.

Over the past years perioperative fluid management has been widely discussed. Present evidence does not allow to give final recommendations on which type of fluid to administer,162,163 since all types of fluid management have not directly been correlated to the development of CAL. More research is needed to successfully distinguish between the different fluid management options. Until then, GDT (albeit unclear what the exact definition of this strategy is) is recommended in particular for high risk populations. The lower the perioperative risks, the lower the GDT gains are. Fluid overload and mesenteric hypoperfusion caused by hypovolemia have a negative impact on the recovery of bowel function.76,164 A lower volume status is a potent cause of gut mucosal hypoperfusion, thereby diminishing nutritional support of the tissues at the anastomotic side.

Surgical damage leads to a combination of decreased vascular supply, high cellularity and an increased oxygen demand. With this knowledge supplemental oxygen perioperatively might reduce colorectal anastomotic dehiscence. However, only two RCT's, one cohort study and two animal studies proved these results. One pilot study showed that the tissue oxygen saturation (StO2) can be accurately measured with the near-infrared spectroscopy (NIRS). It also revealed that a low StO2 on both sides of the anastomosis is associated with complications.165 Targeting StO2 optimization did not improve perioperative outcome in a high risk abdominal surgical population.166 However, especially in critically ill populations arterial hyperoxia is associated with poorer outcomes, although exact cut-off points need to be determined.167 Moreover, there is debate about the interpretation and conclusion of the results of a recent review in favor of higher inspired oxygen fractions due to heterogeneity issues.168 Belda et al explained why just increasing perioperative oxygen fractions in order to prevent surgical site infections today seems too short-sighted based on current literature. At last, detrimental effects of perioperative high oxygen fractions might include increased long-term mortality in cancer patients.64 For these reasons, the exact role of higher supplemental oxygen delivery in humans in clinical daily practice needs to be determined in much larger study populations. Until then, only preventing perioperative hypoxia remains standard practice.

Epidural analgesia is commonly used in colorectal surgery, but the scientific evidence of the correlation towards CAL remains conflicting. Beneficial effects of epidural analgesia may extend to improved pain control, patient satisfaction and blood oxygenation, a reduced risk of pneumonia and reduced need of prolonged ventilation or reintubation.169–171 From an anesthesiological perspective, epidural analgesia does not only reduce the postoperative consumption of systemic opioids but directly improves gastrointestinal function and should be considered where possible, at least for open surgical procedures.172 There is also a low risk of complications due to epidural analgesia.99 But, if technical failure occurs, the complications can be severe, implying careful assessment for indications.

This review summarizes that certain intraoperative non-surgical risk factors of CAL have been determined and could be optimized pre- and intraoperatively. A 'bundle of care' should be introduced including monitoring and adjusting glucose and hemoglobin level, to accurately administer antibiotics prior to surgery and to restrict the amount of blood loss, duration of surgery and intraoperative events by optimizing the operating team and logistics. Unfortunately, still many non-surgical intraoperative parameters remain as undetermined for the risk of developing CAL. This highlights the need to improve collaboration between surgeons and anesthesiologists. It seems rational to improve or optimize patients temperature, fluid status

including cardiac output, MAP and vasopressor use intraoperatively, but evidence is still lacking. Therefore, a prospective registration study is recommended to determine the relation of described common practices and factors on CAL and the additional value of such optimization.

Conclusion

Where unchangeable risk factors are used for CAL risk stratification, identification of modifiable risk factors is necessary to substantially reduce the number of CAL and other complications. Both surgical and non-surgical factors will have their contribution on outcome and quality of life. The exact importance of the individual non-surgical intraoperative risk factor is yet to be determined. Surgeons and anesthesiologists should cooperate on these items in the continuous effort to reduce the number of CAL. Therefore, a registration study is recommended and will now be applied by surgeons and anesthesiologists in a multicenter cohort study in the Netherlands, facilitated by the national Taskforce Anastomotic Leakage.

Highlights

Intraoperative risk factors CAL not yet determined. Registration study recommended and started to identify intraoperative modifiable risk factors

Abbreviations

CAL: Colorectal Anastomotic Leakage
CLS: Colon Leakage Score
MAP: Mean Arterial Pressure
MBP: Mechanical Bowel Preparation
NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

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Figure 1. Flow diagram of study selection.

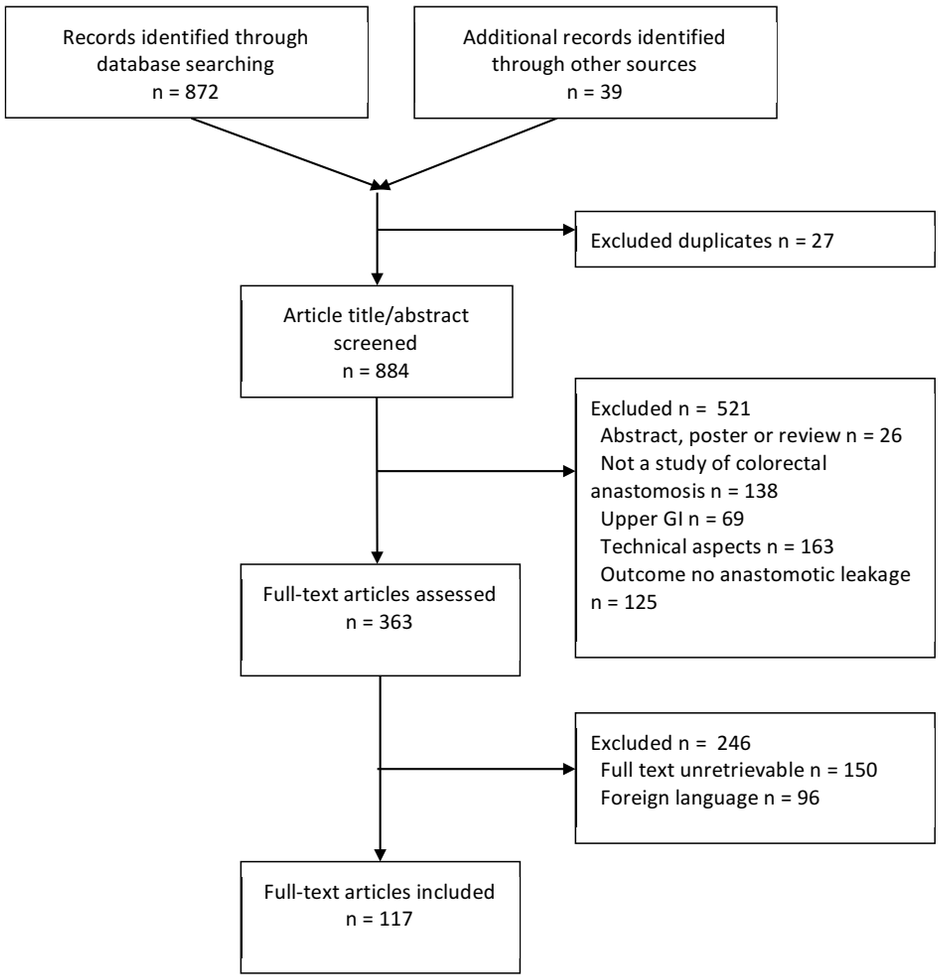


Table 1. This is an overview of literature on intraoperative modifiable risk factors CAL. Risk factors are categorized into three subgroups: general status, tissue perfusion and surgery related risk factors. Reference numbers are given (...) for each intraoperative modifiable risk factor.

General status	Tissue perfusion	Surgery related
Hyperglycemia 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35	Blood loss and anemia 4, 34, 38, 39, 40 ,41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57	Antibiotics 90, 91, 92, 93, 94, 95, 96
Temperature 31, 36, 37	Tissue oxygenation 36, 58, 59, 60, 61, 62, 63	Analgesia 43, 79, 87, 97, 98, 99, 100, 101, 102, 103
	Inotropes / Vasopressors 38, 64, 65	Duration of surgery 104, 105, 106, 107, 108, 109
	Blood pressure 38, 66, 67	Intraoperative events 110, 111, 112, 113, 114
	Fluid management 52, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83	Contamination 41, 84, 106, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127 ,128, 129, 130, 131
	Blood transfusion 45, 84, 85, 86, 87, 88, 89	Surgical experience 45, 132, 133 ,134, 135, 136

Table 2. Modifiable intraoperative risk factors CAL as described in the literature. Comment of the authors is based on the existing literature. Strong evidence group includes determined risk factors of CAL based on high quality studies (level I and II), the moderate group includes potential risk factors of CAL based on experimental studies (level III), weak evidence group are potential risk factors of CAL with level IV or V evidence.

Risk factors	Modifiable	Recommendation	Comment of the authors*
General status			
Hyperglycemia	+	4,4-6.1 mmol/l	Strong
Temperature	+	> 36°C	Moderate
Local perfusion			
Blood loss and anemia	+	Restrict blood los < 100ml Hemoglobin level > 8 g/dl (>5 mmol/l)	Moderate
Tissue oxygenation	+	Supplemental 80% FiO2 during and 6 hours after surgery	Weak
Inotropes / Vasopressors	+	With caution	Weak
Blood pressure	+	- DBP < 90 mmHg preoperatively. - < 40 % decrease in DBP perioperatively. -MAP >60	Weak
Fluid management Cardiac index	+	- Goal directed therapy for high risk patients. - >2,5 L/min/m2	Weak to Moderate
Blood transfusion	+	No transfusion	Strong
Surgery related			
Antibiotics	+	15-60 min prior to surgery	Moderate
Analgesia	+	According to ERAS guidelines (not specifically focused on CAL)	Weak
Duration of surgery	+	< 2 hours, experienced surgeons	Strong
Intraoperative events	-	No intraoperative events	Strong
Contamination	+	No contamination	Strong
Conversion	+/-	No conversion	Strong
Surgical experience	+	- > 50 surgeries a year - Trained operating team	Moderate

Table 3. Characteristics of 117 included studies. Divided into subcategories. First author of study was depicted including year of study and reference number (...). Design of study, study period, country where the study was performed, number of included patients in case it was not a review and main findings of the studies were additionally highlighted in this table. GDT = goal directed therapy, PGDT = protocol goal directed therapy, LOS = length of hospital stay, CAL = colorectal anastomotic leakage, SSI = surgical site infections, DM = diabetes mellitus, MCG = mean postoperative capillary glucose, BG = blood glucose, BMI = body mass index, SV = stroke volume, RCT = randomized controlled trial, SWI = surgical wound infection, CRC = colorectal cancer, NSQIP = National Surgical Quality Improvement Protocol.

Study	Design	Study period	Country	n	Main findings
Hyperglycemia					
Kiran 2013 (20)	*Observational single center study* on hyperglycemia during colorectal surgery in non-diabetic patients.	2010-2011	USA	2.628	Postoperative elevated glucose value is adversely associated with morbidity and mortality; this risk is related to the degree of glucose elevation.
Kwon 2013 (21)	*Observational multicenter study* on perioperative hyperglycemia.	2005-2010	USA	11.633	Perioperative hyperglycemia was associated with adverse outcomes in general surgery patients with and without diabetes.
Frisch 2010 (22)	*Observational single center study* on pre- and post surgery blood glucose levels.	1 January 2007 - 30 June 2007	USA	3.184	Perioperative hyperglycemia is associated with increased LOS, hospital complications, and mortality after noncardiac general surgery.

Turina 2006 (23)	*Experimental study and prospective evaluation* of perioperative blood glucose levels.	2004	USA	20 & 5.285	This may provide a mechanism by which high glucose and insulin impair innate immunity.
McConnell 2009 (24)	*Observational study* on colorectal patients.	April 2001 - May 2006	Canada	149	48-h MCG >11.0 mmol/L is independently associated with increased SSI following colorectal resection in patients with DM.
Lee 2014 (25)	*Clinical review.*	Till 2014	USA	-	Further studies are needed.
Jackson 2011 (26)	*Retrospective analysis* of colorectal surgery patients.	2000-2005	USA	9.638	Perioperative BG target of 80 to 120 mg/dL, although avoiding hypoglycemia, might be appropriate.
Lin 2015 (27)	*Meta-analysis* evaluating DM and CAL risk in patients after gastrointestinal resection.	Till 2014	China	-	Perioperative BG target of 80 to 120 mg/dL, although avoiding hypoglycemia, might be appropriate.
Zaharie 2012 (29)	*Retrospective analysis* of colorectal resections.	1996-2005	Romania	1.743	Diabetes is a significant risk factor of CAL.
Gustafsson 2009 (30)	*Observational study* in major colorectal surgery.	November 2005 - March 2007	Sweden	141	HbA1c may identify patients at higher risk of poor glycaemic control and postoperative complications.
Shaffer 2014 (31)	*Retrospective cohort study* of partial or total colon resections.	January 2009 - December 2012	USA	365	Glucose control is a modifiable risk factor of SSI.
Cong 2009 (32)	*Retrospective analysis* of rectal cancer patients who underwent anterior resection.	2005 - 2008	China	738	Diabetes mellitus is a risk factor for anastomotic leakage after rectal surgery.
Volk 2011 (33)	*Retrospective analysis* on perioperative data of colorectal surgery patients and CAL.	2000 - 2007	Germany	463	High BMI, diabetes mellitus, and hypotensive circulation (i.e., shock) upon admission are also strongly correlated to anastomotic leakage.
Ianca 2008 (34)	*Retrospective analysis* on large bowel resection with primary anastomosis.	2002 and 2006	Romania	933	Serum protein level lower than 5.5 g/dl and serum hemoglobin lower than 9.4 g/dl could be considered as host-related predictive markers for anastomotic leak in large bowel resections for cancer.
Kotagal 2015 (35)	*Retrospective review* in general surgery.	2010–2012	USA	40.836	NDM patients, those with hyperglycemia had significantly higher odds of a composite adverse event.
Temperature					
Shaffer 2014 (31)	*Retrospective cohort study* of partial or total colon resection patients.	January 2009 - December 2012	USA	365	Glucose control is a modifiable risk factor of SSI.
Kimberger 2007 (36)	*Randomized controlled trial* on pigs.	2007	Swiss	16	Supplemental oxygen increased tissue oxygen tension in healthy, peri anastomotic, and anastomotic colon tissue.
Glatz 2014 (37)	*Randomized controlled trial* on rats.	2013	Germany	30	No significant changes were seen in the evaluation of anastomotic stability.
Blood loss and anemia					
Dekker 2011 (4)	*Retrospective cohort study* of left-sided colorectal surgery with primary anastomosis.	2010	Netherlands	121	The CLS can predict the risk of anastomotic leakage following left-sided colorectal surgery.
Lanca 2008 (34)	*Retrospective analysis* on large bowel resection with primary anastomosis.	2002-2006	Romania	933	A serum protein level lower than 5.5 g/dl and serum hemoglobin lower than 9.4 g/dl could be considered as host-related predictive markers for anastomotic leak in large bowel resections for cancer.

Choudhuri 2013 (38)	*Retrospective analysis* of all anastomotic leakages of colorectal patients.	September 2009 - April 2012	India	1.246	Anemia <8 g/dl was independently associated with increased risk of anastomotic leak.
Bertelsen 2010 (39)	*Prospective cohort study* of patients with colorectal adenocarcinoma.	May 2001 - December 2004	Denmark	1.495	Anastomotic leakage after anterior resection for low rectal tumours is related to the level, male gender, smoking and perioperative bleeding.
Nesbakken 2002 (40)	*Prospective observational study* of colorectal patients.	1983-2000	Norway	393	Multiple regression analysis identified a low anastomosis, major bleeding, and age over 75 years as significant risk factors for the development of anastomotic leaks.
Leichtle 2012 (41)	*Prospective observational study* of colorectal patients.	2007-2010	USA	4.340	Risk factors associated with anastomotic leakage were fecal contamination and intraoperative blood loss of more than 100 mL.
Spolverato 2015 (42)	*Retrospective review of prospectively collected data* on pancreatic, hepatic or colorectal resections.	January 2010 - April 2014	USA	4.669	A Hb level of 50% or greater following gastrointestinal surgery was associated with complications, especially ischemic adverse events, even if the nadir Hb level remained at 7 g/dL or greater.
Jestin 2008 (43)	*Case-control study* of rectal resections.	1995-2000	Sweden	372	Adverse intraoperative events, a long duration of surgery and major bleeding, increase the risk of leakage.
Telem 2010 (44)	*Case-control study* with a prospectively maintained administrative database.	January 2002 - December 2007	USA	180	In patients with IBD, preoperative albumin levels lower than 3.5 g/dL, intraoperative blood loss of 200 mL or more, operative time of 200 minutes or more, and/or intraoperative transfusion requirement increased AL risk.
Tang 2001 (45)	*Prospective single center study* of risk-adjusted surgical outcomes.	February 1995 -	Taiwan	2.809	In addition to ASA score and surgical wound class, blood transfusion,

		December 1998			creation of ostomy, types of operation, use of drainage, sex, and surgeons were important in predicting SSIs after elective colorectal resection.
Foster 1985 (46)	*Randomized controlled trial* on rats with colorectal resection.	1984	UK	45	Adequate intra-operative fluid replacement during colonic resection and anastomosis is a prerequisite for successful healing.
Greatorex 1970 (47)	*Retrospective cohort study* on anterior resections and left hemicolectomy.	1957 - 1966	UK	640	It is possible that leakage of anastomosis is related to operative blood loss, and that vasoconstriction produced by haemorrhage has a deleterious effect on the anastomosis.
Zhao 2014 (48)	*Meta-analysis* of 14 randomized controlled trials on laparoscopic versus open surgery in rectal cancer patients.	January 1991 - December 2012	-	-	Compared to the open group, surgical time was prolonged for 31.42 min, the amount of blood loss during the surgery was reduced by 108.95 ml and the proportion of blood transfusion was reduced in the laparoscopic group.
Van der Pas 2013 (50)	*Randomized controlled trial.* Non-inferiority, open-label, comparing open with laparoscopic surgery for rectal cancer patients. COLOR II.	January 2004 - May 2010	Belgium, Canada, Denmark, Germany, the Netherlands, Spain, South Korea, and Sweden	1.044	Laparoscopic surgery was associated with less blood loss, a longer operating time, less use of epidural analgesia, earlier restoration of bowel function, and reduction of the hospital stay.
Kang 2010 (51)	*Randomized controlled trial* comparing open versus laparoscopic surgery after preoperative chemoradiotherapy in patients with mid or low rectal cancer.	April 2006 - August 2009	South Korea	340	Estimated blood loss was less in the laparoscopic group than in the open group, although surgery time was longer in the laparoscopic group.

Hayden et al 2015 (53)	*A retrospective review* was performed on patients who had surgery performed for rectal cancer.	2005-2011	USA	123	Preoperative anemia as possible risk factor for anastomotic leak and neoadjuvant chemoradiation may lead to increased risk of complications overall.
Harju 1988 (54)	*Randomized controlled trial* for iron therapy to improve blood hemoglobin.	1987	Finland	40	Patients with empty iron stores responded well to iron therapy. Not only ferritin (P<0.001) but also blood hemoglobin (P<0.01) concentrations increased.
Saha 2009 (55)	*Retrospective analysis* on medical, anaesthetic and nursing records.	1999-2005	USA	325	Anemia and hypo-albuminemia may be associated with poor outcome.
Abu-Ghanem 2014 (56)	*Prospective data analysis* of patients who underwent laparoscopic colorectal surgery.	2003-2011	Israel	500	Preoperative Charlson score, hemoglobin level, carcinoma, and lower rectum pathologies were found to be independent risk factors for PBT in patients undergoing laparoscopic colorectal surgery.
Dunne 2002 (57)	*Prospective data analysis* (NSQIP) on noncardiac surgical patients.	1995-2000	USA	6.301	High incidence of preoperative en postoperative anemia in surgical patients, with a coincident increase in blood utilization.
Tissue oxygenation					
Kimberger 2007 (36)	*Randomized controlled trial* on pigs.	2007	Swiss	16	Supplemental oxygen increased tissue oxygen tension in healthy, perianastomotic, and anastomotic colon tissue.
Schietroma 2012 (58)	*Randomized controlled trial* on patients with rectal cancer.	February 2008 - February 2011	Italy	72	The overall anastomotic leak rate was 16.6%. 8 patients had an anastomotic dehiscence in the 30% FiO_2 group and 4 in the 80% FiO_2 group ($p < 0.05$). The risk of anastomotic leak was 46% lower in the 80% FiO_2 group vs. the 30% FiO_2.
Schietroma 2014 (59)	*Prospective randomized study* on infraperitoneal anastomosis for rectal cancer.	2008-2013	Italy	81	Supplemental 80% FiO_2 reduced postoperative SSI with few risks to the patient and little associated cost.
Garcia-Botello 2006 (60)	*Randomized controlled trial* on rectal or sigmoid cancer surgery.	June 2003 - January 2005	Spain	45	Perioperative administration of 80% O2 both during surgery and for 6 hours afterwards is associated with an improvement in relative anastomotic hypoperfusion as assessed by the measurement of pHi and PCO2 gap.
Levy 2012 (61)	*Randomized controlled trial* in fluid - optimized patients undergoing laparoscopic colorectal surgery.	2011	UK	75	Anastomotic leakage was significantly higher in patients with a DO_2I of < 400 ml/min/m^2.
Poyrazoglu 2015 (62)	*Randomized controlled trial* on rats.	2013	Turkey	21	The hyperbaric oxygen HBO administration has beneficial effects and contributed to wound healing in colonic anastomosis. Preconditioning-HBO did not alter the results significantly.
Meyhoff 2012 (63)	*Randomized controlled trial* on patients for elective or emergency laparotomy.	October 2006 - October 2008	Denmark	1.386	Administration of 80% oxygen in the perioperative period was associated with significantly increased long-term mortality and this appeared to be statistically significant in patients undergoing cancer surgery but not in non cancer patients.
Inotropes					
Choudhuri 2013 (38)	*Retrospective analysis* of all the anastomotic leakages.	September 2009 - April 2012.	India	1.246	Albumin <3.5 g/dl, anemia <8 g/dl, hypotension, use of inotropes, and blood transfusion independently increased the risk of anastomotic leak.

Zakrison 2007 (64)	*Retrospective analysis* of gastro intestinal anastomosis.	January 2000 - April 2004	USA	259	Vasopressors appear to increase anastomotic leaks threefold, independent of clinical/surgical status or hypotension.
Adanir 2010 (65)	*Randomized controlled trial* on rabbits.	2009	New Zealand	42	Vasopressors appeared to increase the risk of anastomotic leakage. BPA was increased with high doses of vasopressor.
Blood pressure					
Post 2012 (66)	*Prospective observational study* on colorectal surgery patients.	-	Netherlands	285	High preoperative diastolic blood pressure and profound intraoperative hypotension combined with complex surgery, marked by a blood loss of ≥250 mL and the occurrence of intraoperative adverse events, is associated with an increased risk of developing anastomotic leakage.
Varon 2008 (67)	*Review* of pharmacologic agents and strategies commonly used in the management of perioperative hypertension.	1992-2007	-	-	The goal of controlling perioperative hypertension is to protect organ function, and is currently recommended based on the assumption that the risk of complications will be reduced and outcomes improved
Fluid management					
Brandstup 2012 (68)	*Randomized controlled trial*, multicenter and double-blinded, in colorectal surgery patients.	March 2008 - July 2009	Denmark	150	No significant differences between the groups were found for overall, major, minor, cardiopulmonary, or tissue-healing complications, neither length of hospital stay.
Brandstup 2006 (69)	*Review* of evidence behind current standard fluid therapy, and analysis of trials examining the effect of fluid therapy on outcome of surgery.	-	Denmark	-	Fluid lost should be replaced, and fluid overload should be avoided.

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Holte 2007 (70)	*Randomized controlled trial,* double blinded, in colonic surgery.	January 2003 - September 2004	USA	32	Despite improvements in pulmonary function and oxygen saturation with a restrictive fluid regimen, overall functional recovery was not dependent on the amount of fluid administered in the fast-track colonic surgery.
Kirov 2010 (71)	*Review* the perioperative monitoring tools and targets for hemodynamic optimization, assessing the influence of goal-directed therapy in different categories of surgical patients.	-	Israel	-	Based on adequate monitoring, the goal-directed algorithms facilitate early detection of pathophysiological changes and influence the perioperative hemodynamic therapy that can improve the clinical outcome.
Cannesson 2015 (72)	*Prospective data analysis* on patients undergoing open colectomy, pancreatectomy with cancer, participating in a fluid management protocol (PGDT or no PGDT).	June 2011 - September 2013	USA	320	Fluid balance was not significantly different between the two groups. LOS in the hospital in patients in whom PGDT was not fully reported was 8 (6–11) days compared to 8 (5–11) days in patients in whom PGDT was fully reported ($p = 0.21$).
Futier 2010 (73)	*Randomized controlled trial* of patients undergoing major abdominal surgery.	May 2008 - December 2008	France	70	Excessive fluid restriction increased the level of hypovolemia, leading to reduced $ScvO_2$ and thereby increased incidence of postoperative complications.
Giglio 2009 (74)	*Meta-analysis* of the effects of GDT on postoperative GI and liver complications.	Till 2008	-	3.410	GDT, by maintaining an adequate systemic oxygenation, can protect organs particularly at risk of perioperative hypoperfusion and is effective in reducing GI complications.
Bundgaard-Nielsen 2007 (75)	*Review of studies* in which a goal-directed therapeutic strategy was used in surgical patients.	1966 - October 2006	-	725	GDT with the maximization of flow-related haemodynamic variables reduces hospital stay, PONV and

					complications, and facilitates faster gastrointestinal functional recovery.
Pestana 2014 (76)	*Randomized clinical trial* on colorectal surgery patients in 6 tertiary hospitals.	January 2011 - August 2012	Spain, Israel	142	Perioperative hemodynamic protocol guided by a noninvasive cardiac output monitor was not associated with a decrease in the incidence of overall complications or length of stay in major abdominal surgery.
Challand 2012 (77)	*Randomized controlled trial,* double-blinded in major colorectal surgery.	March 2009 - April 2010	UK	179	Intraoperative SV optimization conferred no additional benefit over standard fluid therapy.
Knott 2012 (78)	*Delphi analysis* using three rounds of reiterative questionnaires to obtain consensus.	May 2010 - July 2010	UK	86	Agreement was reached on the role of regional analgesia and the use of esophageal Doppler for intraoperative GDT.
Feldheiser 2015 (79)	*Consensus review* including meta-analyses, randomized controlled trials and large prospective cohort studies.	1966-2014	-	-	This consensus statement demonstrates that anesthesiologists control several preoperative, intraoperative and postoperative ERAS elements.
Gómez-Izquierdo 2015 (80)	*Meta analysis* of randomized clinical trials and cohort studies.	January 1989 - June 2013	-	1.399	GDT facilitated the recovery of bowel function, particularly in patients not treated within enhanced recovery programmes and in those undergoing colorectal operations.
Funk 2015 (81)	*Randomized controlled trial* in elective open repair of abdominal aortic aneurysm.	2014	Canada	40	Despite being associated with fewer complications and improved hemodynamics, there was no difference in the inflammatory response of patients treated with GDT.
Phan 2014 (82)	*Randomized controlled trial* on fluid restriction.	2012-2013	Australia	100	The increased perioperative fluid volumes and increased stroke volumes at the end of surgery in

					patients receiving GDT did not translate to a significant difference in LOS or complications.
Von Heymann 2006 (83)	*Retrospective analysis* of colonic surgery.	2001-2005	Germany	136	The incidence of postoperative complications was not different between patients who were infused 36ml/kg or 53ml/kg of fluids during surgery and post anesthesia care unite stay.
Blood transfusion					
Tang 2001 (45)	*Prospective single center study* of risk-adjusted surgical outcomes.	February 1995 - December 1998	Taiwan	2.809	In addition to ASA score and surgical wound class, blood transfusion, creation of ostomy, types of operation, use of drainage, sex, and surgeons were important in predicting SSIs after elective colorectal resection.
Makela 2003 (84)	*Case control study* on reoperated patients for colorectal anastomosis leakage.	1992-2001	Finland	88	Patients with multiple risk factors have higher risk for anastomotic leakage. When patients have three or more risk factors, the creation of a protective stoma should be considered in cases with a low rectal anastomosis.
Alves 2002 (85)	*Retrospective review* of colorectal resections.	1990-1997	France	707	Blood transfusion intra-operatively is associated with CAL.
Park 2013 (86)	*Retrospective analysis* of patients with rectal cancer.	January 2006 - March 2009	Korea	1.609	Male sex, low anastomosis, preoperative chemoradiation, advanced tumor stage, perioperative bleeding, and multiple firings of the linear stapler increased the risk of CAL after laparoscopic surgery for rectal cancer.

Lai 2013 (87)	*Retrospective study* on colorectal patients.	2000-2011	China	1.312	ASA score, history of hypertension, episodes of hypotension, anastomosis technique, tumor localization, anesthesia duration, and perioperative blood transfusion were significant risk factors for CAL.
Qu 2015 (88)	*Systematic review* on cohort, case–control studies, and randomized controlled trials that examined clinical risk factors for CAL.	Till August 2014	-	4.580	Four operative factors were significantly associated with increased risk of CAL: including longer operative time, number of stapler firings ≥3, intra-operative transfusions/blood loss >100 mL, and anastomosis level within 5 cm from the anal verge.
Boccola 2011 (89)	*Prospective analysis* of patients with colorectal anastomosis.	1984-2004	Australia	1.576	Significant risk factors were anterior resection, anastomosis using an intraluminal stapling device, abdominal drain via laparoscopic port, postoperative blood transfusion, primary cancer site at the rectum, and TNM stage of T2 or higher. Having an LEK showed significant impact on overall, cancer-related, and disease-free survival.
Antibiotics					
Sadahiro 2014 (90)	*Randomized controlled trial* on the effectiveness of oral antibiotics and probiotics in preventing postoperative infection in elective colon cancer procedures.	2008-2011	Japan	300	Recommend oral antibiotics, rather than probiotics, as bowel preparation for elective colon cancer procedures to prevent surgical-site infections.
Abis 2013 (91)	*Review* on studies of selective decontamination of the digestive tract.	1970-2012	Netherlands	-	On the basis of available evidence, the authors have now instigated a large multicenter RCT to evaluate the role of SDD in colorectal cancer

					surgery on anastomotic leakage (SELECT trial).
Abis 2013 (92)	*Randomized multicenter study* comparing preoperative SDD combined with standard antibiotic prophylaxis with standard antibiotic prophylaxis alone in elective CRC surgery patients.	Till 2013	Netherlands	762	Selective decontamination of the digestive tract will reduce clinical CAL, thereby reducing the morbidity and the mortality in CRC patients.
Kobayashi 2014 (93)	*Prospectively data analysis* on patients undergoing colorectal resection.	2002-2010	Japan	918	In patients with anastomotic leakage after surgery, the empirical use of antimicrobial regimens with broad-spectrum activity against both aerobic and anaerobic organisms to treat postoperative intra-abdominal infections following colorectal surgery in accordance with the 2010 IDSA/SIS guidelines is associated with better outcomes.
Rowe-Jones 1990 (95)	*Randomized controlled trial* comparing two prophylactic antibiotic regimens in a parallel group trial.	1987-1989	UK	1.018	A single preoperative dose of cefotaxime plus metronidazole is as efficacious as a three dose regimen of cefuroxime plus metronidazole in preventing wound infection after colorectal surgery and has practical advantages in eliminating the need for postoperative antibiotics.
Nelson 2009 (96)	*Retrospective analysis* to investigate the single, dichotomous outcome of SWI.	-	-	30.880	Antibiotics delivered will reduce the risk of postoperative SWI by at least 75%.
Analgesia					
Jestin 2008 (43)	*Case-control study,* data from the Swedish Rectal Cancer Registry were analysed.	1995-2000	Sweden	402	Except for a protective stoma, none of the variables considered as possible targets for improvement (postoperative epidural anaesthesia,

					observation at intensive care unit for more than 24 h, and intra abdominal drainage) proved to be protective factors.
Feldheiser 2015 (79)	*Consensus review* including meta-analyses, randomized controlled trials and large prospective cohort studies.	1966-2014	-	-	This consensus statement demonstrates that anesthesiologists control several preoperative, intraoperative and postoperative ERAS elements.
Lai 2013 (87)	*Retrospective study* on the risk of anastomotic leakage in colorectal surgery patients.	2000-2011	China	1.312	ASA score, history of hypertension, episodes of hypotension, anastomosis technique, tumor localization, anesthesia duration, and perioperative blood transfusion were significant risk factors for AL.
Popping 2014 (97)	*Systematic Review and Meta-analysis* of randomized controlled trials.	Till July 2012	-	9.044	In adults having surgery under general anesthesia, concomitant epidural analgesia reduces postoperative mortality and improves a multitude of cardiovascular, respiratory, and gastrointestinal morbidity endpoints compared with patients receiving systemic analgesia.
Halabi 2014 (98)	*Retrospective review* of laparoscopic colorectal cases performed with or without epidural analgesia for cancer, diverticular disease, and benign polyps.	January 2002 - December 2010	USA	191.576	Epidural analgesia did not affect the incidence of respiratory failure, pneumonia, anastomotic leak, ileus, or urinary retention.
Halabi 2013 (99)	*Retrospective analysis* on nationwide inpatient sample for elective open colorectal surgeries performed for benign and malignant conditions with or without the use of epidural analgesia.	2002–2010	USA	888.135	Epidural analgesia in open colorectal surgery is safe but does not add major clinical benefits over conventional analgesia.

Piccioni 2015 (100)	*Retrospective study* on colorectal cancer patients and the risk of anastomotic leakage.	May 2008 - December 2011	Italy	1.474	Epidural analgesia does not influence the AL risk after open colorectal surgery for cancer.
Blass 1987 (101)	*Randomized controlled trial* on dogs.	1986	USA	16	Intraoperatively, the epidural-general anesthesia dogs tended to bleed less, making the anastomosis less difficult.
Ryan 1989 (102)	*Three retrospective studies* were conducted to compare the outcomes of colorectal anastomoses, with and without resections, with respect to anaesthetic technique.	1987	Germany	-	Anastomotic leak rates and death rates were lower in the CRAG group, and the lowest incidence of anastomotic leak was reported in the patients receiving CEA.
Holte 2001 (103)	*Review* of randomized controlled trials aiming to investigate postoperative outcome.	1966-May 2000	-	562	There is no statistically significant evidence from randomized controlled trials to indicate epidural analgesia with local anaesthetic to be associated with an increased risk of anastomotic breakdown.
Duration of surgery					
Suding 2008 (104)	*Prospective review* of patient and operative characteristics that contribute to anastomotic leaks.	May 2002 - March 2005	USA	672	Significant risk factors for anastomotic leaks include low preoperative serum albumin level, steroid use, male sex, and increased duration of surgery.
Lipska 2006 (105)	*Review* of the anastomotic leakage rates in a single colorectal Unit to evaluate the risk factors for anastomotic leakage after lower gastrointestinal anastomosis.	1999-2004	New Zealand	541	Male gender, previous abdominal surgery and low rectal cancer are associated with increased anastomotic leakage rates.
Konishi 2006 (106)	*Prospective surveillance* of all elective colorectal resections performed by a single surgeon in a single university.	November 2000 - July 2004	Japan	391	Preoperative steroid use, longer duration of operation, and contamination of the operative field were independent risk factors for developing clinical anastomotic leakage after elective resection for colorectal cancer.
Gervaz 2012 (107)	*Multicenter prospective surveillance program* to assess the incidence of SSI.	October 2008 - November 2010	Switzerland	534	A simple clinical score based on four preoperative variables was clinically useful in predicting the risk of SSI in patients undergoing colorectal surgery.
Midura 2015 (108)	*Retrospective analysis* of patients who underwent segmental colectomy with anastomosis.	2012	USA	13.684	Male sex, steroid use, smoking, open approach, operative time, LOS, 30-day mortality, and preoperative chemotherapy were associated with increased anastomotic leaks and diverting ileostomy with decreased incidence of leaks on multivariate analysis.
Buunen 2009 (109)	*Randomized controlled trial* in 29 European hospitals on patients with solitary cancer of the colon and a body-mass index up to 30 kg/m^2, randomly assigned to either laparoscopic or open surgery as curative treatment.	March 1997 – March 2003	Europe	1.248	The difference in disease-free survival between groups was small and, we believe, clinically acceptable, justifying the implementation of laparoscopic surgery into daily practice.
Intraoperative events					
Kambakamba 2014 (110)	*Retrospective analysis* of elective laparoscopic colorectal resection based on the prospective database of the Swiss Association of Laparoscopic and Thoracoscopic Surgery.	1995-2006	Switzerland	3.928	Patients with an intraoperative adverse event had a significantly higher rate of postoperative local and general morbidity (41.2 and 32.9 % vs. 18.0 and 17.2 %, $p < 0.001$ and $p < 0.001$, respectively).
Goriainov 2008 (111)	*Prospective audit* of all patients undergoing laparoscopic surgery.	January 2003 - August 2006	UK	84	The anastomotic leak rate from intra-corporeal laparoscopic anastomosis is no greater than for open surgery or laparoscopic surgery with extra-corporeal anastomosis.
Casillas 2004 (112)	*Case-Control study* on colectomies.	January 1999 - August 2002	USA	430	Conversion of a laparoscopic colectomy does not result in inappropriately prolonged operative times, increased morbidity or length of stay, increased direct costs, or unexpected readmissions compared with similarly complex laparotomies.
Marusch 2001 (113)	*Multicentric, prospective, observational study* within the Laparoscopic Colorectal Surgery Study Group.	August 1995 - February 1999	Germany, Switzerland, Austria	1.658	Conversion is not considered to be a complication of laparoscopic surgery, it is true that the postoperative course

					after conversion is associated with appreciably poorer results in terms of morbidity, mortality, convalescence, blood transfusion requirement, and postoperative hospital stay.
Kuhry 2005 (114)	*Randomized clinical trial* including patients with colon cancer undergoing either laparoscopic or open operation.	March 1997 - March 2003	Europe	536	Laparoscopic operation for colon cancer at hospitals with high caseloads appears to be associated with improved short-term results.
Contamination					
Leichtle 2012 (41)	*Prospective observational study* of colorectal patients.	2007-2010	USA	4.340	Risk factors associated with anastomotic leakage were fecal contamination and intraoperative blood loss of more than 100 mL.
Makela 2003 (84)	*Case control study* on reoperated patients for colorectal anastomosis leakage.	1992-2001	Finland	88	Patients with multiple risk factors have higher risk for anastomotic leakage. When patients have three or more risk factors, the creation of a protective stoma should be considered in cases with a low rectal anastomosis.
Konishi 2006 (106)	*Prospective surveillance* of all elective colorectal resections performed by a single surgeon in a single university.	November 2000 - July 2004	Japan	391	Preoperative steroid use, longer duration of operation, and contamination of the operative field were independent risk factors for developing clinical anastomotic leakage after elective resection for colorectal cancer.
Ahmad 2003 (115)	*A descriptive, analytical and observational study* on colorectal surgery and MBP.	September 1998 - April 2003	Pakistan	47	Mechanical bowel preparation is not necessary for safe colorectal surgery.
Cao 2012 (116)	*Systematic review* including 14 randomized clinical trials comparing MBP with no MBP before colorectal surgery.	1992-2010	-	5.373	No evidence was noted supporting the use of MBP in patients undergoing elective colorectal

					surgery. MBP should be omitted in routine clinical practice.
De Aguilar-Nascimento 2009 (117)	*Prospective cohort study* on patients who underwent bowel surgery with an anastomosis.	2004-2008	Brazil	53	The multidisciplinary routines of the ACERTO protocol are safe and enhanced recovery in colorectal surgery by reducing both hospitalization and the severity of postoperative morbidity.
Gravante 2008 (118)	*Meta-analysis* of 12 randomized controlled trials.	Till 2007	-	4.919	Compared with mechanical bowel preparation, non-mechanical bowel preparation for colorectal surgery was associated with a non-significant difference in the rate of anastomotic leakage.
Guenaga 2003 (119)	*Meta-analysis* of 6 randomized controlled trials.	Till 2002	-	1.159	The results failed to support the hypothesis that bowel preparation reduces anastomotic leak rates and other complications.
Kovachev 1998 (120)	*Prospective cohort study* on colorectal surgery patients and the use of antibiotic prophylaxis.	1997	Bulgaria	136	In colorectal operations antibacterial prophylaxis applied perioperatively proves effective in combating systemic and local inflammatory complications.
Lins-Neto 2012 (121)	*Prospective cohort study* of patients undergoing abdominal surgery without prior bowel preparation.	January 2007 - June 2011	Brazil	126	Preoperative mechanical bowel preparation is not essential in the routine of colorectal surgeries.
Pineda 2008 (122)	*Meta-analysis* of thirteen randomized controlled trials of colorectal cancer patients and MBP.	1992-2008	UK	4.601	MBP is of no benefit to patients undergoing elective colorectal resection and need not be recommended to meet "standard of care."
Pirro 2006 (123)	*Comparative study* of MBP in colorectal surgery.	2001-2004	France	190	Colorectal surgery without MBP may be safely performed and could improve the quality of life of patients in the peri-operatory period.

Young Tabusso 2002 (124)	*Prospective cohort study* of MBP in colorectal surgery.	2001	Spain	47	The results show that mechanical preparation of the colon does not provide any benefit and may result in a higher incidence of complications in colorectal surgery.
Nasirkhan 2006 (125)	*Review* of anastomotic disruption after large bowel resection.	1953-2005	-	-	Male gender, obesity, level of anastomosis, peritoneal contamination, age, operative time and blood transfusions, have all been implicated as potential risk factors for CAL.
Kim 2014 (126)	*Retrospective analysis* of prospectively collected data in colorectal surgery.	September 2010 - August 2012	Korea	380	Colon cancer surgery can be performed safely without an MBP with respect to anastomosis leakage, SSI and the severity of surgical complication.
Muller-Stich 2006 (127)	*Systematic review* of 10 RCT and 7 meta-analyses comparing orthograde bowel cleansing to no preoperative bowel preparation.	-	-	-	Routine preoperative orthograde bowel cleansing is no longer justified prior to colorectal surgery in general due to increased risk of anastomotic leakages.
Moghadamyeghaneh 2015 (128)	*Retrospective analysis* of the NSQIP database to examine the clinical data of colon cancer patients undergoing scheduled colon resection.	2012-2013	USA	5.021	Solitary mechanical bowel preparation and solitary oral bowel preparation had no significant effects on major postoperative complications after colon cancer resection. However, a combination of mechanical and oral antibiotic preparations showed a significant decrease in postoperative morbidity.
Kiran 2015 (129)	*Retrospective analysis* of the NSQIP colectomy data.	2012	USA	8.442	On multivariable analysis, MBP with antibiotics, but not without, was independently associated with reduced anastomotic leak, SSI, and postoperative ileus.

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CHAPTER 7

CAN ANASTOMOTIC LEAKAGE IN LEFT SIDED COLORECTAL SURGERY BE PREDICTED?

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ABSTRACT

Background

Colorectal anastomotic leakage (CAL) is a potentially devastating complication following colorectal surgery. An optimized CAL risk analysis may aid in tailoring postoperative colorectal management. Aim of the present study was to prospectively validate a previously developed colon leakage score (CLS).

Methods

Pre- intra- and postoperative data of patients undergoing left sided colorectal surgery with a primary anastomosis were collected during a five-year time period in a single hospital (2012-2016). CAL was defined as proposed by the international study group of rectal cancer (ISREC). The CLS and a modified-CLS (mod-CLS, not including intraoperative risk factors) were calculated. Potential risk factors for CAL were analyzed using standard techniques including conditional logistic regression and Cox-regression.

Results

A total of 384 patients (67% male, age 67 range 19-93) fulfilled inclusion criteria. CAL was diagnosed in 42 (10.9%) patients, and in 26% a diverting stoma was constructed. Median CLS and mod-CLS scores of CLS were not different between patient groups (CLS in CAL: 7 vs non-CAL 7; mod-CLS in CAL: 6 vs non-CAL 6, both NS). Cut off CLS or mod-CLS scores associated with stoma construction were not identified. However, a >500 ml blood loss predicted CAL (26% vs. 13%, $p<0.05$).

Conclusion

The colon leakage score did not predict anastomotic leakage in left sided colorectal resections in the present study cohort. An accurate anastomotic leakage risk assessment is crucial for tailoring details of surgery for an individual patient as outcome may be improved.

Key words: colorectal anastomotic leakage, surgery, colorectal cancer, complications, colon
leakage score, prediction.

What does this paper add to the literature?

This study addresses the importance of differentiating between high or low risk of anastomotic leakage. A prediction model can support the clinical decision making process, performing an anastomosis or a (deviating) stoma. Risk assessment is crucial for tailoring details of surgery for an individual patient as outcome may be improved.

Introduction

Colorectal anastomotic leakage (CAL) is still one of the major complications after colorectal surgery. CAL may result in severe sepsis, requirement for further surgery and longer hospitalization, significant morbidity with lower reported health related quality of life (HRQoL) and even mortality (1,2). The incidence of CAL varies from 1.5 to 23 percent, depending on definition, patient risk factors and anatomical site of surgery (2–5). A clinical preoperative risk assessment by the operating surgeon has a low predictive value as the risk of CAL is always underestimated (6). Differentiating between high or low risk on CAL can support the clinical decision making process concerning the construction of an anastomosis or a (diverting) stoma. Therefore, an accurate risk assessment is crucial for tailoring details of surgery for the individual patient as outcome may be improved.

Two clinical CAL risk assessment tools were previously developed, a colon leakage score (CLS) and a prognostic colorectal leakage index (PROCOLE) (7,8). The CLS score is based on potential risk factors that were identified following a systematic literature search that are tabulated prior to surgery. The PROCOLE score uses similar parameters but also includes possible risk factors related to patient comorbidity. Both the CLS and the PROCOLE scores also include intraoperative parameters to eventually determine the risk on CAL. Furthermore, several other scores or predictors have been proposed to assess the clinical risk on anastomotic leakage in the early postoperative phase (9,10). However, a simple score that is useful as a preoperative counselling tool is currently not available.

The CLS was initially developed for left sided colorectal surgery. A strong association between CLS scores and risk of leakage was demonstrated in a patient series but validation was not performed (8). The goal of the present study was to determine whether CLS scores predicted colorectal anastomotic leakage in an observational cohort in a large Dutch teaching hospital.

Methods

Data of consecutive patients undergoing elective and emergency left sided colorectal surgery with primary anastomosis for malignant and benign disease in Máxima Medical Center (MMC) between January, 2012 and December, 2016 were analyzed (figure 1). The MMC is a 550-bed community and teaching hospital situated in the southern part of The Netherlands, serving a population of approximately 200.000 inhabitants. In MMC, laparoscopic surgery is the standard operative technique for colon abnormalities. Elective patients receive bowel preparation prior to surgery although selective decontamination of the digestive tract (SDDs) was not used. Open surgery was performed in case of previous major abdominal surgery, tumor growth into nearby organs (T4 tumors), or in case of conversion as deemed necessary by the operating surgeon. In MMC, colorectal surgery is only done by certified gastrointestinal surgeons dedicated to this type of operations since 2006.

Data were retrospectively collected in the 2012 (January) -2014 (December) cohort and obtained prospectively in the 2015 (April) -2016 (December) cohort. Preoperative data accrual including characteristics such as age, sex, American society of anesthesiologists (ASA) physical status classification, body mass index (BMI), cigarette smoking, alcohol use, corticosteroid use, neoadjuvant therapy (yes or no), medical history (any) and hemoglobin level that were retrieved from electronic patient files and peroperative registration data. Intraoperative data assessment included type of surgery, emergency surgery (yes or no), cause of emergency surgery (bleeding, obstruction, perforation), laparoscopic or open surgery, conversion, additional intervention, type of anastomosis, distance anastomosis to anal verge, blood loss and stoma. These data were retrieved from electronic surgical and anesthesiological sources and operative notes. Postoperative characteristics including colorectal anastomotic leakage, other postoperative complications as scored by Clavien Dindo (11), and in hospital mortality were also tabulated.

Definitions

The colon leakage score was developed based on information from the literature and expert opinions. They have chosen a set of 13 easily accessible clinical items and weighted the risk factors by a collective expertise of three dedicated colorectal surgeons. It was tested in a retrospective cohort of consecutive patients undergoing left-sided colorectal surgery with primary anastomosis.

As there is no uniform, worldwide accepted definition of colon

and rectal anastomotic leakage, we adhered to the gradation system as proposed by the International Study group of Rectal Cancer (ISREC) (12,13). To determine the CLS score, CAL was defined (as in the paper of Dekker et al.) by clinically relevant operative and/or radiological findings requiring relaparotomy (ISREC Grade C anastomotic leakage). Patients whose leak was only detected on radiological examination and was not clinically relevant were not considered to have CAL. A CT scan with contrast enema was in the majority of cases used to detect CAL, unless clinical deterioration of the patient required immediate reoperation by decision of a dedicated colorectal surgeon. Routine contrast enema or radiodiagnostics were not performed after surgery.

Left sided colorectal surgery was defined as an operation that was aimed to remove the left sided hemicolon, a sigmoid resection or a low anterior resection. Ileus was defined as the lack of passage of stool or flatus within 4 days after surgery (14). Cigarette smoking (yes/no) was defined as patients who previously and/or currently smoked cigarettes or cigars and was also expressed in number of pack years. Alcohol use was categorized as more or less than three units daily. Steroids were scored as the present use of corticosteroids excluding exhalers. Distance of the anastomosis to anal verge was specified by the operating surgeon (<5, 5-10 or >10cm). Additional procedures were defined as procedures that were additionally required during the standard resection including intraoperative radiotherapy and multi organ resection.

Outcome

The primary outcome of this study was the performance of the CLS as a predictor of colorectal anastomotic leakage. The CLS ranges from 0 to 43 points. For the present study, we additionally developed the modified-CLS score (mod-CLS) that includes all items of the original CLS but omitted intraoperative parameters (duration of operation, blood loss, distance of anastomosis to anal verge and additional procedures) (8). It was reasoned that such a mod-CLS might also be more useful for counseling of patients in the preoperative phase. A mod-CLS score ranges from 0- 32 points.

Possible relations between scores of CLS and mod-CLS and postoperative outcome were assessed. Postoperative outcome parameters included colorectal anastomotic leakage, in hospital mortality, complications including ileus, anastomotic leakage, wound infection, urinary tract infection, pneumonia, thromboembolic complication, delirium, abdominal abscess. Also, the comprehensive complication index (CCI) was determined. The CCI is a combined outcome measure reflecting morbidity and mortality. A CCI score above or equal to 20 is associated with clinically relevant morbidity (15,16).

Statistical analysis

All analyses were done in SPSS version 22 (IBM IBM Corp., Armonk, NY, USA). Baseline characteristics of CAL and non-CAL patients were compared using the Pearson Chi-square test for categorical variables. An unpaired t-test analyzed normally distributed continuous variables whereas the Mann-Whitney U test was used for non-normally distributed continuous variables.

The potential value of the CLS as a predictor of CAL was analyzed by logistic regression analysis using CLS as the independent variable and CAL as the dependent variable. Results were expressed as odds ratios (OR) with 95% confidence intervals (95%CI). The strength of the CLS in predicting CAL was assessed by the area under the receiver-operating characteristics (ROC) curves (AUC). To explore the influence of a stoma on the observed associations, we subsequently stratified the analyses for presence and absence of a diverting stoma. In addition, logistic regression analysis was used to describe the association of CLS with the occurrence of postoperative complications, mortality and a CCI score above 20. Statistical significance was accepted at a two-sided p-value <0.05.

Results

From 2012 until 2016, 366 patients underwent left sided colorectal surgery with a primary anastomosis of which 35 (9.6%) developed colorectal anastomotic leakage, grade C (figure 1). Items that contributed to the CLS score in CAL and non-CAL patients are listed in table 1. Data sets for all items were complete, except for distance of the anastomosis to the anal verge (complete 73%, missing 27%).

A total of 22% (n=82) of the patients received a diverting stoma during the index operation (table 2). Of these, 9% (n=7) developed CAL, while CAL also occurred in 10% (n=28) not receiving a diverting stoma (p=0.833). In colon surgery, the leakage rate was 13% compared to 5% in rectal surgery (p<0.05). The difference in CLS score between CAL patients and non-CAL patients was not significant (CAL: 7 vs non-CAL: 7). Figure 2 presents a scatter plot of individual CLS scores illustrating the absence of a difference between CAL and non-CAL patients. Mod-CLS scores of CAL patients and non-CAL patients were also not significantly different (Mod-CLS, CAL: 6 vs Mod-CLS non-CAL: 6, table 3).

Patients without a diverting stoma (n=284)

CLS scores in patients without a diverting stoma having CAL or not having CAL were almost identical (mean; CAL: 6.8 vs non-CAL, 6.9, p=0.822, table 4). When colon and rectum patients were analyzed separately, there were again no differences in CLS scores. Area under the curve (AUC) calculations demonstrated that the onset of CAL was not related to CLS (figure 3). A multiple regression analysis was not possible as the univariate analysis identified just blood loss >500ml as the only parameter that was different between CAL and non-CAL patients (CAL: 26% vs non-CAL: 13%, p<0.05).

Patients with a diverting stoma (n=82)

In patients with a diverting stoma (n=82), mean CLS in the leakage group was 9 versus 9.6 in patients without CAL (p=0.672). ROC curve and logistic regression did not identify a correlation between CLS and onset of CAL (figure 3).

Laparoscopic surgery

A statistically significant difference was found between patients who were operated laparoscopically compared to patients who underwent a conversion to open surgery, and open surgery (conversion 17%, open: 15% vs lapsc: 6%, p<0.01, table 2). The number of stoma's constructed in the converted surgery group was comparable to the laparoscopic group. Converted patients however did encounter a higher rate of constructed stoma's compared to non-converted patients (37% vs. 23%). In addition, similar CLS values were found in patient with or without a stoma (table 4).

Discussion

Colorectal anastomotic leakage following bowel resection (CAL) remains a feared complication. Unfortunately, a simple and valid tool predicting CAL does not exist at present. The colon leakage score (CLS) tabulating simple parameters such as age, sex and BMI was reportedly sound in a selected group of patients, but external validation had not occurred yet. The present study shows that this CLS did not have predictive value in a Dutch left sided colorectal patient series. Moreover, a relevant CLS cut off value discriminating between a CAL and a non-CAL patient could not be determined. Omitting intraoperative parameters from the CLS score (mod-CLS) also did not improve these predictive properties.

The CLS was originally designed to improve risk stratification of patients undergoing left sided colorectal resections in two ways. First, it examined whether the score could predict CAL per se. Second, it sought to determine a clinically relevant cut off value possibly guiding the decision making process whether or not to construct a diverting stoma. In a relatively small patient cohort (n=121), a CLS score < 11 had a low 3% risk of CAL. It was therefore suggested that stoma formation was not required in patients with such low scores. Another study did confirm the CLS < 11 to be the best cut-off value (17). In this study cohort however, no relevant cut off value could be determined.

There are several possible reasons for the invalidity of the CLS in this patient series. First, population characteristics varied as a substantially higher number of high risk patients were included in Dekker's original study as 17% of patients underwent emergency surgery of which 10% were due to bowel perforation. Second, 4% had a ASA 4 status that is associated with a substantial postoperative morbidity and mortality. Finally, no patients with an anastomosis lower than 5cm from the anal verge participated in the present study. It is known that short distance to the anus results in a higher CAL risk (5). Therefore, the factor patient mix may likely explain the dismal predictive properties of the CLS in the present series.

There is clearly a need for a proper intraoperative tool predicting the necessity of constructing a diverting stoma. A simple score predicting the onset of CAL that can be used in the preoperative phase is even more important. Surely, a preoperative period may serve as a 'window of opportunity' to optimize all modifiable risk factors that are associated with complications including CAL (4,18–20). However, the CLS is not useful for preoperative risk stratification as it also considers intraoperative risk factors (additional procedures, blood loss, distance anastomosis from the anal verge, and duration of operation). The present study proposed a modified CLS score omitting these intraoperative risk factors thus only including preoperative parameters. Unfortunately however, even this mod-CLS model did not predict the risk of CAL in the present patient cohort.

The CLS prognostic index has a few important limitations to address. First, the CLS was constructed from a systematic literature review and involved identifying the risk factors of anastomotic leakage and selecting those that, according to the CLS' authors, could be considered as readily available clinical variables. As such, the selection process was subjective. Second, the weight of the CLS prognostic variables were assigned subjectively based on the experience of several colorectal surgeons through a heuristic iteration method. Probably, it would be better that weights of the prognostic variables were based on the results obtained from meta-analysis, although this might be a challenge based on the minimal available literature. Also, the predictive ability of the CLS prognostic index may have been overestimated because it was only assessed in a sample with 10 anastomotic leaks.

The present study suffers from limitations including a mix of retrospective and prospectively accumulated data. Moreover, it studied a limited number of patients in a single hospital model. A prediction model is ideally built on big data obtained from prospectively collected datasets, preferably in a multicenter and international study setting. Such an approach may help to identify whether the current or modified CLS has a potential of predicting CAL in these patients. To this end, the Dutch 'Taskforce Anastomotic Leakage' initiated a prospective observational cohort study (Leak Check N16.092) to analyze the possible advantages of a prediction model on such a bigger scale. Accurate prediction models may aid clinicians including surgeons in their choice whether to operate only under certain improved conditions, to construct a diverting stoma, or to even not operate at all, to finally prevent the occurrence of colorectal anastomotic leakage and mortality.

Conclusion

The colon leakage score (CLS) does not predict the risk of CAL after left sided colorectal resections in the present study cohort. There remains the need for an improved risk model allowing for counselling and stratifying patients aimed at reducing the onset of CAL. If these models are sound once prospectively tested, preoperative work up and surgical approach may be optimized.

Figure 1. Flow diagram of left-sided colorectal surgery patients included in the study.

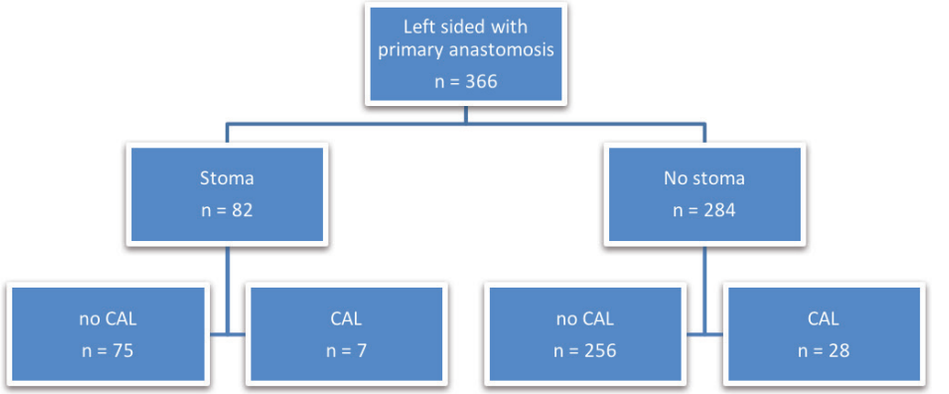


Figure 2. Scatter plot of the colon leakage score for all patients who received left-sided colorectal surgery with (blue) and without (green) anastomotic leakage.

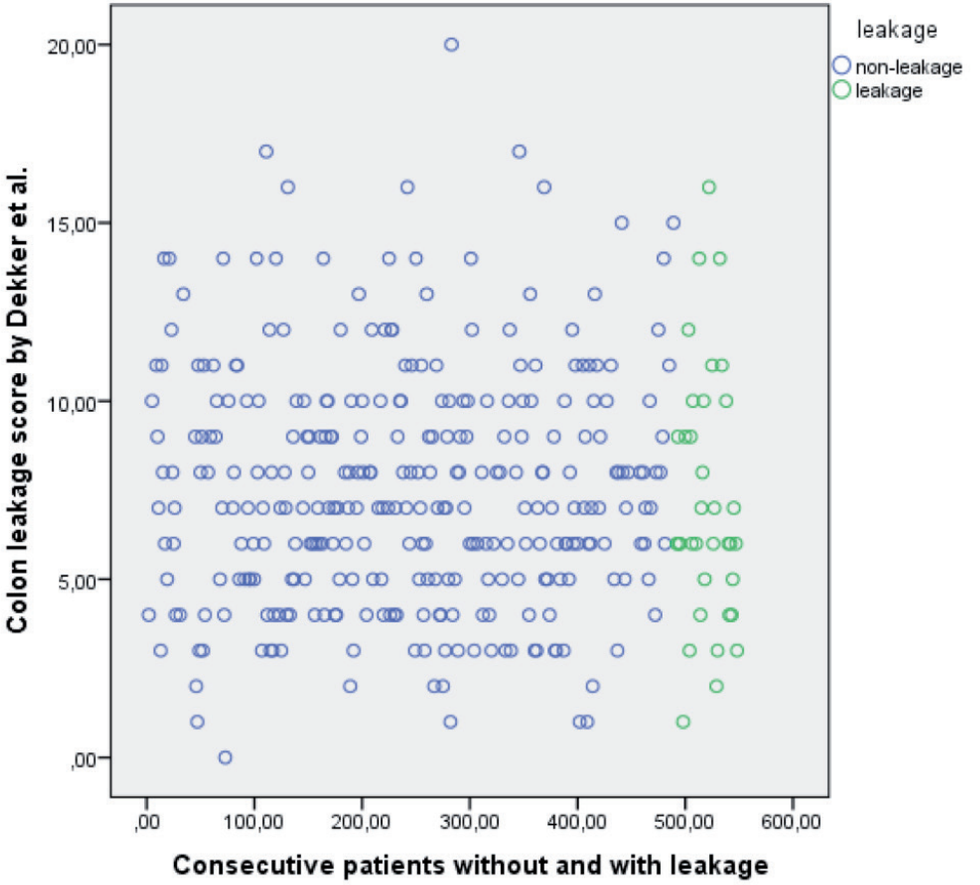


Figure 3. Receiver operating characteristic (ROC) curve for the colon leakage score versus anastomotic leakage for all patients in left-sided colorectal surgery with primary anastomosis without (fig.3a, n=1-2) and with (fig.3b, n = 284) a non-functional stoma. The area under de curve is 0.491 (95%CI: 0.379 – 0.603) and 0.441 (95%CI: 0.225-0.657) respectively.

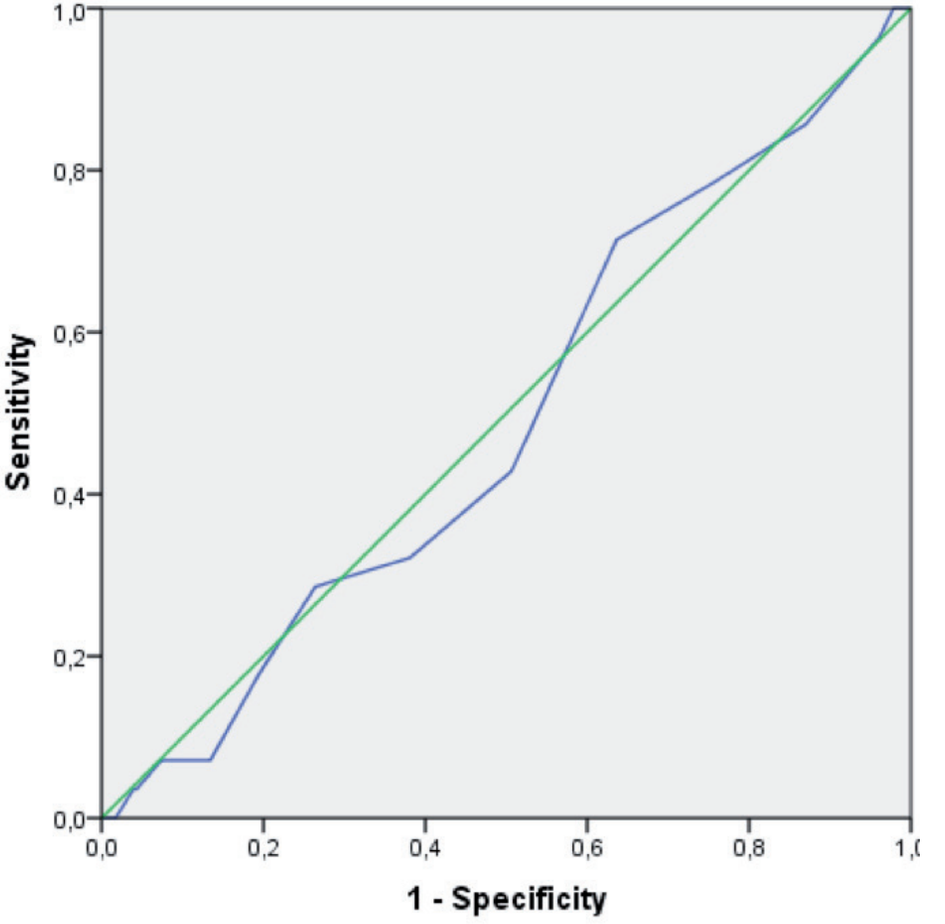


Table 1. Baseline characteristics derived from the colon leakage score for patients undergoing left-sided colorectal surgery with and without anastomotic leakage.

	Total N=366	Non-leakage N=331	Leakage N=35	P-value
Age in years, median (range)	68 (19-93)	68 (35-93)	67 (19-84)	0.427
Male	207 (5)	186 (56)	21 (60)	0.666
ASA grade (%)				0.806
I	78 (22)	71 (22)	7 (20)	
II	238 (67)	213 (66)	25 (71)	
III	40 (11)	37 (12)	3 (9)	
IV	0	0	0	
BMI category (%)				0.859
<19 kg/m^2	9 (3)	8 (2)	1 (3)	
19-24.9 kg/m^2	157 (43)	144 (44)	13 (37)	
25-30 kg/m^2	128 (39)	128 (39)	14 (40)	
>30 kg/m^2	51 (15)	51 (15)	7 (20)	
Intoxications (%)				
Smoking*	154 (43)	137 (42)	17 (49)	0.466
Alcohol use#	16 (5)	16 (5)	0	0.170
Corticosteroid use^	10 (3)	10 (3)	0	0.296
Neoadjuvant therapy (%)				
None	360 (95)	312 ()	38 (86)	
Radiotherapy	45 (12)	44 (13)	1 (3)	0.073
Chemoradiation	19 (5)	18 (6)	1 (3)	0.511
Emergency surgery (%)				
Bleeding	0	0	0	-
Obstruction	13 (4)	0	1 (4)	0.882
Perforation	0		0	-
Distance of anastomosis to anal verge= (%)				0.107
<5	11 (3)	11 (3)	0	
5-10	39 (11)	37 (11)	2 (6)	
>10	224 (61)	196 (59)	28 (80)	
missing	92 (25)	87 (26)	5 (14)	
Additional procedures**	66 (18)	58 (18)	8 (23)	0.440
Median blood loss (IQR)***				0.002
<500 ml	315 (86)	289 (87)	26 (74)	
500-999 ml	39 (11)	35 (11)	4 (11)	
1000-2000 ml	10 (3)	6 (2)	4 (11)	
>2000 ml	2 (1)	1 (0.3)	1 (3)	
Median duration of operation (IQR)				0.513
<2:00 hours	57 (16)	49 (15)	8 (23)	
2:00-2:59 hours	191 (52)	173 (52)	18 (51)	
3:00-3:59 hours	91 (25)	85 (26)	6 (17)	
≥4:00 hours	28 (8)	25 (8)	3 (9)	

Legend 1. IQR = Inter Quartile Range; ASA = American Society of Anesthesiologists score; BMI = Body Mass Index; *current cigarette smoking at cancer diagnosis; #alcohol use of more than 3 units a day; ^present use of corticosteroids, excluding exhalers; =distance of anastomosis to anal verge in centimeters; **additional procedures during surgery including intraoperative radiotherapy and multi organ resection; ***blood loss and/or blood transfusions in milliliters.

Table 2. Treatment characteristics of patients undergoing colorectal surgery. Patients with anastomotic leakage compared to non-leakage.

	CLS	Mod-CLS***
Colorectal anastomotic leakage		
Yes	7 (5-10)	6 (4-8)
No	7 (5-10)	6 (4-8)
Postoperative complications^		
Yes	8 (6-10)	6 (4-8)
No	7 (5-9)	5 (3-7)
Comprehensive complication index* >=20		
Yes	8 (6-11)	6 (4-8)
No	7 (5-9)	5 (3-7)
Mortality**		
Yes	9 (8-12)	7 (6-10)
No	7 (5-9)	5 (3-7)

Legend 2. *Colorectal cancer including any disease stage; median duration of surgery with interquartile ranges 25 and 75%; ^diverting ileostoma.

Table 3. Colon leakage score and the modified colon leakage score (mod-CLS) according to postoperative outcome of patients undergoing colorectal surgery.

	Total	Non-leakage	Leakage	P-value#
Patients	366	331 (90)	35 (10)	
Malignant disease (%)*	315 (86)	290 (92)	25 (8)	0.010
Duration of surgery (IQR)	154 (75-420)	155 (75-420)	140 (76-300)	0.769
Laparoscopic resection (%)	231 (63)	218 (94)	13 (6)	0.003
Conversion to open resection (%)	70 (19)	58 (83)	12 (17)	
Open resection (%)	65 (18)	55 (85)	10 (15)	
Stoma (%)^	82 (22)	75 (91)	7 (9)	0.833
No stoma (%)^	284 (78)	256 (90)	28 (10)	
Colonic anastomosis (%)	210 (57)	183 (87)	27 (13)	0.018
Rectal anastomosis (%)	156 (43)	148 (95)	8 (5)	

Legend 3. Medians with interquartile ranges (IQR) 25 and 75%. ^Complications are registered as one or more complications postoperatively, occurring within 30 days (ileus, anastomotic leakage, wound infection, urinary tract infection, pneumonia, thromboembolic complication, delirium, abdominal abscess); *mean comprehensive complication index greater than or equal to 20 [13, 14]; **in hospital mortality until discharge; ***modified colon leakage score without the following intraoperative parameters: duration of operation, blood loss, distance of anastomosis to anal verge and additional procedures.

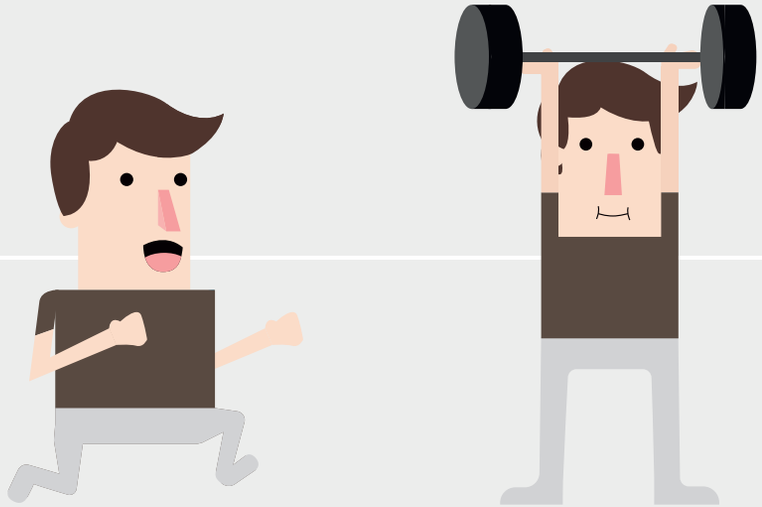
Table 4. Colorectal anastomotic leakage (CAL) in patients with and without a nonfunctional diverting stoma in left-sided colorectal surgery.

Without stoma (n=284)	**Non-CAL (n=256, 90%)**	**CAL (n=28, 10%)**	**P-value**
CLS	6.89 (0-20)	6.75 (2-14)	0.822
CLS colon only	6.73 (0-20)	6.74 (2-14)	0.921
CLS rectum only	7.26 (0-20)	7.25 (4-10)	0.997

With stoma (n=82)	**Non-CAL (n=75, 95%)**	**CAL (n=7, 5%)**	**P-value**
CLS	9.56 (2-17)	9 (1-16)	0.672
CLS colon only	8 (2-14)	8.67 (1-14)	0.686
CLS rectum only	9.60 (3-17)	8.50 (4-16)	0.450

Chapter 8 Prehabilitation versus no prehabilitation to improve functional capacity and reduce postoperative morbidity and mortality in patients undergoing elective colorectal cancer resection.
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Chapter 9 Making patients fit for surgery: introducing a four pillar multimodal prehabilitation program in colorectal cancer.
Submitted.



PART III

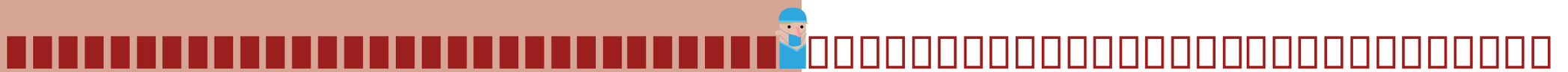
IMPROVING COLORECTAL OUTCOME WITH PREHABILITATION

CHAPTER 8

PREHABILITATION VERSUS NO PREHABILITATION TO IMPROVE FUNCTIONAL CAPACITY AND REDUCE POSTOPERATIVE MORBIDITY AND MORTALITY IN PATIENTS UNDERGOING ELECTIVE COLORECTAL CANCER RESECTION (PROTOCOL)

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Accepted at Cochrane Database of Systematic Reviews.



ABSTRACT

This is a draft and post-peer review version of a Protocol for a Cochrane Review (Intervention). Upon completion and approval, the final version is expected to be published in the Cochrane Database of Systematic Reviews (www.cochranelibrary.com).

The objectives are as follows:

To assess the effectiveness of a prehabilitation program versus no prehabilitation (current care) for cancer patients undergoing colorectal cancer resection to enhance functional capacity and to reduce postoperative mobidity.

Editorial group: Cochrane Colorectal Cancer Group

Background

Description of the condition

Colorectal cancer (CRC) is the second most prevalent type of cancer in the World causing over 700.000 deaths yearly (Torre 2015). The cornerstone in treatment of CRC remains surgery. Unfortunately, postoperative complications occur in up to 50% of patients and are associated with an increase in mortality- and recurrence rate, increased hospital costs and a decrease in Health Related Quality of Life (HRQoL) (Govaert 2015; Kirchhoff 2010; McDermott 2015). One of the most severe complications is colorectal anastomotic leakage with a reported incidence between 1.5-23%. Anastomotic leakage is associated with high rates of morbidity and mortality, poor HRQoL and increased health expenditures (Kirchhoff 2010; Govaert 2015; Bertelsen 2010; McArdle 2005; Hammond 2014). Even in the absence of complications, major surgery is associated with a 20% to 40% reduction in physiological and functional capacity when measured by energy expenditure, endurance time, workload and heart rate during maximum exercise (Snowden 2010). The enhanced recovery after surgery (ERAS) program has significantly accelerated functional recovery and made patients less care dependent on high level care after surgery (Gustafsson 2013). The period before surgery however may in fact be a better time to intervene in the factors that contribute to recovery including ERAS program (Carli 2010; van Rooijen 2017).

Description of the intervention

Poor functional capacity, malnutrition, cigarette smoking and unstable mental status, have all been put forward as factors which are associated with major complications after colorectal surgery. Prehabilitation focuses on those four parameters may therefore contribute to an improved functional capacity (Figure 1), a reduction of complications, less morbidity and an improved Health Related Quality of Life (HRQoL) (Gillis 2014). While pilot studies suggest that prehabilitation might offer significant benefits, large differences exist in the content of prehabilitation programs and no comparisons (prehabilitation versus no prehabilitation) are conducted to date. Therefore, a Cochrane systematic review in this field will add value.

Since it has been established that the number and severity of complications are closely related to patients' preoperative functional capacity, nutritional status, smoking behavior and psychological well-being (West 2016; Gillis 2014; Moghadamyeghaneh 2015; Baucom 2015; Rosenberger 2006), there is a growing need to target these issues with the implementation of a multimodal intervention program. The time frame between diagnosis and operation is limited in most countries to 4-5 weeks. Pilot studies have used this time period with multimodal prehabilitation. They found significant improvements in functional capacity prior to surgery, potentially enabling faster recovery and less dependency in activities of daily living post-surgery (Mayo 2011; Gillis 2014; Chen 2016) (Figure 1).

They additionally suggest that exercise training alone is not sufficient to attenuate the stress response in all patients and that it is important to also address factors that promote beneficial adaptations to training like nutrition and coping behavior (Mayo 2011). Moreover, they propose that if functional capacity can be increased preoperatively, you may expect a reduction in postoperative morbidity and mortality (Gillis 2014). However, this has never been investigated.

How the intervention might work

Based on the notion that preoperative exercise would have an impact on recovery of functional capacity after colorectal surgery (Figure 1), a randomised controlled trial has been performed (Carli 2010). This trial, the first and largest trial with surgical prehabilitation, compared two exercise regimens (intense exercise on a stationary bike as opposed to walking and deep breathing) for several weeks before colorectal surgery. The primary outcome was functional walking capacity, as measured with the six-minute walk test (6MWT) between 5 to 9 weeks postoperatively. The 6MWT is a validated tool for assessing physical conditioning of patients, does not require expensive equipment or extensive testing, and strongly correlates with more precise test for functional capacity, such as cardio-pulmonary exercise testing (Moriello 2008; Lee 2013). Due to this practical approach, it is used in most studies investigating clinical prehabilitation before major abdominal surgery (O'Doherty 2013). Subgroup analysis showed that patients whose functional exercise capacity improved preoperatively recovered well in the postoperative period, regardless of exercise technique (Mayo 2011). However, one-third of patients deteriorated preoperatively despite the exercise regimen, and these patients were also at greater risk for prolonged recovery after surgery. Poor preoperative physical function (fatigue and physical performance) and the presence of anxiety and depression were also significant confounding predictors of prolonged recovery. These results suggest that exercise training alone is not sufficient to attenuate the stress response in all patients and that it is also important to address factors like nutrition and coping behavior that promote the beneficial adaptation to training.

The role of nutritional status and psychological well-being in surgical recovery may not be underestimated. Evidence from cancer rehabilitation suggests that exercise attenuates fatigue by facilitating the incorporation

of nutrients and improves HRQoL by reducing the impact of anxiety and depression (Spence 2007). The nutritional status of patients affected by colorectal cancer is directly influenced by the presence of cancer (Barbosa 2014). This impacts on all aspects of intermediary metabolism (proteins, carbohydrates, lipids, vitamins). Other factors such as age, adjuvant cancer therapy and stage of the disease also impact nutritional status (Arends 2016; Barbosa 2014; Garth 2010). The greater sensitivity of protein catabolism to nutritional support, in particular to amino acids, could have important implications for the nutritional management of these patients during the period of catabolic stress, with particular emphasis on substrate utilization and energy requirement (Waitzberg 2006).

Psychological status may also play an important role in surgical recovery. It is well documented that patients awaiting major surgery experience anxiety about their upcoming operation, the outcome, and their course of healing and recovery (Kiecolt-Glazer 1998; Munafo 2001). They may also feel depressed, have unrealistic expectations (overly optimistic or pessimistic) about their health status, and lack adequate strategies for coping with the pre- and postoperative periods. Any of these factors may influence pain (Munafo 1998) and interfere with postoperative functioning (Rosenberger 2006; Wallace 1984). For this reasons, patients might be seen and trained by a psychologist to reduce anxiety and avoid depression by putting the patients in a well-informed active coping role in beating their disease.

Evidence exists that preoperative smoking interventions reduce postoperative morbidity (Sorensen 2012). Smoking cessation a few weeks before surgery is likely to reduce the risk of complications, since cessation restores the inflammatory cellular functions within 4 weeks (Sorensen 2010). A period of 4 to 8 weeks smoking cessation prior to surgery has already been shown to significantly reduce postoperative complications (Thomson 2014). However, only when intensive counseling and nicotine replacement therapy are combined (Sorensen 2010; Sorensen 2012; Thomson 2014).

Why it is important to do this review

Prehabilitation may raise in clinical importance the upcoming decade. The last systematic review was published in 2011 and mostly included single modal programs and surgeries other than colorectal. This delivers a heterogenic patient population and limits the ability to generalize study results (Santa Mina 2014). Multimodal prehabilitation may be most promising since the expected synergic effect. Additionally, prehabilitation may enhance patient empowerment and shared decision making thereby putting the patient in a central role. This all addresses the need to perform a Cochrane systematic review, to investigate the current prehabilitation initiatives in colorectal surgery. In this way we may deliver recommendations of the elements of an optimal prehabilitation program and preferable outcome measures for future study purposes on prehabilitation.

Objectives

To assess the effectiveness of a (multimodal) prehabilitation program versus no prehabilitation for cancer patients undergoing colorectal cancer resection. We will investigate whether prehabilitation is safe and effective to enhance functional capacity and to reduce postoperative morbidity and mortality.

Methods

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) will be included in this review to maintain the best level of evidence. Cluster CTs will be included as well. Trials will be included irrespective of whether an intention to-treat analysis has been carried out. Prehabilitation programs reporting on a combination of the following interventions will be included: physical exercise (endurance and resistance training), nutrition, psychological support and smoking cessation. Studies with a prehabilitation program of less than 14 days will be excluded. Multi-arm studies will be included if they report on at least two of the four prehabilitation interventions. Pilot studies will be included if the patients are randomised. If not all data is reported, we will ask the authors to send the data for further analysis. Only RCTs with follow-up of at least four weeks' duration will be included in this review. Four weeks after surgery additional therapy (chemotherapy, surgery for metastasis) may be considered which requires an optimal functional capacity of patients.

Types of participants

Studies with adult patients (> 18 years) receiving elective surgery for colorectal cancer will be included. Studies with patients undergoing primary resection for colorectal cancer and (neo)adjuvant therapy will be included as well. No studies will be included with patients receiving additional intraoperative therapy and/or multi-organ resection, neither patients with metastatic disease. If possible subgroup and sensitivity analysis will

be performed on patients receiving neoadjuvant therapy, open versus laparoscopic surgery, and colon versus rectum surgery.

Types of interventions

All interventions identified in studies as part of a prehabilitation program to improve functional capacity, patients' nutritional, mental and smoking status, will be analysed and compared to a control group (usual care or no prehabilitation). Multimodal (e.g. exercise and nutrition) and single modal programs (e.g. exercise alone) will be included. If different prehabilitation interventions are compared with each other as well as to a control group, the study will be included. Studies should list frequency and duration of the intervention programs.

Types of outcome measures

Primary outcomes

The effect on 6-minute walk distance (6MWT) (meters walked in 6 minutes in a corridor of at least 20 meters) just before surgery (T1).

Secondary outcomes

Functional capacity:

- VO2peak (ml/kg)
- hand grip strength (kg)

Follow up:

- length of hospital stay (in days)
- overall mortality at maximal follow up period (in months)
- overall complication rate (Clavien Dindo scale 1-5, Comprehensive Complication Index (Slankamenac 2013))
- overall safety of prehabilitation interventions (dropouts, serious adverse events)
- patient reported HRQoL (SF-36, HADs, EQ5d, EORTC QLQ 29/30)
- return to normal activities (RNA) as measured by PROMIS (van der Meij 2016; Hedrick 2017)

Outcomes should be available at baseline (T0, 3-6 weeks prior to surgery), just before surgery (T1, <1 week), and 4 (T2) and/or 8 weeks (T3) after surgery.

Search methods for identification of studies

Electronic searches

Two authors (SJvR and GT) will conduct a comprehensive literature search with no language restriction by searching the following electronic databases:

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library) (Appendix 1) MEDLINE (Ovid, 1950 to present) (Appendix 2) Embase (Ovid, 1974 to present) (Appendix 3).

In addition, we will search for trials on ClinicalTrials.gov, Google scholar, Chinese trials registry, and the WHO's International Clinical Trials Registry Platform (ICTRP). We will also contact colleague experts in the field of prehabilitation to request their point of view.

Searching other resources

A hand search of references lists of relevant studies will be carried out.

Data collection and analysis

Selection of studies

Three review authors (SJvR, GT and HJPF) will independently screen the titles and abstracts of all articles we identify in the literature searches. Disagreements regarding inclusion/exclusion of selected trials will be resolved by discussion.

We will retrieve the full-text papers of articles where we consider the titles and abstracts to be relevant or where eligibility is unclear. Two review authors (SJvR and HJPF) will independently assess these articles for inclusion and will resolve any discrepancies by discussion. In case of disagreement, we will consult a third review author (GT).

When necessary, additional or missing information will be requested from the authors of the included trials. We will collate multiple reports of one study and we will indicate a primary data source.

Trials that compare three or more different therapy programs (several prehabilitation programs vs control) with other kinds of programs, will be included. From these trials, only participants treated with prehabilitation and the control group shall be noted.

We will present the study selection process in a PRISMA flow chart. We will list the excluded studies and their reasons for exclusion in a 'Characteristics of excluded studies' table. We will include studies irrespective of whether the study presents outcome data.

Data extraction and management

Two review authors (GT and HJPF) will extract data independently using a standard data collection form and enter data into Review Manager (RevMan 2016).

The data collection form will contain the following items.

• General information: study title, study author(s), source, publication date, contact address, language, funding sources and author declaration(s) of interest;
• Study characteristics: number, age, gender, comorbidity, study setting, application of an ERAS program will be registered, statistical power, type of surgery, adherence, number of drop-outs;
• Outcomes: 6MWT, VO2peak, hand grip strength, length of hospital stay, overall mortality at maximal follow up period, overall complication rate (Clavien Dindo scale 1-5), comprehensive complication index, patient reported quality of life (SF-36, HADs, EQ5d, EORTC QLQ 29/30)).

When necessary, additional or missing information will be requested from the authors of the included trials. We will extract the number of participants and all relevant outcome measures per follow up period with accompanying standard errors and 95% confidence intervals for each treatment group. We will resolve any disagreements regarding data collection by consulting a third review author (SvR).

Assessment of risk of bias in included studies

Two review authors (GT, HJPF) will independently assess and three other review authors (SvR, RR and GS) will confirm the methodological quality of the trials, primarily for adequacy of allocation concealment, bias, and follow-up. As in most trials that compared prehabilitation with a reference group, blinding of staff and participants is not possible, this will therefore not be considered.

We will use the Cochrane 'Risk of bias' Tool for assessing risk of bias of included trials (Chapter 8, Higgins 2011). We assessed risk of bias of the following domains:

· Random sequence generation;

• Low risk of bias (the method used is adequate (e.g. computer-generated random numbers, table of random numbers) or is unlikely to introduce confounding)
• Uncertain risk of bias (information is insufficient to permit assessment of whether the method used is likely to introduce confounding)
• High risk of bias (the method used (e.g. quasi-randomised trials) is improper and is likely to introduce confounding)

· Allocation concealment;

• Low risk of bias (the method used (e.g. central allocation) is unlikely to induce bias on the final observed effect)
• Uncertain risk of bias (information is insufficient to permit assessment of whether the method used is likely to induce bias on the estimate of effect)
• High risk of bias (the method used (e.g. open random allocation schedule) is likely to induce bias on the final observed effect)

· Blinding of participants and outcome assessors;

• Low risk of bias (blinding was performed adequately, or the outcome measurement is not likely to be influenced by lack of blinding)
• Uncertain risk of bias (information is insufficient to permit assessment of whether the type of blinding used is likely to induce bias on the estimate of effect)
• High risk of bias (no blinding or incomplete blinding, and the outcome or the outcome measurement is likely to be influenced by lack of blinding)

· Incomplete outcome data;

• Low risk of bias (underlying reasons for loss of data are unlikely to make treatment effects depart from plausible values, or proper methods have been employed to handle missing data)
• Uncertain risk of bias (information is insufficient to permit assessment of whether the missing data mechanism in combination with the method used to handle missing data is likely to induce bias on the estimate of effect)
• High risk of bias (the crude estimate of effects (e.g. complete case estimate) will clearly be biased because of underlying reasons for the loss of data, and the methods used to handle missing data are unsatisfactory)

· Early stopping;

• Low risk of bias (sample size calculation was reported and the trial was not stopped, or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was low)
• Uncertain risk of bias (sample size calculations were not reported, and it is not clear whether the trial was stopped early
• High risk of bias (the trial was stopped early because of an informal stopping rule, or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was high)

· Other bias;

The extent of contamination (switching between treatment arms) will be estimated. Study quality will be graded in a Risk of bias table on the basis of a checklist of design components. The adequacy of each category shall be qualified as "low", "unclear", or "high" risk according to the criteria provided in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) (Appendix 4).

Measures of treatment effect

The primary outcome that will be considered is 6MWT at T1. We will

express the treatment effect as the pooled weighted average difference in 6MWT at T1 (i.e. meters) with 95% confidence intervals between patients with and without prehabilitation.

As a secondary measure we will assess time-to-event data (e.g. overall morbidity and mortality), we will calculate the hazard ratios (HR) and their 95% confidence intervals (CI) for each trial. If no HRs are reported, we will extrapolate them from the reported Kaplan-Meier curves (Parmar 1998). For dichotomous variables (e.g. toxicity rates), we will calculate relative ratios (RR) and their 95% CI's. For categorical outcomes (e.g. Clavien Dindo scale) we will use the proportional odds model, which assumes there is an equal odds ratio for all dichotomies of the data as proposed in the Cochrane Handbook (Higgins 2011). For continuous outcomes (e.g. functional outcomes, quality of life measurements), we will use raw mean differences along with their 95% CI as summary statistic. If results are expressed on different scales standardized mean differences (SMD) with 95% CI will be used (Higgins 2011). We will check both the magnitude and the direction of the effect size reported by the included studies to ensure that we do not include any incorrect values in the pooled analysis. For time-to-event outcomes, we will extract log Hazard ratio where possible, using preferably the standard error, and alternatively the CI or p-value. If we do not obtain sufficient data to calculate the Hazard ratio, data will be dichotomized.

Unit of analysis issues

We will pool data and perform a meta-analysis using the aggregated effect parameters and confidence intervals as reported by the investigators. If individual data are available, we will create a long format dataset based on one record per patient-measurement that will account for repeated measurements within patients and address design effects. We do not expect to find either cross-over RCTs or cluster-RCTs.

However, if we identify any cluster-RCTs that meet the inclusion criteria of this review, we will include them in the analyses along with individually RCTs. We will adjust their sample sizes using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011, chapter 16.3.4 or 16.3.6) using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-RCTs and individually RCTs, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and we consider the interaction between the effect of intervention and the choice of randomization unit to be unlikely.

Should we find cross-over RCTs that meet the inclusion criteria of this review, we will perform sensitivity analysis by excluding those trials to assess whether this type of trial significantly affects the pooled estimates. We will use preferably the data from the first period, if reported.

Dealing with missing data

In case of missing data, we will contact the study authors to request any missing information. We will analyze all data based on the intention-to-treat (ITT) principle as far as possible. We will report the level of loss-to-follow-up and assess this as a potential source of bias. When participants dropped out from the trial before the endpoint assessment, or if data from separate time points is missing, we will analyze only the available data. In the case of any assumptions and imputations by the authors, we will assess methods -including whether imputations are performed using best case, worse case or mean imputation strategies - and their effects using sensitivity analyses.

Assessment of heterogeneity

We will assess heterogeneity visually in forest plots and statistically using the Chi2 test ($P < 0.10$). We will set the P value to 0.10 to determine statistical significance because the Chi2 test has low power to assess heterogeneity when studies have small sample sizes or are few in number (Higgins 2011).

We will calculate the I2 statistic as a measure of heterogeneity. The I2 statistic represents the percentage variation across studies explained by heterogeneity. To limit the influence of clinical and methodological heterogeneity, we will pool studies with similar study design and with a comparable patient population (e.g. indication for surgery, type of surgery, age, sex). We will interpret the I2 statistic value according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011, chapter 9.5.2). The I2 statistic will be interpreted as follows: 0% to 40% low heterogeneity, 30% to 60% moderate heterogeneity, 50% to 90% substantial heterogeneity and 75% to 100% considerable heterogeneity. We will apply this for all outcomes as suggested in the Cochrane Handbook (Higgins 2011). We will not pool data if heterogeneity is high (i.e. if the I2 statistic value is greater than 75%). We will investigate potential sources of between-study heterogeneity by means of subgroup analysis (see Subgroup analysis and investigation of heterogeneity). Statistical heterogeneity will be addressed in the analysis by including a random effect into the model if possible. If studies are clinically heterogeneous, we will not pool them in meta-analysis.

Assessment of reporting biases

To prevent language bias, we do not impose a language restriction. If sufficient studies are found (more than 10 studies), we will aim to identify publication bias by making funnel plots.

Data synthesis

When possible, we will pool summary data for dichotomous, ordinal, continuous and time-to-event outcomes to create an overall effect size (ES) with an 95% CI at various periods of follow-up using a random-effects model (Dersimonian 1986). To explore the effect of small effect sizes at the extremes of power we will compare other methods to pull the data such as a restricted maximum likelihood model (Hardy 1996) or permutations model (Follman 1999). The estimation of between study heterogeneity might be inaccurate when we identify a small number of trials for inclusion and the random-effects model might be biased. If the number of included trials is lower than 10, we will perform a meta-analysis using a fixed-effect model. In case of dichotomous outcome, we will use the Mantel-Haenszel method to run both the fixed-effect and random-effects model. The inverse variance method will be used in case of ordinal and continuous data for both models. In case of inclusion of cluster RCTs, we will use the generic inverse variance method as well (Higgins 2011).

If standard errors (SEs) are reported (and authors will not reply on our request to send unpublished data), we shall convert these to standard deviations (SD). Normal distribution of data will be assumed according to the authors statement in the publication. If individual data are available, we will visually check the distribution using histograms. For articles with non-parametric results, SDs will be calculated by dividing the width of the interquartile range by 1.35, according to Chapter 7.7.3.5 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Data of each study will be summarized in forest plots and calculated summary estimates with a 95% CI. We consider using a two-sided $P < 0.05$ as statistically significant, except for the test of publication bias for which the recommended levels are $P < 0.10$. Statistical analyses are done by using the Review Manager software (RevMan 2016).

To minimize the chance of a random error, due to sparse data and repetitive testing of accumulating data, a trial sequential analysis will be performed (Thorlund 2011). The required information size needed to detect or reject the effect of our intervention will be based on the event proportion in the control group (Wetterslev 2008).

Subgroup analysis and investigation of heterogeneity

We may find studies in which a preoperative exercise program is used instead of a multimodal preoperative program (prehabilitation). If a significant number of studies is found, we will perform a subgroup analysis between studies that only use preoperative exercise testing only and studies that uses a formal prehabilitation program. If possible, sub analysis will be performed on patients receiving neoadjuvant therapy, high-risk patients, elderly patients (>70 years), and comparison on disease stage, type of surgery (colon versus rectum), and type of intervention (supervised versus non-supervised, home-based versus facility-based).

Summary of findings

We will assess the overall quality of evidence of the main review outcomes, subgroup and sensitivity analyses using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach in summary of Findings Table(s).

We will evaluate the quality of evidence using the GRADE approach for the following outcomes (Schünemann 2009):

· postoperative complications
· overall survival
· colorectal cancer-specific survival
· relapse-free survival
· functional performance measures
· length of hospital stay
· health-related quality of life
· adverse events

The SoF table(s) will highlight the overall quality of the body of evidence for the main review outcomes, using the GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, indirectness, imprecision and publication bias). Judgements about the quality of the evidence (high, moderate, low or very low) will be justified, documented and incorporated into the reporting of results for each outcome.

The GRADE system classifies the quality of evidence in one of four grades:

Grade	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence on the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

A Summary of the GRADE approach to rating the quality of evidence, addressing five possible reasons for downgrading, and three possible reasons for upgrading:

Downgrades the evidence*	Upgrades the evidence
Study limitation	Large magnitude of effect
Inconsistency of results (unexplained heterogeneity, inconsistency of results)	All plausible confounding would reduce the demonstrated effect
Indirectness of evidence (indirect population, intervention, control, outcomes)	Dose-response gradient
Imprecision (wide confidence intervals, single trial)	
Publication bias	

*If there are very serious concerns (for example if most information is from studies at high risk of bias), we will rate down two levels (applied to all five reasons listed)

Sensitivity analysis

Individual study effects on the results will be examined by excluding trials with high heterogeneity, missing data and high risk of bias, as this will allow us to determine if these factors influence the study results significantly.

Results

Description of studies

Results of the search

Included studies

Excluded studies

Risk of bias in included studies

Allocation (selection bias)

Blinding (performance bias and detection bias)

Incomplete outcome data (attrition bias)

Selective reporting (reporting bias)

Other potential sources of bias

Effects of interventions

Discussion

Summary of main results

Overall completeness and applicability of evidence

Quality of the evidence

Potential biases in the review process

Agreements and disagreements with other studies or reviews

Authors' conclusions

Implications for practice

Implications for research

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Declarations of interest

No conflicts of interest.

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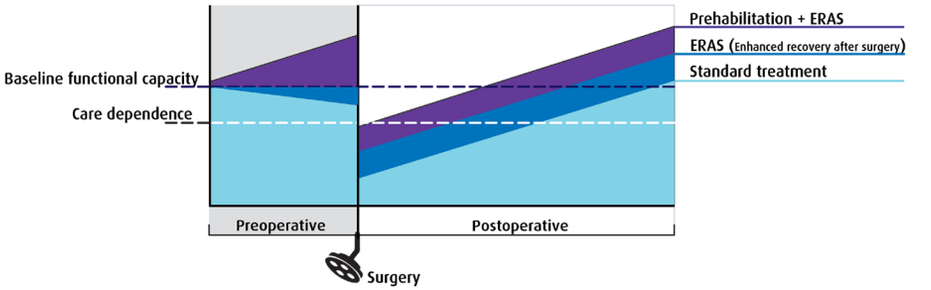
Data and analyses

1 prehab vs no-prehab

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 after 3 months	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Figures

Figure 1. Functional capacity baseline level of patients undergoing elective surgery for colorectal cancer during treatment. Level of Activities Daily Living (ADL), Enhanced Recovery After Surgery (ERAS). (Adapted from Carli 2005 with permission). Standard treatment is considered surgery alone without additional perioperative intervention. Level of Activities Daily living is the minimal required energy level to function normally.



Appendices

1 CENTRAL search strategy

1. MeSH descriptor Intestine, Large explode all trees and with qualifier: Surgery
2. MeSH descriptor Colonic Diseases explode all trees and with qualifier: Surgery
3. MeSH descriptor Rectal Diseases explode all trees and with qualifier: Surgery
4. MeSH descriptor Abdomen explode all trees and with qualifier: Surgery
5. MeSH descriptor Colorectal Surgery explode all trees

6. MeSH descriptor Colectomy explode all trees
7. (colectom* or protectom*):ti,ab,kw
8. ((colorect* or colon* or rect* or anorect* or anus* or anal* or intestin* or bowel* or abdomen or abdominal) NEAR/2 (resection or surgery or operat* or surgical*)):ti,ab,kw
9. OR/1-8
10. Prehabilitat*:ti,ab,kw
11. ((Pre-operat* or preoperat*) NEAR/2 (care or period or intervention or exercise or fitness or program)):ti,ab,kw
12. 10 or11
13. 9 and 12

2 MEDLINE search strategy

MEDLINE (Ovid, 1950 to present)
1. Exp colonic diseases/su
2. Exp rectal diseases/su
3. Exp intestine, Large/su
4. Exp abdomen/su
5. Exp colorectal surgery
6. Exp colectomy/
7. (colectom* or protectom*).mp.
8. ((colorect* or colon* or rect* or anorect* or anus* or anal* or intestin* or bowel* or abdomen or abdominal) adj2 (resection or surgery or operat* or surgical*)).mp.
9. OR/1-8
10. Prehabilitat*.mp.
11. ((Pre-operat* or preoperat*) adj2 (care or period or intervention or exercise or fitness or program)).tw,kf.
12. 10 or 11
13. 9 and 12
14. Randomized controlled trial.pt.
15. Controlled clinical trial.pt.
16. Randomized.ab.
17. Placebo.ab.
18. Clinical trials as topic.sh.
19. Randomly.ab.
20. Trial.ti.
21. OR/14-20
22. Exp animals/ not humans.sh.
23. 21 not 22
24. 13 and 23

3 Embase search strategy

Embase (Ovid, 1974 to present)
1. Exp Large intestine/su
2. Exp colon disease/su
3. Exp rectum disease/su
4. Exp abdominal surgery
5. (colectomy* or protectom*).mp.
6. ((colorect* or colon* or rect* or anorect* or anus* or anal* or intestin* or bowel* or abdomen or abdominal) adj2 (resection or surgery or operat* or surgical*)).mp.
7. OR/1-6
8. Prehabilitat*.mp.
9. ((Pre-operativ* or preoperativ*) adj2 (care or period or intervention or exercise or fitness or program)).tw,kw.
10. OR/8-9
11. 7 and 10
12. CROSSOVER PROCEDURE.sh.
13. DOUBLE-BLIND PROCEDURE.sh.
14. SINGLE-BLIND PROCEDURE.dk
15. (crossover* or cross over*).ti,ab.
16. Placebo*.ti,ab.
17. (doubl* adj blind*).ti,ab.
18. allocat*.ti,ab.
19. trial.ti.
20. RANDOMIZED CONTROLLED TRIAL.sh.
21. random*.ti,ab.
22. OR/12-21
23. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)
24. 22 not 23
25. 11 and 24

4 Criteria for judging risk of bias in the 'Risk of bias' assessment tool

RANDOM SEQUENCE GENERATION
Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.

Criteria for a judgement of ‘Low risk’ of bias.	The investigators describe a random component in the sequence generation process such as: · Referring to a random number table; · Using a computer random number generator; · Coin tossing; · Shuffling cards or envelopes; · Throwing dice; · Drawing of lots; · Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgement of ‘High risk’ of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: · Sequence generated by odd or even date of birth; · Sequence generated by some rule based on date (or day) of admission; · Sequence generated by some rule based on hospital or clinic record number. · Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: · Allocation by judgement of the clinician; · Allocation by preference of the participant; · Allocation based on the results of a laboratory test or a series of tests; · Allocation by availability of the intervention.

Criteria for the judgement of ‘Unclear risk’ of bias.	Insufficient information about the sequence generation process to permit judgement of ‘Low risk’ or ‘High risk’.
ALLOCATION CONCEALMENT Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.	
Criteria for a judgement of ‘Low risk’ of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: · Central allocation (including telephone, web-based and pharmacy-controlled randomization); · Sequentially numbered drug containers of identical appearance; · Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of ‘High risk’ of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: · Using an open random allocation schedule (e.g. a list of random numbers); · Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); · Alternation or rotation; · Date of birth; · Case record number; · Any other explicitly unconcealed procedure.
Criteria for the judgement of ‘Unclear risk’ of bias.	Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
BLINDING OF PARTICIPANTS AND PERSONNEL Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	

Criteria for a judgement of ‘Low risk’ of bias.	Any one of the following: · No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; · Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of ‘High risk’ of bias.	Any one of the following: · No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; · Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgement of ‘Unclear risk’ of bias.	Any one of the following: · Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’; · The study did not address this outcome.
BLINDING OF OUTCOME ASSESSMENT Detection bias due to knowledge of the allocated interventions by outcome assessors.	
Criteria for a judgement of ‘Low risk’ of bias.	Any one of the following: · No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; · Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of ‘High risk’ of bias.	Any one of the following: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; · Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Criteria for the judgement of ‘Unclear risk’ of bias.	Any one of the following: · Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’; · The study did not address this outcome.
INCOMPLETE OUTCOME DATA Attrition bias due to amount, nature or handling of incomplete outcome data.	
Criteria for a judgement of ‘Low risk’ of bias.	Any one of the following: · No missing outcome data; · Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); · Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; · For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; · For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; · Missing data have been imputed using appropriate methods.

Criteria for the judgement of ‘High risk’ of bias.	Any one of the following: · Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; · For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; · For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; · ‘As-treated’ analysis done with substantial departure of the intervention received from that assigned at randomization; · Potentially inappropriate application of simple imputation.
Criteria for the judgement of ‘Unclear risk’ of bias.	Any one of the following: · Insufficient reporting of attrition/exclusions to permit judgement of ‘Low risk’ or ‘High risk’ (e.g. number randomized not stated, no reasons for missing data provided); · The study did not address this outcome.
SELECTIVE REPORTING Reporting bias due to selective outcome reporting.	
Criteria for a judgement of ‘Low risk’ of bias.	Any of the following: · The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; · The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for the judgement of ‘High risk’ of bias.	Any one of the following: · Not all of the study’s pre-specified primary outcomes have been reported; · One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; · One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); · One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; · The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of ‘Unclear risk’ of bias.	Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’. It is likely that the majority of studies will fall into this category.
OTHER BIAS Bias due to problems not covered elsewhere in the table.	
Criteria for a judgement of ‘Low risk’ of bias.	The study appears to be free of other sources of bias.
Criteria for the judgement of ‘High risk’ of bias.	There is at least one important risk of bias. For example, the study: · Had a potential source of bias related to the specific study design used; or · Has been claimed to have been fraudulent; or · Had some other problem.
Criteria for the judgement of ‘Unclear risk’ of bias.	There may be a risk of bias, but there is either: · Insufficient information to assess whether an important risk of bias exists; or · Insufficient rationale or evidence that an identified problem will introduce bias.

CHAPTER 9

MAKING PATIENTS FIT FOR SURGERY: INTRODUCING A FOUR PILLAR MULTIMODAL PREHABILITATION PROGRAM IN COLORECTAL CANCER

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ABSTRACT

Background

Following surgery for colorectal cancer, up to half of patients may develop complications such as anastomotic leakage, ileus and wound infection. Number and severity of complications are closely related to preoperative functional capacity. Enhancing patients' functional capacity prior to surgery -prehabilitation- may facilitate faster recovery and improve quality of life. However, time before surgery is short, mandating a multimodal and high-intensity training approach. This study investigated feasibility and safety of a prehabilitation program for colorectal cancer.

Methods

Fifty patients undergoing elective colorectal surgery for cancer were included. Patients were assigned to an intervention (n=20, prehabilitation) or control group (n=30, standard care) according to availability of the program. Both groups received perioperative care in accordance with the enhanced recovery after surgery guidelines. Prehabilitation consisted of a multimodal program: high-intensity training, high-protein nutrition, smoking cessation and psychological support. Program attendance, patient satisfaction, adverse events and parameters assessing functional capacity were determined.

Results

Program evaluation revealed a high (88%) attendance rate and high level of patient satisfaction. No significant adverse events related to the program occurred. After prehabilitation, significant improvements were observed for all patients in terms of endurance, strength, or both. Eighty-six versus forty percent of patients recovered to baseline functional capacity within four weeks after surgery (intervention versus control, $p<0.01$).

Conclusion

A comprehensive multimodal and multidisciplinary prehabilitation program including high-intensity training for colorectal cancer patients is feasible and effective. A randomized controlled trial (NTR5947) was initiated to determine whether multimodal prehabilitation may lower morbidity and mortality rates in colorectal surgery.

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Keywords: prehabilitation, feasibility, functional capacity, colorectal cancer, surgery

Background

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

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

To date, trials with preoperative home-based training programs showed small effect sizes and had low compliance (16,17). Moreover, moderate exercise programs have not yielded beneficial effects in a preoperative setting (17). These findings may not be unexpected, as the preoperative training period is relatively short (maximum of 5 weeks) (18). In such a short time span, high-intensity training is needed to attain a sufficient cardiopulmonary response for the improvement of postoperative outcome. Due to the load of this high-intensity training, thorough guidance of patients is needed to enhance feasibility and compliance to such a training program. Furthermore, evidence shows that prehabilitation should be multimodal including supervised high-intensity exercise training, adequate nutrition, smoking cessation, and psychological support for an optimal benefit (19). In terms of nutrition, protein supplementation as an addition to training may lead to more effectiveness (20–23). Psychological support and cessation of smoking may further enhance the effects of such a program (24,25).

This pilot study was initiated to test feasibility, effectiveness, and safety of such a prehabilitation program being contemplated for a randomized controlled trial (NTR5947).

Methods

Subjects

This study was conducted between June 2016 and June 2017 at Máxima Medical Center (MMC), Veldhoven, the Netherlands. Eligible participants were over 18 years of age and scheduled for elective resection for colorectal cancer without neoadjuvant treatment. Patients with metastatic disease, chronic renal failure, ASA score 4 or 5, conditions interfering with the ability to perform exercise, and the inability to understand informed consent were excluded.

Study design

This non-randomized prospective, hospital-based observational cohort study was approved by MMC Ethics Committee (NL54547.015.15). After providing verbal and written consent, patients were assigned to the prehabilitation program or standard care (control) depending on program availability. The sample size was set to 30 in the control group and 20 in the intervention group based on previous studies (17).

Both groups received perioperative care according to enhanced recovery after surgery (ERAS) guidelines (26). Patients were screened for anemia and optimized using iron injections (ferinject) if needed (threshold >7 mmol/l or 12 mg/dL). A smoke cessation program, which included intensive counselling (group and/or telephone sessions weekly) in combination with nicotine replacement therapy, was offered to all patients. Both groups were assessed at standardized time points before and after surgery (figure 1).

Exercise intervention

The prehabilitation group followed a 4-week program including 3-weekly hospital-based high-intensity endurance (interval) training, and upper body and lower body resistance training. Participants were also encouraged to walk or bike for 60 minutes on the days between the supervised training sessions.

The endurance training was performed on a stationary bicycle with 3 blocks of moderate intensity and 3 blocks of high intensity, and personalized using cardiopulmonary exercise testing (CPET) data (ECG, VO2max, HF, AT and RQ (27,28). The workload (watt) for the high intensity block was chosen to start at 65% of the maximum workload (at VO2peak). This intensity will result in a metabolic response in the range of 85-100% of VO2peak (Borg scale 15-17) at the end of the high-intensity interval – which is considered an appropriate range for high-intensity training. For recovery at moderate

intensity we chose a workload (watt) at 75% of VO2 AT (or, if AT was not visible, 20% of VO2peak). The workload was increased with 10% when Borg RPE was below 13 and/or heart rate <85% of the maximum heart rate and decreased with 10% when the exercise intensity in the first block could not be achieved in the last block.

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

Nutritional intervention

A protein supplement (Refit®TMP 90 Shake, Friesland Campina) was given to the prehabilitation group two times daily: 1) within one hour after exercise and 2) before bedtime (0.4 gram/kg body weight per serving).
A 3-day-food diary was completed by all participants before the start and at the end of the prehabilitation program. Participants in the intervention group received a tailored dietary advice aiming at a total protein intake of 1,5-1,8 g/kg/day (23,31,32).

Vitamin D and multivitamins (50% of RDA) were provided daily during prehabilitation (33–35).

Psychological support

Preoperatively, patients in the intervention group were scheduled for a 90-minute visit with a trained psychologist to address patients' anxiety level, provide coping strategies, teach relaxation techniques, and discuss postoperative expectations. If desired, more sessions were offered during the 4 weeks of prehabilitation. Also, patients were phoned weekly to increase adherence to the program.

Outcomes

The primary outcomes were feasibility, determined as adherence to training session, and number of dropouts and safety, determined as occurrence of adverse events (36,37). Dropouts received a short questionnaire to assess the reason for non-participation or drop-out from the study. Satisfaction after the completion of the intervention programs was assessed using a brief self-designed questionnaire.

A secondary outcome was functional capacity after prehabilitation and 4 weeks postoperatively, as measured by 6MWT. During the 6MWT, the patient was asked to walk as far as possible along a fifty-meter stretch of corridor in six minutes (38,39). An increase of 20 meters was considered clinically relevant (40–42).

Another secondary outcome was muscle strength as measured with 1RM. Because determining 1RM directly (by lifting the maximum weight achievable for the patient) has been questioned due to a risk of serious muscular injury, we chose to define the 1RM by indirect measures using the Brzycki formula (1RM=weight*36/(37-repetitions)) (43,44).

Further information was extracted using screening methods and tests for functional capacity (CPET, hand grip strength test, stair climb test and sit-to-stand test), physical activity level (modified CHAMP-S (19)), nutritional status (PG-SGA SF, anthropometry, BMI and food diary), health-related quality of life (SF-36, EORTC QLQ-C30 and EORTC QLQ-CR29), vulnerability of older patients (fried frailty score and G8 score) and depression and anxiety (GAD-7 and PHQ-9). These tests and questionnaires were captured so complete logistics could be tested for feasibility, but the number of patients in this pilot study were considered to be too small to draw definitive conclusions on the effect of prehabilitation based on outcomes of these questionnaires.

Statistical analysis

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

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

A two-tailed $p<0.05$ was considered statistically significant. Categorical and non-categorical data on feasibility were analyzed as qualitative measures. Statistical analysis was performed using SPSS for Windows software (version 22.0) and Graphpad Prism software for Windows.

Results

Patient characteristics

Patient characteristics are described in table 1. Patients in the prehabilitation group had a lower average 6MWT (535 vs. 568, ns), VO2peak (23 vs. 27, ns) and 1RM leg press (97 vs. 116, ns) – suggesting a lower baseline functional capacity in the intervention group compared to controls. The number of anastomoses constructed, laparoscopy and conversion rate, duration of surgery etc. were similar in both groups. In addition, postoperative complications, length of hospital stay, and rates for mortality, reintervention and readmission for both groups were similar to rates from hospital administration after standard care (table 2).

Feasibility, safety and program satisfaction

No adverse events as a result of the study or prehabilitation interventions were reported. Three of the 20 patients in the intervention group did not complete the whole program. One patient dropped out indicating that she did not have time for the program due to illness of her husband; the two others could not complete the program because their surgery was rescheduled to an earlier moment (due to logistical challenges). No patients dropped out because of fatigue or inability to perform the exercise or nutritional intervention. Ninety percent of patients indicated that they felt less tired because of the program. Program evaluation revealed a high attendance rate at the training sessions: of the 17 patients who completed the program, 12 patients attended 90% or more of training sessions. The remaining 5 patients also attended more than 75% of training sessions, and overall, 88% of training sessions were completed by patients. A high level of patient satisfaction was also observed (mean score of 4.6, 1= not satisfied, 5= very satisfied). Most important factors (>= 70%) affecting program satisfaction, the reasons to join a prehabilitation program, and major challenges in completing the program are given in Figure 2. Forty percent of the participants perceived no obstacles to the completion of the program as offered. When asked if they would follow the program again in retrospect, all patients confirmed, and all patients would recommend the program to family or friends.

Functional capacity

The majority of patients in the prehabilitation group improved their endurance capacity after four weeks of prehabilitation, as measured by the 6MWT. Strength (1RM) increased for all patients. Sixty-four percent of patients showed a clinically relevant progression in 6-MWT (>=20 meters) after prehabilitation (14,17,45). There were two non-responders. Both these patients had a baseline 6-MWT which was slightly above mean baseline functional capacity. Overall, more than half of patients in the intervention group progressed on all tests. There were no patients who progressed on less than 3 tests for endurance and strength.

Four weeks after surgery, mean functional capacity of patients in the intervention group increased compared to baseline, whereas the control group showed a decline in functional capacity (Figure 3). A mean increase of 30.3 meters compared to baseline is seen in the intervention group, and -16.3 meter decrease in walking distance is seen in controls. This suggests that patients recover above their baseline functional capacity after prehabilitation, whereas the control group shows a slight decline in condition ($p<0.05$). We also observed that 86 percent of patients in the prehabilitation group recovered to baseline functional capacity within four weeks after surgery, versus only 40 percent in the control group ($p<0.01$).

Discussion

This study was initiated to test the feasibility and safety of multimodal prehabilitation including high-intensity training for colorectal cancer patients undergoing elective surgery. We show that prehabilitation is feasible and safe, enables patients to become fit for surgery, and that it is highly appreciated by patients.

Feasibility, safety, and effectiveness

Previous studies on prehabilitation have shown that patients may benefit most of a multimodal program (25). Exercise, nutritional, psychological and smoking cessation interventions seem most effective when combined, and tailored to the individual patient. Earlier studies using lower-intensity and home-based programs resulted in only modest or no improvement in functional capacity (17). We therefore opted for a supervised and personalized high-intensity training (HIT) approach including protein supplementation. This approach resulted in improved functional capacity in patients after only four weeks of prehabilitation. The implementation of multimodal prehabilitation high-intensity training was feasible to implement in daily practice. There were no adverse events due to the program. The nutritional intervention did not result in any major obstacles as perceived by the patients. However, protein ingestion just before sleep was found to be uncomfortable and we therefore changed our protocol to supplement intake one hour before sleep. Four patients in the control group were active smokers at the moment of inclusion and successfully quit smoking. Mental support by a psychologist was only beneficial for a few patients. Our psychologists therefore recommend not to offer support of this kind to all patients in future prehabilitation programs. However, patients have considerable anxiety levels after cancer diagnosis which they need to cope with during the preoperative period. Therefore, we keep advising psychological screening for high anxiety and depression (using validated questionnaires such as PHQ-9 or GAD-7) so that any psychological care that is needed is not withheld from patients. Additionally, optimal information regarding treatment, support of a case manager during treatment and the visits to the physiotherapist may help patients to cope with their situation. For this, we recommend at least weekly contact with patients by a case manager – physically or by phone. During these contacts, coping mechanisms and psychological complaints should be addressed, and training perseverance should be further encouraged. Giving patients the opportunity to change their own behavior and have an effect on their own treatment was thought to be extremely important. Since these patients felt actively engaged with their treatment, they were better informed, had more confidence in their treatment, and shared decision-making became standard practice.

Collaboration and logistics

Although this prehabilitation program proved feasible, it could only succeed due to the collaboration of involved medical disciplines and hospital management. Most hospitals tend to work in “silo’s” (46,47). Such a restricted approach discourages collaboration where effective logistics are required. The successful completion of the program required secure planning, coordination, and flexible resources to facilitate all appointments for patients during prehabilitation. Regular meetings with representatives of all the disciplines allowed us to instigate and implement an appropriate framework for prehabilitation. Enthusiasm of patients was communicated to the whole research team, and was indispensable factor in further enhancing and sustaining commitment of involved health care practitioners.

In the present study, prehabilitation was limited to a maximum of 5 weeks from cancer diagnosis to surgery due to national and international legislation. There are also countries where the government compels surgeons to operate within 2 weeks (Denmark) or where it is customary to be operated within several days (China). Also, ‘waiting time’ targets for hospitals, which are publicly available, result in the expectation of patients that they will be operated within this period. Recent studies show that oncological outcome does not improve when colorectal patients are operated within these 5 weeks (18). Moreover, the present study indicates that prehabilitation results in substantial benefits for patients in terms of improving functional capacity and this finding should be investigated on a larger scale. The planned RCT aims to show an association between increasing preoperative functional capacity using prehabilitation, and better postoperative outcome. Consequently, it may even be advisable to prolong the prehabilitation period further for individual patients.

Limitations

Although patients were very satisfied with the prehabilitation program and even though there was an improvement in functional capacity, this study had several limitations. The aim of this study was to test feasibility of a multimodal prehabilitation program and therefore only fifty patients were included. Due to these small numbers and lack of randomization, limited conclusions can be drawn on the postoperative effects of the program. Especially for the analysis of postoperative outcome, a larger sample number is needed. A larger patient population may also facilitate analysis of responsiveness in different subgroups of patients.

Future perspectives

Prehabilitation may be seen as a new era in healthcare focusing on prevention and lifestyle changes. The combination of current knowledge may allow us to improve care before any type of intensive treatment such as surgery or chemoradiotherapy (5,17,49,50). Prehabilitation improves patient education, and gives patients a central role (patient empowerment), and it may even enhance recovery and facilitate the earlier start of adjuvant treatment, improving outcome (48).

This pilot study included a small number of patients and was not set up to determine whether prehabilitation may reduce postoperative morbidity and mortality rates. Since this is a clinically relevant question, we initiated a randomized controlled trial, to investigate whether multimodal prehabilitation could reduce postoperative complications and improve functional capacity pre- and postoperatively for patients undergoing surgery for colorectal cancer. This study will also investigate the impact of such a program on HRQoL, length of hospital stay and cost-effectiveness. The principal of future prehabilitation research and implementation includes support throughout the healthcare organization and the involvement of all relevant stakeholders (such as medical specialists, management, finance and health insurance companies), in order to allow patients to prepare optimally for any type of major treatment.

This study demonstrated the feasibility and preliminary effectiveness of a comprehensive multimodal and multidisciplinary prehabilitation program using high-intensity training, optimal nutrition, smoking cessation and psychological support for colorectal cancer patients. Further research in the form of a large-scale worldwide randomized controlled trial (NTR5947) is needed to relate the potential of prehabilitation to postoperative morbidity and mortality.

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List of abbreviations

BMI: Body Mass Index
CAL: Colorectal Anastomotic Leakage
CPET: CardioPulmonary Exercise Testing
CRC: ColoRectal Cancer
EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30
EORTC QLQ-CR29: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire ColoRectal cancer 29
ERAS: Enhanced Recovery After Surgery
GAD-7: Generalized Anxiety Disorder 7
G8: Geriatrician 8 questionnaire
HIT: High Intensity Training
HRQoL: Health Related Quality of Life
LOS: Length Of hospital Stay
6MWT: six Minute Walk Test
MMC: Máxima Medical Center
NRT: Nicotine Replacement Therapy
1RM: one Repetition Maximum
PG-SGA: Patient Generated Subjective Global Assessment
PHQ-9: Patient Health Questionnaire 9
SD: Standard Deviation
SF-36: Short Form health survey 36

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

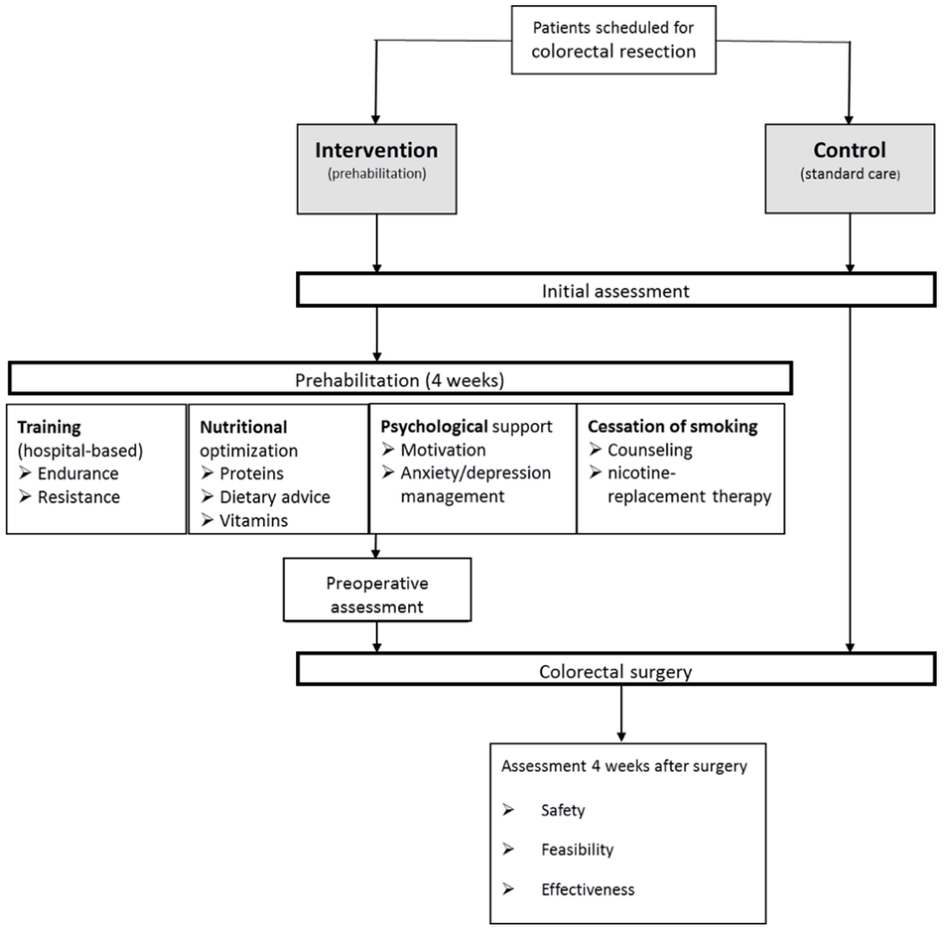


Figure 2. Program evaluation for all 20 patients in the prehabilitation intervention group undergoing surgery for colorectal cancer.

A. Main reason for participating in the program
B. Which factors contributed to the usefulness of the program in your experience?
C. Main challenge in completing the program

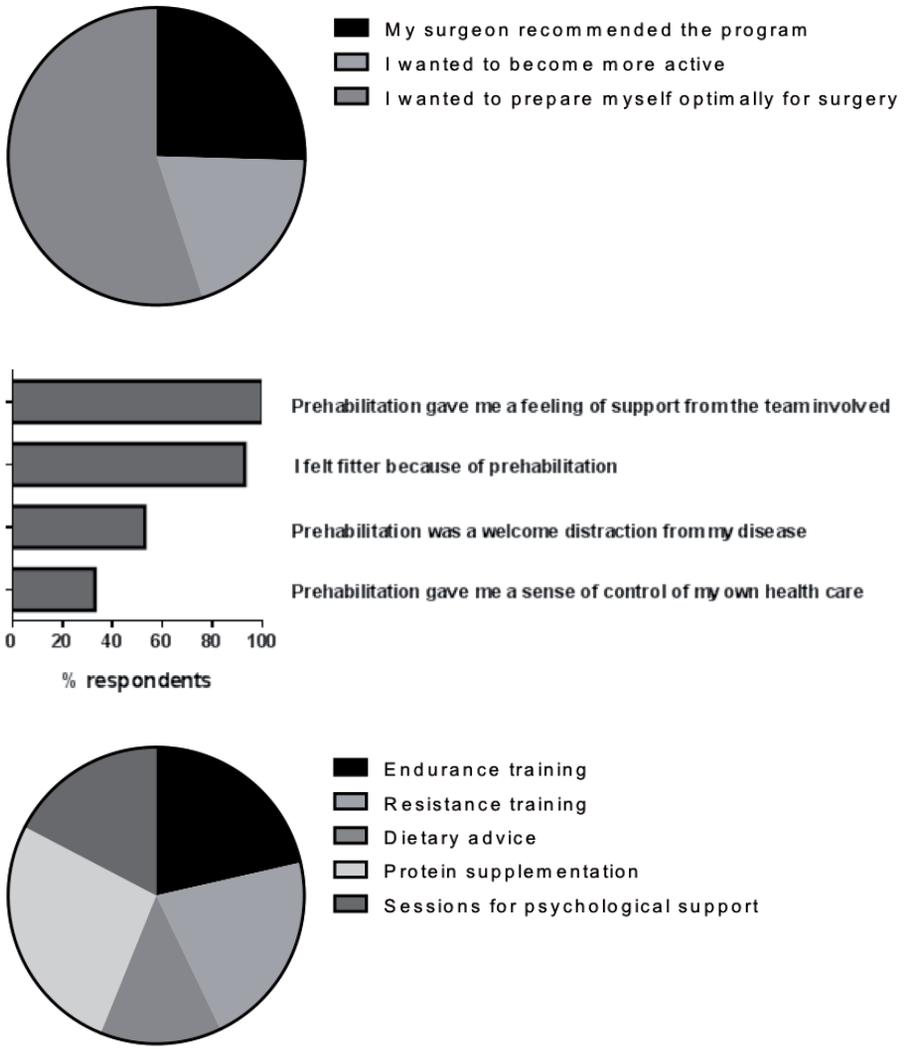


Figure 3. Patients undergoing a 4 week prehabilitation program prior to colorectal surgery showed progress after training, and performed better postoperatively (ANOVA, p<0.05) on functional capacity (6MWT) compared to controls receiving standard care.

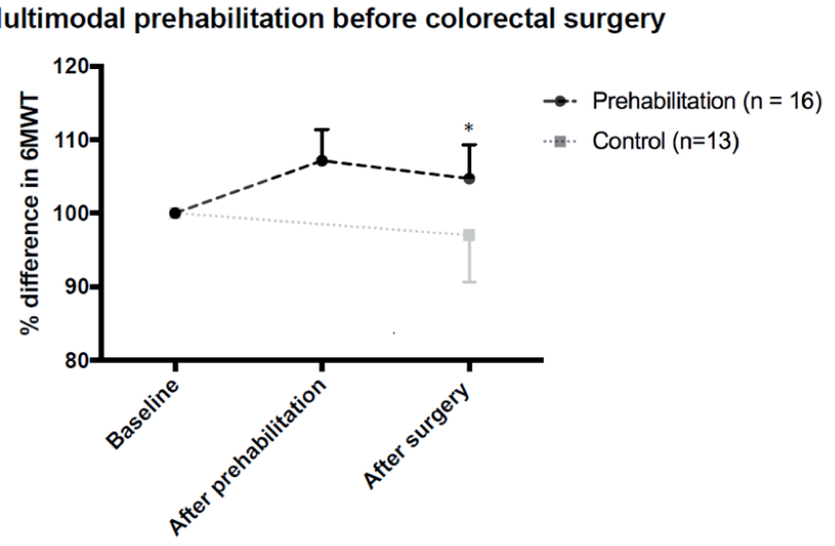


Table 1. Patient characteristics of 50 patients undergoing elective colorectal surgery for cancer. Prehabilitation intervention versus control group.

	Total group n = 50	Prehab n = 20	Control n = 30
Male sex (%)	27 (54)	10 (50)	17 (57)
Age (range)	71 (46-89)	75 (62-89)	71 (46-84)
Charlson Comorbidity Index* (range)	3 (2-7)	3 (2-7)	2 (2-7)
ASA (%)**			
0	-	-	-
I	5 (10)	2 (10)	3 (10)
II	39 (78)	15 (75)	24 (80)
III	6 (12)	3 (15)	3 (10)
BMI[#] (median)	26 (18-35)	26 (18-29)	26 (19-45)
Cigarette smoking^ (%)	4 (8)	0	4 (14)
Pack years (IQR)	1 (0-15)	0 (0-19)	5 (0-15)
Disease stage[-]			
0	1 (2)	0	1 (3)
I	16 (32)	6 (30)	10 (33)
II	13 (26)	8 (40)	5 (17)
III	19 (38)	6 (30)	13 (44)
IV	1 (2)	0	1 (3)
Mental status			
PHQ-9[$] (IQR)	3 (1-6)	4 (2-10)	2 (1-4)
GAD-7[!] (IQR)	3 (1-8)	6 (3-13)	3 (0-7)
Functional capacity			
6MWT[&] (IQR)	568 (518-598)	535 (498-586)	568 (521-605)
VO2peak[&] (IQR)	26 (20-28)	23 (18-26)	27 (24-30)
1RM leg press[&] (IQR)	113 (89-133)	97 (81-130)	116 (93-157)
1RM chest press[&] (IQR)	33 (26-47)	27 (18-35)	39 (31-61)
1RM lateral pull down[&] (IQR)	36 (32-48)	33 (30-39)	44 (34-58)
Stoma[+] (%)	9 (18)	2 (10)	7 (23)
Colonic surgery (%)	37 (74)	18 (90)	19 (76)
Laparoscopic (%)	46 (92)	19 (95)	28 (93)
Conversion (%)	7 (15)	3 (16)	4 (16)
Anastomosis (%)	46 (92)	19 (95)	22 (88)
Duration of surgery (min)	161 (82-354)	159 (82-268)	163 (83-315)

Legend 1. Medians with percentages or interquartile ranges (IQR) 25 and 75%. *Comorbidity was defined using the Charlson comorbidity index; **American Society for Anesthesiologists score; ^cigarette smoking at time of cancer diagnosis; ***smoking cessation in the four weeks before surgery; -disease stage defined by the TNM classification of malignant tumours; $Patient Health Questionnaire number 9; !Generalised Anxiety Disorder number 7; &One Repetition Maximum as measured four weeks preoperatively; #Body Mass Index; +diverting stoma.

Table 2. Postoperative characteristics of 50 patients undergoing elective colorectal surgery for cancer. Prehabilitation intervention group versus control group.

	Total group n = 50	Prehab n = 20	Control n = 30
CCI* (range)	6 (0-36)	7 (0-36)	5 (0-36)
Complications (%)**	11 (22)	5 (25)	7 (23)
Anastomotic leakage* (%)**	2 (4)	0	2 (7)
Hospital stay$ (range)	5 (2-41)	5 (3-16)	4 (2-41)
Reintervention= (%)	2 (4)	1 (5)	2 (7)
Readmission+ (%)	1 (2)	0	1 (3)
Mortality=	0	0	0

Legend 2. *Mean comprehensive complication index; **number of patients with postoperative complications as defined by Clavien Dindo; ***colorectal anastomotic leakage as defined by the international study group of rectal cancer (ISREC) classification grade C; $length of hospital stay in days; =reintervention and mortality during hospital stay; +readmission within 30 days after surgery; #start adjuvant chemotherapy, number of days after surgery.

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Chapter 10 Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: The first international randomized controlled trial on multimodal prehabilitation.
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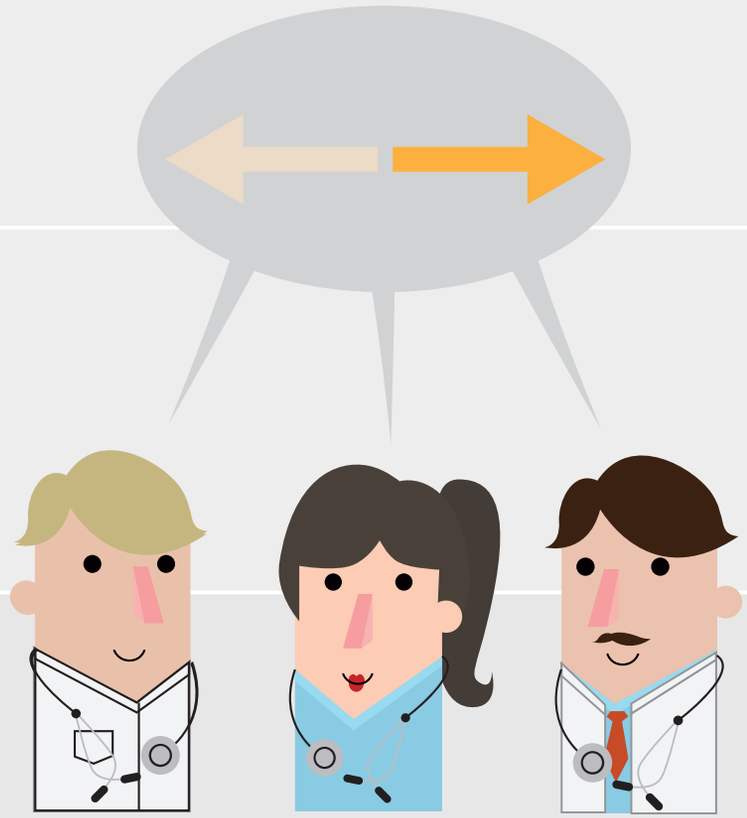
Chapter 11 Systematic review of exercise training in colorectal cancer patients during treatment.
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Chapter 12 Improving outcomes in oncological colorectal surgery by prehabilitation: a group effort to establish a tailor-made approach.
Submitted.

Chapter 13 Summarizing discussion, future perspectives and conclusions.

Chapter 14 Valorization - Valorisatie

Chapter 15 Overview of research projects
List of publications
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Word of thanks - Dankwoord
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Colorectal patient journey



PART IV

FUTURE PERSPECTIVES OF PREHABILITATION

CHAPTER 10
MULTIMODAL PREHABILITATION VERSUS REGULAR CARE IN COLORECTAL CANCER PATIENTS TO IMPROVE FUNCTIONAL CAPACITY AND REDUCE POSTOPERATIVE COMPLICATIONS:
THE FIRST INTERNATIONAL RANDOMIZED CONTROLLED TRIAL FOR MULTIMODAL PREHABILITATION

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ABSTRACT

Background

Colorectal cancer (CRC) is the second most prevalent type of cancer in the world. Surgery is the only curative option. However, postoperative complications occur in up to 50% of patients and are associated with higher morbidity and mortality rates, lower health related quality of life (HRQoL) and increased expenditure in health care. The number and severity of complications are closely related to preoperative functional capacity, nutritional state, psychological state, and smoking behavior. Traditional approaches have targeted the postoperative period for rehabilitation and lifestyle changes. However, recent evidence shows that the preoperative period might be the optimal moment for intervention. This study will determine the impact of multimodal prehabilitation on patients' functional capacity and postoperative complications.

Methods and design

This international multicenter, prospective, randomized controlled trial will include 714 patients undergoing colorectal surgery for cancer. Patients will be allocated to the intervention group, which will receive 4 weeks of prehabilitation (group 1, prehab), or the control group, which will receive no prehabilitation (group 2, no prehab). Both groups will receive perioperative care in accordance with the enhanced recovery after surgery (ERAS) guidelines. The primary outcomes for measurement will be functional capacity (as assessed using the six-minute walk test (6MWT)) and postoperative status determined with the Comprehensive Complication Index (CCI). Secondary outcomes will include HRQoL, length of hospital stay (LOS) and a cost-effectiveness analysis.

Discussion

Multimodal prehabilitation is expected to enhance patients' functional capacity and to reduce postoperative complications. It may therefore result in increased survival and improved HRQoL. This is the first international multicenter study investigating multimodal prehabilitation for patients undergoing colorectal surgery for cancer.

Trial registration: Trial Registry: NTR5947 – date of registration: 1 August 2016.

Keywords: prehabilitation, colorectal surgery, functional capacity, enhanced recovery after surgery, comprehensive complication index, postoperative complications, colorectal cancer.

Background

Colorectal cancer (CRC) is the second most prevalent type of cancer in the world, with over 1.4 million cases and 693.900 deaths a year. The only way to cure this condition is by surgical removal of the tumor. However, postoperative complications occur in up to 50% of patients and they are associated with higher morbidity and mortality rates, increased expenditure on health care and poorer health related quality of life (HRQoL).[2,3,4] Even in the absence of complications, major surgery is associated with a 20% to 40% reduction in physiological and functional capacity when measured by energy expenditure, endurance time, workload and heart rate during maximum exercise. This reduction in physiological reserve is experienced as a higher level of fatigue 4-6 weeks after hospital discharge.[5] Only 40% of patients return to their preoperative baseline functional capacity (as measured by VO2 peak).

Moreover, a proportion of operated colorectal cancer patients are eligible for adjuvant chemotherapy. The physical endurance required for completion of chemotherapy becomes more challenging when functional capacity has already been impaired due to surgery. Patients that have an impaired recovery might not start with chemotherapy at all or might have a delayed start. A delayed start (> 6 weeks after surgery) is known to compromise survival.[6,7] Therefore, there might be a secondary gain in survival if patients recover prosperously.

There is emerging evidence suggesting that many of the negative effects of major surgery can be reduced through the attenuation of surgical stress.[8] Efforts to improve the recovery process have primarily focused on the intraoperative factors (such as minimally invasive surgery and afferent neural blockade[9]) and postoperative interventions (examples being "fast track" early nutrition and mobilization[10]). The latter protocols have been designed to facilitate the return of functional activities and accelerate convalescence. However, the postoperative period may not be the best time to ask surgical patients to make significant changes in their nutrition and exercise since patients are tired and concerned about perturbing the healing process. As well as anxious about possible additional treatments for their underlying condition. The preoperative period may in fact be a better time to intervene in the factors that contribute to recovery, both physical and mental, and alleviate some of the emotional distress associated with the anticipation of surgery and the recovery process. [11,12]

The process of improving the functional capacity of the individual in order to enable them to withstand an incoming stressor has been termed prehabilitation.[13,14] Although some approaches have focused on education to prepare patients for procedures,[15] few steps have been taken to systematically enhance functional capacity before surgery. To investigate the impact of preoperative exercise on the recovery of functional capacity after colorectal surgery, Carli et al. performed a randomized controlled pilot study.[13] This trial, the first and largest trial with surgical prehabilitation, compared two exercise regimens (intense exercise on a stationary bike as opposed to walking and deep breathing) for several weeks before colorectal surgery. The primary outcome was functional walking capacity, as measured with the six-minute walk test (6MWT) between 5 to 9 weeks postoperatively. This trial showed that our target population has an average age of 60 with a low exercise capacity (VO2-peak of 18 ml/kg: an anaerobic threshold (AT) of around 10 ml/kg), and a 6MWT around 70% of normal. In terms of the risk for postoperative complications, this is exactly the most relevant range clinically (a threshold value of VO2 at AT of 10 ml/kg/min gives 0.88 specificity and 0.79 sensitivity with an area under curve of 0.85 for the risk of complications).[16]

Subgroup analysis showed that patients whose functional exercise capacity improved preoperatively, recovered relatively well in the postoperative period - regardless of the exercise technique.[17] However, one-third of patients deteriorated preoperatively despite the exercise regimen, and these patients were also at greater risk of prolonged recovery after surgery. Poor preoperative physical function (fatigue, malnutrition and physical performance) and the presence of anxiety and depression were also significant confounding predictors of prolonged recovery.[18,19,20,21,22] These results suggest that exercise training alone is not sufficient to attenuate the stress response in all patients and that it is also important to address factors such as nutrition and coping behavior that promote beneficial adaptation to training. Gillis et al. conducted a pilot study that showed that significant changes in postoperative functional exercise capacity can be achieved with a prehabilitation program.[38] However, they did not address the clinically relevant relationship between preoperative functional capacity, and the postoperative outcome. If functional capacity can be improved preoperatively, we may expect a reduction in postoperative complications.

Since it has been established that the number and severity of complications are closely related to preoperative functional capacity, nutritional status, smoking behavior and psychological well-being, there has been increasing interest in targeting these issues with a multimodal intervention program.[11] From a physiological point of view and based on limited practical experience, it seems feasible to achieve clinically relevant effects during the period of 4-5 weeks between diagnosis and operation.[12,13,16,38] However, this can only be achieved with targeted interventions that include exercise, nutrition, stopping smoking, and psychological support.

Study objectives

The general aim of this study is to investigate whether multimodal prehabilitation could enhance postoperative outcome using the comprehensive complication index (CCI) and 6-minute walk test (6MWT). Secondary outcomes will include patient reported outcome measures (PROMs) such as HRQoL and depression and anxiety scores, functional capacity measurements, nutritional and smoking status, length of hospital stay, study compliance, patients satisfaction and a cost-effectiveness analysis.

Methods/design

This is an international multicenter, randomized controlled trial with two study groups. Written informed consent will be obtained from all patients. The trial will be conducted according to the rules of Good Clinical Practice and a Data Safety Monitoring Board (DSMB) has been appointed to monitor (serious) adverse events. The Netherlands Comprehensive Cancer Organisation will be responsible for quality control and data management. Ethical approval for this study was granted by the Medical Ethics Committee of the Máxima Medical Center (Veldhoven, the Netherlands) under reference number W16.100/NL58281.015.16. Important protocol modifications will be addressed to relevant parties.

Study population

Adult patients (>18 years) undergoing elective colorectal resection for cancer are eligible for inclusion. We will include 714 patients: 357 in each arm. We expect a dropout rate of 10%. The estimated duration of the recruitment period is two years. Exclusion criteria are metastatic disease known preoperatively, paralysis or patients with mobility problems (who are unable to exercise), premorbid conditions or orthopedic impairments that contraindicated exercise, cognitive disabilities, chronic renal failure (dialysis or creatinine >250 mmol), ASA score 4 or higher, and illiteracy (inability to read and understand the language of the country where the study will be performed).

Participating centers

Patients from the Máxima Medical Center (coordinating hospital, Eindhoven-Veldhoven, the Netherlands), the Montréal General Hospital (Montréal, McGill, Canada), Zealand University Hospital (Zealand Region, Denmark), Foch Hôpital (Paris, France), the Saint Anna University Hospital of Ferrara (Ferrara, Italy), and Hospital Clinic de Barcelona (Barcelona, Spain), will be included in this study.

Randomization

Patients will be block randomized with a 1:1 allocation by means of randomization software (Research Manager clinical trial data management system, Deventer, the Netherlands), stratified by study sites, tumor location and neoadjuvant treatment. Patients will be allocated either to the intervention group, which will receive 4 weeks of prehabilitation, or to the control group, which will receive no prehabilitation.

In all participating centers, both the investigator and the surgeon responsible will verify eligibility. If the indication for surgery is established, patients will be screened by the medical research team for health conditions that prohibit participation in the program. They will then be called by the research investigator and an appointment will be made to provide written and oral information about the trial during a scheduled outpatient appointment. Patients will be given enough time to enquire about the details of the trial and to decide whether or not they wish to participate. Patients will be required to sign the informed consent form in the presence of the surgeon or investigator. A participant flow diagram is shown in Figure 1. After the study has been explained and consent is obtained, there will be a multidisciplinary assessment. Based on intake by the sports physician, the physiotherapist/kinesiologist, the nutritionist and the case manager/ psychologist, an individual prehabilitation program will be started during for weeks in the intervention group.

Study outline

Routine standard preoperative and postoperative clinical care in the participating institutions do not currently include special nutrition, exercise and psychological support to cope with anxiety before surgery. As usual, patients are evaluated in the preoperative clinic before surgery to determine whether they are fit for surgery and to adjust their medication for co-morbid conditions. It is not common practice after surgery to offer them an in-hospital exercise program but patients are given generic instructions by the surgeons about mobilization and returning to normal activities. Some patients may be referred to a physiotherapist by their surgeon. Nutrition, exercise and coping strategies will be introduced solely for research purposes. All patients will be screened four weeks before surgery to capture insufficient hemoglobin levels (thresholds in Canada: >11.2 g/dl, Europe: >7 mmol/l). Hemoglobin levels in patients with iron insufficiency will be optimized using iron injections (ferinject).

Perioperative care will be based on a standardized, multi-element, evidence-based, comprehensive, ERAS guideline in line with the consensus review of optimal care for patients undergoing colorectal surgery.[23] The guideline will be applied in all participating centers to improve generalizability.

The diagnostic work-up for patients with a tumor suspected for malignancy at colonoscopy will be finalized within one week while awaiting definitive pathology. An individual treatment strategy will then be proposed by the multidisciplinary team. Patients that meet the criteria for the trial will be scheduled approximately five weeks after the final diagnosis. This schedule allows for the implementation of a four-week prehabilitation program.

The multidisciplinary multimodal prehabilitation program is composed of 4 elements: exercise training, nutritional intervention, smoking cessation and psychological support. The exact interventions are shown in table 1 and described jn detail below:

1. Exercise program

An exercise specialist (kinesiologist, sport physician) will assess the patients mobility and his/her capacity to exercise using a cardiopulmonary exercise test (CPET). The CPET values will be used to establish an individualized program based on the standardized program.[24] In addition to the preoperative exercise program, patients will receive information about breathing techniques to prevent pneumonia.

Patients in the intervention group will have three supervised in-hospital training sessions per week during four weeks. They will include four three-minute blocks of high-intensity interval training (HIT) aimed at achieving 90% of the VO2peak and two blocks of resistance training (2 series of 10 repetitions of 6 exercises targeting all major muscle groups). Patients will also be given instructions about how to conduct aerobic exercises at home: either walking or cycling, at moderate intensity. The aim will be 60 minutes four times a week. Patients in both the intervention and control group will wear an accelerometer for four weeks to count the number of steps walked in order to record the overall activity.

The conventional wisdom is that training blocks of 3–5 minutes are particularly effective in terms of enhancing exercise capacity. Most of the nine studies that produced the largest increases in VO2max (~0.85/min) used blocks of 3–5 minutes and HIT. Many of these studies presented either individual data or ranges for VO2max values pre- and post-training, and an appraisal of these data suggests that a marked training response was seen in all subjects.[25]

In the intervention group we expect to achieve the following improvements after four weeks of prehabilitation compared to baseline measurements: a 10% increase in VO2 peak, a 15% increase in VO2 at anaerobic level, a 20-40% increase in 1-RM tests and an increase of >20 meters in the 6MWT.

2. Nutritional assessment and intervention

The nutritionist will complete nutritional assessments at baseline appointments and during the prehabilitation program using the patient-generated subjective global assessment (PG-SGA), body composition (skinfold measurements, mid upper-arm muscle area), hand grip strength and nutritional intake (caloric and protein intake), and a patients' three-day food diary.

We aim to establish an anabolic condition preoperatively. In cachectic and sarcopenic patients we try to increase lean body mass by 1-2 kg or more during four weeks of prehabilitation. In order to achieve this goal, the target dietary protein intake will be 1.5-1.8 gr/kg body weight in all patients.

Participants will receive high-quality protein supplements containing 30 grams of protein following exercise and before sleep. Dietary advice will be given in order to achieve adequate oral protein intake spread properly across meals. Since vitamin D is associated with muscle mass and muscle strength,[26,27] vitamin D will be supplemented daily according to guidelines of the Health Council of the Netherlands (10 µg for women aged 50-69y, for men <70y and women <50y with colored skin and/or little sun exposure and 20 µg for women and men aged 70 y or older).[28] Besides vitamin D, many elderly patients may have other micronutrient deficiencies or ingest vitamins and minerals below recommended doses before and after surgery. Therefore, all other vitamins and minerals are supplied in a multivitamin/mineral supplement containing 50% of the recommended daily allowance.

During the period of hospitalization, the time (in days) that patients consume nil per mouth is recorded. Also, on the day of discharge, a trained dietician performs a 24-hour recall questionnaire to estimate oral protein- and energy intake. Nutritional status assessment (PG-SGA) will be performed at 4 and 8 weeks post-surgery by an investigator – trained by a registered dietician.

3. Smoking cessation

A smoking cessation program with intensive counseling and nicotine replacement therapy (NRT) will be offered to all patients during the weeks of prehabilitation. Approximately 15-20% of our patients are smokers when cancer is diagnosed.11 The goal is to achieve a smoking cessation rate of 80% before surgery.

4. Psychological coping

It is expected that patients undergoing surgery for cancer are anxious with some component of depression. Since both anxiety and depression can influence the motivation to carry out social and functional activities, psychological strategies can be put in place to help patients to cope with the stress of surgery and disease. Therefore, patients will be screened for anxiety and depression using the GAD-7 and PHQ-9 questionnaires. If these questionnaires result in a high score (GAD-7 of 10 or higher; PHQ-9 score 15 or higher), patients are considered high-risk and will be offered a referral to a psychologist. Referred patients will receive a total of 1.5 hours of psychological intervention in the first session and more sessions during the 4 weeks of prehabilitation if necessary.

All patients in the intervention group will be given instructions on relaxation and breathing techniques by a trained investigator. They will be given an instruction CD, which they can use for relaxation techniques at home. After the program, patients will be asked if their perceived usefulness of these techniques. For psychological support, the intervention group will be contacted weekly by the investigator by phone. During these 5-15 minute phone calls, a researcher will shortly evaluate personal progression by a standardized set of questions. In order to enhance adherence to the prehabilitation program, all patients in the intervention group will receive an instructional brochure that includes information about all elements of the program.

Study outcomes

The initial primary outcome will be postoperative complications, as scored by the Comprehensive Complication Index,[29] with the relevant data being collected as a continuous variable and calculated using the sum of morbidity and mortality presented on the Clavien Dindo classification.[30] The CCI score will be calculated at the 30 days of follow-up. The second primary outcome will be the 6MWT measured at 4 weeks after surgery and compared to baseline. The 6MWT will additionally be measured directly after prehabilitation and 8 weeks after surgery.

Secondary outcomes will include patient reported outcome measurements (PROMs) such as health related quality of life (HRQoL) (EORTC QLQ-CR29 and EORTC QLQ-C30 and RAND questionnaires) and depression and anxiety scores (GAD-7, PHQ-9 questionnaires), functional capacity (CPET including VO2max, VO2peak, AT, the sit to stand test, stair climb test, hand grip strength and activity questionnaire), nutritional status (3-day food diary, PG-SGA, anthropometry), postoperative complications, length of hospital stay, study compliance, patient satisfaction and a cost-effectiveness analysis. All secondary outcomes are measured at baseline, the week before surgery, 4 and 8 weeks and 1 year post-surgery.

Statistical analysis

Baseline characteristics of both groups will be compared to assess the adequacy of the randomization. Data will be analyzed on an intention-to-treat basis. In addition, a per-protocol analysis will be performed. Trial results will be published in a respective journal. Primary and secondary outcomes for the intervention and control groups will be compared.

The primary outcome CCI will be described as the mean plus the standard deviation (SD). Since we expect CCI to be right skewed we will also describe CCI as the median plus interquartile range (IQR) and percentage

above 20. To test the hypothesis (H0) that the study arms result in similar CCIs (in other words, prehabilitation does not prevent postoperative complications), we will use the Student's T-test if data are normally distributed. Mann-Whitney U if data are not normally distributed or statistical methods that take into account the possible zero-inflated nature of the data. The second primary outcome 6MWT is a continuous variable. This data will be stated as means, plus SD, at each time point. To accommodate the repeat measurements for individuals, we will use a generalized linear mixed model to statistically test the hypothesis of both study arms being equal in terms of functional capacity over time.

All secondary outcomes will be described as means plus SD or median plus IQR, with the data being continuous, and measures for each time point being normally and non-normally distributed respectively. Categorical parameters will be described as number plus percentage per time point. Statistical methods will include t-test and the Mann-Whitney U test for continuous parameters, distributed either normally or not normally respectively, at a single postoperative time-point. Categorical outcomes will be analyzed with Chi-square testing or regression analysis (logistic, ordinal or nominal, depending on the definition of the parameter) for single time points. The size of the sample will be calculated on the basis of the primary aim: the reduction of postoperative complications as determined with the CCI score. With our population variables, the CCI mean is 10.4 (SD 14), and the target reduction is 30%. We use an alpha of 0.05 and power of 0.80 (two-sided test). We expect a dropout rate of 10%. We therefore need 714 patients: 357 in each arm. This gives us sufficient statistical power to demonstrate the expected proportion of difference (55% versus 20%) in the 6MWT between baseline and surgery based on previous studies.[13,58] Approximately 600 eligible CRC patients undergo surgery in one of the six participating hospitals annually. This implies that we will complete inclusion within two years with the inclusion period being followed by a year of follow-up.

Due to limited clinical data regarding effect size of the primary endpoint – CCI - an interim analysis will be performed. The interim analysis is planned if half of the intended number of subjects have completed the 4-week assessment (i.e. timing of the primary endpoint assessment). The intention of the interim analysis is to terminate the study if there is a statistical significant difference between study arms.

Economic evaluation

To analyze cost-effectiveness, we will focus on the results of the program defined as reduction of complications, improving survival, less need for postoperative care and improvements in social productivity. The economic evaluation will be performed per participating center and includes incremental cost-effectiveness and cost-utility analysis using the RAND and iMTA-PCQ questionnaires. The cost-effectiveness ratio will be calculated by dividing the difference between the mean total costs for the exercise and control groups by the difference in the mean effect in the groups. The cost-utility ratio expresses the additional costs of the intervention compared with the control group per quality-adjusted life years.[32]

Discussion

Despite advances in surgical techniques and improvements in postoperative care, morbidity and mortality remain high in CRC patients undergoing surgery. Postoperative complications occur in up to 50% of patients and surgery is associated with a 20% to 40% reduction in physiological and functional capacity.

Since we know that the number and severity of complications are, or may be, associated with preoperative functional capacity, nutritional status, smoking behavior and psychological well-being, it is incumbent on us to test a multimodal intervention program that targets these issues. Traditional approaches have focused on the postoperative period for rehabilitation and lifestyle changes. However, recent evidence has shown that the preoperative period is a better time to intervene.[33] Therefore, we initiated the first international randomized controlled trial on multimodal prehabilitation for patients undergoing colorectal surgery for cancer.

Patient lifestyle (stated as inactivity, obesity, dietary pattern, and smoking behavior) is an important contributor to the development of CRC.[34] Moreover, CRC patients often develop problems with their nutritional status which may aggravate deconditioning and muscle wasting (sarcopenia).[26] This implies that, particularly in this group of patients, there is considerable potential for improvement in both nutritional status and functional exercise capacity.[35,35,37] A recent review indicated that optimizing functional exercise capacity in the surgical population can, by comparison with controls, result in fewer postoperative complications, shorten the length of hospital stay, reduce disability, and improve quality of life.[38] However, there have been no previous studies rigorously evaluating the impact of multimodal prehabilitation prior to digestive surgery.

Interventions that involve physical exercise training for endurance and strength, nutrition, mental support and smoking behavior have all found an independent and clinically relevant effect on the reduction of postoperative complications in small studies. If all these interventions are orchestrated in an innovative prehabilitation program, it may prove feasible to design a highly effective and comprehensive intervention. Synergy may result from these individual interventions if they are applied in a multimodal program since it is known that protein supplements one hour after exercise improve uptake and enhance anabolic effects.[39,40,41,42,43,44] Nutritional supplementation four weeks before and after surgery has been shown to enhance preoperative functional walking capacity and recovery in patients undergoing colorectal resection for cancer.[45] Moreover, the release of dopamine during exercise improves the psychological mindset and smoking cessation improves the ability to perform exercise.

After the diagnosis of CRC, there is a relatively short period of 4-5 weeks before the actual surgery. A rigorous intervention program of prehabilitation is therefore required that is closely coordinated with the entire medical treatment program. An additional potential benefit is the empowerment of patients, who may then play an active role in coping with their disease. From a physiological point of view and based on limited practical experience, it seems feasible to achieve clinical relevant effects during the period of four weeks between diagnosis and surgery. However, this is possible only with a combination of robust innovative interventions involving nutrition, physiological support, smoking cessation and exercise training. These ideas are supported by Carli et al., who stated that a multidisciplinary prehabilitation program needs to be developed, tested, implemented and delivered to patients. [46,47]

Another reason why optimal recovery after surgery is important is because it will increase the potential of patients to withstand additional therapies such as chemotherapy, targeted immunotherapy, metastatic disease resection and/or hyperthermic intraperitoneal chemotherapy (HIPEC).[48,49] A study by the Dutch cancer register included 11.000 stage-3 CRC patients (2008-2013).[6] 4899 of whom were not treated with chemotherapy. The five-year survival rate in this group was only 39%. If chemotherapy started >12 weeks postoperatively, the five-year survival rate increased to 54%. When chemotherapy began <6 weeks after the operation, this rate increased further to 76%. Improved functional capacity may facilitate an earlier start of adjuvant chemotherapy and thereby increasing survival. Finally, functional exercise capacity in cancer survivors is closely correlated to HRQoL.[50,51]

Despite previous evidence from small-scale trials, there are currently no standardized prehabilitation programs and they are therefore not mentioned in current medical guidelines. This highlights the need to design, test, optimize, and implement a multimodal program for maximizing improvements in nutritional status and functional capacity prior to surgery. We expect to see a reduction in postoperative complications, Length Of hospital Stay (LOS), intensive care stay, 30-day mortality rate, and health expenditure due to the multimodal prehabilitation program. The sum of all these separate outcomes will be measured using the Comprehensive Complication Index (CCI), which is a relatively new and interesting outcome measure.[28] As stated in the literature, patients with postoperative complications report a lower HRQoL than patients without. We will be the first to determine whether the HRQoL of patients with postoperative complications is inferior both preoperatively and 1 year postoperatively than the HRQoL of patients without complications. We expect poorer HRQoL in patients with complications preoperatively and one year postoperatively than in patients without complications.

Limitations of the study should be noted as well. Due to its nature

this study is performed non-blinded. This may result in higher dropout rates or an increased activity level in the control group, due to the growing and intuitive understanding of the benefits of exercise training and optimal nutrition. To limit this potential bias of increased activity, we will introduce activity trackers to all patients. We do realize patient characteristics, social circumstances and healthcare facilities will not be the same in all countries. Therefore we will stratify per participating center. Our international approach of the randomized controlled trial will demonstrate that a worldwide implementation may be possible. In case our multimodal program proves to enhance postoperative outcome, it will be impossible to discover which element of the program attributed most. A large sample size and different outcome measurement will facilitate subgroup analyses, to determine effects of the program within different areas, such as functional capacity, body composition, and quality of life. Our large sample size will also give us the possibility to analyze the possible effect differences of an intensive hospital-based prehabilitation program in different patient groups. This way, prehabilitation in the current form can be implemented for patient groups who will benefit the most from intensive hospital-based training. For less high-risk patients, future research could focus on programs in which training is less intensively monitored, such as home-based programs.

Our study investigating prehabilitation is a good example of research in prevention and it will be the first to systematically implement existing knowledge from a variety of different medical specialties and basic science into a four-element multimodal preoperative program for CRC patients with the aim of improving functional capacity and reducing the postoperative complication rate.

Ethics approval and consent to participate

Medical ethical reviewing committee Máxima Medical Center number: NL58281.015.16. Ethical reviewing committees of all participating centers have additionally reviewed and approved the protocol. A written informed consent form for publication will be available for every study participant.

Consent for publication

Written informed consent has been obtained from all study participants. Availability of data and material: Not applicable. Competing interests: No competing interests. Funding: Each participating center is responsible for their own funding. Máxima Medical Center is supported by the Dutch Cancer Society (KWF), for local organization costs and materials used in the study. The KWF has peer reviewed the protocol to grant the subsidy, however they did not have impact on the design of the study. The Peri-Operative Program (POP) will provide funding for the research conducted by the McGill group in the Montréal General Hospital. The funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Authors' contributions

SR and FC conceived the study. SR, FC, SD, SB, RL, RR, GS, GDS drafted the manuscript. SR, FC, SD, RL, RA, EM, CS, GS, GDS designed the study. SR, FC, SD, GT, RB, MG, NB, RA, EM, SB, GM, RL, CF, IG, JC, CS, RR, GS, GDS, are local investigators at the participating centers. The study is supervised and coordinated by SR, FC, SD and GDS. GDS is responsible for accurate execution of the study. All authors approved the final manuscript.

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GDS is a surgeon at Máxima Medical Center, Veldhoven, the Netherlands

Trial status

Open for inclusion since June 2017.

Figure 1. Flow diagram for study participants.

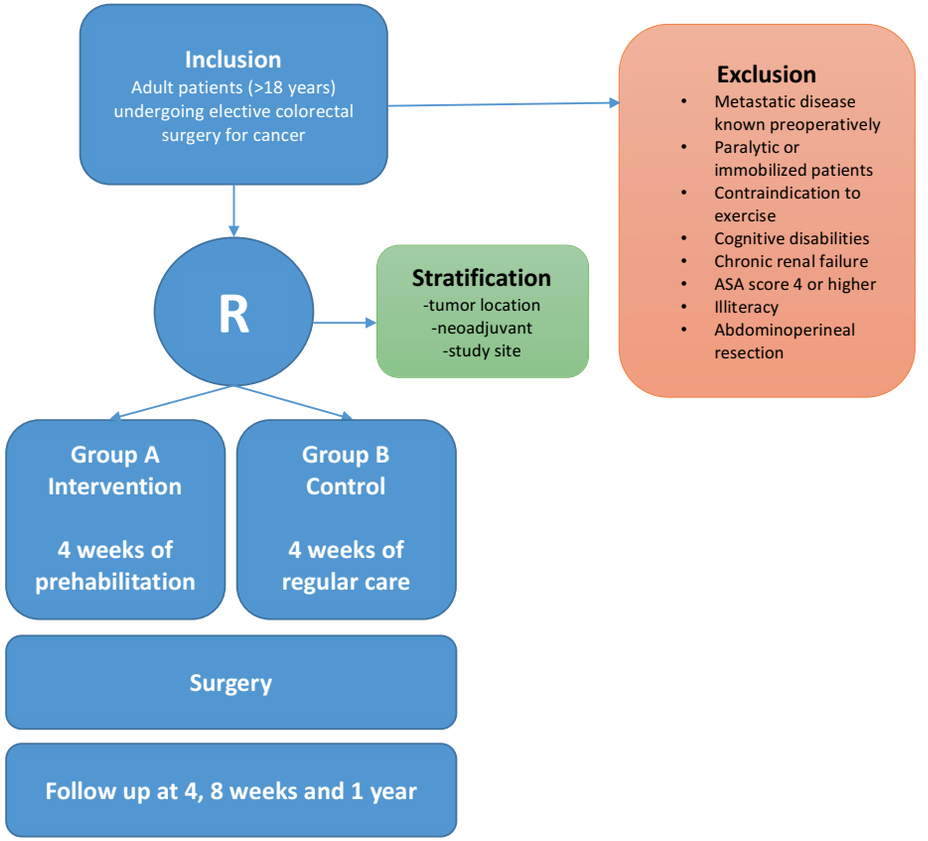


Table 1. Prehabilitation interventions.

PREHABILITATION RANDOMIZED CONTROLLED TRIAL SCHEME							
	Preoperative			Operation	Postoperative		
Weeks	**-5**	**-4**	**-1**	**0**	**4**	**8**	**52**
	Before start	**Baseline (t0)**	**Preoperative (t1)**	**Surgery**	**30 day follow up (t2)**	**8 weeks follow up (t3)**	**1 year follow up (t4)**
Gastroenterologist	Inform patient	-	-	-	-	-	-
Casemanager	Inclusion patient	G8 score	-	-	-	-	-
Sport physician	-	Informed consent VO2max Anaerobic threshold Exercise-ECG	VO2max Anaerobic threshold Exercise-ECG	-	VO2max Anaerobic threshold Exercise-ECG	-	-
Physiotherapist	-	6MWT Stair climb test Sit-to-stand test 1-RM Activity questionnaire Fried Frailty Score	6MWT Stair climb test Sit-to-stand test Activity questionnaire	-	6MWT Stair climb test Sit-to-stand test Activity questionnaire	6MWT Stair climb test Sit-to-stand test Activity questionnaire	-
Dietician	Food diary	Height, weight Weight loss %* Anthropometry Hand grip strength PG-SGA	Food diary Height, weight Weight loss %* Anthropometry Hand grip strength PG-SGA	-	Height, weight Weight loss %* Hand grip strength PG-SGA	Height, weight Weight loss %* Wrist/abdominal/ Hand grip strength PG-SGA	-
Psychologist	-	Intake Coping with anxiety***	-	-	-	-	-
Anesthesiologist	-	-	Preoperative screening**	ERAS**	-	-	-
Surgeon	-	-	ERAS**	-	-	-	-
Surgical resident	-	-	-	-	Outpatient data	-	-
Researcher	-	HRQoL GAD-7 PHQ-9	HRQoL GAD-7 PHQ-9	-	30-day morbidity and mortality HRQoL GAD-7 PHQ-9	HRQoL GAD-7 PHQ-9	Mortality HRQoL GAD-7 PHQ-9

* weight loss in the past 3-6 months. ** Following Enhanced Recovery After Surgery (ERAS) guidelines. *** when indicated, as stated in the protocol.

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CHAPTER 11

SYSTEMATIC REVIEW OF EXERCISE TRAINING IN COLORECTAL CANCER PATIENTS DURING TREATMENT.

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ABSTRACT

Background

Colorectal cancer surgery results in considerable post-operative morbidity, mortality and reduced quality of life. Since many patients will undergo additional (neo)adjuvant chemo or radiation therapy, it is imperative that each individual optimize their physical function. To elucidate the potential of exercise in patient optimization, we investigated the evidence for an exercise program before and after surgical treatment in colorectal cancer patients.

Methods

A systematic review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011) the guidelines of the Physical Therapy Journal (PTJ) and the PRISMA guidelines.

Results

No literature pertaining to exercise training during preoperative neoadjuvant treatment was found. Seven studies, investigating the effects of regular exercise during adjuvant chemotherapy for patients with colorectal cancer or a mixed population, were identified. A small effect (Effect Size (ES) 0.4) of endurance/interval training and strength training (ES 0.4) was found in 2 studies conducted in patients with colorectal and gastrointestinal cancer. In 5 studies that included a mixed population of cancer patients, interval training resulted in a large improvement (ES 1.5; $p \leq 0.05$). Endurance training alone was found to increase both lower extremity strength and endurance capacity. The effects of strength training in the lower extremity are moderate whereas, in the upper extremity, the increase is small.

Conclusion

There is limited evidence available on exercise training during treatment in colorectal cancer patients. One study concluded exercise therapy may be beneficial for colorectal cancer patients during adjuvant treatment. The possible advantages of training during neoadjuvant treatment still need to be explored by prehabilitation trials.

Key words: surgery; neoadjuvant; chemoradiotherapy; endurance training; strength training; functional capacity; prehabilitation

Introduction

In 2015, 15.253 new patients were diagnosed with colorectal cancer (CRC) in the Netherlands (Integraal Kankercentrum Netherlands, 2016). Elimination of the cancer requires surgical removal of the tumor. Unfortunately, CRC surgery is associated with a rate of complications that may approach 35% (Brown et al., 2014). The most feared complication remains colorectal anastomotic leakage with a reported incidence of 1.5-23%. (Bakker et al., 2014; McDermott et al., 2015). Complications are most frequently dependent on disease activity, poor functional capacity, multiple patient and treatment-related variables, (Brown et al., 2014; West et al., 20141; McDermott et al., 2015) and the use of neoadjuvant chemoradiation therapy (NACRT) (West1 et al., 2014; West et al., 2015; McDermott et al., 2015, Morielli et al., 2016).

To decrease postoperative complications, focus has been primarily on changes in surgical techniques and assessment of risk factors (Kirchhoff et al., 2010; Dekker et al., 2011; Erb et al., 2014; Daams et al., 2014; McDermott et al., 2015; Van Rooijen et al., 2016). Evidence indicates that the functional capacity of patients is of extreme importance for the preservation of Health Related Quality of Life (HRQoL) and should be optimized, both before and after surgery, as well as during additional treatment such as chemoradiation therapy (Van Moll et al., 2016). As supported by the prehabilitation literature, the preoperative phase has been identified as the ideal timeframe in which to enhance patients' physical status (Van Rooijen et al., 2016).

The functional capacity of patients mainly consists of aerobic endurance capacity and muscular strength (as demonstrated by resistance training) and can be considered essential in the preparation of patients for surgery. This is especially important for patients with colorectal cancer, since their functional capacity is lower at the time of diagnosis as compared to their healthy counterparts (Kahn et al., 2007; Beaton et al., 2013). VO2peak is one of the main indicators of functional capacity and is generally considered a predictive value for perioperative morbidity and mortality (West1 et al., 2014; West2 et al., 2014). If optimal preparation of patients for surgery could enhance functional recovery, training during neoadjuvant therapy may also improve outcome by increasing the functional capacity. Since neoadjuvant therapy significantly decreases objectively measured VO2peak (West1 et al., 2014) patients may greatly benefit from exercise training during therapy. Since patients with rectal cancer receive neoadjuvant treatment in the period between diagnosis and surgery, there is ample time for physical training. This relatively long timeframe can support the optimization of functional capacity in individual patients, thus allowing for improved recovery (Carli et al., 2010; van Eeghen et al., 2016).

This review was initiated because of the lack of evidence for exercise training at a time point in cancer treatment when great improvements may be possible (Morielli et al., 2016). We aimed to critically analyze the state of the literature that addresses the types of exercise training during treatment in colorectal cancer patients. By this, the results of this systematic review may serve as a proof of principle of an optimal exercise prescription that can be used for this little explored period during the trajectory of cancer treatment.

Methods

A systematic review was conducted in studies up to November 17th 2015 according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011). In addition, the guidelines of the Physical Therapy Journal (PTJ) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were also adhered to.

Data sources and searches

Randomized Controlled Trials and Control Trials (RCTs and CCTs) that were based on colorectal cancer patients receiving (neo)adjuvant chemotherapy were included in this review without date restriction. We did not include articles describing exercise during prehabilitation programs since we were particularly interested in the value of exercise training during additional chemoradiotherapy.

The electronic databases Pubmed, Embase and Cinahl were searched consisting the following terms:

- Pubmed: (("Drug Therapy"[Mesh] OR "drug therapy"[Subheading]) AND ("Exercise"[Mesh] OR "Exercise Therapy"[Mesh]) AND ("Neoplasms"[Mesh])) OR ((neoplasm*[tiab] OR cancer[tiab]) AND (chemotherapy[tiab] OR drug therapy[tiab]) AND (exercise[tiab] OR training[tiab] OR strength[tiab])) (filters activated: Humans)
- Embase: 'exercise' OR 'exercise'/exp OR exercise AND ('chemotherapy' OR 'chemotherapy'/exp OR chemotherapy) AND [humans]/lim.
- Cinahl: MH ((chemotherapy, adjuvant) OR TI chemotherapy OR AB chemotherapy OR TI drug therapy OR AB drug therapy OR TI during active treatment OR AB during active treatment) AND MH ((therapeutic exercise) OR TI strength OR AB strength OR TI endurance OR AB endurance).

Articles were screened based on title and abstract by two independent reviewers (SR, ME), after removal of duplicates. Full articles of potentially eligible studies were included and assessed by two reviewers (SR, ME). The literature search is summarized in the flow chart as presented in figure 1.

Given the limited coverage of studies on exercise interventions in patients with colorectal cancer during adjuvant chemotherapy, we decided to also include studies on exercise interventions (endurance-, interval- and muscle strength training) of a mixed population of cancer patients- colorectal, gastrointestinal and abdominal cancer- during adjuvant chemotherapy. Control groups consisted of subjects that either received no intervention or interventions for comparison of different training types and intensities.

Unfortunately, no studies for exercise training in patients with rectal cancer during Neoadjuvant ChemoRadiation Therapy (NACRT) were found.

Exercise interventions and study outcomes

Exercise training was defined as a structured form of either aerobic, interval or strength training based upon validated measurements describing training intensity. Studies only involving promotion of more physical activity e.g. with help of pedometers were not included in this review.

Validated study outcomes included were endurance capacity (VO2peak, 6MWD) if exercise frequency and duration were specified, and muscle strength (kg). All studies that included exercise interventions with the aim of reducing adverse events and complications, predictors of adherence, safety, barriers to training and moderators were eligible.

Quality assessment

Two reviewers (ME, WO) independently screened titles and abstracts. Two reviewers (SR, ME) assessed the included articles on risk of bias and methodological quality independently using the Cochrance Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011). When discrepancies were found between judgments, consensus was achieved with the third reviewer (GS). Reference lists of systematic reviews and included articles were scrutinized for further eligible studies. Ratings of RCT's was conducted by the Dutch translation of Physiotherapy Evidence Database (PEDro) (Verhagen et al., 1998; Maher et al., 2003; De Morton, 2009). Levels of evidence were determined according to EBRO- guidelines. Inter-observer agreement for PEDro was assessed using Cohen's Kappa ((k); 95% CI).

Data synthesis

Due to the inclusion of both studies with patients with CRC and a mixed population pooling of data was not possible. Best evidence synthesis (Slavin, 1995) was used to present the results of this review followed by a descriptive analysis. Data were analyzed and categorized by outcome and was done according to the information necessary to develop an exercise program in consultation with two experts (SR, GS).

Data analysis

Excel was used for the data analysis. The Effect Size (ES) for strength training and endurance/interval training was calculated using Cohen's Δ (d) as the average difference divided by the pooled standard deviation of both measurements. Where results were given for the individual strength exercises, the means and standard deviations for the individual exercises for

the lower and upper extremity were pooled and Cohen's Δ (d) was assessed. The magnitude of the ES was calculated using the categories: d 0.2-0.5= small; d 0.5-0.8= moderate; and d >0.8=large (Cohen, 1988).

Results

The initial search yielded 4669 studies. As previously indicated, no studies that were based on exercise training during preoperative treatment (e.g. neoadjuvant therapy) were found. After removing duplicates and exclusion based on title and abstract, 37 studies were included and screened in full text. Finally, 7 studies remained for analysis and critical appraisal (figure 1). No additional studies were detected by screening the references of the previously identified work.

Subjects

Demographic characteristics of the included studies are shown in table 1. The 7 studies included in this review involved a total number of 606 participants, with 423 (69.8%) women and 183 (30.2%) men. Participants were between 47-60 years old. Adherence for aerobic exercise training ranged from 67.6% to 94%. Adherence to the resistance training was lower; ranging from 65.0% to 70.8%. Three studies focused on aerobic training and 4 studies included a combination of resistance and aerobic training. One study assessed the same exercise intervention during treatment as well as after treatment in 2 different groups. In 3 studies, participants received a combination of chemotherapy and radiotherapy.

Aerobic capacity

Aerobic capacity was assessed in all 7 studies and beneficial effects were reported in 6 studies. There was no significant effect of endurance/ interval training on functional capacity in the studies conducted for patients with colorectal or gastrointestinal cancer. The 6 MWD improved in both colon cancer and mixed population groups. There is only a high effect size for the aerobic exercise group reported by Lin et al. (2014) The combination of endurance and interval training on a cycle ergometer gives a significant and clinical relevant effect (ES 1.5; $p \leq 0.05$), increasing aerobic capacity in the mixed population (Adamsen et al., 2009; Glass et al., 2015). Also a home-based weight bearing (walking, jogging, dancing) exercise intervention increased 12MWD (ES 0.9, no specific p-value reported) (Schwartz et al., 2009). Moreover, this study demonstrated that moderate intensity endurance training alone increased both lower extremity strength and endurance capacity (Schwartz et al., 2009). One study stands out by using light to moderate intensity exercise that resulted a decrease in VO2peak among the aerobic exercise group and an increase among the control group (-1,4 ml/kg/min; ES -1.7 vs + 0.7 ml/kg/min; ES 0.3; p=0.26) (Griffith et al., 2009).

Muscle strength

Muscle strength was assessed in four studies and beneficial effects for lower extremity strength was consistently reported. None of these studies reported significant and clinical effects (ES) for upper extremity strength. There is no significant effect and a small ES (ES 0.4) (Lin et al., 2014; Jensen et al., 2014) for lower extremity strength in the studies conducted for patients with colorectal and gastrointestinal cancer. Two studies assessed strength in a mixed population of patients with cancer: both showed significant and clinical effects in lower extremity strength (ES 0.7; p=0.053 and ES 0.9; p≤0.01). The largest effect was reported when exercise was prescribed according to 1RM and if the exercise interventions were predetermined, including program, repetitions and weights (Adamsen et al., 2009; Jensen et al., 2014). Schwartz et al. (2009) showed that both cardiovascular endurance training and resistance training can lead to an increase of strength of the lower extremity (+6 kg; ES 1.0 vs. +24.1 kg; ES 0.7), also compared to a control group (+3.7 kg, ES 0.1; p≤0.05). Results of this study also indicated resistance training may lead to an increased endurance capacity (+122.3 mtr, ES 0.7; p≤0.05). One study did not report the results of strength training, although the exercise program consisted of cardiovascular exercises and resistance training. Only the results on cardiovascular function and fatigue were given (Schneider et al., 2007).

Quality assessment

Results of the critical appraisal for each included study were assessed according to the Pedro-score and risk of bias assessment (Cochrane) (tables 1 and 5). Overall, the Pedro-score was between 4/10-7/10 (k=0.54; CI 0.35-0.72). Only one study reported a low risk of selection bias on both items (Adamsen et al., 2009), 3 studies reported a high risk (Schneider et al., 2007; Lin et al., 2014; Glass et al., 2015) and 3 studies an unclear risk (Schwartz et al., 2009; Griffith et al., 2009; Jensen et al., 2014). Performance bias was reported as high risk in one study (Adamsen et al., 2009) and reported as unclear and high risk in 6 studies (Schneider et al., 2007; Schwartz et al., 2009; Lin et al., 2014; Jensen et al. 2014; Glass et al., 2015). Detection bias was reported as high or unclear in all included studies. Attrition bias was reported as low risk on both items in 4 studies (Adamsen et al., 2009; Lin et al., 2014; Jensen et al., 2014; Glass et al., 2015). Reporting bias was not appointed.

Discussion

The aim was to investigate the current evidence for aerobic and resistance strength training during treatment of colorectal cancer patients, with the aim of improving functional capacity and diminishing postoperative complications. Only 7 studies that investigated the effects of regular exercise during adjuvant chemotherapy for patients with colorectal cancer or a mixed cancer population (that included colorectal patients) met the criteria for analysis.

Based on this systematic review, a supervised combined strength- and endurance/interval training appears to be potentially effective to improve functional capacity (VO2peak) and muscle strength (lower extremity). Strength training that focuses on the lower extremity appears to be very important for the enhancement of both strength and endurance capacity and should, at least, consist of the leg press (Adamsen et al., 2009; Jensen et al., 2014) knee extension/flexion (Schneider et al., 2007; Adamsen et al., 2009; Jensen et al., 2014) and exercises that target the gluteus region/ thigh region (Lin et al. 2014).

Although the methodological quality of the included studies was poor-average, an important result is that no adverse events following the strength and endurance/interval training interventions have been reported. This is in accordance with the results of the study of Morielli et al. specifically conducted for rectal cancer patients during and after NACRT. According to Morielli et al. (2016) and Van Waart et al. (2015), exercise during or after chemoradiation therapy in the preoperative period could be the most effective because they are not influenced by postoperative functional disabilities that result from abdominal surgery (Hornsby et al., 2014). Since no primary studies which assess endurance and strength training during preoperative treatment such as neoadjuvant chemoradiaton therapy (NACRT) are available, recommendation for exercise during or after NACRT can therefore only be based on extrapolation of information from training modalities during adjuvant chemotherapy.

The clinical importance of prehabilitation

It may seem obvious to optimize the functional capacity of patients prior to surgery. Although our literature search yielded almost no results, there is currently much more awareness and pilot studies that prove safety and efficacy are forthcoming (Morielli et al., 2016). However, to date, no detailed programs- other than exercise training alone- exist. Our team is increasingly interested in a multimodal prehabilitation program, which combines exercise training with nutritional supplements, as well teaching anxiety reducing techniques and a smoking cessation program. Through

this multimodal approach, the patients' functional capacity is enhanced preoperatively, thus promoting an accelerated recovery after surgery. In order to further our knowledge about the potential of prehabilitation, we have initiated a multicenter randomized controlled trial (NTR5947) that aims to elucidate the most effective and efficient means to improve functional capacity in the period of time from diagnosis to surgery (Van Rooijen et al., 2017). Prehabilitation, a multimodal program that enhances the patients' preoperative status, may thereby contribute to substantial improvement in functional capacity (VO2peak) in patients with colorectal cancer (West et al., 2015). Prehabilitation also results in greater 6 minute walk distances (6MWD, as recorded in meters), enhanced recovery, decreased length of hospital stay (LoS) and improvements in HRQoL, as investigated in small pilot studies (Singh et al., 2013; Chen et al., 2016; Minella et al., 2016). Despite this potential, no reductions in postoperative complications have been identified to date (Mayo et al., 2011; Stottmeier et al., 2012) due to limitations of studies and small numbers of included patients.

Aerobic capacity

An overall increase in aerobic capacity (VO2peak and 6 or 12MWD) has been previously reported. The largest improvement of VO2peak has been shown by Glass et al. (2015) using a 12 week, three weekly supervised, high intensity regimen (+32.5%; interval training). This study used mid-term assessments throughout the chemotherapy period and investigated adaptation of loads accordingly. This study suggests that the most effective way to increase functional capacity is the combination of endurance and interval training, and progressing the load during the training period, depending on the individual progress. The exercise program is in concordance of the exercise program used in West et al. (2015) after NACRT.

In general, improvements of strength and aerobic capacity are seen mostly in both the intervention and control groups. Schwartz et al. (2009) is the only study that reports inactivity throughout the chemotherapy period. It shows a clinical relevant decrease of 12MWD in the first six months (-5,1%; ES-0.6). The overall improvements in the control groups may underline limitations in the original studies. The non-randomized study designs let patients in the control group get a different 'mind-set' for exercising (Lin et al., 2014), a high crossover to the exercise training group (Griffith et al., 2009) or allowed to freely increase physical activity (Adamsen et al., 2009). This may have positively influenced the results in the control groups.

Aerobic training can be performed on a cycle ergometer or a treadmill (weight bearing exercises), depending on the capabilities of the patient. In all studies, the intensity of the aerobic training starts with a moderate intensity (endurance), which progressively changes to a higher, heavy-maximal, intensity (interval). Both moderate (endurance) and heavy-maximal (interval) training seem to be effective, in which the interval training favors. A combination of supervised interval training and endurance training seems logic from a practical point of view. Since patients perform the less complex endurance aspect of the training more easily at home, while for optimal dosing of the interval training supervision seems more mandatory.

Muscle strength

A general increase in lower extremity strength has been reported by Schwartz et al (2009). They found both an increase in endurance capacity and lower extremity strength due to lower extremity strength training. However, patients in the resistance training group reported beginning a self-initiated cardiovascular endurance training program, which could explain the improvements in both strength and endurance capacity. For upper extremity strength, the clinically relevant effect is low (ES ranging from 0.1-0.4). This may suggest training of the upper extremity strength is less meaningful for the overall outcome in this population. Studies with low or unspecified intensities had lower effect sizes. This is in line with general knowledge since strength training is most effective when prescribed with higher intensities and lower repetitions (ACSM Guidelines for exercise prescription 9th edition, 2014). This seems to be also the case in this population since the program of Schwartz et al. (2009) and Adamsen et al. (2009), using high intensity and low repetition training (70-100% 1-RM in 3 series of 5-8 repetitions), gave the most substantial effect sizes (ES 0.9).

Methodological quality

The results of the Pedro-score are poor-average. However, important aspects of the methodological quality of randomized controlled trials are blinding of participants and therapists. Due to the research design, true blinding was not feasible in these type of studies. This results in a high or unclear risk of performance bias in all studies. All, except one study, scores high or unclear on selection bias and performance bias. High risk of selection- and performance bias could influence the effectiveness of the intervention, due to more motivated and relatively fit patients.

Limitations and strengths

The main limitation of this review is that there is no literature available on preoperative exercise training during neoadjuvant therapy. Regarding the included studies for training during adjuvant chemotherapy, studies are heterogeneous in terms of population and training modalities. Five of the

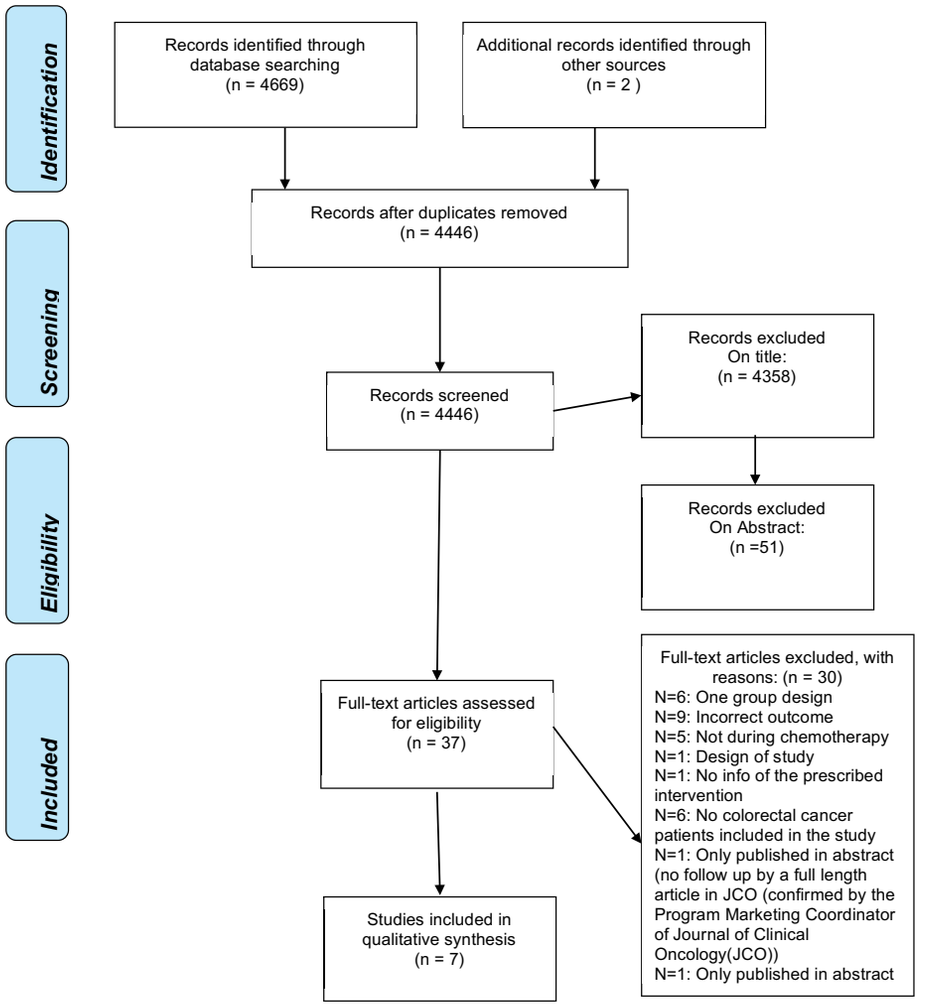
seven studies included a mix of cancer patients with limited colorectal cancer patients. Therefore, pooling of data was also not possible. Furthermore, five studies used a small sample size (<50) which could influence the external validity and increase the possibility of type II error. To assess Cohen's Δ for the individual strength exercises, the means and standard deviations were categorized in exercises of the lower- and upper extremity and pooled. Also, the age of included patients was between 47 and 60 years. This is over ten years younger than the reported median age for colorectal cancer patients. This review may therefore not reflect the best exercise training methods for older patients.

The strengths for the systematic review is the use of PRISMA guidelines and the recommendations of the Cochrane collaboration. The level of evidence is determined according to established recommendations. The methodological quality was assessed in association with an expert. The literature search was done without date restriction, however included studies where all recently published (2009-2014). This review is the first to describe the best evidence for a potential training program at a point in cancer treatment when great improvements may be possible. It clarifies what seems to be the most feasible and effective training form to increase physical capacity in colorectal cancer patients undergoing treatment.

Perspective

Exercise therapy may be beneficial for colorectal cancer patients during adjuvant treatment. However, this is based on limited research quality of the included studies (table 5). A combination of supervised high/moderate intensity strength training and interval training with additional counseling for home based endurance training seems to be the most effective. To customize the recommended exercise interventions following this review, the next step is to apply structured exercise training interventions during additional treatment of colorectal cancer patients, both before and after surgery. This, in order to test feasibility and safety (including adverse events) and to optimize the dose of training (registering feasibility and training effect) including optimization of nutrition in combination with training. Given the clinical benefit that may be expected from such training during adjuvant chemotherapy (e.g. the low risks and, the potential benefits which are presented in this review), research should also be initiated to test the effects of exercise training during neoadjuvant chemoradiotherapy. Current prehabilitation trials may therefore include this, establishing the possible advantages of exercise treatment during neoadjuvant therapy.

Figure 1. Flow Chart.



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Table 1. Demographic characteristics of study population.

Table 1 Demographic characteristics of the study population

Author	Population	N. of participants	Stage	Age (mean/yrs, SD)	Treatment	Design	Pedro-score
Lin et al, 2014[28]	CRC	E=21 C=24 CRC=45	IIA-IIIC	E= 59.0 (9.5) C= 54.3 (10.6)	Ch	RCT	5/10
Jensen et al, 2014[29]	Gastrointestinal	AET=13 RET=13 CRC=11	II-III	AET= 51.6 (13.6) RET= 58.7 (12.0)	Ch/R-Ch	CCT	4/10
Griffith et al, 2009[32]	CRC, Breast, Prostate, Different	E=73 C=65 CRC=7	I-III	E= 59.8 (10.8) C= 60.6 (10.8)	Ch/R-Ch	RCT	6/10
Glass et al, 2014[31]	Abdomen, Breast, Lung, Bladder, Peritoneal, Primary Unknown, Rectum, Uterus, Nasopharynx	E=23 C=21 CRC=4	II-III	E= 56 (10) C= 54 (11)	Ch	CCT	6/10
Adamsen et al, 2009[30]	Oncological malignancies, Hematologic malignancies	E=135 C=134 CRC=35	I-III	E= 47.2 (10.7) C= 47.2 (10.6)	Ch	RCT	7/10
Schwartz et al, 2009[33]	Colon, Breast, Lymphoma	E=34 R=34 C=33 CRC=13	I-III	E= 48(12.6%) R= 47(8.7%) C=48 (9,8%)	Ch	RCT	5/10
Schneider et al, 2007[34]	Colon, Rectal, Prostate, Lymphoma, Lung, Bladder, Melanoma, Pancreatic, Testicular, Throat	Dtm=8 Ftm=37 CRC=10	Nr	Dtm= 67.1 (9.5) Ftm= 64.0 (12.5)	Ch/Ch-R	CCT	5/10

Abbreviations: CRC, colorectal cancer; E, Exercise group; C, Control group; AET: aerobic exercise training; RET, resistance exercise training, R, resistance group; Dtm, during treatment; Ftm, following treatment; Ch, chemotherapy; R-Ch, Chemoradiation; RCT, randomized controlled trial; CCT, clinical controlled trial; nr, not reported.

Table 2. Overview of the training programs.

Primary author	Duration (weeks/minutes)	Frequency (Session/week)	Supervised/ Homebased
Lin et al, 2014[28]	12/40-60	2	Supervised
Jensen et al, 2014[29]	12/45	2	Supervised
Griffith et al, 2009[32]	During chemotherapy Period/20-30	5	Homebased
Glass et al, 2014[31]	12/20-45	3	Supervised
Adamsen et al, 2009[30]	6/90	3	Supervised
Schwartz et al, 2009[33]	52/20-30	4	Homebased
Schneider et al, 2007[34]	26/60	2-3	Supervised

Table 3. Overview of training modalities and intensities of the studies, including effect sizes (Cohen's Δ).

Resistance training					Aerobic training				
Primary author	**Resistance exercises**	**Sets and reps**	**intensity**	**ES (cohen's Δ) RET**	**Aerobic exercises**	**Duration(min)**	**Intensity**	**ES (cohen's Δ) AET**	**Classification intensity**
Lin et al, 2014[28]	Arms, abdominal muscles, thigh, gluteus region	Us	Theraband, dumbbell, sandbags	UE=0,1 LE=0,2	Cycle ergometer	20-30	40/55%- 60/75% HRR	**0,7**	Moderate-Heavy
Jensen et al, 2014[29]	Leg, biceps, triceps, back, knee flexor, knee extensor	2-3 sets 15-25 reps	60-80% 1RM	UE=0,4 LE=0,4	Bicycle ergometer	10-30	60-80% max HR	Na	Moderate-Heavy
Griffith et al, 2009[32]					Walking	20-30	50-70% max HR	**-1,7**	Light-Moderate
Glass et al, 2014[31]					Stationary cycle ergometer	20-40	55-100% Vo2max	**1,5**	Moderate-Maximal
Adamsen et al, 2009[30]	leg press, chest press, pull down, abdominal crunch, lower back, knee extension	3 sets 5-8 reps	70-100% 1RM	UE=0,4 LE=**0,9**	Stationary bycycle	15	85-95% maxHR	0,3	Very Heavy
Schwartz et al, 2009[33]	Overhead press, seated row, leg extension	3 sets of 12 reps / 2x sets of 18-20 reps	Theraband, dumbbell	UE=**1,0** LE=**0,9**	Walking, jogging, dancing	20-30	Symptom limited, moderate intensity range RPE scale	**0,9**	Na
Schneider et al, 2007[34]	chest press, shoulder press, lat pulldown, triceps, step ups, hamstring curl, calf raise, pelvic motion fit ball, crunches fit ball	2 sets 10 reps	RPE 3 (0-10 scale)	Nr	Underwater treadmill	20	30%-55% HRR	0,3	Light-Moderate

Abbreviations: Us, unspecified; NA, not applicable; Nr, not reported; UE, upper extremity; LE, lower extremity, HR, heart rate; 1 RM, one repetition maximum; HRR, heart rate reserve; RET, resistance exercise training; AET, aerobic exercise training; RPE scale, rated perceived exertion scale.

Table 4. Results of endurance - and strength training in the included studies.

Primary author	**Results endurance training**	**Results strength training (kg)**
Intervention groups		Intervention groups
Lin et al, 2014[28]	Pre: 491.3(91.5) mtr Post: 550.2(85.3) mtr Int vs con: p=0.02	UE: Pre: 28.8(13.0) Post: 30.5(12.5). Int vs con p=0.001 LE: Pre: 16.5(3.6) Post: 17.1(3.4). Int vs con p=0.004
Jensen et al, 2014[29]	Pre: 85.1Wmax / Post (6 weeks): 90.3Wmax (ns)	UE: Biceps: Pre: 13.0 / Post: 19.0 p=0.017 Triceps: Pre: 11.1 / Post: 14.5 p=0.072 LE: Leg: Pre: 33.5 / Post: 49.0 p=0.001 knee flexion: Pre: 13.7 / Post: 16.0 p=0.002 Knee extension: Pre: 14.5 / Post: 15.0 p=0.841
Griffith et al, 2009[32]	Pre: 13.13(0.59) l/kg/min Post: 12.04(0.69) l/kg/min Intervention vs control: p=0.26	
Glass et al, 2014[31]	Pre: 15,5(3,7) ml/kg/min Post: 20,5(2,9) ml/kg/min. p<0,05	
Adamsen et al, 2009[30]	Pre: 1.82(0.4) l/min Post: 1.96(0.5) l/min. Intervention vs control: p=<0.0001	UE: Pre: 37.9(15.6) / Post: 45.2(17.9) LE: Pre: 100.8(30.5) / Post: 132.4(42.3). Int vs con p<0.0001
Schwartz et al, 2009[33]	Pre: 1017.3(210) mtr Post: 2101(183) mtr Strength and endurance vs control: p<0.05	UE: Overhead press: Pre: 24.1(13.6) / Post: 25.4(13.6) Seated row: Pre: 36.7(15.8) / Post: 44.9(13.2) LE: Pre: 74.8(34.8) / Post: 98.9(30.8) Strength/endurance vs con p<0.05 for lower- and upper extremity.
Schneider et al, 2007[34]	Pre: 25.6(5.0) ml/kg/min Post: 27.1(4.4) ml/kg/min. p<0.05	
Control group/Other Intervention group		Control group/Other Intervention group
Lin et al, 2014[28]	Pre: 505.6(117.9) mtr Post: 550.2(121.2) mtr	UE: Pre: 29.5(11.7) / Post: 31.4(12.2) Int vs con p=0.001 LE: Pre: 16.3(3.6) / Post: 16.5(4.3) Int vs con p=0.004
Jensen et al, 2014[29]		
Griffith et al, 2009[32]		
Glass et al, 2014[31]	Pre: 16,2(4,3) Post: 17,1(3,2). No p-value available	

Adamsen et al, 2009[30]	Pre: 1.90(0.5) l/min Post: 1.88(0.5) l/min	UE: Pre: 40.2(18.0) / Post: 39.7(17.2). LE: Pre: 107.6 (33.3) / Post: 110.4(36.0)Int vs con p<0.0001
Schwartz et al, 2009[33]	Pre: 1035.4(200) mtr Post: 983(193) mtr	UE: Overhead press: Pre: 22.7(9.9) / Post: 23.6(10.4) Seated row: Pre: 33.6(17.1) / Post: 32.2(15.8) LE: Pre: 73.9(35.8) / Post: 76.2(29.5)
Schneider et al, 2007[34]	Pre: 21.3(5.0) ml/kg/min Post: 24.8(5.0) ml/kg/min. p<0.05	

Abbreviations: mtr, meters; kg, kilogram; UE, upper extremity; LE, lower extremity.

Table 5. Results of risk of bias assessment of the included studies.

Table 5: Results of risk of bias assessment of the included studies

	Bias							
	Selection bias		Performance bias	Detection bias		Attrition bias		Reporting bias
Author, Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (patient reported outcomes)	Blinding of outcome assessment	Incomplete outcome data addressed (Short-term outcomes (2-6 weeks))	Incomplete outcome data addressed (Longer-term outcomes (>6 weeks))	Selective reporting
Lin et al.[28]	High	High	High	Low	Low	Low	Low	Low
Jensen et al.[29]	Unclear	Unclear	High	Unclear	Unclear	Low	Low	Low
Griffith et al.[32]	Unclear	Unclear	Unclear	Unclear	High	Low	Low	Low
Glass et al.[31]	High	High	Unclear	Low	Low	Low	Unclear	Low
Adamsen et al.[30]	Low	Low	High	Low	Low	Low	Low	Low
Schwartz et al.[33]	Unclear	Unclear	High	Unclear	Unclear	Low	Low	Low
Schneider et al.[34]	High	High	High	High	High	Low	Low	Low

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CHAPTER 12

IMPROVING THE OUTCOMES IN ONCOLOGICAL COLORECTAL SURGERY BY MEANS OF PREHABILITATION: A GROUP EFFORT TO ESTABLISH A TAILOR-MADE APPROACH

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ABSTRACT

Background

The cornerstone in the treatment of colorectal cancer is surgery. A surgical event poses a significant stressor to the life of a patient with the risk of decreased functional decline and impaired health related quality of life. Prehabilitation is defined as the multimodal preoperative enhancement of a patient's condition. It may serve as a strategy to improve postoperative outcomes. Prehabilitation requires a multidisciplinary effort of medical health care professionals and a behavioral change of the patient.

Methods

The goal of prehabilitation is threefold: first, to reduce postoperative complications, second, to enhance and accelerate the recovery of the patient and third, to improve overall quality of life. In this article, we introduce the FIT-model illustrating a possible framework towards the implementation of both evidence-based and tailor-made prehabilitation for patients undergoing surgery for colorectal cancer.

Results

The model is comprised of three pillars: 'Facts' (how to screen patients and evidence on what content to prescribe), 'Integration' (data of own questionnaires assessing motivation of patients and specialists) and finally 'Tools' (which outcome measurements to use).

Discussion

Developing implementable methods and defining standardized outcome instruments will help to establish a solid base for patient centered prehabilitation programs. Any party introducing prehabilitation requiring multidisciplinary teamwork and behavioral change can potentially use this framework.

Introduction

Colorectal cancer is the third most common type of cancer in men and the second most common in women, with over 1,3 million new cases diagnosed annually worldwide. Over 80 per cent of these patients are over 60 years old.[1] Currently, surgery remains the cornerstone of treatment. However, the physical stress associated with surgery brings significant morbidity and mortality, especially in patients with diminished physical reserves.[2],[3]

The rate of complications is considerably increased (up to 50%) in vulnerable patients.[4] Recent studies have identified several modifiable risk factors for complications in patients undergoing colorectal surgery (such as malnutrition, poor functional capacity, cigarette smoking, anemia, and anxiety).[5],[6],[7],[8] The preoperative period can serve as a window of opportunity to enhance the condition of high-risk patients and consequently decrease surgery-associated morbidity and mortality.[9], [10]

This preoperative enhancement has been coined prehabilitation and can consist of any form of patient optimization before surgery.[11] The research group of Carli et al. has proposed a model illustrated in figure 1, demonstrating the potential benefit of prehabilitation.[12] The enhanced recovery after surgery (ERAS) program has significantly accelerated recovery and made patients less care dependent on high level care after surgery.[13], [14] However, ERAS specifically focuses on the postoperative period and only starts 48 hours prior to operation. Prehabilitation can shift the classic 'waiting period' to a time frame in which patients can influence their own treatment outcomes. The waiting period prior to surgery is a salient time for patients to improve their lifestyle choices. The patient's functional capacity may thereby be improved before surgery, leading to a smaller decline of function during the postoperative period and possibly even faster recovery. [12] [Figure 1]

The goal of prehabilitation is threefold: first, to reduce postoperative complications, second, to enhance and speed up recovery and third, to improve overall health related quality of life (HRQoL). To date, research has been performed on single modal programs mostly focusing on nutritional status or exercise training.[15] However, taking into account the multifactorial origins of a patient's vulnerability, a multimodal approach combining nutritional support, exercise training, psychological support, smoking cessation and anemia correction, might be more effective.[16]

Prehabilitation requires the multidisciplinary collaboration of medical experts and to support behavioral changes of a patient. Optimal implementation will be indispensable to ensure optimal compliance amongst patients. This narrative review introduces the FIT-model (Facts, Integration, Tools) to assess the current screening methods, prehabilitation contents, user assessment and outcome measurement of prehabilitation in patients undergoing surgery for colorectal cancer (figure 2). In Facts, we describe the need for triage and the different components considered essential in a multimodal prehabilitation program. In Integration, we present questionnaires which we used to assess the motivation of patients and specialists regarding prehabilitation. In Tools, we describe the available outcomes measurements. [Figure 2]

I. FACTS - PREHABILITATION SCREENING AND CONTENTS

Based on the prehabilitation hypothesis, patients with poor overall wellbeing may benefit most from a prehabilitation program. In some cases, surgical intervention should be reconsidered, or surgery should be postponed to substantially improve the patients' functional capacity. Currently, five modifiable risk factors have been described in colorectal cancer surgery: poor functional capacity, malnutrition, cigarette smoking, anemia and anxiety. [5],[6],[7],[8]

1. Physical Condition

Screening

Declined preoperative functional capacity is an independent risk factor for postoperative complications and delayed recovery in patients undergoing colorectal surgery.[17],[18] Impaired functional capacity (decreased muscle performance, poor cardiorespiratory state) leads to impaired functional performance. Especially older patients are at an increased risk for adverse outcome due to comorbidities, sarcopenia and functional impairment.[19] Physical performance can be assessed in multiple ways, ranging from questionnaires (e.g. KATZ-ADL), to physical tests (grip strength, cardiopulmonary exercise testing [CPET], 6-minute walk test [6MWT]).

Contents

Preoperative exercise interventions can increase physical performance in colorectal cancer patients.[20], [21] Current physical programs vary from a complete training program involving both cardiorespiratory exercises combined with strength training in a sports facility to at-home exercise programs.[22]–[24] Since physically frail patients are often not used to exercise on a daily basis, researchers should strive to construct a feasible but exerting workout[25]. An example of a program is provided in Table 1.

2. Nutrition

Screening

About 55% of all patients and 25-40% of surgical patients are undernourished on admission to the hospital[26],[27],[28]. Moreover, malnutrition is further intensified during hospitalization especially in patients undergoing major surgery.[29] Malnutrition has been recognized as an independent risk factor for perioperative morbidity and severe postoperative complications.[30],[31] Nutritional support is therefore recommended, sometimes even in seemingly well-nourished patients to target relative deficiencies (e.g. protein).[32]–[34]

There are various screening instruments to assess nutritional state of which the Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) is an example of a screening tool that can be used to identify malnutrition. It is an internationally validated instrument that identifies malnutrition in oncologic patients by assessing weight loss, comorbidity, metabolic stress combined with a physical examination.[35],[36] The Short Nutritional Assessment Questionnaire (SNAQ) is another validated instrument to identify patients at risk for postoperative complications due to a poor nutritional state (also in non-oncological patients).[37] The SNAQ score consists of three questions assessing weight loss, appetite and need for supplemental nutrition such as parental or tube feeding. A recent study showed that a score >3 is specifically associated with postoperative complications in patients undergoing surgery for colorectal cancer.[8]

More specifically in the case of colorectal cancer patients, it should be noted that impaired nutritional status can also refer to a state of relative protein deficiency which manifests itself as sarcopenia or loss in lean body mass.[38] Sarcopenia is defined as a combination of loss of muscle mass and muscle strength.[39] Importantly, it is often not detected with standard malnutrition screening tools that measure low body mass index (BMI) or recent weight loss, as many sarcopenic colorectal cancer patients are overweight or obese.[40] Various methods to screen for sarcopenia have been described by the European Working Group of Sarcopenia in Old People (EWSGO) including measurement of psoas density on CT-scan, hand grip strength measurement etc.[41]

Contents

It is not only challenging to measure the contents of a patient's diet, but also to interfere with it. Diets are notoriously difficult to adhere to and each patient will likely require tailor-made optimization. Regarding protein intake, the European Society of Enteral and Parenteral Nutrition (ESPEN) advices a total of 1.5g/kg/day in cancer patients.[42] Recent studies aim for a total protein intake of 1.5 to 1.8 g/kg/day.[16] The daily estimated habitual protein intake can be estimated and a dietary specialist can provide patients with a tailored dietary advice aiming at a total intake of two portions of 20-40g/protein a day. Since colorectal cancer patients are often able to eat normally, severe cachexia requiring tube or parenteral feeding is not frequently encountered.

At the level of micronutrients, vitamin D is associated with muscle mass and muscle strength.[43] Vitamin D will be supplied daily immediately after cancer diagnosis according to guidelines of the World Health Organization (10µg for men <70 years and for women aged 50-69 years or for women <50 years with coloured skin or little sun exposure, and 20µg for women and men aged 70 years and older). Many elderly patients may have other micronutrient deficiencies or ingest vitamins and minerals below recommended doses before and after surgery.[44] Therefore, it

may be recommended to provide the patients with a multivitamin/mineral supplement.

3. Smoking

Screening

Cigarette smoking is a well-known risk factor for postoperative complications.[45] Smoking has a transient effect on the tissue microenvironment and a prolonged effect on inflammatory and reparative cell functions leading to delayed healing and complication.[46] Wound contraction and collagen metabolism are also affected by a smoking-induced alteration in vitamin C turnover and by a change in inflammatory cell response.[45] Evidence has shown that preoperative smoking cessation interventions reduce postoperative morbidity. [47]

Contents

A period of 4 to 8 weeks smoking cessation prior to surgery has already been shown to significantly reduce postoperative complications and morbidity.[47] Patients may be referred to institutes that can help them to stop smoking. Successful smoking cessation may be achieved in just a few weeks as long as the patient is offered a combination of intensive counseling and nicotine replacement therapy.[48]

4. Anemia

Screening

Preoperative iron deficiency anemia is associated with increased morbidity and mortality.[49], [50] Furthermore, anemia is associated with overall fatigue and impaired physical performance.[51] As the most common cause of anemia in colorectal cancer patients in case of iron deficiency anemia, low hemoglobin levels (men <8g/dl, women< 7.5g/dl) should be assessed in combination with low ferritin (<10ug/l) and low transferrin saturation (<16%) levels.[52]

Contents

Patients should be preoperatively screened to identify insufficient hemoglobin levels. In case of iron insufficiency, optimization of hemoglobin levels using iron injections is preferable. Oral iron supplementation suffers from low compliancy and has more side effects whereas red blood cell transfusions are associated with higher perioperative morbidity and inferior long-term oncological outcomes.[53], [54] The specific dose is calculated according to the severity of anemia and the weight of the patient.[55][53], [54] By using iron injections, anemia may be corrected in a relatively short timeframe. In order to first achieve sufficient hemoglobin levels, postponing surgery may also be considered. Importantly, an optimal hemoglobin level may enhance patients' fitness levels, thereby also allowing for optimal exercise training.

5. Anxiety and mood disorders

Screening

Psychological status (mood, motivation, knowledge) may also play an important role in surgical recovery. It is well documented that patients awaiting major surgery experience anxiety concerning their upcoming operation, its outcome, and their course of healing and recovery.[56], [57] They may also feel depressed, hold unrealistic expectations (overly optimistic or pessimistic) about their health status, and possess inadequate strategies for coping in the pre- and postoperative periods. Any of these factors may influence pain and interfere with postoperative functioning. [58] Furthermore, high levels of cortisol induced by anxiety might have a negative effect in muscle strengthening.[59] Various instruments have been developed to assess mood and anxiety state. The Generalized Anxiety Disorder (GAD)-7 questionnaire for anxiety, the Patient Health Questionnaire (PHQ)-9 for depression and the Hospital and Depression Scale (HADS) combining both are examples of international validated questionnaires. The GAD-7 is a valid and efficient tool for screening for generalized anxiety disorder and assessing its severity in clinical practice and research.[60] The PHQ-9 including nine questions is half the length of many other depression measures, has comparable sensitivity and specificity, and consists of the actual nine criteria on which the diagnosis of DSM-IV depressive disorders is based.[61] HADS is a 14-question measure with seven items each for depression and anxiety.[62] It generates separate scores for anxiety and depression as well as a combined score of psychological distress and has been shown to have good psychometric properties for factor structure, homogeneity, and internal consistency and has been used in studies of patients with a variety of healthcare problems.[63]

Contents

Patients can experience stress and anxiety prior to and after surgery. Cognitive training in the form of psychological counselling, meditation or yoga can reduce anxiety and stress perioperatively.[58] Furthermore, providing the patient with detailed information of the upcoming treatment and course of hospitalisation and the opportunity to contact former colorectal cancer patients can reduce preoperative anxiety.[64]

A summary of all screening methods and interventions is provided in Table 1.

II. INTEGRATION: IMPLEMENTATION IN THE FIELD

In order to achieve successful integration and implementation of a prehabilitation program, behavioural change is required in both patients and those providing the care. Therefore, we investigated the attitude of patients and surgeons towards prehabilitation.

Patients

In 2016-2017, a prehabilitation pilot study in patients undergoing colorectal surgery for cancer took place in Maxima Medical Center, Veldhoven/Eindhoven, the Netherlands (NL54547.015.15, submitted data). This pilot study was initiated to test the feasibility and safety of a multimodal prehabilitation program at both patient and organizational level.

Fifty patients were assigned to intervention (n=20) or control group (n=30). They participated in a multimodal prehabilitation of four weeks in hospital physical training (high intensity endurance and strength training, 3x per week), tailored dietary advice and supplements (total protein intake of 1.5 to 1.8 g/kg/day, 0.4 gram/kg/day after strength training and daily before sleep, 50% of recommended daily allowance for multivitamins, and extra vitamin D), a smoking cessation program (including intensive counselling and any nicotine replacement therapy), and psychological support (one session at the psychologist providing strategies to cope with stress and anxiety). Perioperative care and rehabilitation were given according to the ERAS guidelines.[65] Four weeks after surgery, patients were asked to give feedback on the prehabilitation program.

Evaluation of the program showed high patient appreciation. The attendance rate to the weekly training sessions by the physiotherapist was 88% and patient satisfaction was high (4 on a scale of 1 to 5). Reasons for joining the prehabilitation program were the motivation to optimally prepare for surgery (90%), distraction from the disease in the period before surgery (70%), and to be able to self-manage and change the condition (90%). Overall, these results suggest that prehabilitation could be of additional value to patients undergoing colorectal cancer surgery. A full description of the pilot study is provided in the original article.

Colorectal surgeons

In 2016, a questionnaire was distributed to explore colorectal surgeons' intentions to cooperate in prehabilitation programs. Dutch colorectal surgeons were contacted via email to respond to an online questionnaire (Supplementary Table 1). A link to the survey was also distributed via the online newsletter of the Dutch Colorectal Cancer Group. The questionnaire contained items related to the surgeons' attitudes concerning the content, the design and the delivery of prehabilitation programs. Descriptive statistics were used to analyse these data. A total of 29 colorectal surgeons responded (27% response rate). Prehabilitation was considered an essential part of optimal care by 93% of the surgeons. Aerobic training (97%), optimization of medication (79%) or improved nutrition (79%) were the most popular forms of prehabilitation. A total of 86% were willing to postpone the operation in order to optimize the patient. Seventy-six percent considered a period of 2-4 weeks sufficient, and 93% agreed that insurance companies should cover the costs of prehabilitation. A prehabilitation program was available in 15 of the 29 responding hospitals (52%) and consisted most often of optimization of medication (80%), smoking cessation (60%) and/or psychosocial support (60%). A total of 90% of the surgeons was willing to participate in research on prehabilitation. Seven hospitals (24%) were already performing research. [Figure 3]

Networks

In 2016, the Fit4Surgery project group was founded in The Netherlands with the aim of creating the first online platform bringing together scientific evidence, clinical expertise and evidence/data from all other stakeholders (ranging from personal trainers to supermarkets). The merging of clinical, scientific and personal data will result in the design of an optimal multimodal prehabilitation program for each individual patient facing surgery. The current state of the healthcare system is characterized by divided coordination and the lack of overview for the individual patient. The Fit4Surgery platform aims to be a wisely accessible platform, providing all knowledge and tools required to participate in prehabilitation. The Fit4Surgery platform focuses on patients' interests and the empowerment of caretakers, thereby exceeding organizational, political and financial incentives.

Future prehabilitation may not take place within the hospital. To achieve sustainability in healthcare, it in the interest of all to aim for more cost-effective quality, prevention of disease, and the introduction scalable healthcare solutions. Although the targets seem clear, and do fit the prehabilitation concept completely, there is still a gap towards clinical practice. To facilitate these changes a new collaboration has to be created between the different parties, such as hospitals, patient organizations, health insurance companies, technical developers for patient monitoring devices and business developers to support the financial plans and business modal. In this way, we may achieve a prehabilitation concept which may improve sustainability in treatment for a large number of patients.

III. TOOLS: OUTCOME MEASUREMENT

The goal of prehabilitation is threefold: first, to reduce postoperative complications, second, to enhance and speed up recovery and third, to improve overall quality of life. The chosen instruments to measure outcome should reflect these three dimensions. Furthermore, measuring compliance to the prehabilitation program is vital to ensure its effect. Based on previous literature on prehabilitation, we propose validated and frequently used measurement instruments in each domain.

Compliance

Since prehabilitation is a behavioural intervention, adherence and correct implementation of the intervention might be a challenge. It is therefore recommended that research groups objectify adherence to specific prehabilitation contents.[66] Compliance can be defined as the percentage of attendance to the prehabilitation program (e.g. attendance to training sessions or exercise modalities, compliance to protein intake). Besides compliance, a sufficient quality of execution or so-called fidelity will be essential in order for the program to be successful.[66] Furthermore, measuring compliance for scientific purposes is important but it should be noted that a prehabilitation program is also largely based on the patient's intrinsic motivation. An overly present paternalistic approach with police-like compliance measurement can be potentially harmful.

Regarding the different components of prehabilitation, both active and passive ways to register compliance and fidelity remain scarce. Physical activity can be easily quantified by wearables with sensors. However, adequate methods to monitor nutritional intake, smoking cessation and adherence to a psychological program without too much interference with the patient's daily life remain to be a field of pioneering research for the years to come.[67], [68]

Reduction of postoperative complications

Considering the use of postoperative complications as a measurement tool, it should be noted that the definitions for complications are extremely heterogeneous between studies. For example, one of the most serious complications of colorectal surgery is anastomotic leakage and currently no consensus on the definition exists.[69] Therefore, it might be of more use to implement the Comprehensive Complication Index (CCI) which calculates the sum of morbidity and mortality presented on the Clavien-Dindo scale.[70] Since the CCI assesses the resulting action that was undertaken to treat a complication, interference due to heterogeneity of definitions is diminished.

Enhancement of recovery

At minimum, the goal after surgery is to return the patient to his original level of functioning prior to diagnosis. Cardiopulmonary exercise testing serves as a gold standard in measuring physical performance. It provides an objective assessment of the integrative exercise responses involving the pulmonary, cardiovascular, and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function.[71] Overall recovery is currently expressed in standardized tests such as the 6-minute walk test which has been proven to be strongly correlated with postoperative outcomes in colorectal surgery.[72], [73]

However, it remains a major challenge to develop a validated outcome instrument that allows patients to track their progress according to their own baseline rather than a population-based mean. Previous literature has introduced the concept of "time to return to normal activities", in which normal activities (e.g. getting dressed, cycling, shopping for groceries) are defined by a comprehensive item bank (Supplementary Table 2) reflecting physical performance based on information from validated patient reported outcomes measurements.[74], [75] Ideally, information regarding functional performance could be registered by activity diaries or passively by using sensors and mobile devices.

Increasing quality of life

Questionnaires remain to be the most frequently used and validated way to assess quality of life in patients. In colorectal surgery, the EORTC-QLQ-CR29/C30, including physical, emotional and social functioning and mobility and overall well-being, is most commonly used.[76] Overall quality of life can be measured by the Short Form Health Survey (SF-36) questionnaire.[77]

Conclusion

By failing to prepare, we prepare to fail. The preoperative period maintains a window of opportunity to address modifiable risk factors such as nutrition, functional capacity, anemia, cigarette smoking and mood/anxiety and to optimize a patient's condition prior to surgery. This can be achieved by implementing a prehabilitation program, defined as the multimodal preoperative enhancement of a patient's condition. The goal is to reduce postoperative complications, to enhance recovery and to improve overall quality of life. This review offers an integrative FIT-model (Facts, Integration, Tools) in order to successfully investigate and implement prehabilitation in the coming years. The basis of the current prehabilitation method should focus adjusting modifiable risk factors such as malnutrition, poor physical state, smoking, anemia and poor cognitive state. However, a standard prehabilitation program should only serve as a starting point. A tailored approach focusing on specific individual risk factors of each patient could potentially be more effective. Future research should focus on the value of prehabilitation as optimal preparation for colorectal surgery and other abdominal surgical procedures. Developing implementable methods and defining standardized outcome instruments will help to establish a solid base for patient centered prehabilitation programs.

Perspective

A surgical intervention poses similar stress to the body as a performance in sports. As a consequence, any preoperative patient can be considered as an athlete. Results improve by optimal preparation and thus involve the introduction of exercise, optimizing nutritional state, quitting smoking and optimal psychological support. As a consequence, cross-linking knowledge between the field of prehabilitation and sports medicine could serve both parties in gaining insight in ways to optimally prepare patients and athletes for their game day.

Figure 1. A model describing the functional capacity of patients during their treatment journey and showing the potential of prehabilitation.

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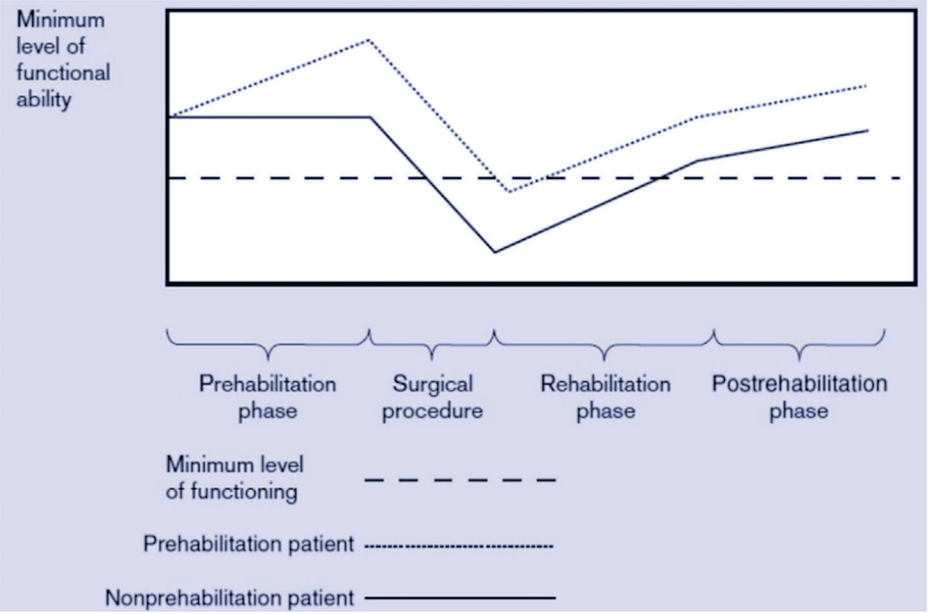


Figure 2. Introduction of the FIT-model (Facts, Integration, Tools) to assess the current screening methods, prehabilitation contents, user assessment and outcome measurement of prehabilitation in patients undergoing surgery for colorectal cancer.

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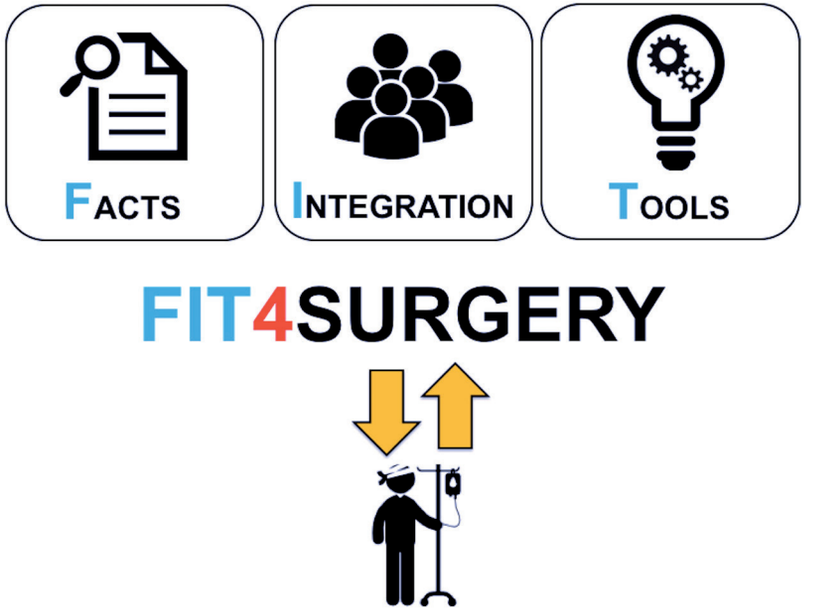


Figure 1. Outcome of questionnaire among Dutch colorectal surgeons and their perspective on the essential content of multimodal prehabilitation.

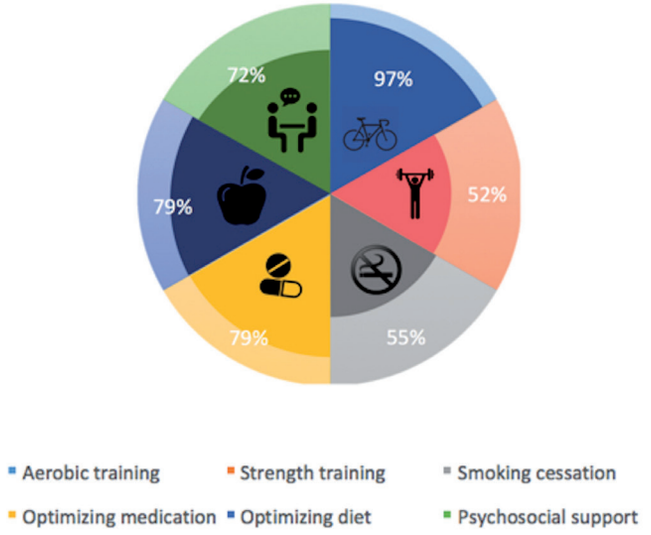


Table 1. Prehabilitation Content Elements.

Content	Measurement	Intervention	Compliance
Exercise			
Cardiovascular	6MWT*, CPET*, TUG*	3x/week HIT* 30 min bicycle	Activity Tracker (e.g. Actigraph)
Strength	Muscle Mass, Hand Grip Strength	Strength 10-15 min arms (flex/ext), trunk (chair rise), legs (knee raising, heel raises), 6-10 reps, 1-2 reps	(Digital) Diary
Functional	KATZ-ADL*		
Nutrition			
Protein intake	MNA*, SNAQ*, PG-SGA*	2x day snack/supplement containing 40g protein, 1.5-1.8g/kg/protein/day	(Digital) Diary
Micronutrients	Diary	multivitamin supplement	Product registration
Psychological			
Anxiety	GAD-7*, HADS*	Psychological counseling, meditation, yoga	Daily logging of mood
Depression	PHQ-9*, HADS*		
Knowledge	Patient interview	Information sessions, Former patient contact	
Social	Anamnesis		
Smoking	Anamnesis	Personalized counseling	(Digital) Diary Intoxication Screening
Anemia	Hemoglobin Transferrin saturation	Diet optimalisation Iron supplementation	Medication accountability tracking

Legend 1. * 6MWT= six minute walking test[72], CPET=cardiopulmonary exercise test[73], TUG=Timed Up and Go[74], KATZ-ADL=questionnaire about daily living dependency[21], HIT=high intensity interval training[75], MNA=Mini Nutritional Assessment[76], SNAQ=Short Nutritional Assessment Questionnaire[43], PG-SGA=Patient-Generated Short Global Assessment[42], GAD-7= Generalized Anxiety Disorder Assessment[67], HADS=Hospital and Depression Scale[70], PHQ-9=Patient Health Questionnaire[68]

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CHAPTER 13

SUMMARIZING DISCUSSION, FUTURE PERSPECTIVES AND CONCLUSIONS



The journey to improve colorectal care

Why do we need to improve?

Decades of research have substantially improved care for patients undergoing colorectal surgery for cancer. Despite these efforts, the incidence of major complications such as colorectal anastomotic leakage (CAL) remains stable, which highly impacts both postoperative outcome and especially patients' health related quality of life (HRQoL) 1–3.
To enhance patient related outcomes, this vast amount of (scientific) knowledge needs to be translated into clinical practice. This translation includes implementation research from both medical as well as patient perspective. This thesis was initiated to identify possible improvements and to fasten implementation of the most recent evidence for patients undergoing surgery for colorectal cancer.

How did we improve?

A 3-year program was defined to improve care at patient level. The first year (2015) mainly consisted of analysis of retrospective data of a single medium volume hospital, creation of a database for prospective data collection, patient interviews, and initiation of the definition of outcomes such as CAL (part 1 of this thesis). The second year (2016) included the development and execution of a 12-month improvement program (modifiable risk factors, part 2) and collection of prospective data. The third year (2017) was used to analyze data, to publish results and to initiate and implement the next steps in colorectal care such as prehabilitation (part 3 and 4).

What did we do to improve?

Within these 3 years, we further defined specific improvement programs within the preoperative, intraoperative and postoperative phase. Furthermore, we initiated several networks and collaborations to facilitate scientific collaboration between in-hospital departments and medical centers in various countries around the globe.

The improvement programs and their results as well as initiated networks, together with our future perspectives will be discussed in the thesis and some final conclusions of this thesis are made.

Preoperative improvements

Preoperatively, there is a window of opportunity to optimally prepare any patient for surgery. With today's knowledge, we have the obligation to the society to improve our preoperative care by defining patient related treatment outcomes, to improve risk assessment, to enhance patient information and facilitate optimal preparation.

Defining outcomes

No uniform and generally used definition for both colon and rectal anastomotic leakage in the clinical setting was found to exist 4. This lack of consensus complicates the comparison of study results and to translate current knowledge into the clinical decision-making process 5. Since CAL remains the worst complication after colorectal surgery 2,6–9, we initiated three studies that were aimed at arriving at a universally accepted definition for CAL.

In the first study we questioned both Dutch and Chinese surgeons whether they agreed on the current available definitions of CAL (study 1, chapter 3). Since we found no agreement, these findings were a prompt to review all available literature using CAL as its primary outcome (study 2, chapter 4). This systematic review of over 3000 papers surprisingly demonstrated that more than half of the papers did not consider or define CAL, although this complication was the primary outcome measure. In this review, only for rectal but not for colon anastomotic leakage a more commonly used definition was found 10,11. We categorized all available definitions into 11 different classifications of CAL. We identified 14 clinical symptoms associated with CAL and 14 different grading systems related to the severity of CAL. We strongly believe that implementation of a graded system with treatment recommendations for the different severity grades of CAL will enhance uniformity in patient care and may lead to less treatment delay. An initial step is to exactly define the terminology that properly describes a leak. It is probably more appropriate to refer to a leak as impaired gut healing. Secondly, the exact timing of CAL occurrence requires description. What is considered an early or a late anastomotic leak? Is early anastomotic leakage due to technical failure? Since the European snapshot study on CAL after low anterior resection demonstrated a surprisingly high incidence (20%) of CAL >30 days postoperatively 12, we have to be aware of these 'late' leakages, their mechanism of occurrence, and possible therapies. Furthermore, colon and rectal anastomotic leakage may possibly be regarded and described as two entities. Reasons to consider rectal and colonic anastomotic leakage as two separate problems include the different reported incidence rates, the range of surgical techniques and microbial composition 13. Standardizing

the method of reporting data on type of surgery, relative location of anastomosis and way of testing of anastomosis integrity both during and after surgery (prior to temporary stoma reversal) are advised. Moreover, we need to reach consensus on the various approaches of construction of deviating ostomies and type of ostomy, clinical symptoms associated with the diagnosis of CAL, diagnostic tools for establishing the diagnosis of CAL, separate leakage rates for colon and rectal anastomoses, median interval of CAL diagnosis from day of surgery, the use of a grading system and associated treatment plan. The results of this systematic review, together with the outcome of the consensus assessment, will be proposed in a worldwide Delphi analysis (study 3, in preparation). Using this systematic approach, we hope to arrive at a uniformly accepted definition of CAL. These endeavors will not only improve the quality and comparability of research projects but will additionally facilitate to a proper diagnosis and optimal treatment of CAL.

Risk assessment

In general, there is a need for more individualized treatment of colorectal cancer. Although many risk factors for colorectal complications and CAL were identified, a portion is non-modifiable. In contrast, this thesis focuses on the identification of modifiable risk factors (chapter 5 and 6). If determined, an individual risk on the development of major complications may be calculated before surgery. Such an approach may improve preoperative counseling and may facilitate shared decision. Anesthesiologists and even gastroenterologists, are thus involved in an earlier phase of treatment to address and possibly influence potential risk factors together with their colleague surgeons. Medication, anemia, functional capacity, smoking- and nutritional status may all be optimized in the weeks before surgery. Unfortunately, no valuable prediction model is currently available. The studies in this thesis support the creation of a new risk model. As we were not able to validate the existing colon leakage score in our patient cohort (chapter 7), we suggest to increase the volume of patients thus creating an effective prediction model. We therefore initiated the international LEAK CHECK study that is discussed below. This study will include over 2000 patients and hopefully will enable us to identify intraoperative and modifiable risk factors of CAL.

Prehabilitation

The preoperative period is a window of therapeutic opportunity to prepare patients to better withstand the stresses of surgery 14–19. Despite the overwhelming evidence demonstrating improvements in functional capacity 15,20–24, nutritional 25–31, physiological 32–35, and smoking status 36–38, we currently do not offer any structural patient programs enabling them to enhance their preoperative status themselves. This thesis investigated the evidence regarding the potential benefits a program termed prehabilitation (chapter 8) and sought to initiate measures a to aid patients in taking charge of their own treatment. We identified various interventional elements that may contribute to patient adherence and provided suggestions on ways for improvement during the limited period of 4 weeks before surgery strikes.

Regarding the program's content, efforts are being made to gain more evidence on the efficacy of specific elements of prehabilitation as well as in the execution of a multimodal program in the form of pilot studies 39–43. We initiated such a pilot study to validate a multimodal prehabilitation program (chapter 9) which may be used in an international randomized controlled trial (chapter 10). This pilot study showed feasibility, safety and preliminary effectiveness of a multimodal and high intensity training program for colorectal cancer patients awaiting surgery. High adherence (88%) to this program and high patient satisfaction was found. Interestingly, patients undergoing prehabilitation returned to their baseline functional capacity significantly faster compared to the control group 4 weeks after surgery (86% vs 40%, $p<0.05$). A currently running international trial will hopefully provide us with information regarding the relationship between prehabilitation and the possible reduction of postoperative complications, enhanced functional recovery (return to normal activities, RNA) and improved health related quality of life (HRQoL).

Future prehabilitation studies may focus on programs that are offered closer to the patients' habitat, and not or just partially in hospitals. Local programs may lower the costs, but more importantly, may increase program accessibility. Distance monitoring with proper devices might be key to maintain optimal adherence to a program. Interestingly, prehabilitation may merge into such a home- or environmental based rehabilitation program. These approaches fit into a continuum of care where patients are optimally treated from diagnosis until full recovery at home. Moreover, specific patient target groups have to be defined ideally benefitting from prehabilitation. Neoadjuvant patients, for example, might greatly improve following these programs since their functional capacity prior to surgery is often impaired (chapter 11) 44. We are convinced that prehabilitation may also be beneficial for many other (oncological) patient groups facing surgery or other intensive treatment. These hypotheses however should all be tested in new trials.

Since the current state of the Dutch healthcare system is characterized by a lack of coordination and overview for an individual patient, we are launching the Fit4Surgery platform that is widely accessible for patients and professionals and provides all knowledge and tools required in prehabilitation. We released a FIT model that is based on 3 pillars:

Facts (how to screen patients and what content to prescribe), Integration (assess motivation of patients and professionals and the development of a platform), and lastly Tools (which outcome measures to use) (chapter 12). In this way, we may reach sustainability in healthcare that is wished for by the Dutch government: more care for less costs, prevention of disease, and the introduction of e-health. Although the targets seem clear and do fit within the prehabilitation concept, there is still a gap with clinical practice. We therefore questioned Dutch colorectal surgeons for their attitude regarding prehabilitation which was found predominantly positive. Ninety-three percent of the responding surgeons indicated prehabilitation should be part of regular treatment. Moreover, 86% would be willing to postpone surgery if a prehabilitation program was offered to their patients.

To facilitate all needed changes and to reach implementation of prehabilitation, the Fit4Surgery foundation aims for further collaboration between all different parties, such as hospitals, patient organizations, health insurance companies, technical developers of patient monitoring devices and business developers to support the financial plans and business model. In this way, we may possibly come up with a valuable prehabilitation concept for a large number of patients.

Patient involvement

During the execution of this thesis, we developed a patient information application to optimally inform both patients and their relatives on the various aspects of surgery. The goal was to combine all information folders (>20) into one single application. This 'app' comprises information of all important stakeholders in colorectal care and sends push notifications to patients at the time they (and their relatives) need it. Using this approach, we optimally prepare patients before surgery, explaining about the importance of prehabilitation a few weeks before surgery, providing information a few days before admission to the hospital on what to expect during hospitalization, and sending notifications on how to smoothly recover during the postoperative days at the ward. By enhancing the patients' information level and of their relatives, they will possibly have less anxiety, and will be better prepared not only for the in-hospital stay, but also for their return to home, which is often associated with logistical challenges 45. After its introduction, patients were found to frequently refer to the application during their recovery to discuss their mobilization and pain control with nurses and surgical residents.

We also started an initiative to provide patients the real experience of 'having been there'. By the use of 360-degree virtual reality (VR) videos, patients and their relatives can virtually visit the hospital as 'if they were there' (www.infor-med.nl). For colorectal cancer patients, we produced 5 VR video's to optimally guide them through their treatment. The set of VR's starts with a video on the national bowel screening program (Bevolkingsonderzoek, BVO), continues with a video on the colonoscopy, explains about bowel cancer and its possible treatment strategies (endoscopic resection, surgery) and ends with a video explaining the use of adjuvant chemotherapy. All videos are produced with a panel including patients and professionals to optimally fit to patients' needs. The goals are to improve information levels of both patients and their relatives, to reduce anxiety and to increase treatment efficiency by the reduction of time needed for patient instruction. Answers to these questions are now being investigated in 6 separate randomized controlled trials although preliminary data were not available at the time of thesis conception.

Intraoperative improvements

Intraoperatively, surgeons have put focus on surgical techniques in both experimental and clinical research settings trying to improve outcome of surgery. To date however, little knowledge is available regarding the anesthesiological aspects of perioperative care, especially during surgery. We therefore initiated a collaboration between surgeons and anesthesiologists and performed a literature review on modifiable intraoperative risk factors of CAL (chapter 6). There appears to be only scarce knowledge on risk factors that are possibly modifiable during surgery. Additionally, there are many anesthesiological factors (such as use of inotropes, neuromuscular blockage (NMB), goal directed therapy [GDT]), which need to be further investigated on their potential benefits or risks 46–48. Anesthesiologists and surgeons should act together to study potential improvements during surgery 49. Since there are no specific protocols worldwide available on the optimal anesthesiological approach in perioperative care, we decided to initiate the creation of one. In this protocol we included all relevant items (risk stratification, preoperative optimization, medication, fasting protocol, antibiotics, temperature, induction, GDT, depth of anesthesia, NMB, postoperative nausea and vomiting prophylaxis (PONV), multimodal analgesia including the epidural and lidocaine, nasogastric tube, glucose, postoperative shivering and pain targets) that are considered important to facilitate an optimal recovery after surgery 50–53. New items such as deep NMB and GDT are still under debate, but may possibly soon prove their value 46,47. A recent systematic review and meta-analysis showed that deep NMB during laparoscopic surgeries improved the surgical 'work space' when compared with moderate NMB 54. Additionally, deep NMB may reduce postoperative pain. Whether these measures lead to fewer intraoperative complications or improved recovery of surgery should be further studied.

Another recent meta-analysis showed the potential of GDT to facilitate the recovery of bowel function, particularly in patients who did not participate in 'enhanced recovery programs' 48.

After we intensified collaboration between surgeons and anesthesiologists within our own hospital and on national level with the Taskforce Anastomotic Leakage, a better understanding was created on optimal treatment for patients undergoing colorectal surgery. By making anesthesiologists, surgeons and their assistants more aware of the potential interrelationship of a range of risk factors, we experienced a change in a diverse set of parameters. The introduction of the simple LEAK CHECK questionnaire, to be completed at the time of anastomosis construction, made the entire operating team aware of the status of the patient. This 'time out' taking just a minute or two, introduced the so called - Hawthorne or observer effect – which is known as a type of reaction of individuals modifying an aspect of their behavior in response to their awareness of being observed 55,56. Without giving the operating crew any clue on how to adjust several parameters (such as mean arterial pressure, body temperature, administration of inotropes), but just to let them check the status of the patient on these several items, we for instance observed an increase of body temperature at the beginning of operation with more than 1 degree Celsius.

To further support normothermia during the perioperative phase, we introduced warmth jackets. Since the maintenance of normothermia decreases the incidence of surgical site infections (SSI) and shortens length of hospital stay, all our patients were offered such a warmth jacket 57. Approximately 30 minutes before transfer from the ward to the operating theatre, patients undressed completely and put the jacket on. A controller device enabled patients to choose a comfortable temperature. During surgery, the jacket could be easily transformed to a regular 'bair hugger'. After surgery, patients wake up having their warmth jacket again controlling their own temperature. The use of this simple device supported us to further increase and regulate body temperature of all colorectal patients, reaching 100% normothermia.

On a surgical level, there may also be additional improvements during the intraoperative phase. The role of stapled anastomosis in right colonic resections and a defunctioning stoma are still under debate 58,59. Fluorescence-guided surgery may add in lowering CAL rates 60,61. Although randomized controlled trials are absent, indocyanine green fluorescence (ICG-FA) seems like a promising method to intraoperatively assess perfusion at the site intended for anastomosis 62. More research is needed to relate ICG-FA to a potential reduction of CAL. ICG-FA may additionally serve as a method to identify peritoneal metastasis and small lymph nodes 63. Use of this method was found to modify planned surgery in up to 29% of the cases 64.

Postoperative improvements

After surgery, patients are awaiting a challenge to recover as soon as possible. The goal is to optimally recover after hospital discharge and to reach baseline (preoperative) functional status, needed to perform activities of daily living (ADL) independently, within a few weeks.

Early diagnosis

A uniform diagnosis of CAL remains a clinical challenge as signs and symptoms preceding a clinical deterioration of patients with anastomotic leakage are often nonspecific. The diagnosis is often delayed due to lack of definition, misdiagnosis and false negative radiological examinations 4,65. An earlier diagnosis is important since early intervention can prevent the development of severe sepsis. Currently, patients with CAL are on average diagnosed at day 4-6 postoperatively.

Diagnostic methods of CAL include clinical examination (i.e. DULK score), laboratory measurements (i.e. CRP, leukocytes), radiological investigations (i.e. X-thorax, CT-scan) and/or an immediate re-intervention (i.e. drainage, reoperation). Clinical examination using the DULK score and performing a CT scan were insufficient as early predictors of CAL 65. Although baseline CRP and leukocytes levels substantially rise due to surgical stress and abdominal infection, both are not specific for CAL. Therefore, there is an urgent need to find an efficient biomarker early reflecting anastomotic leakage, allowing safe and early discharge of patients after colorectal surgery.

Procalcitonin

Procalcitonin (PCT), a prohormone of calcitonin produced by C cells in the thyroid gland, is possibly a sensitive and specific biomarker to diagnose CAL in an earlier phase 66. PCT increases during severe bacterial, parasitical or fungal infections and remains normal in viral infection and noninfectious inflammatory reactions 67. Using PCT as an early predictor of bacterial infections in thoracic and oncologic surgery was more accurate than the determination of CRP and leukocytes 68. Nevertheless, literature about the value of PCT as an early biomarker of CAL remains conflicting necessitating more research 69. In this thesis we initiated a study on procalcitonin as an early biomarker of CAL. Results are being analyzed and will be prepared for publication in the year of 2018.

Volatile organic compounds

As part of the ongoing REVEAL study initiated by the Maastricht

University Medical Center, we studied Volatile Organic Compounds (VOCs) in exhaled breath as a potential tool for the early diagnosis of anastomotic leakage 70. The composition of VOCs in exhaled breath depends on health status. Various metabolic processes within the body produce volatile products that are released into the blood and will be passed on to the airway once the blood reaches the lungs 71. Moreover, the occurrence of chronic inflammation and/or oxidative stress can result in the excretion of volatile compounds that generate unique VOC patterns. In this study, we measured a substantial number of VOCs in exhaled air as a potential method of prediction of CAL prior to primary surgery, and/or a predictor for CAL during the first days (day 1-6) after surgery. The VOC study included 20 CAL patients in 2017 and data are currently being analyzed.

Late anastomotic leakage

The incidence of late (>30 days after surgery) anastomotic leakage, is underestimated as was found in a registration study initiated by our Dutch collaborative research group Snapshot 12. A total of 71 hospitals included 998 patients undergoing low anterior resection. The incidence of CAL within 30 days after surgery was 13.4% compared to 20% after 30 days. This highlights the need to intensively follow up patients, possibly even beyond the three to four-week time period.

Collaboration is key to improve

A profound change in colorectal care requires collaboration between the various (para)medical disciplines and medical institutes. 'Silo thinking', a term that refers to the unwillingness to share information between departments, is common in healthcare 72,73. This from of thinking restricts implementation of multidisciplinary programs and should be discouraged. Referral of colorectal cancer patients to a sports physician, psychologist or geriatrician is not common practice and requires substantial changes in the organizational structure. It took our MMC hospital two years for achieving an optimal collaboration between a variety of departments involved in colorectal care (surgeon, anesthesiologist, gastroenterologist, oncologist, case manager, sports physician, physiotherapist, dietician, geriatrician, psychologist). Collaboration between medical centers was even more challenging, since each center relies on its own protocols and preferences. Collaboration is one of the key factors to truly change (colorectal) practice. It may now seem rather old-fashioned to adhere to your own specialism and your own medical center, when treating multimodal and multidisciplinary problems. Because of the many specialists involved in colorectal care, collaboration could renovate the actual treatment plan, thereby improving outcome for the individual patient. Additionally, collaboration in research projects may facilitate generalizability of study outcomes, thereby providing essential information to a substantial larger group of patients. To bring this ideology into action, we initiated the Dutch Taskforce Anastomotic Leakage, created the Fit4Surgery foundation, established an international prehabilitation consortium and cooperation between Máxima Medical Center and a Dutch health insurance company.

Taskforce Anastomotic Leakage

The 'Taskforce Anastomotic Leakage' was initiated to commonly diminish major complication rates after colorectal surgery in over 30 (out of 81) participating hospitals in the Netherlands. Surgeons, anesthesiologists, residents and researchers are involved in this Taskforce. Collaboration between surgeons and anesthesiologists on the improvement of intraoperative items may be key in a continuous effort to reduce the number of major complications in colorectal surgery such as CAL 3,49,74–78. The initiated prospective LEAK CHECK study is currently being performed in 20 hospitals including two in Belgium (the Antwerp University Hospital) and Italy (Ferrara University Hospital), respectively. Based on the results of 2000 included patients, conclusions may be drawn to initiate a new study. This follow up study may promote an active change in intraoperative modifiable parameters which deviate from the normal. The Taskforce will also further contribute to the search for a uniform definition of CAL.

Fit4Surgery foundation

To bring all knowledge together - regarding prehabilitation - we founded a Dutch collaboration group in 2016: Fit4Surgery. The Fit4Surgey foundation launched a 'FIT' model (Facts, Integration and Tools), which may help to translate existing knowledge into practice. In this way, patients may directly benefit from science, which normally takes 17 (!) years to bring an idea into clinical practice 79–81. Facts stands for science, in which several (international) research projects on prehabilitation have been initiated. This may help us to describe the different components considered essential in a multimodal prehabilitation program 39,40. Integration consists of implementation aspects of prehabilitation and assesses motivation of patients and healthcare professionals. And tools refer to the development of technical instruments to support, encourage, and monitor patients during their prehabilitation program. The Fit4Surgery group will continue in its efforts to facilitate collaboration in order to investigate and optimize prehabilitation in the Netherlands and abroad.

International prehabilitation consortium

To coordinate the international prehabilitation randomized controlled trial in over six participating countries (Canada, Denmark, France, Italy, Spain and the Netherlands), and to generate a state of the art regarding prehabilitation (including definitions and models), the 'PREHAB' consortium was initiated. Research questions may be proposed to and will be discussed by the principal investigator group of six leading experts on prehabilitation. Outcome measures will be continuously discussed to create the gold standard.

Together defining a business case

New initiatives and innovations in healthcare need to be proven, preferably cost-effective. After the introduction of the concept of prehabilitation, we started a collaboration between our hospital and one of the 3 large Dutch health insurance companies (CZ) to define a business case. To create an overview of total health expenditures of a patient treated for colorectal cancer, both in-hospital (i.e. treatment costs) and out of hospital (i.e. societal costs) are being investigated. Potential benefits of the program will be highlighted (such as reduction in length of hospital stay, complications and an improved HRQoL) and compared to the extra costs of a prehabilitation program (such as triage, exercise training and protein supplements). In this way, the optimal business case may be defined for prehabilitation to facilitate optimal implementation in the (Dutch) healthcare system.

If prehabilitation is indeed successful in not only improving functional capacity but also by reducing the postoperative complication rate, postponing an operation in order to further optimize the patient's condition may become an option82. These endeavors are possibly interesting for health insurance companies in considering prehabilitation as part of a standard treatment stratagem.

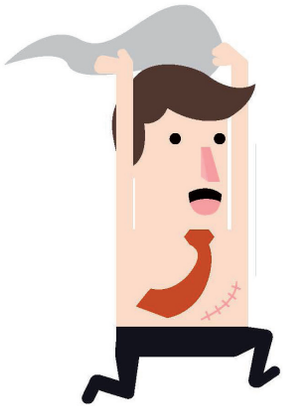
Results of improvements: ERAS 3.0

Studies that are presented in this thesis report on patient specific programs increasing the ability to healthy undergo surgery, to enhance collaboration of specialists and expert centers in the Netherlands and abroad, and to create value based programs for curbing healthcare expenditures. The programs and studies resulted in a significant reduction of complications (50 to 30%; unpublished data), the number of colorectal anastomotic leakage (9% to 2.5%) and length of hospital stay (8 to 4 days), in just a period of two years (2016 and 2017). Above all, both patient and employee satisfaction were increased by changing the mindset and improving collaboration. Together we feel that we revolutionized colorectal care.

This change is reached by the effort of all disciplines together. It started by creating awareness. 'Average is not enough', 'we want to become outperformers', 'we do have a problem', 'and we are all problem owner'. Second, we analyzed our current performance state, analyzed retrospective data and created a consortium with leaders of all medical specialties involved in colorectal care. Together with this team we increased the ERAS protocol compliance, creating a good start to further improve.

In our second year of change we launched a 12-month program facilitating a real improvement. Each month another theme was designed to improve part of the patients' treatment journey. The content was based on the analysis of own patient data and delivered valuable insights in ways to improve. With this program we created a multimodal and multidisciplinary approach that enabled us to further improve the ERAS protocol by adding the latest available evidence. The 12-months program included optimization of compliance to the ERAS program (I), a multidisciplinary protocol to improve the preoperative hemoglobin level if lower than 7 mmol/l (II), temperature regulation introducing warmth jackets (III), optimal perioperative nutrition and fluid management (IV), introduction of a smoke cessation program (V), enhanced postoperative mobilization (VI), introduction of chewing gum and coffee on the ward to support bowel movement (VII), the introduction of prehabilitation (VIII), improved discharge logistics (IX), optimization of patient information (X), the introduction of a data management system (XI) and the report to the multidisciplinary team of final outcomes of the improvement program (XII).

In our third year of studies we started to share our knowledge and results. ERAS 3.0 was our goal. After the introduction of ERAS in the late '90s by Prof. dr. H. Kehlet 51,83, the most contributing changes in colorectal care were the introduction of laparoscopy, differentiation of surgeons and the obligation for national data registration in the Netherlands (ERAS 2.0) 84,85. Adding the latest evidence in perioperative care, supplemented with the introduction of next steps (i.e. optimal patient information and prehabilitation), a continuum of care is created allowing for an optimal patient benefit (ERAS 3.0).



CONCLUSIONS

1. Several perioperative modifiable risk factors of CAL in colorectal patients may be identified including BMI (<20 or >30+=), comorbidities, presence of an epidural catheter, delayed antibiotics administration, volume of intravenous fluids, blood loss and blood transfusions.

2. Consensus on definitions regarding CAL is lacking among Dutch and Chinese colorectal surgeons and there exist important differences between the countries.

3. A worldwide accepted definition of both colon and rectal anastomotic leakage is currently not available.

4. The risk of developing severe complications is related to number of modifiable preoperative risk factors.

5. Collaboration between surgeons and anesthesiologists is key in addressing potential modifiable intraoperative risk factors.

6. The 'colon leakage score' is not predictive of CAL.

7. The period before surgery may in fact be a better time to intervene in factors that contribute to recovery and is referred to as a 'window of opportunity'. Measures in a so called prehabilitation program will prove of utmost clinical importance in the upcoming decade.

8. A comprehensive 4-pillar multimodal and multidisciplinary prehabilitation program including high-intensity exercise training, nutritional support, smoking cessation and mental coaching for colorectal cancer patients is feasible and effective.

9. Exercise therapy may be beneficial for colorectal cancer patients during (neo)adjuvant treatment.

10. Prehabilitation requires a multidisciplinary effort of medical health care professionals and a behavioral change of the patient.

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CHAPTER 14

VALORIZATION - VALORISATIE



VALORIZATION

Creating opportunities in colorectal care

This thesis was initiated to improve outcome of colorectal surgery with the main aim to lower the number of a feared complication termed anastomotic leakage (CAL) in a Dutch teaching hospital (Maxima Medical Center, MMC). A 3-year program was defined to systematically study the current patient population and to explore the existing literature. These endeavors were all aimed to initiate an improvement program and to translate the current knowledge into clinical practice for immediate patient benefit.

The literature suggests that several windows of opportunity during surgical treatment of colorectal cancer patients may be present. The studies in this thesis started with a simple improvement program in a single institution but eventually resulted in the creation of several valuable programs in a multidisciplinary, multicenter and worldwide collaboration setting.

The MMC hospital's outcome of colorectal surgery significantly improved due to the initiation of these projects. For instance, CAL rates dropped over a period of one year from 9% to 2.5%, complication rates diminished from 50% to 30%, and the length of hospital stay was shortened from 8 to 4 days. Above all, patient and health care workers' satisfaction increased by changing their respective mindsets and optimizing collaboration. By proving the concept of prehabilitation by literature reviews, lobbying and pilot studies, several grants were received resulting in approximately 1 million euro's to further develop and coordinate a global study on prehabilitation. We re-founded the 'Taskforce Anastomotic Leakage' in over 30 hospitals and several medical disciplines and aim to reach consensus on the worldwide definition of CAL. Via the Taskforce we are the first to initiate a prospective international multicenter study (LEAK CHECK) to study larger volumes of patients to further predict and prevent the risk of CAL. Together with our (inter)national colleagues and initiated networks we will continue to create opportunities to improve care for all patients facing colorectal cancer.

58 millions of savings

Most patients with colorectal cancer can undergo a successful operation. The 5-year survival of patients not having metastatic disease is 60 to 95%. However, these operations are extensive and associated with high rates of morbidity and mortality, with CAL the most feared complication. Postoperative complications occur in up to 50% of patients 1. The incidence of CAL is reported 1-21% in worldwide literature, in the Netherlands on average 5.8% for colon and 9.4% for rectal operations. These suboptimal results reduce the health related quality of life (HRQoL) and significantly increase health expenditure. Costs due to complications such as CAL were not studied extensively yet. We therefore investigated our own patient cohort and encountered a 3 to 4-fold increase in costs compared to a patient not having CAL. In the Netherlands, yearly about 2250 leakages occur. If these CAL's were all prevented, a total of 58 million euros was saved. This figure highlights the need to improve and support the idea of constructing a relevant business case. Even if a zero leakage rate was not attained, every 1% CAL reduction may result in a 6-10 million decrease in costs. Moreover, a reduction of other postoperative complications may result in even higher cost-savings making a serious investment worthwhile.

Value based healthcare: Yes we care

With a possible savings of millions of euro's, value based programs for colorectal cancer treatment may be designed. We may adhere to a strategy which maximizes value for patients by achieving the best outcomes at the lowest cost. Since there are worldwide 1.400.000 new colorectal cancer cases per year (17.000 in the Netherlands) and 700.000 deaths (5.000 in the Netherlands), there is a potential to maximize value for many patients. Together with the Dutch insurance company Centraal Ziekenfonds (CZ) we started a collaboration to create a business case for colorectal care. Both in-hospital (i.e. treatment costs) and out of hospital (i.e. societal costs) are currently being investigated. Potential benefits of an optimal prehabilitation and enhanced recovery after surgery (ERAS) program will be highlighted (reflected in reduction in length of hospital stay and complications, improved HRQoL, better 5-year survival) and compared to the extra costs of a prehabilitation program (such as triage, exercise training, proteins). These outcomes were selected together with patients and healthcare professionals in sessions guided by the decision group 7. In this way, optimal outcome parameters for patients, and business case for hospitals and health insurance companies, may be defined. This may finally lead to an optimal implementation of value based innovations in the (Dutch) healthcare system.

The colorectal patient decides

Healthcare exists because of patients. Healthcare is there for

patients. And if healthcare doesn't work for patients, it doesn't work. Along with the Hippocrates' Oath to help or not to harm the patient, we need to develop a healthcare system where patients are put in first place whereas doctors have the freedom to care for them the best way they can.

An optimal preparation of patients before treatment is crucial to achieve these goals. In this thesis we introduced a patient information application and the concept of prehabilitation. Both are designed to optimally inform patients regarding their upcoming surgery and explains how patients can optimize their own situation while waiting for surgery. This frame of mind encourages patients (and their relatives) to be in charge of their own treatment, to actively participate in their treatment and to reach shared decisions on treatment.

Revolution in colorectal care introducing prehabilitation

As the concept of prehabilitation (multimodal approach to get patients fit for surgery) did not exist in the Netherlands, we contacted Prof. F. Carli of the Montreal General Hospital, Canada prior to the initiation of studies that are described in this thesis. He was the first to publish on the potential of prehabilitation for cancer patients 8,9. We were invited to join his first multidisciplinary expert meeting on prehabilitation in the fall of 2015 and together decided to design the first international multicenter randomized trial on multimodal prehabilitation. Combined with sufficient compliance to the ERAS program, optimal care for colorectal cancer patients is guaranteed. It is anticipated that this collaboration and study initiation will support further research on the potential of prehabilitation. Home based training programs, individualized training advice and prehabilitation for other types of (oncological) disease may now be investigated.

Collaboration is key

Collaboration is key to a variety of projects initiated in this thesis. Local, national and international collaborations guarantee further improvements in colorectal care. We challenged the existing silo's by building interconnecting bridges, creating collaboration between many medical professionals within our hospital. On a national level, the Taskforce Anastomotic Leakage provides a platform for researchers and clinicians to share knowledge and experience on the prevention of complications including CAL. In her almost 3 years of existence, many projects were established, both clinical and experimental. Together with the Dutch Cancer Society (KWF) and the National Fund against Cancer (NFtK), Friesland Campina, Philips Healthcare and health insurance company CZ, we investigate the potential of prehabilitation. Our Fit4Surgery foundation launched its FIT-model, creating a platform which is widely accessible for patients and professionals, providing all knowledge and tools required for prehabilitation. On an international level, we will continue research projects with our international consortium in over 30 hospitals in 8 different countries leading to the LEAK CHECK study and PREHAB randomized controlled trial.

Valorization of improvements: ERAS 3.0

ERAS 3.0 has been introduced by our research team to challenge the current suboptimal morbidity and mortality rates in colorectal care. It aims for a zero complication tolerance policy and optimal patient involvement. A zero complication rate may be a utopia. However, utopia offers a goal to reach out for and a vision to be realized. It provides a compass point to determine which direction to move toward and a measuring stick to determine how far one has come. This utopia has been politically necessary to get everyone on board and to reach our goals.

We've reached our goals by refurbishing the ERAS program. ERAS 1.0 refers to the enhanced recovery program introduced by Prof. dr. H. Kehlet in the late 1990s and implemented in our center in 2005. The success of ERAS has been its multimodal approach, challenging many different risk factors of complications in perioperative care at the same time 11. Since then, the most contributing changes in colorectal care have been the introduction of laparoscopy, differentiation of surgeons and the obligation for national data registration in the Netherlands (ERAS 2.0). ERAS 3.0 is our goal. The measuring sticks included optimal adherence to the ERAS 1.0 program, the addition of latest evidence in perioperative care, completed with the introduction of next steps in colorectal care; optimal patient information and prehabilitation (ERAS 3.0). We have had a first chance to share our thoughts with the Akershus University Hospital in Oslo, Norway. We've visited their hospital to determine their need for improvement and organized a 2-day program for their multidisciplinary staff in our hospital to inform and inspire. Altogether, we believe this ERAS 3.0 concept will optimally serve the continuum of care for both patients as healthcare professionals.

VALORISATIE

Benutten en creëren van mogelijkheden binnen darmkankerchirurgie

Dit proefschrift geeft de onderzoeken weer die zijn opgezet om de uitkomsten van zorg bij de behandeling van colorectale tumoren te verbeteren. Het belangrijkste doel was om het aantal naadlekkages - de meest gevreesde complicatie bij darmchirurgie - in een Nederlands opleidingsziekenhuis, het Máxima Medisch Centrum (MMC), te verlagen. Een driejarig programma werd opgesteld om de huidige patiëntenpopulatie systematisch te bestuderen en de bestaande literatuur te verkennen. Deze inspanningen waren gericht op het initiëren van een verbeterprogramma en het vertalen van de huidige kennis naar de klinische praktijk. Dit zou dan uiteindelijk moeten resulteren in meer patiëntgerichte zorg en minder complicaties.

De literatuur suggereert dat, in de periode rondom chirurgische behandeling van patiënten met een colorectale maligniteit, diverse kansen tot verbetering bestaan. Hoewel de studies in dit proefschrift zijn opgezet om een verbeterprogramma te ontwikkelen en te implementeren in één enkele instelling, heeft dit uiteindelijk geresulteerd in de creatie van verschillende waardevolle programma's in een multidisciplinair, multicenter en zelfs een wereldwijd samenwerkingsverband.

De uitkomsten voor colorectale chirurgie binnen Máxima Medisch Centrum zijn aanzienlijk verbeterd door een multidisciplinaire aanpak binnen het zorgpad colorectale tumoren. Zo daalde het percentage naadlekkages in een periode van één jaar van 8% naar 2,5%, namen de postoperatieve complicaties af van 50% naar 30% en werd de duur van het verblijf in het ziekenhuis verkort van gemiddeld acht naar vier ligdagen. Bovenal steeg de tevredenheid van patiënten en medewerkers doordat wederzijdse participatie in het postoperatief herstel werd gestimuleerd en de samenwerking werd geoptimaliseerd.

Met het hele onderzoeksteam hebben we het concept prehabilitatie geïmplementeerd gebaseerd op literatuuronderzoek en internationale samenwerking. Op basis van een pilotstudie (gefinancierd door het Nationaal Fonds tegen Kanker (NFtK)) werd een grote internationale randomized controlled trial (RCT) opgezet. Hiervoor werden tevens verschillende subsidies ontvangen, waaronder een Grant van het Koningin Wilhelmina Fonds (KWF Kankerbestrijding) die bedoeld is om de internationale vervolgstudie te coördineren.

We hebben een belangrijke bijdrage gehad in de oprichting van de landelijke 'Taskforce Naadlekkage'. Met participatie van meer dan dertig ziekenhuizen en verschillende medische disciplines streven we binnen deze organisatie naar consensus over een wereldwijde definitie van naadlekkage. Via de Taskforce zijn wij het eerste centrum dat een prospectieve internationale multicenter studie initieert (LEAK CHECK) waarbij grotere aantallen patiënten worden bestudeerd om het risico op naadlekkage verder te voorspellen en te voorkómen. Samen met onze (inter)nationale collega's en geïnitieerde netwerken zullen we mogelijkheden blijven creëren om de zorg voor alle patiënten met darmkanker te verbeteren.

58 miljoen besparing

De meeste patiënten met colorectale kanker kunnen een succesvolle operatie ondergaan. De vijf-jaars overleving van patiënten zonder gemetastaseerde ziekte is 60 tot 95%. Deze operaties zijn echter complex en geassocieerd met hoge percentages morbiditeit en mortaliteit, met naadlekkage als de meest gevreesde complicatie. Postoperatieve complicaties, ernstig en minder ernstig, komen voor bij soms 50% van de patiënten. In de literatuur wordt de incidentie van naadlekkage wordt gerapporteerd als zijnde 1 tot 21%, in Nederland bedraagt dit gemiddeld 5,8% voor colon en 9,4% voor rectum operaties. Deze suboptimale resultaten verminderen de gezondheid gerelateerde kwaliteit van leven (HRQoL) en verhogen de gezondheidsuitgaven aanzienlijk. Kosten als gevolg van complicaties zoals naadlekkage werden nog niet uitgebreid bestudeerd. We hebben daarom ons eigen patiënten cohort onderzocht en een drie tot viervoudige kostenstijging gevonden in geval van naadlekkage, ten opzichte van een situatie zonder deze complicatie (36.000,- versus 9.000.- euro). In Nederland doen zich jaarlijks circa 2250 naadlekkages voor. Als deze naadlekkages allemaal voorkomen zouden worden, zou in potentie 58 miljoen euro bespaard kunnen worden. Dit cijfer benadrukt de noodzaak om de zorg te blijven verbeteren en een juiste business case te beschrijven. Zelfs als een lekkagepercentage van nul procent niet wordt bereikt, kan elke een procent naadlekkage-verlaging resulteren in een kostenvermindering van 6 tot 10 miljoen euro. Bovendien kan een vermindering van andere postoperatieve complicaties leiden tot nog hogere kostenbesparingen.

Op waarde gebaseerde gezondheidszorg: Yes, we care

Met een mogelijke besparing van miljoenen euro's kunnen op waarde gebaseerde programma's voor de behandeling van colorectale kanker worden ontworpen. We kunnen ons richten op een strategie die de waarde voor patiënten maximaliseert door de beste resultaten te behalen tegen de laagste kosten. Aangezien er wereldwijd jaarlijks 1.400.000 nieuwe gevallen van colorectale kanker zijn (17.000 in Nederland) en 700.000 sterfgevallen (5.000 in Nederland), is er in potentie voor veel patiënten veel waarde toe te voegen. Samen met de Nederlandse verzekeringsmaatschappij Centraal Ziekenfonds (CZ) zijn we een samenwerking gestart om een business case voor colorectale zorg te creëren. Zowel de kostenfactor in het ziekenhuis (dat wil zeggen behandelingskosten) als buiten het ziekenhuis (dat wil zeggen maatschappelijke kosten) wordt momenteel onderzocht. Potentiële voordelen van een optimaal prehabilitatie en verbeterd herstel na chirurgie (Enhanced Recovery After Surgery, ERAS) programma zullen worden benadrukt. Dit wordt weerspiegeld in verminderde verblijfsduur in het ziekenhuis, complicaties, verbeterde kwaliteit van leven en vijf-jaars overleving en wordt vergeleken met de extra kosten van een prehabilitatie-programma (zoals patiënttriage, training, voedingssupplementen, mentale coaching en stoppen met roken). Deze uitkomsten werden samen met patiënten en zorgprofessionals geselecteerd in sessies geleid door de Value Based Healthcare beslissingsgroep (the Decision Group). Op deze manier kunnen optimale uitkomstparameters voor patiënten en een business case voor ziekenhuizen en zorgverzekeraars worden gedefinieerd. Dit kan uiteindelijk leiden tot een optimale implementatie van waarde-gebaseerde innovaties in de (Nederlandse) gezondheidszorg.

De colorectale patiënt beslist

Gezondheidszorg bestaat omdat er patiënten zijn. Gezondheidszorg is er voor patiënten. Als de aangeboden zorg niet werkt voor de patiënten, dan werkt het hele systeem niet. Op basis van de Eed van Hippocrates: "om de patiënt te helpen en niet te schaden", moeten we een gezondheidszorgsysteem ontwikkelen waarbij patiënten op de eerste plaats komen, terwijl artsen de vrijheid hebben om op de best mogelijke manier voor hen te zorgen.

Een optimale voorbereiding van patiënten vóór de behandeling is cruciaal om deze doelen te bereiken. In dit proefschrift hebben we een digitale applicatie voor patiëntinformatie en het begrip prehabilitatie geïntroduceerd. Beide zijn ontworpen om patiënten optimaal te informeren over hun aanstaande operatie en leggen uit hoe patiënten hun eigen situatie kunnen optimaliseren in de wachttijd voor een operatie. Deze opzet moedigt patiënten (en hun familieleden) aan om zelf verantwoordelijkheid te nemen over hun eigen behandeling, om actief deel te nemen aan hun behandeling en om gedeelde beslissingen over de behandeling te nemen.

Revolutie in colorectale zorg met prehabilitatie

Aangezien het concept prehabilitatie (multimodale benadering om patiënten geschikt te maken voor operaties) in Nederland niet bestond, hebben we contact opgenomen met Prof. F. Carli van het Montreal General Hospital, Canada, voorafgaand aan de start van onderzoeken die in dit proefschrift worden beschreven. Hij was de eerste die publiceerde over het potentieel nut van prehabilitatie voor kankerpatiënten. We werden uitgenodigd om deel te nemen aan zijn eerste multidisciplinaire expertmeeting over prehabilitatie in het najaar van 2015 en besloten samen om de eerste internationale multicenter RCT over multimodale prehabilitatie te ontwerpen. Gecombineerd met voldoende naleving van het ERAS-programma, is optimale zorg voor patiënten met dikke darmkanker op deze wijze gegarandeerd. Verwacht wordt dat deze samenwerking en studie-initiatie verder onderzoek naar het potentieel van prehabilitatie zal ondersteunen. Ook thuissituatie trainingsprogramma's, geïndividualiseerd trainingsadvies, en prehabilitatie voor andere soorten (oncologische) ziekten kunnen nu verder worden onderzocht.

Samenwerking is de sleutel tot succes

Samenwerking is de sleutel tot succes in de verschillende projecten die in dit proefschrift zijn geïnitieerd. Lokale, nationale en internationale samenwerkingen garanderen verdere verbeteringen in de colorectale zorg. We daagden de bestaande silo's uit door bruggen te bouwen, waardoor er samenwerking ontstond tussen vele verschillende medische disciplines in ons eigen ziekenhuis. Op nationaal niveau biedt de Taskforce Naadlekkage een platform voor onderzoekers en clinici om kennis en ervaring te delen over de preventie van complicaties, waaronder naadlekkage. In haar bijna drie-jarig bestaan werden veel projecten opgezet, zowel klinisch als experimenteel. Samen met het Koningin Wilhelmina Fonds (KWF Kankerbestrijding), het Nationaal Fonds tegen Kanker (NFtK), Friesland Campina, Philips Healthcare en zorgverzekeraar CZ onderzoeken we de potentie van prehabilitatie. Onze Fit4Surgery-stichting lanceerde het FIT-model en creëert een platform dat breed toegankelijk is voor patiënten en professionals, dat alle kennis

en hulpmiddelen biedt die nodig zijn voor prehabilitatie. Op internationaal niveau zullen we onderzoeksprojecten voortzetten met ons internationaal consortium in meer dan 30 ziekenhuizen in 8 verschillende landen, leidend tot de LEAK CHECK-studie en PREHAB RCT.

Valorisatie van verbeteringen: ERAS 3.0

ERAS 3.0 (Enhanced Recovery Around Surgery) is door ons onderzoeksteam geïntroduceerd om de huidige suboptimale morbiditeit en mortaliteit bij colorectale zorg aan te vechten. Het streeft naar een 'nul complicatie tolerantiebeleid' en een optimale betrokkenheid van de patiënt. Nul procent complicaties kan een utopie zijn. Het gaat echter om de visie om dit te willen realiseren. Het biedt een kompas om te bepalen in welke richting we moeten gaan en een meetstok om te bepalen hoe ver we zijn gekomen. Deze "utopie van nul procent complicaties" was politiek noodzakelijk om iedereen aan boord te krijgen en onze doelen te bereiken.

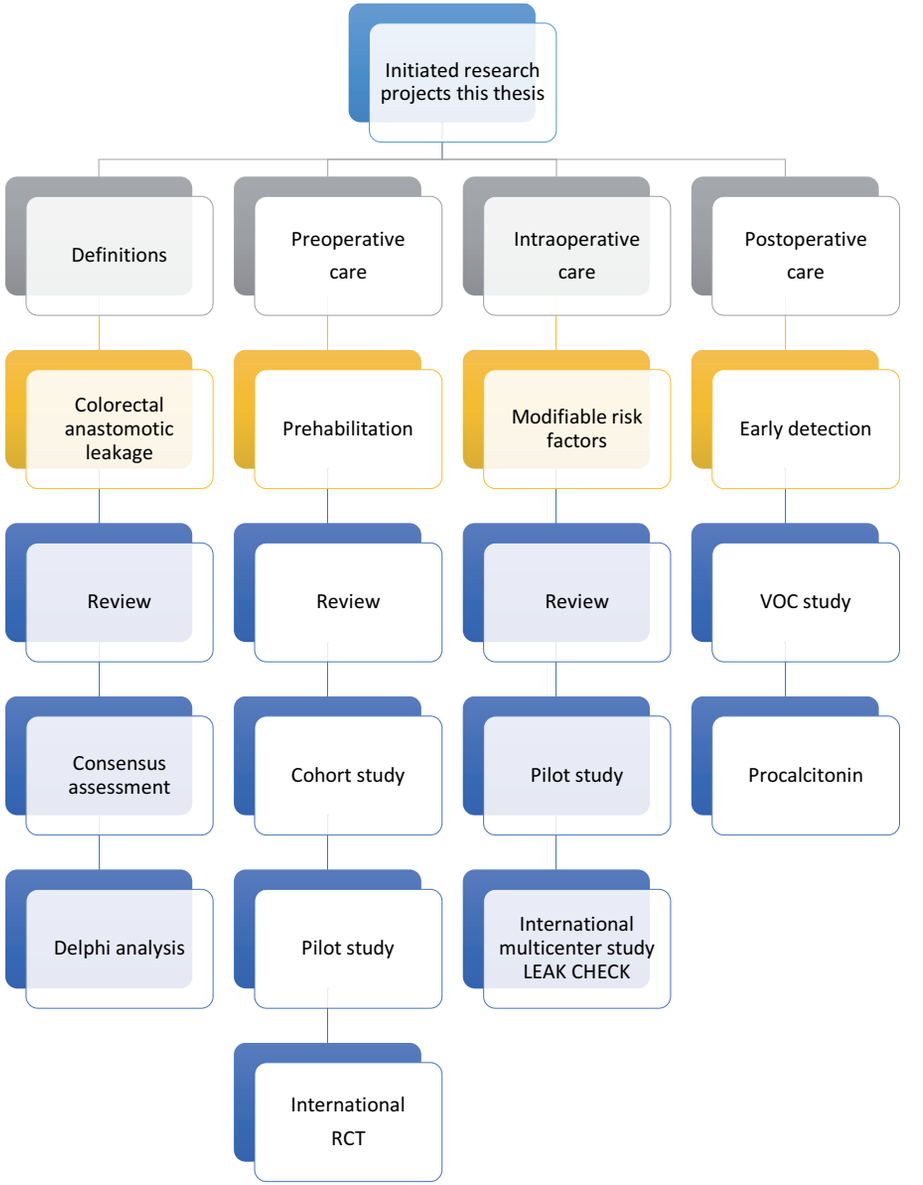
We hebben een deel van onze doelen bereikt door het ERAS-programma te vernieuwen. ERAS 1.0 verwijst naar het optimale herstelprogramma geïntroduceerd door Prof. H. Kehlet aan het eind van de jaren negentig en geïmplementeerd in ons centrum in 2005. Het succes van ERAS was de multimodale aanpak, waarbij tegelijkertijd veel verschillende risicofactoren van complicaties in de perioperatieve zorg werden uitgedaagd. Sindsdien zijn de meest bijdragende veranderingen in colorectaal zorg geweest: de introductie van laparoscopie, verdere differentiatie van chirurgen en de verplichting tot nationale dataregistratie in Nederland (ERAS 2.0). ERAS 3.0 is ons nieuwe doel. De meetstokken omvatten optimale naleving van het ERAS 1.0-programma, de toevoeging van de nieuwste kennis in de perioperatieve zorg, aangevuld met de introductie van de volgende stappen in colorectale zorg: optimale patiëntinformatie en prehabilitatie (ERAS 3.0). We hebben een eerste kans gehad om onze gedachten te delen met het Akershus University Hospital in Oslo, Noorwegen. Dat ziekenhuis werd bezocht om hun behoefte aan verbetering te inventariseren en we organiseerden een tweedaags programma voor hun multidisciplinaire team in ons ziekenhuis MMC om te informeren en te inspireren. Al met al zijn wij overtuigd dat dit ERAS 3.0-concept het continuüm van zorg voor zowel patiënten als zorgprofessionals optimaal zal dienen.

CHAPTER 15

OVERVIEW OF RESEARCH PROJECTS
LIST OF PUBLICATIONS
LIST OF CO-AUTHORS
WORD OF THANKS - DANKWOORD
CURRICULUM VITAE
COLORECTAL PATIENT JOURNEY



OVERVIEW OF RESEARCH PROJECTS



LIST OF PUBLICATIONS

Publications

1. **van Rooijen SJ,** van Workum F, Boll B, Rosman C. Aorto esophageal fistula after minimally invasive esophagectomy with intrathoracic anastomosis: report of 3 cases and review of the literature. Journal of case reports in Medical Science. 2016.

2. Cottaar MEJ, **van Rooijen SJ,** Doomernik D, Tan ECTH. Bilateral acute myotendinous rupture of the rectus abdominis muscle: case report and review of the literature. Annals of Sports Medicine and Research. 2016.

3. **van Rooijen SJ,** Wegdam J, de Vries Reilingh T, Slooter GD. Fitte patiënt voor beter behandelresultaat. Risico op complicaties lager door actieve voorbereiding van darmkankerpatiënt. Medisch Contact. Mei 2016.

4. **van Rooijen SJ,** Huisman D, Stuijvenberg M, Stens J, Roumen RMH, Daams F, Slooter GD. Intraoperative modifiable risk factors of colorectal anastomotic leakage: why surgeons and anesthesiologists should act together. International Journal of Surgery. 2016 Dec;36(Pt A):183-200.

5. **van Rooijen SJ,** Carli F, Oksbjerg Dalton S, Johansen C, Dieleman J, Roumen RMH, Slooter GD. Preoperative modifiable risk factors in colorectal surgery: an observational cohort study identifying the possible value of prehabilitation. Acta Oncologica. 2017 Feb; 56 (2): 329-334.

6. **van Rooijen SJ,** Bosch SL, Braam HJW, Bökkerink GMJ, Nagtegaal ID, de Wilt JHW. Acute toxicity and surgical complications after preoperative (chemo)radiation therapy for rectal cancer in patients with inflammatory bowel disease. Radiotherapy and Oncology. 2017 Apr;123(1):147-153.

7. Stuijvenberg M, Plomp R, **van Rooijen SJ,** Boekema P, Roumen RMH, Slooter GD. Bevolkingsonderzoek naar darmkanker: eerstejaars resultaten uit Máxima Medisch Centrum. Medisch Journaal. April 2017.

8. **van Rooijen SJ,** Carli F, Oksbjerg Dalton S, Johansen C, Dieleman J, Roumen RMH, Slooter GD. Preoperatieve beïnvloedbare risicofactoren voor complicaties na colorectale chirurgie: de waarde van prehabilitatie. Medisch Journaal. Juli 2017.

9. **van Rooijen SJ,** Engelen MA, Scheede-Bergdahl C, et al. Systematic review of exercise training in colorectal cancer patients during treatment. Scand J Med Sci Sports. 2017; 00:1–11.

10. **van Rooijen SJ,** Jongen ACHM, Wu ZQ, Ji JF, Slooter GD, Roumen RMH, Bouvy ND. Definition of colorectal anastomotic leakage: A consensus survey among Dutch and Chinese colorectal surgeons. World J Gastroenterol 2017; 23(33): 6172-6180.

11. Ferreira V, Agnihotram RV, Bergdahl A, **van Rooijen SJ,** Awasthi R, Carli F, Scheede-Bergdahl C. Maximizing patient adherence to prehabilitation: what do the patients say? Supportive Care in Cancer 2018 Feb 24.

12. **van Rooijen SJ,** Carli F, Dalton SO, Thomas G, Bojesen RD, Le Guen M, Barizien N, Awasthi R, Minnella EM, Beijer S, Martinez-Palli G, van Lieshout RHMA, Gogenur I, Feo CV, Johansen C, Scheede-Bergdahl C, Roumen RMH, Schep G, Slooter GD. Multimodal prehabilitation versus regular care in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized trial for multimodal prehabilitation. Accepted BMC Cancer. 2018.

13. **van Rooijen SJ,** Thomas G, Fokkenrood HJP, Roumen RMH, Slooter GD. Prehabilitation versus no prehabilitation to improve functional capacity and reduce postoperative morbidity and mortality in patients undergoing elective colorectal cancer resection. Accepted Cochrane Database of Systematic Reviews 2018.

14. **van Rooijen SJ,** Bruns ERJ, Argillander TE, van der Zaag ES, Grevenstein WMU, van Duijvendijk P, Buskens CJ, Bemelman WA, van Munster BC, Slooter GD, van den Heuvel B. Improving outcomes in oncological colorectal surgery by prehabilitation: a group effort to establish a tailor-made approach. Submitted.

15. **van Rooijen SJ,** Jongen ACHM, Schuermans VNE, Wu Z, Roumen RMH, Slooter GD, Bouvy ND. Use of colorectal anastomotic leakage definitions in literature: results of a systematic review and recommendations for future reporting. Submitted.

16. **van Rooijen SJ,** Dieleman J, Bouvy ND, Slooter GD, Roumen RMH. Perioperative modifiable risk factors for colorectal anastomotic leakage. Submitted.

17. **van Rooijen SJ**, Hartmans SA, Dieleman J, Bouvy ND, Slooter GD, Roumen RMH. Can anastomotic leakage in left sided colorectal surgery be predicted? Submitted.

18. **van Rooijen SJ**, Thomas G, Schep G, van Lieshout RHMA, Beijer S, Dubbers R, Rademakers N, Papen-Botterhuis NE, van Kempen S, Carli F, Roumen RMH, Slooter GD. Making patients fit for surgery: introducing a four pillar multimodal prehabilitation program in colorectal cancer. Submitted.

19. Dutch Snapshot research group. Benchmarking recent national practice in rectal cancer treatment with landmark randomized controlled trials. Colorectal Disease. 2017 Jun;19(6):O219-O231.

20. Dutch Snapshot research group. Anastomotic Leakage and Chronic Presacral Sinus Formation After Low Anterior Resection: Results From a Large Cross-sectional Study. Ann Surg. 2017 Nov;266(5):870-877.

21. Dutch Snapshot research group. The influence of hospital volume on long-term oncological outcome after rectal cancer surgery. Int J Colorectal Dis. 2017 Sep 7.

Awards

2018 Wetenschapsprijs Maxima Medisch Centrum
'Pilot studie prehabilitatie'
2017 Winner 'Best innovation story' Interface Health Society
2017 Prehabilitation data monitoring and value based healthcare project Grant
2017 Nationale Zorginnovatieprijs 2017, nomination
2017 Doctorpreneur Award 2016 VvAA, nomination
2017 Winnaar cliënten jaarprijs Máxima Medisch Centrum
2016 Samsung Bright Virtual Reality Awards, nomination
2016 Koningin Wilhelmina Fonds, research Grant prehabilitation
2016 National Fonds tegen Kanker, research Grant prehabilitation
2016 Metropool Regio Eindhoven, Stimuleringsfonds
2016 Brabantse Ontwikkel Maatschappij, Haalbaarheidssubsidie
2016 Stichting DaDa, innovatiegelden Virtual Reality
2016 NutsOhra, Klein Geluk, innovatiebeurs
2016 Innovation Price, Reshape Center for Innovation and Human Centered Design
2014 Koninklijke Nederlandse Academie voor Wetenschap, research Grant
2011 Dr. E Dekker programma, Hartstichting

Presentations and conferences

2017	Interface Health Summit invited speaker. 'Story of a Dutch Doctorpreneur.'	Vancouver
2017	Worldwide webinar 'Breaking barriers in colorectal laparoscopic adoption: innovations in perioperative management.'	Zurich
2017	European Society of Coloproctology conference. 'Prehabilitation and colorectal anastomotic leakage.'	Berlin
2017	First World surgical prehabilitation conference: to improve postoperative outcome. 'Prehabilitation for abdominal surgery.' Faculty and invited speaker.	Montréal
2017	Health Innovation School. 'Health innovation experiences of a Doctorpreneur.'	Nijmegen
2017	Zorg en ICT congres lezing. 'Why don't we ask patients.'	Utrecht
2017	Chirurgendagen.	Veldhoven
2017	Taskforce Naadlekkage vergadering. 'Colon leakage score en definitie naadlekkage.'	Amstelveen
2017	Staflunch Maxima Medisch Centrum. 'Toekomst Colorectale zorg: Een revolutie met ERAS 3.0 en prehabilitatie.'	Veldhoven
2017	ICT&Health congres. 'Virtual reality voor patiënten.'	Utrecht
2016	European colorectal congress. 'Definition colorectal anastomotic leakage.'	St Gallen
2016	Zorgvisie congres. Gastheer en spreker Thema middag Strategische Positionering in de Zorg. 'Patient Involvement, De toekomst is nu.'	Soesterberg
2016	Prehabilitation McGill University. Audit colorectale zorg en prehabilitatie.	Montréal
2016	St Anna University Hospital. 'Leak Check study' and 'Prehabilitation for colorectal cancer patients.'	Ferrara
2016	Taskforce Naadlekkage vergadering. 'Definitie colorectale naadlekkage.'	Rotterdam
2016	European Society of Coloproctology conference. 'Fit4Surgery: the best start to a great finish.'	Milaan
2016	European Cancer Rehabilitation & Survivorship. 'Prehabilitation for colorectal cancer patients.'	Copenhagen
2016	Stichting Topklinische Ziekenhuizen Lustrum. 'Innovaties vanuit de zorg: Virtual Reality voor patienten.'	Amsterdam
2016	Ingendael Discours, Blommestein Groep, Lezing 'Innovaties voor en door patiënten.'	Château St. Gerlach
2016	Dutch Technology Week. 'Innovatie in de gezondheidszorg.'	Veldhoven
2016	Our Future Health, patients included conference. 'VisitU: welcome home.'	Nijmegen
2016	Chirurgendagen en symposium Taskforce Naadlekkage.	Veldhoven
2016	Wetenschapsavond Máxima Medisch Centrum. Prehabilitatie, perioperatieve beïnvloedbare risicofactoren naadlekkage, resultaten darmkanker bevolkingsonderzoek 2015.	Veldhoven
2016	Taskforce Naadlekkage vergadering. 'LEK CHECK studie'.	Nijmegen
2016	Werkgroep Coloproctologie zuid Nederland. 'Verbetermanagement perioperatieve zorg.'	Kasteel Elsloo
2016	Networks in Anesthesiology and Surgery. Conference perioperative care.	Rome
2015	European Society of Coloproctology conference.	Dublin
2015	Vereniging voor sportgeneeskunde jaarcongres. 'Darmkanker en het potentieel nut van prehabilitatie.'	Eindhoven
2015	Expert meeting prehabilitation.	Montréal
2015	Chirurgendagen.	Veldhoven
2015	Nederlandse Vereniging voor Endoscopische Chirurgie jaarcongres.	Amsterdam
2015	Nederlandse Vereniging voor Gastroenterologie jaarcongres.	Veldhoven
2014	European Society of Surgical Oncology 34th congress. 'Inflammatory bowel disease: neaodjuvant therapy and postoperative complications.'	Liverpool
2014	Chirurgendagen. 'Inflammatory bowel disease: neaodjuvant therapy and postoperative complications.'	Veldhoven
2014	Society of Surgical Oncology conference. 'Acute toxicity and surgical complications after preoperative (chemo)radiation therapy for rectal cancer in patients with inflammatory bowel disease.'	Phoenix

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CURRICULUM VITAE AUCTORIS

Stefanus Johannes van Rooijen was born on September 20th, 1989 in Tiel, the Netherlands; he is the eldest of two. After attending primary school in Maurik, he graduated in 2007 from high school (Atheneum, o.r.s. Lek en Linge, Culemborg). Since an early age, Stefan demonstrated a strong proclivity towards the combination of technology and human interaction. This typical combination urged him to join an education program entitled 'Technical Medicine' (University of Twente, Enschede). After earning his propaedeutics, he became progressively convinced that the medical aspect mattered the most to him, he therefore, decided to pursue medicine as his chosen career. He elected to start his medical school at the Radboud University, Nijmegen. During his Bachelor degree, he noticed that surgery, and oncological surgery in particular, best suited his interests. He started conducting research during the last year of his Bachelor's at the Department of Surgery at the Radboud University Medical Center (Prof. dr. J.H.W. de Wilt, Drs. G.M.J. Bökkerink). During his Master's, he continued his oncological research projects and gained further interest in the combination of technology and human centered design. He started master classes at the REshape Innovation Center (director L.J.L.P.G. Engelen) to further develop his entrepreneurial skills. After graduating medical school in January 2015, he was offered a position as PhD student at the Department of Surgery at Máxima Medical Center (Eindhoven/ Veldhoven) and the Maastricht University Medical Center (Maastricht), the Netherlands (Dr. R.M.H. Roumen, Dr. G.D. Slooter, Prof. N.D. Bouvy). His research focused on improvements in colorectal care, in particular to find practical solutions to lower the morbidity – especially anastomotic leakage – and mortality rates following major oncological surgery and to improve patients' long-term quality of life. From the start of his PhD, he believed in multidisciplinary collaboration and was offered a position on the board of the Dutch Taskforce Anastomotic Leakage (Dr. F. Daams, Dr. M. den Dulk, Dr. M.N. Sosef). He has further developed his fascination and penchant for technology by introducing a patient information application. He has designed a novel and worldwide prehabilitation program based on the needs of patients, together with a research team at the Montréal General Hospital in Canada (led by Prof. F. Carli). The Reshape Center in Nijmegen and Health Innovation Campus in Veldhoven provided Stefan with the right tools to further develop patient directed technologies, such as virtual reality for patients (VisitU and Infor-Med). He is also involved in health innovation as a lecturer at the first Health Innovation School (Ministry of Health, Welfare and Sport and Reshape innovation). At the moment he is working at the Department of Surgery at Máxima Medical Center (ANIOS). Stefan will apply for a resident position in the field of surgical oncology. He is living with his wife Maudi in Eindhoven, the Netherlands.



COLORECTAL CARE:
“GREAT THINGS ARE DONE BY A SERIES OF SMALL THINGS BROUGHT TOGETHER”
-VINCENT VAN GOGH