PREVENTION, EARLY DIAGNOSIS AND TREATMENT OF COMPLICATIONS AFTER COLORECTAL SURGERY

KEVIN TALBOOM

Prevention, early diagnosis and treatment of complications after colorectal surgery

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Prevention, early diagnosis and treatment of complications after colorectal surgery

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General Introduction and Thesis Outline

INTRODUCTION

Colorectal cancer remains one of the most common types of cancer worldwide and still occurs in around 12.000 new cases yearly in the Netherlands, of which 3.200 are rectal cancer.[1] The primary goal in colorectal cancer treatment is to achieve long-term cancer-free survival and in an ideal scenario this has to be achieved without causing too much collateral damage. Oncological outcomes after colorectal cancer surgery have improved in recent decades and therefore focus has shifted to mitigating the negative consequences, such as surgical complications. As a consequence, there is sufficient literature on how to improve oncological outcomes, while evidence remains limited whether complications after colorectal cancer surgery (especially anastomotic leakage) can be prevented and when it does occur, how it can be diagnosed early and treated effectively.

Anastomotic leakage – incidence, presentation and risk factors

Anastomotic leakage (AL) remains one of the most feared complications after low anterior resection (LAR) for rectal cancer and a nationwide cross-sectional study showed an incidence around 20%.[2] Development of AL leads to increased morbidity rates, increased reintervention rates, increased healthcare costs and is associated with worsened functional and oncological outcomes.[3-5] AL can be defined as “a breach in a surgical joint between two hollow viscera, with or without active leak of luminal contents” and symptoms include abdominal/pelvic pain, bloating, nausea, vomiting, fever, tachycardia, blood or pus per anum and signs of peritonitis.[6]

An ileostomy created during index surgery can mask early symptoms of AL and these leaks are often only diagnosed during work-up for stoma closure. Conventionally, there is a fear of an increase in rate and severity of AL after selective diversion. However, in several comparative studies long term stoma-rates are similar and selective diversion prevents creation of unnecessary stomas.[7, 8] Furthermore, up to one third of all stoma’s that are created with temporary intention, become permanent.[9]

The aetiology of AL is complex and multifactorial and is caused by multiple modifiable and non-modifiable risk factors, related to various patient-, tumor- and intraoperative technical characteristics. Among known risk factors are male gender, large tumor size, smoking status, obesity, comorbidities, an unfavorable

microbiome, previous neoadjuvant radiotherapy, poor bowel perfusion, low colo-anal anastomosis, and use of inotropics during surgery.[10, 11]

The location of the surgical site within the boney pelvis, makes it difficult to reach, perform an effective resection and create the perfect anastomosis. Some risk factors are non-modifiable, but some can be addressed. To prevent tension on the anastomosis, additional length of the afferent colon can be obtained by performing a splenic flexion mobilization, which can increase the length of the afferent colon up to 30 centimeters.[12] To assess intraoperative perfusion of the bowel, a new technique called fluorescence angiography (FA) can be used. By injecting indocyanine green (ICG), perfusion of the bowel can be assessed with a near infrared camera and appears to reduce AL-rate.[13]

Some studies suggest that an unfavorable microbiome (the consistency of all microorganisms in the gut) is involved in the development of anastomotic leakage.[14-16] Some *enterococcus faecalis* and *pseudomonas* species can produce collagenase, which impairs wound healing and can be influenced by giving preoperative mechanical bowel preparation and oral antibiotics.

Preoperative anemia

Up to 1 in three patients undergoing surgery for colorectal cancer has a preoperative anemia and can lead to increased morbidity, mortality and decreased convalescence.[17, 18] In oncological patients, development of anemia is multifactorial and is caused by impaired iron absorption, nutritional deficiency and chronic disease from a cytokine mediated disorder. Adequate iron reserves are essential for erythroblast production and is an important component is many other human metabolic enzymes.[19] Iron deficiency, with or without anemia, can lead to fatigue and impaired physical and cognitive outcomes.[20, 21] Despite these serious consequences it is rarely corrected before surgery and leaves room for improvement.

Preoperative iron deficiency anemia can be treated with blood transfusion, erythropoietin stimulating agents (ESA) and iron supplementation. Blood transfusion and ESA are effective at correcting anemia levels, but are less suitable for colorectal cancer patients, because of an increased risk of oncological recurrence[22, 23]. Iron supplementation seems attractive to correct anemia before surgery, but no clear evidence on the optimal treatment strategy in the preoperative setting is available.

Anastomotic leakage - treatment

Whenever AL after rectal cancer surgery occurs, its location also makes it difficult to treat effectively. The presacral abscess is difficult to reach and the anal sphincter hampers passive drainage, causing debris to accumulate in the presacral cavity. Conventional treatment of anastomotic leakage consists of creation of a diverting ileostomy (if not created primarily) and radiological or transanal drainage of any present collections. This treatment is successful in only half of all patients developing AL, and leaves a chronic presacral sinus at 1 year in 9.5%.[2] New emerging treatments include the introduction of endoscopic vacuum therapy (EVT) in which a poly-urethane sponge is placed into the abscess cavity, which is connected to a negative pressure system.[24] This cleans the cavity by suctioning away debris and pus and promotes growth of healthy granulating tissue. After the cavity is clean, it can be closed surgically with transanal sutures, called endoscopic vacuum assisted surgical closure (EVASC).[25, 26]

Early initiation of AL-treatment is important to ensure good results. When a leak it diagnosed in the late postoperative phase, chronic inflammation has often caused fibrosis of the cavity and retraction of the anastomotic edges, which impairs the healing capacity and possibility of reconstruction. To ensure early diagnosis of AL, measurement of C-Reactive protein (CRP) is possibly an effective biomarker. This inflammatory marker can be increased as early as day 3 after primary surgery, and has a negative predictive value of 97% at a cutoff value of 172 mg/l.[27] If CRP is elevated, additional imaging and/or endoscopy can be performed to confirm AL.

THE AIM AND THESIS OUTLINE

In this thesis, several components to prevent, facilitate early detection and treat complications of colorectal surgery were evaluated, including preoperative iron treatment, selective diversion, postoperative imaging, EVT, EVASC and other treatment modalities. A special focus was placed on anastomotic leakage after rectal cancer surgery.

In **chapter 2**, the multifactorial etiology of AL was addressed in a protocol for a multi-interventional program for prevention, early diagnosis and treatment of anastomotic leakage (IMARI-trial).

In **chapter 3**, preoperative iron supplementation was evaluated in the treatment of preoperative iron-deficiency anemia for patients undergoing curative resection for colorectal cancer.

In **chapter 4**, the omission a diverting ileostomy after low anterior resection for rectal cancer was evaluated to ensure that selective diversion could safely be performed, without increasing the incidence and severity of AL. Highly selective diversion is important to enable early diagnosis of AL and subsequent early treatment.

In **chapter 5**, the efficacy of CRP-guided imaging was evaluated to determine if anastomotic leakage could be detected early and effectively.

In **chapter 6**, a protocol is described for the TENTACLE-Rectum study, which aims to develop an AL-severity score and investigate effective treatment strategies for different subgroups of AL.

In **chapter 7**, treatment variety and optimal treatment principles for AL were investigated by asking colorectal surgeons worldwide to participate in a case vignette study. This chapter will be used to guide development of the AL-severity score and subsequent optimal treatment strategies of the study described in **chapter 6.**

In **chapter 8***,* an overview of the different facets of treating AL by performing transanal surgery are presented in a narrative review.

In **chapter 9**, the efficacy and extensive experience over the last decade of performing EVASC to treat AL is evaluated. The development of a proactive treatment strategy for AL is described.

In **chapter 10**, conventional treatment and four proactive treatment strategies are compared in a multicenter cohort study to determine if there is a benefit of increasing treatment intensity for long-term continuity rates.

In **chapter 11**, the literature on EVT (with or without early surgical closure) is evaluated in a systematic review with meta-analysis to determine the efficacy in restoring continuity after developing AL.

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CHAPTER 2

IMARI: multi-Interventional program for prevention and early Management of Anastomotic leakage after low Anterior resection in Rectal cancer patIents: rationale and study protocol

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ABSTRACT

Background: Anastomotic leakage (AL) is still a common and feared complication after low anterior resection (LAR) for rectal cancer. The multifactorial pathophysiology of AL and lack of standardised treatment options requires a multi-modal approach to improve long-term anastomotic integrity. The objective of the IMARI-trial is to determine whether the one-year anastomotic integrity rate in patients undergoing LAR for rectal cancer can be improved using a multi-interventional program.

Methods: IMARI is a multicentre prospective clinical effectiveness trial, whereby current local practice (control cohort) will be evaluated, and subsequently compared to results after implementation of the multi-interventional program (intervention cohort). Patients undergoing LAR for rectal cancer will be included. The multi-interventional program includes three preventive interventions (mechanical bowel preparation with oral antibiotics, tailored full splenic flexure mobilization and intraoperative fluorescence angiography using indocyanine green) combined with a standardised pathway for early detection and active management of AL. The primary outcome is anastomotic integrity, confirmed by CT-scan at one year postoperatively. Secondary outcomes include incidence of AL, protocol compliance and association with AL, temporary and permanent stoma rate, reintervention rate, quality of life and functional outcome. Microbiome analysis will be conducted to investigate the role of the rectal microbiome in AL. In a Dutch nationwide study, the AL rate was 20%, with anastomotic integrity of 90% after one year. Based on an expected reduction of AL due to the preventive approaches of 50%, and increase of anastomotic integrity by a standardised pathway for early detection and active management of AL, we hypothesised that the anastomotic integrity rate will increase from 90 to 97% at one year. An improvement of 7% in anastomotic integrity at one year was considered clinically relevant. A total number of 488 patients (244 per cohort) are needed to detect this difference, with 80% statistical power.

Discussion: The IMARI-trial is designed to evaluate whether a multi-interventional program can improve long-term anastomotic integrity after rectal cancer surgery. The uniqueness of IMARI lies in the multi-modal design that addresses the multifactorial pathophysiology for prevention, and a standardised pathway for early detection and active treatment of AL.

BACKGROUND

Anastomotic leakage (AL) is still a common and feared complication after low anterior resection (LAR) for rectal cancer. A nationwide cross-sectional study with more than 3-years follow-up revealed an overall incidence of 20%[1]. Occurrence of AL leads to significant increase of postoperative morbidity, prolonged hospital stay, increased healthcare costs, and adversely affects oncological and functional outcome with an increased risk of a permanent stoma[2-4]. The underlying aetiology for AL is a complex multifactorial mix of both modifiable and non-modifiable risk factors that relate to various patient- and tumour characteristics, neo-adjuvant protocols and intraoperative technical aspects[1, 5-7]. Examples of modifiable surgical factors include tension on the anastomosis and anastomotic perfusion. Lately, the impact of the gut microbiome on AL has been studied and a pivotal role seems plausible[8, 9].

While better understanding and modification of risk factors will undoubtedly drive AL rates down, the risk will never be completely non-existent as a result of non-modifiable and currently unknown factors. Hence, besides focus on prevention, limiting the impact of AL is equally important and can be achieved by early detection and appropriate management. However, no international consensus exists on a diagnostic pathway for early detection of AL, even though evidence is building for the use of C-reactive protein (CRP) in the early postoperative period[10, 11]. Regarding management of AL, this usually involves a deviating ileostomy if not yet performed primarily, in combination with “passive” drainage of the abscess cavity via transanal or percutaneous route[1, 12]. Using this aforementioned approach, almost half of the leaks do not heal and may require major salvage surgery, including the creation of a permanent stoma[1, 12].

We hypothesised that a multi-interventional program with a focus on prevention, diagnosis and management of AL would improve the one-year anastomotic integrity rate in patients undergoing LAR for rectal cancer. In the IMARI trial, the chosen set of interventions aiming at reduced risk of AL were: (1) mechanical bowel preparation (MBP) with oral antibiotics (AB) to optimise the microbiome [13-16]; (2) splenic flexure mobilization to optimise a tension-free anastomosis[17]; (3) intraoperative real-time fluorescence angiography (FA) using indocyanine green (ICG) to assess adequate perfusion[18, 19]. These preventive measures are combined with clinical pathways for early detection and “active” management of AL. Serial CRP measurements in the early postoperative period in combination with a CT-scan with rectal contrast will be employed for early detection. On confirmation of AL, endoscopic vacuum-assisted closure therapy (EVAC) of the abscess

cavity is initiated to control pelvic sepsis followed by early transanal closure or restorative re-do surgery to restore anastomotic integrity. This quality controlled multi-interventional program will be implemented within existing institutional enhanced recovery programs and prehabilitation initiatives.

METHODS

This study protocol is written in accordance with the SPIRIT guidelines[20, 21] and the SPIRIT checklist is provided in Appendix 1

Study objectives

The primary objective of this study is to determine whether the one-year anastomotic integrity rate in patients undergoing LAR for rectal cancer can be improved using a multi-interventional program which includes: (1) MBP/AB; (2) tailored full splenic flexure mobilisation; (3) intraoperative FA using ICG; (4) routine CRP measurements postoperatively and CT-scan with rectal contrast on indication; (5) EVAC with early transanal closure of the anastomotic defect or restorative re-do surgery.

Secondary objectives include the evaluation of the multi-interventional program on the AL rate and quality of life until one year after the index operation, and the establishment of the IMARI biobank. The rationale for sample collection in the IMARI biobank is to investigate the role of the rectal microbiome in AL.

Study design

The IMARI trial is a multicentre prospective clinical effectiveness trial, whereby current local practice (control cohort) will be evaluated, and subsequently compared to results after implementation of the multi-interventional program (intervention cohort). The flow diagram for the study is shown in figure 1.

Ethical consideration

The trial will be conducted according to Good Clinical Practice guidelines and the principles of the declaration of Helsinki (2013)[22]. This study is approved by the Medical Ethical Committee and Biobank committee of the Amsterdam UMC, location AMC. The protocol is registered by the Dutch Central Committee on Research Involving Human Subjects (NL67600.018.18) and is submitted to the trialregister.nl database (NL8261).

Study population

Eligibility criteria for study participation are: (1) planned to undergo LAR for either one of the following diagnoses: a) primary rectal cancer as defined by the international consensus definition for rectal cancer[23] or b) regrowth of rectal cancer in a watch and wait protocol or c) completion/salvage surgery after local excision for rectal cancer; (2) willing to complete quality of life questionnaires and comply with schedule of outpatient follow-up visits; (3) ≥ 18 years old.

A subject is not eligible for inclusion in case of presence of one of the following exclusion criteria: (1) LAR without colorectal or coloanal anastomosis; (2) locally advanced rectal cancer, expected to require beyond-total mesorectal excision approach or multi-visceral excision; (3) synchronous colonic resections.

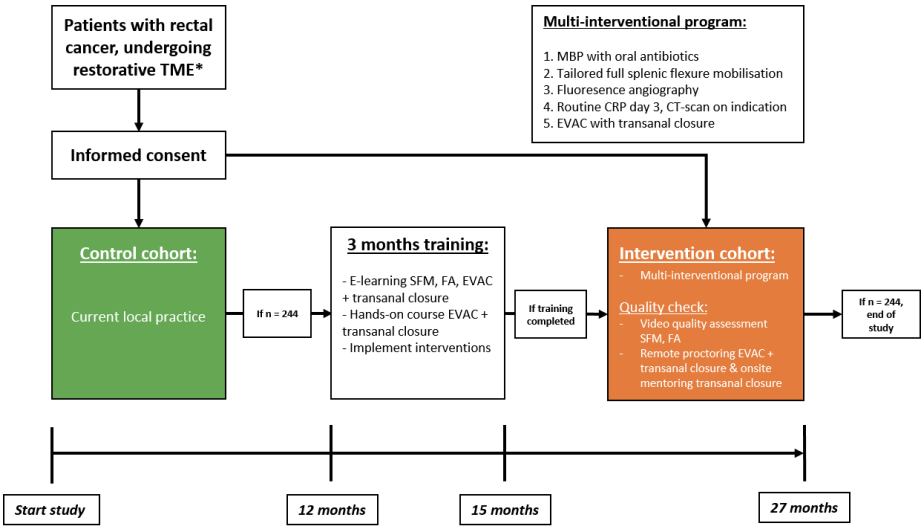

Figure 1: Flow diagram study. MBP, Mechanical Bowel preparation; CRP, C-reactive protein; CT, computed tomography; EVAC, endoscopic vacuum-assisted closure; FA, Fluorescence angiography; SFM, Splenic flexure mobilisation; TME, Total Mesorectal Excision.

Informed consent procedure

Patients meeting all eligibility criteria stated above will be informed on the trial at the outpatient clinic by a member of the research team. Written informed consent will be obtained for participation in the trial and separate consent obtained for storage of samples in the IMARI biobank. Every included patient will be assigned a three-digit study number and only local sites have access to a decryption code.

Study Outline

Control cohort

The study will start in all participating hospitals with accrual into the control cohort, whereby patients will receive care according to standard local protocol. The local protocol may well include one or more components of the multi-interventional program and this will be recorded in the case-report form (CRF) for each patient.

Intervention cohort

When accrual of the control cohort has been completed (n=244, figure 1), all participating hospitals will start a training period of 3 months before implementation of the multi-interventional program and accrual of patients into the intervention cohort. A standardised protocol for MBP/AB and postoperative surveillance of patients for AL will be distributed among centres, enabling timely implementation before start of the intervention cohort. Staff from participating centres will be trained via online educational modules and hands-on training sessions on tailored splenic flexure mobilization, intraoperative FA and EVAC management of AL combined with early surgical closure of anastomotic defects. Random checks of procedural videos and use of a system for remote proctoring will be employed to ensure quality control throughout the entire trial period.

Multi-interventional program:

1. Mechanical bowel preparation with oral antibiotics

MBP will start the day before surgery by oral administration of 2 liters of polyethylene glycol (Moviprep©) or sodium phosphate. Based on the results from the SELECT-trial[24] and unpublished work from the pre-caution trial[25], 10ml of selective digestive decontamination (SDD) solution will be administered four times daily during the three days prior to surgery. The SDD suspension (10ml) will contain: colistine 100 mg, tobramycine 80 mg and amphotericine B 500 mg.

2. Tailored full splenic flexure mobilization

For low rectal cancers, defined according to the LOREC definition, a full splenic flexure mobilisation is mandatory[26, 27]. For all other rectal cancers a full splenic flexure mobilisation is at the discretion of the operating surgeon. Full splenic flexure mobilisation entails the following essential and mandatory steps: (1) division of the inferior mesenteric vein at the lower border of the pancreas just lateral to the angle of Treitz; (2) full release of the distal transverse colonic mesentery from the body and tail of the pancreas; (3) division of the gastro-colic

ligament to release omentum from distal transverse colon. These steps can be completed either in a medial to lateral or lateral to medial approach

3. Intraoperative fluorescence angiography using indocyanine green

Intraoperative FA using ICG will be performed in all patients before and after construction of the anastomosis using a standard intravenous injection of ICG (0.1mg/kg/bolus). Near infrared imaging can be performed by different imaging platforms, and all relevant FA characteristics will be recorded in the CRF. The first assessment is done after rectal mobilisation, but prior to bowel division. The proximal colon will be assessed under conventional white light and the point of planned transection will be marked. Subsequently, FA will be performed using either an intracorporeal or extracorporeal FA technique. The decision whether or not to change the planned anastomotic site will be made according to the surgeon's subjective interpretation of FA.

Anastomotic reconstruction is performed according to the surgeon's preference, followed by an intracorporeal or intraluminal FA assessment of the anastomosis after a second bolus of ICG. Any anastomotic revision, or additional manipulation of the anastomosis (i.e. sutures) will be recorded. The creation of a deviating stoma will be at the surgeon's discretion. A third dose of ICG is allowed, if deemed necessary by the operating surgeon.

4. Routine CRP measurement

CRP measurement will be performed routinely on day 3 postoperatively. A CRP level above the threshold of 172mg/l[10], combined with any clinical aberrant observations, will trigger a CT Abdomen with rectal contrast. Otherwise, CRP measurement will be repeated at day 4 postoperatively. In case of a stable or higher CRP level, a CT abdomen with rectal contrast will be performed to exclude AL, irrespective of clinical findings. Any extraluminal air and/or fluid at the level of the anastomosis will at least be considered as suspicious of AL based on CT, requiring further investigation. Any extravasation of contrast will be defined as clear AL. The algorithm for clinical decision making according to CRP level is displayed in figure 2.

5. Endoscopic vacuum-assisted drainage with early transanal closure of the anastomotic defect

When the CT-scan reveals clear AL, clinical management depends on the presence of a primary diverting stoma. If not created primarily, a diverting ileostomy will be constructed with abdominal lavage in case of purulent or fecal peritonitis, preferably using a laparoscopic approach, and combined with intraoperative

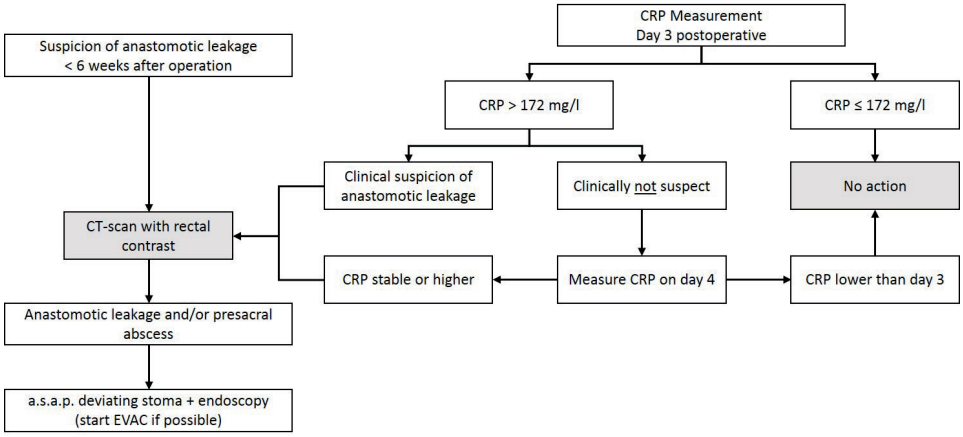

Figure 2: Flow diagram postoperative algorithm.

endoscopic assessment of the anastomosis with EVAC if indicated. In patients with primary diversion, endoscopic assessment of the anastomosis can be performed under general anaesthesia, especially if surgical management of peritonitis is required, or under sedation at the endoscopy room. For a pelvic fluid collection on CT without any obvious extraluminal contrast, an endoscopy is preferred as first step to assess whether an actual defect can be identified before return to theatre for diversion. At endoscopy, potential signs of ischaemia and characteristics of the anastomotic defect (extent circular dehiscence, retraction) will determine further steps to control pelvic sepsis (figure 3).

Patients deemed suitable for EVAC will have endosponge exchanges every 3-4 days, with assessment of the anastomotic defect and associated cavity by the gastroenterologist and/or surgeon. Usually after two to four endosponge exchanges, the anastomotic defect should be ready to be closed transanally as previously described[28-30]. The transanal closure will be checked by endoscopy two weeks postoperatively. If no defect is identified at endoscopy, a further assessment will follow by CT with rectal contrast. At the time of endoscopy a CRP check will also be included.

If the initial endoscopic evaluation reveals ischaemia or significant retraction of the afferent colon, a different pathway will be followed: (1) early or late re-do of the anastomosis, with use of EVAC for initial control of pelvic sepsis; or (2) take down of the anastomosis; preferred technique will be intersphincteric resection of the rectal remnant, permanent colostomy and filling of the pelvis with an omentoplasty.

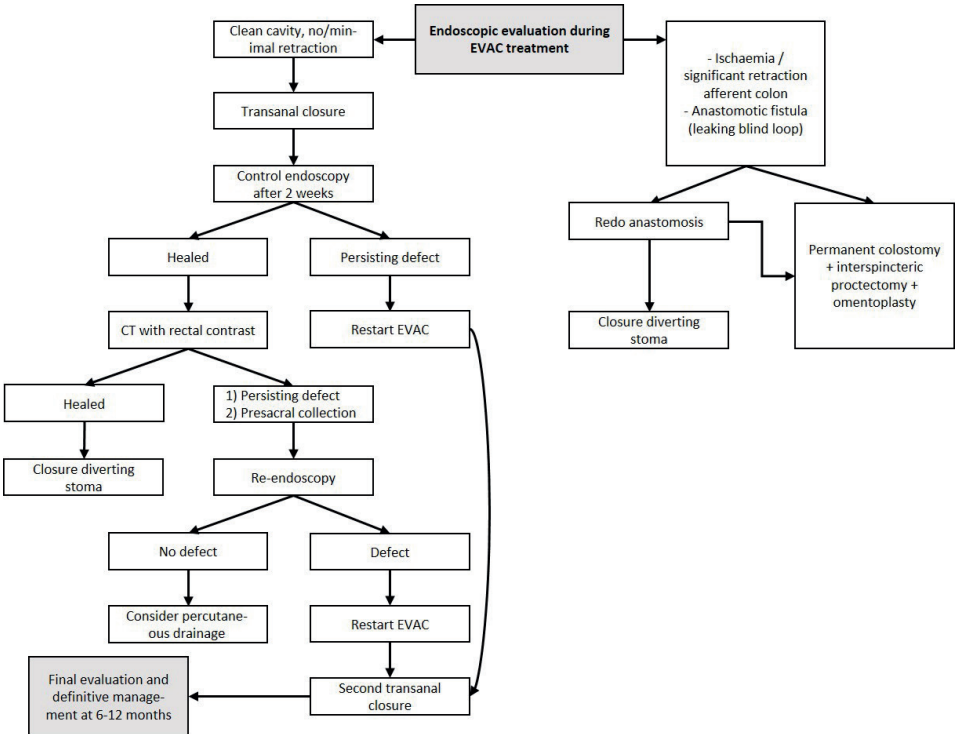

Figure 3: Flow diagram pro-active leak management.

At any point in time, participating centres can contact the initiating centre for advice, assessment of endoscopy images and the most appropriate further step in management of the AL and sepsis.

Outcomes

The primary outcome of this study is anastomotic integrity one year after the index operation. This will be determined in all included patients by CT-scan at one year as part of regular follow-up of patients after rectal cancer surgery[31].

Secondary outcomes include: (1) incidence of AL within 30 days, 90 days, and one year post-operative; (2) protocol compliance to any intervention; (3) protocol compliance in association to AL; (4) changes in rectal microbiome and association with AL; (5) permanent stoma rate; (6) temporary stoma rate and total time of having a stoma during one year; (7) length of hospital stay after index surgery and total stay during one year; (8) overall and stoma-related readmission and reintervention rates; (9) quality of life (EQ-5D, QLQ-C30, QLQ-CR29); (10) bowel, urinary and sexual function (LARS, UDI-6, IIQ-7, IIEF for male and MFSFQ for female)

pre-operatively, at 90 days and one year; (11) diagnostic accuracy of serial CRP at day 3-4; (12) efficacy of EVAC with early transanal closure of the anastomotic defect; (13) change of management related to FA: site of proximal bowel division used for anastomosis, re-do anastomosis, reinforcement of anastomosis after construction, decision for diverting stoma, or decision for a non-restorative procedure; (14) operative and post-operative complications within 90 days of index surgery; (15) 1-year local recurrence and overall survival rate.

To assess the rectal microbiome, the following samples are collected for the IMARI biobank: stool samples before start MBP/AB and at day 4 postoperative, the anastomotic donut (colonic side) from the operation, intraoperative rectal swab from the anastomotic site, and for patients that develop AL an endoscopic rectal swab from the abscess cavity. Samples will be stored centrally in the IMARI biobank at the Tytgat Institute in the Amsterdam UMC, location AMC. Microbiota profiling will be done using an Illumina Miseq platform. In addition, metatranscriptomics will be performed on selected samples to look for presence and activity of collagenolytic Enterococcus faecalis and additional detrimental species for anastomotic integrity. Collection points of all outcomes are summarised in Table 1.

Sample size calculation

In a Dutch nationwide study, the AL rate was 20%, with anastomotic integrity of 90% after one year[1]. Meta-analysis of MBP/AB revealed that preoperative antibiotics were associated with lower AL rates (OR 0.59, 0.53-0.67; p<0.001)[14]. Pooled analysis of studies using routine FA showed an OR of 0.34 (0.16-0.74;p=0.006)[18]. Together with full splenic flexure mobilisation, the estimated reduction in AL rate is 50%. In the CLEAN-study, treatment with EVAC and early surgical closure resulted in anastomotic healing in two thirds of the patients within the first year[32]. Therefore, we hypothesised that the combination of all interventions will increase the anastomotic integrity rate from 90% to 97% at one year. Applying a Fisher exact test with a two-sided 0.05 significance level and 80% power, and with an estimated drop-out of 10%, a total number of 488 patients (244 per cohort) are needed to be able to detect a 7% increase in anastomotic integrity by implementation of the combined interventions.

Statistical analysis

The primary endpoint, anastomotic integrity, will be compared between the two trial cohorts using a two-sided Fisher exact test. AL rates will be compared

Table 1: Timing of enrollment, interventions and assessments. IC, informed consent.

	Study period										
	Preoperative					**Postoperative**					
TIMEPOINT *Days in relation to primary resection*	**Pre IC**	**- x**	**- 3**	**-1**	**0**	**1**	**3**	**4**	**+ x**	**90**	**365**
Enrolment											
Eligibility screen	X										
Information	X										
Informed consent	X										
Interventions *(only during intervention cohort)*											
MBP				X							
Oral AB			●	●							
SFM					X						
FA					X						
CRP-measurement							X				
EVAC + transanal closure									X		
Assessments											
Baseline variables		X									
Follow-up variables					X				X	X	X
Microbiome samples		X			X	X		X	X		
Quality of Life questionnaires		X								X	X
Abdominal CT									X		X

between the cohorts using generalised estimating equations model adjusting for stratification factors. This approach will be used to test the two-sided hypothesis that the AL rate is equal in both cohorts (i.e. an odds ratio of 1), considering the 95% confidence interval and a p-value of 0.05. Other secondary endpoints with binary measures will be analysed using multi-variable logistic regression adjusting for stratification factors. Secondary endpoints with continuous measures will be analysed using linear regression models adjusting for stratification factors. When the data is not normally distributed, the data will be transformed to achieve normal distribution. The secondary endpoint 'duration of temporary stoma' will be analysed using a cox-regression model with adjusting for stratification factors. Quality of life and function outcome will be calculated as domain and summarised scores according to the manuals, and graphically represented across all time points. Comparisons of questionnaire outcomes will be analysed using linear mixed models. Statistical analyses will be performed using the latest version of SPSS software for Windows.

The statistical analysis plan will be finalised before data is locked for analysis, and decision will be made on stratification factors and planned subgroup analysis, and on how to deal with application of components of the multi-interventional program in the control cohort, protocol violations, and baseline imbalance.

Safety reporting

This IMARI trial is considered a low-risk study, because any of the interventions are already being used in routine daily practice. Serious adverse events will not be reported for the control cohort, since patients will receive standard care. Serious adverse events will be recorded until 30 days after index surgery or any study related procedure for the intervention cohort.

Data handling and monitoring

Data will be digitally collected using the electronic data management system Castor EDC (www.castoredc.com). In all participating hospitals, one surgeon acts as local investigator who is primarily responsible for execution of trial interventions, and for accuracy and completeness of the CRF. Quality of life questionnaires will be collected through the data collection initiative of the Prospective Dutch ColoRectal Cancer (PLCRC) group (clinicaltrials.gov NCT02070146). This study will be monitored as described in a monitoring plan by an independent monitor to ensure quality and adherence to the protocol. If patients are only willing to participate in the IMARI-trial, questionnaires will be collected by the investigators

Public disclosure and publication policy

IMARI was registered at the trialregister.nl database (NL8261). The results of IMARI will be submitted to a peer-reviewed journal regardless of study outcome. Co-authorship will be based on the international ICMJE guidelines. Besides the key authors (coordinating investigators as first authors and principal investigators as senior authors), authorship is granted to the local investigator of each centre when at least ten patients are included in the trial and when substantial contribution to the trial is made.

DISCUSSION

In contrast to improvements over the last decades regarding oncological outcomes after rectal cancer surgery, AL and ensuing long-term sequelae remain common. A cross-sectional study in the Netherlands revealed an AL rate of 20% after long-term follow-up, with nearly half of AL not healing and giving rise to a chronic sinus. In the IMARI trial we propose a multi-interventional program, not only being designed to reduce AL, but also to increase the chance of long-term anastomotic integrity. The uniqueness of the IMARI trial lies in the multi-modal design that addresses the multifactorial pathophysiology, early detection and active treatment of AL.

Thus far, many risk factors have been associated with AL and a complex multifactorial pathophysiology has emerged[1, 5-7, 9]. Most interventional studies up till now only evaluated the impact of a single risk factor on AL[17, 24, 33, 34]. The IMARI trial addresses three modifiable risk factors to ensure a tension-free, adequate perfused anastomosis, under optimal condition of the microbiome: (1) MBP/AB that could lead to a reduction in AL by reduction of the fecal bulk and bacterial load [13-16]; (2) Splenic flexure mobilization to optimise a tension-free anastomosis, particularly for low rectal cancer[17, 35]; (3) Intraoperative real-time FA using ICG to assesses adequate perfusion of the afferent colon and anastomosis. Routine use of this FA technology has been associated with reduced AL rates, although no data from large randomised controlled trials (RCT) are available[18, 19].

If AL occurs, prompt detection is crucial to allow for immediate treatment initiation and control of pelvic sepsis. Rapid sepsis control avoids further morbidity and should also limit long-term functional sequelae. Although transanal and/or radiological transgluteal drainage of pelvic sepsis does allow for some degree of sepsis control, leakage is not actively treated and the anastomotic defect is not likely to heal spontaneously. In contrast, after 2-4 EVAC exchanges, which takes approximately 1-2 weeks, well vascularised granulation tissue is often visible inside the cavity. This allows for subsequent transanal closure of the anastomotic defect with a suction drain positioned behind the anastomosis with its tip inside the cavity, after which the cavity collapses and the neo-rectum expands[30, 32]. As such, EVAC in combination with early transanal closure allows for a more active, rapid control of pelvic sepsis and at the end mucosal approximation. This pathway should allow for more anastomoses to be preserved, prevent chronic presacral sinuses and improve functional outcomes by limiting peri-anastomotic fibrosis with preservation of compliance of the neo-rectum.

Even though RCTs are considered the most robust research strategy for establishing a causal relationship, a comparative cohort design was chosen for the IMARI trial. In the setting of a classical RCT, contamination is likely to occur in the control arm. Surgeons are likely to change their daily practice, when observing benefits from the multi-interventional program. We consider this also a problem in a stepped-wedge cluster RCT, a frequently used variant of a classical RCT. Thus, a comparative cohort design was selected in the form of a prospective clinical effectiveness trial, where crossover to the intervention cohort occurs after completion of accrual in the control cohort. Participating centres will simultaneous start recruitment for the intervention arm, after completion of a 3 month training period. Furthermore, in the set-up of a clinical effectiveness trial the true impact of utilising the multi-interventional program can be evaluated under real conditions[36].

For the purpose of the IMARI trial, a multidisciplinary scientific study-group was composed, including surgeons from both academic and peripheral centres, gastroenterologists, radiologists, specialised nurses and researchers. In this way hospital-wide awareness is created and a broadly supported multi-modal approach was made possible.

Successful implementation of the IMARI multi-interventional program within existing enhanced recovery and prehabilitation programs would have a positive influence on morbidity, mortality, and possibly oncological outcomes. By increasing the chance of long-term anastomotic integrity and decreasing permanent stoma rates, the IMARI trial should contribute to a better quality of life for patients undergoing rectal cancer surgery.

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CHAPTER 3

Ferric carboxymaltose infusion versus oral iron supplementation for preoperative iron deficiency anaemia in patients with colorectal cancer (FIT): a multicentre, open-label, randomised, controlled trial

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ABSTRACT

Background: A third of patients with colorectal cancer who are eligible for surgery in high-income countries have concomitant anaemia associated with adverse outcomes. We aimed to compare the efficacy of preoperative intravenous and oral iron supplementation in patients with colorectal cancer and iron deficiency anaemia.

Methods: In the FIT multicentre, open-label, randomised, controlled trial, adult patients (aged 18 years or older) with M0 stage colorectal cancer scheduled for elective curative resection and iron deficiency anaemia (defined as haemoglobin level of less than 7·5 mmol/L (12 g/dL) for women and less than 8 mmol/L (13 g/dL) for men, and a transferrin saturation of less than 20%) were randomly assigned to either 1-2 g of ferric carboxymaltose intravenously or three tablets of 200 mg of oral ferrous fumarate daily. The primary endpoint was the proportion of patients with normalised haemoglobin levels before surgery (≥12 g/dL for women and ≥13 g/dL for men). An intention-to-treat analysis was done for the primary analysis. Safety was analysed in all patients who received treatment. The trial was registered at ClincalTrials.gov, NCT02243735, and has completed recruitment.

Findings: Between Oct 31, 2014, and Feb 23, 2021, 202 patients were included and assigned to intravenous (n=96) or oral (n=106) iron treatment. Treatment began a median of 14 days (IQR 11-22) before surgery for intravenous iron and 19 days (IQR 13-27) for oral iron. Normalisation of haemoglobin at day of admission was reached in 14 (17%) of 84 patients treated intravenously and 15 (16%) of 97 patients treated orally (relative risk [RR] 1·08 [95% CI 0·55-2·10]; p=0·83), but the proportion of patients with normalised haemoglobin significantly increased for the intravenous treatment group at later timepoints (49 [60%] of 82 vs 18 [21%] of 88 at 30 days; RR 2·92 [95% CI 1·87-4·58]; p<0·0001). The most prevalent treatment-related adverse event was discoloured faeces (grade 1) after oral iron treatment (14 [13%] of 105), and no treatment-related serious adverse events or deaths were observed in either group. No differences in other safety outcomes were seen, and the most common serious adverse events were anastomotic leakage (11 [5%] of 202), aspiration pneumonia (5 [2%] of 202), and intra-abdominal abscess (5 [2%] 202).

Interpretation: Normalisation of haemoglobin before surgery was infrequent with both treatment regimens, but significantly improved at all other timepoints following intravenous iron treatment. Restoration of iron stores was feasible only with intravenous iron. In selected patients, surgery might be delayed to augment the effect of intravenous iron on haemoglobin normalisation.

Research in context

Evidence before this study

We searched PubMed using the terms ("intravenous iron" OR "oral iron") AND "anaemia" AND "surgery" with no language or date restrictions on June 1, 2022. Previous studies were mainly done in orthopaedic and cardiac surgeries and focused on reducing allogenic blood transfusion. This might not be a relevant outcome in colorectal surgery because the incidence of transfusion is low and is more likely to be associated with the complexity of the surgery rather than the preoperative haemoglobin level. Transfusion is also less suitable for patients with colorectal cancer because it is associated with cancer recurrence. A 2019 Cochrane review including six randomised controlled trials (RCTs) was difficult to interpret due to the large heterogeneity in iron regimens, the inclusion of patients with and without anaemia, and the use of thresholds for haemoglobin normalisation other than those recommended in WHO guidelines. An RCT from 2000 comparing intravenous iron and placebo for major abdominal surgery included a wide variety of indications, hampering extrapolation of the results to daily practice. The efficacy of intravenous versus oral iron in patients with colorectal cancer and with iron deficiency anaemia currently remains unknown.

Added value of this study

This study is the first RCT to provide data on the efficacy of intravenous and oral preoperative iron supplementation in patients with colorectal cancer to improve preoperative haemoglobin levels and iron stores, together with clinical outcome variables (eg, complications, reinterventions, and postoperative stay). The results show that both intravenous and oral iron do not normalise haemoglobin levels just before surgery, but intravenous iron increases haemoglobin levels significantly more effectively during follow-up. Only intravenous iron was shown to be able to reverse iron deficiency, and in patients with mild anaemia, the rate of postoperative reinterventions and admission to intensive care units were lower after intravenous iron compared with oral iron, indicating that sufficient iron stores might be more important than haemoglobin levels.

Implications of all the available evidence

In the FIT study, the increased haemoglobin levels, restored iron stores, and improved clinical outcomes observed postoperatively in a well defined group of patients with colorectal cancer after intravenous iron compared with oral iron suggest a potential benefit of intravenous iron preoperatively. Other available literature is indefinite due to heterogeneity in study design and outcomes. Restoration of iron stores is feasible with intravenous iron, justifying intravenous iron infusion as part of a prehabilitation programme for patients undergoing colorectal surgery to reduce postoperative negative sequelae. In selected patients, surgery might be delayed for 3 weeks to augment the effect of intravenous iron on haemoglobin normalisation.

INTRODUCTION

Preoperative anaemia affects up to one third of patients undergoing resection for colorectal cancer.[1, 2] Despite the increased risk of mortality, length of stay and complications associated with preoperative anaemia, it is unclear if correction of anaemia produces a corresponding correction in the associated risk to patients in terms of perioperative morbidity.[3-6]

Cancer-related anaemia is a multifactorial problem caused by impaired iron absorption from the gut, impaired iron availability, blood loss and deficiency of multiple nutrients.[7] Iron-deficiency anaemia is the most common type of anaemia in colorectal cancer patients.[8, 9] Having sufficient iron stores is necessary for adequate erythropoiesis and is an essential component of many other metabolic enzymes involved in basic cellular processes and mitochondrial function.[10-12]

Preoperative iron-deficiency anaemia can be treated with iron supplementation. Despite the association of anaemia with adverse outcomes of colorectal surgery, there is relative undertreatment of preoperative iron deficiency anaemia.[3-6] A possible explanation for this is that the need for acute perioperative blood transfusion is only around 4% in colorectal cancer surgery.[2] However, even a mild preoperative anaemia is associated with an increased risk of morbidity and 30-day mortality.[6, 13] Iron deficiency can also occur in the presence of normal haemoglobin (Hb) levels, causing fatigue and impaired physical and cognitive functioning.[11, 12] Another explanation for the undertreatment of iron anaemia may be that the time until surgery is perceived to be insufficient for preoperative optimization of Hb levels. Intravenous (IV) iron increases Hb levels faster than oral iron supplementation, but requires an infusion, sometimes necessitating an extra hospital visit. Studies in other surgical populations have shown that Hb-normalisation can be accomplished in a few weeks in patients scheduled for gynaecological surgery.[14]

A recent Cochrane review comparing different iron regimes found no clear advantage of any type of iron treatment, but was difficult to interpret due to heterogeneity in design of the included studies.[15] A recent RCT comparing IV iron and placebo for major abdominal surgery found no difference in postoperative blood transfusions. [16] One RCT comparing IV iron and usual care in patients undergoing major abdominal surgery found lower blood transfusion rates after IV iron.[17] Both included a wide variety of indications, which makes it difficult to extrapolate results to specific patient groups. Colorectal cancer patient undergoing surgery are specifically at higher risk of having specific iron-deficiency

anaemia, especially right-sided tumours, and have additional issues with oral iron absorption. One RCT comparing oral and IV iron in anaemic colorectal cancer patients found no difference in blood transfusion rates, but did find that IV iron resulted in restored iron stores and correction of anaemia, but this study used different cut-offs for anaemia and also included patient without iron-deficiency.[18]

There is no strong evidence regarding the efficacy of iron supplementation in patients with colorectal cancer who have a narrow preoperative time period, and there is no consensus on the optimal treatment strategy in the preoperative setting. We therefore aimed to compare the efficacy of intravenous and oral iron supplementation for correction of anaemia in patients with iron deficiency anaemia before elective colorectal cancer surgery. We hypothesised that intravenous iron would lead to a higher percentage of patients with a normalised haemoglobin level (≥7·5 mmol/L [12 g/dL] for women and ≥8 mmol/L [13 g/dL] for men) at the day of surgery, compared with oral iron.

METHODS

Study design and participants

FIT was an international, multicentre, open-label, randomised, controlled superiority trial, done in 14 centres in the Netherlands and one centre in Italy (appendix p 18), investigating which type of iron administration is superior in the treatment of iron deficiency anaemia in patients with colorectal cancer undergoing surgery. Details on the protocol were published earlier.[19] Available literature at the time of conception of this study appeared to show a benefit of both oral and intravenous iron, and we considered it unethical to include a placebo group that would withhold optimal treatment from these patients. Ethical approval was gained before this trial from the medical ethical committee of Amsterdam UMC, location University of Amsterdam, and from all local ethical committees in participating centres. All patients provided written informed consent before trial participation.

Patients aged 18 years or older were eligible if planned for curative resection for M0 stage colorectal cancer and with a proven iron deficiency anaemia, without the need for immediate blood transfusion according to local protocol. Iron deficiency anaemia was defined as haemoglobin level of less than 7·5 mmol/L (12 g/dL) for women and less than 8 mmol/L (13 g/dL) for men,[20] and a transferrin saturation of less than 20%. Exclusion criteria were palliative surgery or metastasised

disease; blood transfusion within 1 month before screening; serum ferritin more than 800 µg/L; pregnancy; contraindication to use ferric carboxymaltose or ferrous fumarate; American Society for Anesthesiology classification score of more than 3; the use of erythropoietin stimulating drugs within 3 months before screening; chronic kidney disease (glomerular filtration rate <30 mL/min per 1·73 m2); myelodysplastic syndrome; elevated liver enzymes (>3 times the normal value); hereditary hemochromatosis; thalassaemia; and haemolytic anaemia or chronic haemolysis. Detailed inclusion and exclusion criteria are shown in the appendix (p 2).

Randomisation

Patients were screened, informed, and asked to sign informed consent in the outpatient clinic of the participating centre by local study personnel. Patients were then computer randomised (1:1) in random block sizes of two or four for either intravenous or oral iron with an online web-based tool (Alea) by the study personnel at the initiating study site. Randomisation was stratified for age, colon or rectal carcinoma, open or laparoscopic operation, and baseline haemoglobin levels (5·0–6·2 mmol/L [8–10 g/dL] vs 6·3–8·0 mmol/L [10–13 g/dL]). Patients and treating physicians were not masked to the outcome of the randomisation, because it was not deemed feasible.

Procedures

Details of the study procedures are in the appendix (p 2). Iron treatment was initiated as soon as possible following randomisation. Patients who received ferric carboxymaltose were given doses according to the summary of product characteristics depending on bodyweight and haemoglobin level. Patients with severe anaemia (haemoglobin ≤6·2 mmol/L [10 g/dL]) received a dose of 1500 mg if their weight was 35–70 kg and 2000 mg if it was more than 70 kg. Patients with mild anaemia (haemoglobin >6·2 mmol/L [10 g/dL]) received a dose of 1000 mg if their weight was 35–70 kg and 1500 mg if it was more than 70 kg. A maximum of 1000 mg was given per week as per package inserts, and if a second infusion was necessary, this was planned at least 1 week apart. The first infusion consisted of 1000 mg and the second infusion the remainder of the dose. Intravenous iron was given in a short-stay setting or colon care unit and infused over 15 min under supervision of a physician or registered nurse. Patients who received the oral iron treatment received three 200 mg ferrous fumarate tablets daily from randomisation until the day before surgery, and patients were asked about medication adherence at admission. The planned surgery was not postponed for intravenous or oral iron treatment. When patients were randomly

assigned to receive oral iron remained anaemic after surgery, the oral iron treatment was continued.

Clinical outcome data were collected preoperatively, during admission, and at 30 days and at 6 months postoperatively. Patients received health-related quality of life and fatigue questionnaires (EQ-5D, EORTC-C30, EORTC CR29, the iMTA Medical Consumption Questionnaire, and the iMTA Productivity Cost Questionnaire at baseline, 4 weeks, and 6 months, and Brief Fatigue Inventory at baseline, admission, 2 weeks, 4 weeks, 3 months, and 6 months). Blood samples to assess haemoglobin and iron values were taken at baseline, admission, and at day 1 and 7 postoperatively, and after 1, 2, and 3 months. All measurements were done by local laboratories. All serious adverse events that were possibly related to the protocol treatment were reported to the coordinating investigator within 24 h and reported to the regulatory authorities. All other adverse events were recorded in the case report form. Adverse events were classified as Common Terminology Criteria for Adverse Events (version 5).

Outcomes

The primary outcome of this study was the proportion of patients whose haemoglobin level normalised (≥7·5 mmol/L [12 g/dL] for women and ≥8 mmol/L [13 g/dL] for men) from the beginning of treatment to surgery. Secondary outcomes included morbidity (assessed with the Clavien-Dindo classification and the Comprehensive Complication Index [CCI]), reintervention rate, number of blood transfusions needed, total number of readmissions, length of hospital stay, admissions to intensive care units (ICUs), absolute change in haemoglobin from baseline before surgery and postoperatively, time needed to reach normalisation of haemoglobin level, change in baseline of other iron or haematological parameters (ie, transferrin saturation, ferritin, and C-reactive protein), and health-related quality of life and fatigue scores. Cutoffs for normal iron stores were defined as above normal local value (ferritin >800 µg/L or transferrin saturation >20%).

Statistical analysis

For a reasonable calculation of the required sample size, a dichotomous outcome was chosen as a primary endpoint. The trial was designed as a superiority trial, hypothesising that a greater percentage of patients would reach a normalised haemoglobin level with intravenous, rather than oral, iron supplementation. The calculation was based on a previous RCT comparing intravenous and oral iron supplementation in post-partum women with iron deficiency anaemia.[14]

After 2 weeks of treatment, normalisation of haemoglobin was seen in 55% of the intravenous group and 35% of the oral group. A somewhat lower rate of normalisation of haemoglobin would be expected in patients with colorectal cancer compared with post-partum women, and therefore, the percentage of patients expected to reach normalised haemoglobin (≥7·5 mmol/L [12 g/dL] for women and ≥8 mmol/L [13 g/dL] for men) was 45% in the intravenous iron group and 25% in the oral iron group. On the basis of these proportions, a sample size of 89 patients per group was needed for a $\chi 2$ test to achieve 80% power at a two-sided α of 0·05. With an estimated loss to follow-up of 10%, a sample size of 198 was calculated. After the inclusion of 152 patients, the actual loss to follow-up rate for the primary endpoint was 23% (35 of 152). At the beginning of the study, blood samples on the day of admission were not taken from several patients. The number of patients affected appeared to be similar for both groups and was mainly due to logistical issues, such as earlier rescheduling of the resection without notification of the study team. After adjustment, a sample size of 220 patients was recalculated. nQuery Advisor (version 7.0) was used to calculate the sample size.

Data were collected by local study personnel in a secure web-based case report form system (OpenClinica). Patients were included in the intention-to-treat analysis if they received the first dose of study medication. The primary outcome and dichotomous outcomes were calculated using a two-sided $\chi 2$ test at a significance level of 0·05 and presented with relative risk (RR) ratios and 95% CIs. If the observed count was less than 10, a Fisher's exact test was used for the dichotomous outcomes. Depending on distribution, continuous outcomes were reported by means and standard deviations, analysed with a Student's t test and presented with a mean difference and 95% CIs or reported by medians and interquartile ranges and analysed using the Mann–Whitney U test. An as-treated analysis was done on patients that received the allocated treatment in the correct dose, with the first dose at least 2 weeks before surgery. A subgroup analysis was done for the following factors used for stratification in the randomisation process: aged 70 years or younger, aged older than 70 years, baseline haemoglobin 6·2 mmol/L (10 g/dL) or less, baseline haemoglobin more than 6·2 mmol/L (10 g/dL), and sex. For the continuous quality of life outcomes, a linear mixed model was used with autoregressive structure and time, and the baseline score and randomisation results were used as fixed effects. A Bonferroni correction was used to correct for multiple testing. Patients with missing data were excluded from analysis. Available patients with complete data were reported per outcome. Statistical analysis was done with SPSS Statistics, version 26.0.

A data safety monitoring board was instituted to guard the safety of included patients, give advice on the continuation of the study upon superiority of one of the types of treatment, and guard the methodological quality of the study. The data safety monitoring board did the interim analyses to ensure these goals. The study was monitored independently by a clinical research unit as described in a monitoring plan to ensure quality and adherence to the protocol. During the first COVID-19 wave in 2020, the trial was halted for 3 months to ensure safety of patients and study personnel and resulted in a slightly decreased inclusion rate afterwards. The trial was registered at ClinicalTrials.gov, NCT02243735.

Role of funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Between Oct 31, 2014, and Feb 23, 2021, a total of 220 patients were included in the study, of whom 110 were randomly assigned to intravenous iron and 110 to oral iron treatment. 14 patients were excluded from the intravenous iron group after randomisation and four were excluded from the oral iron group (figure 1). In the intravenous iron group, 95 (99%) of 96 patients received the allocated treatment, and one patient crossed over to the oral iron treatment because of personal preference. In the oral iron group, 104 (98%) of 106 patients received the allocated treatment, and two patients crossed over to the intravenous iron treatment.

Baseline characteristics among the treatment groups were comparable (table 1). The median age was 71 years (IQR 62–80) and 105 (52%) of 202 patients were men. Mean BMI was 26 kg/m2 (SD 5), and most patients had tumours in the ascending colon (74 [37%] of 202) or caecum (41 [20%] of 202). According to the American Society for Anesthesiology classification, 44 (22%) of 202 patients were scored 1, 107 (53%) were scored 2, and 51 (25%) were scored 3. Anticoagulant medication was used by 53 (26%) patients, and six (3%) patients had received a previous blood transfusion. Baseline albumin levels were the same in both groups (38 g/L vs 38 g/L).

The median interval from randomisation to intervention with iron supplementation was 5 days (IQR 2–7) in the intravenous iron group and 0 days (IQR 0–1) in the oral iron group (p<0·0001). The median interval from intervention to surgery was

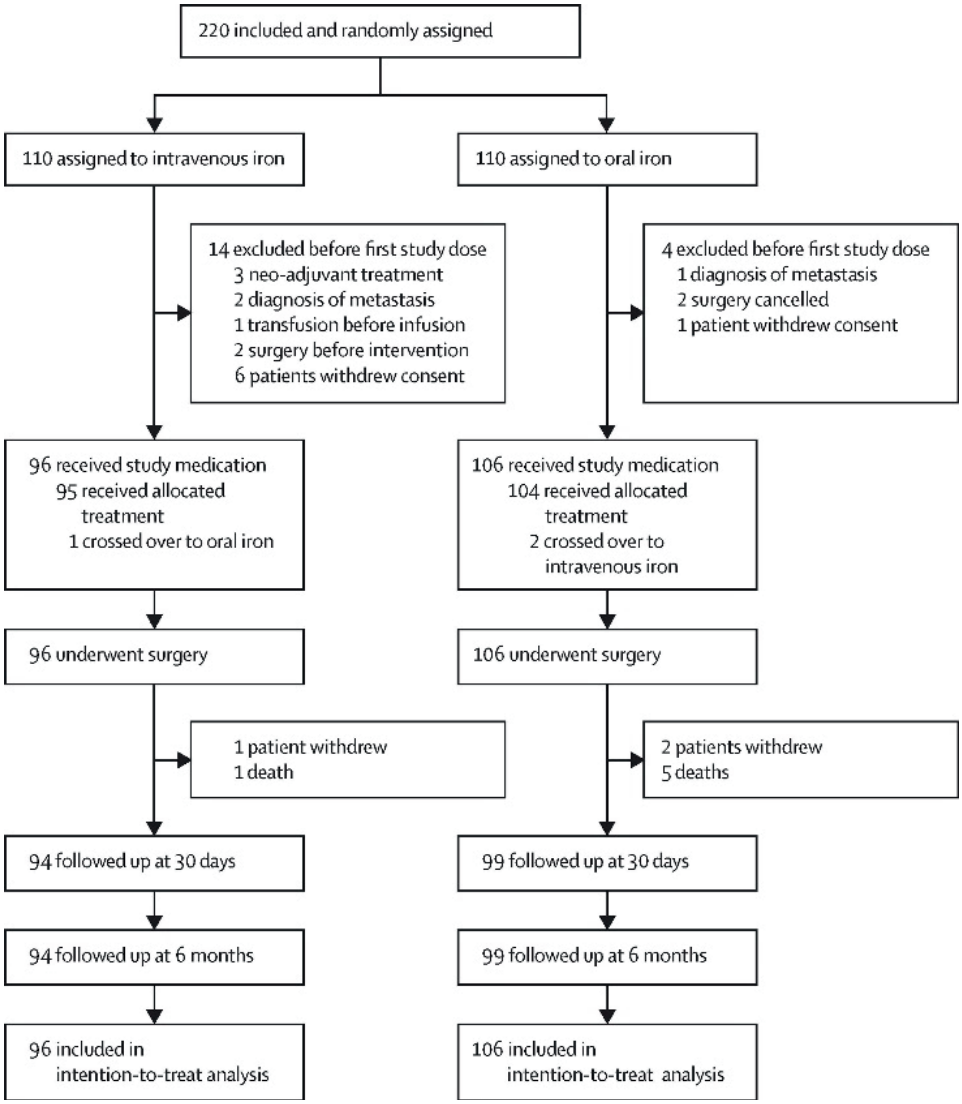


Figure 1: Trial profile

14 days (IQR 11–22) in the intravenous iron group and 19 days (IQR 13–27) in the oral iron group (p=0·0064). The most prevalent treatment-related adverse event was discoloured faeces (grade 1) after oral iron treatment (14 [13%] of 105), and no treatment-related serious adverse events or deaths were observed in either group. Most patients (136 [67%] of 202) had a right hemicolectomy, and the type of surgery was similar in both groups (table 1; appendix pp 5–6).

Table 1: Baseline, treatment and surgical characteristics *Data are n (%), n/N (%), mean (SD), or median (IQR).*

	Total (n=202)	Intravenous iron (n=96)	Oral iron (n=106)
Sex			
Men	105 (52%)	49 (51%)	56 (53%)
Women	97 (48%)	47 (49%)	50 (47%)
Age, years	71 (62–80)	72 (63–79)	70 (61–81)
BMI, kg/m²	26 (5); n=192	27 (6); n=92	26 (5); n=100
American Society for Anesthesiology score			
1	44 (22%)	20 (21%)	24 (23%)
2	107 (53%)	54 (56%)	53 (50%)
3	51 (25%)	22 (23%)	29 (27%)
Smoker			
Current	25/198 (13%)	15/96 (16%)	10/102 (10%)
Former	54/198 (27%)	28/96 (29%)	26/102 (25%)
Never	119/198 (60%)	53/96 (55%)	66/102 (65%)
Tumour location			
Colon ascendens	74 (37%)	36 (38%)	38 (36%)
Caecum	41 (20%)	22 (23%)	19 (18%)
Sigmoid	26 (13%)	15 (16%)	11 (10%)
Colon transversum	19 (9%)	11 (11%)	8 (8%)
Flexura hepatica	15 (7%)	3 (3%)	12 (11%)
Colon descendens	14 (7%)	5 (5%)	9 (8%)
Rectum	10 (5%)	3 (3%)	7 (7%)
Flexura lienalis	3 (1%)	1 (1%)	2 (2%)
Tumour stage			
TX	17/188 (9%)	11/90 (12%)	6/98 (6%)
T1	7/188 (4%)	4/90 (4%)	3/98 (3%)
T2	37/188 (20%)	17/90 (19%)	20/98 (20%)
T3	107/188 (57%)	51/90 (57%)	56/98 (57%)
T4	20/188 (11%)	7/90 (8%)	13/98 (13%)
Node stage			
NX	23/186 (12%)	12/90 (13%)	11/96 (12%)
N0	95/186 (51%)	47/90 (52%)	48/96 (50%)
N1	56/186 (30%)	22/90 (24%)	34/96 (35%)
N2	12/186 (6%)	9/90 (10%)	3/96 (3%)
Metastasis stage			
M0	0	0	0
Preoperative radiotherapy	0	0	0
Previous blood transfusion	6 (3%)	3 (3%)	3 (3%)
History of cardiac disease	42 (21%)	19 (20%)	23 (22%)
Anticoagulant medication use	53 (26%)	23 (24%)	30 (28%)
Treatment type			
Intravenous	97 (48%)	95 (99%)	2 (2%)
Oral	105 (52%)	1 (1%)	104 (98%)
Median interval from randomisation to intervention, days	1 (0–5); n=196	5 (2–7); n=95	0 (0–1); n=101

→

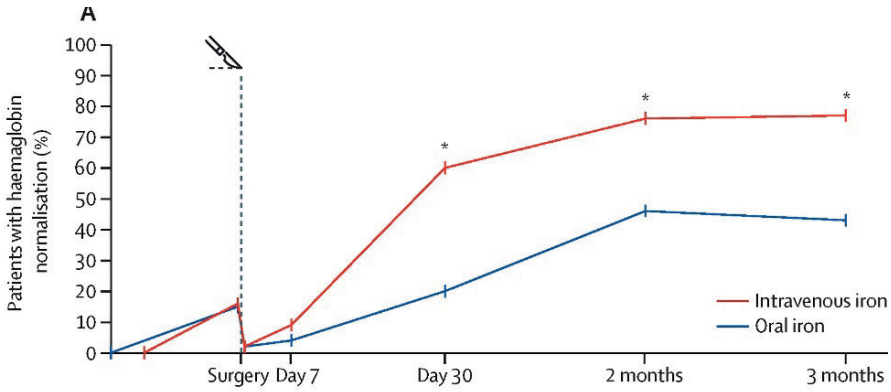
Median interval from intervention to surgery, days	17 (12–24); n=198	14 (11–22); n=94	19 (13–27); n=104
Surgery approach			
Open	18 (9%)	10 (10%)	8 (8%)
Laparoscopic	184 (91%)	86 (90%)	98 (92%)
Conversion	21/183 (11%)	7/85 (8%)	14/98 (14%)
Operation type			
Right hemicolectomy	136 (67%)	64 (67%)	72 (68%)
Transversum resection	1 (<1%)	0	1 (1%)
Left hemicolectomy	28 (14%)	14 (15%)	14 (13%)
Subtotal colectomy	4 (2%)	2 (2%)	2 (2%)
Low anterior resection	22 (11%)	11 (11%)	11 (10%)
Abdomino–perineal resection	1 (<1%)	0	1 (1%)

**In one patient, the tumour could not be resected because of ingrowth in surrounding tissues and a diverting stoma was created. NA=not available.*

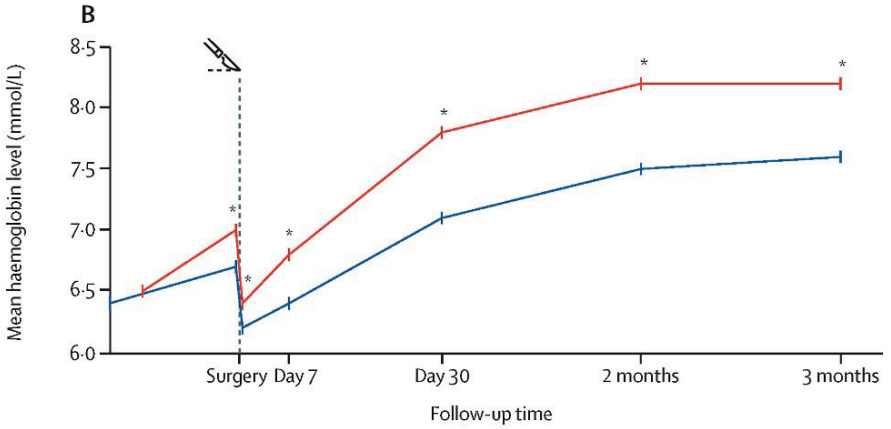
Haemoglobin levels were similar at randomisation for intravenous iron (mean 6·5 mmol/L [SD 10·5 g/dL]) and oral iron (haemoglobin 6·4 mmol/L [10·3 g/dL], p=0·48), and were higher at day of admission in the intravenous iron group (7·0 mmol/L [11·3 g/dl] vs 6·7 mmol/L [10·8 g/dL], p=0·041) compared with the oral iron group. Mean absolute change in haemoglobin from baseline until admission was similar after intravenous iron compared with oral iron (0·53 mmol/L [0·85 g/dl] vs 0·36 mmol/L [0·58 g/dL]; p=0·13). The number of patients with complete normalisation of haemoglobin at day of admission was low and did not differ between the intravenous iron and oral iron groups at admission (14 [17%] of 84 vs 15 [16%] of 97; RR 1·08 [95% CI 0·55–2·10]; p=0·83), or in the first postoperative days.

The proportion of patients with a normalised haemoglobin level was significantly greater in the intravenous group than the oral iron group at 30 days (49 [60%] of 82 vs 18 [21%] of 88; RR 2·92 [95% CI 1·87–4·58]; p<0·0001), 2 months (56 [76%] of 74 vs 37 [45%] of 83; RR 1·69 [95% CI 1·29–2·23]; p<0·0001), and 3 months (56 [76%] of 74 vs 37 [43%] of 86; RR 1·76 [95% CI 1·34–2·32]; p<0·0001) follow-up (figure 2). Serum transferrin saturation, ferritin and haematocrit levels were similar at baseline, but were significantly higher in the intravenous iron group at day of admission and most postoperative timepoints (figure 3; appendix pp 3, 7–8).

The postoperative cumulative complication rate at 6 months was 46 (48%) of 96 patients in the intravenous iron group and 60 (57%) of 106 in the oral group, and complications at Clavien–Dindo score of 3 or higher were seen in 12 (13%) of 96 patients in the intravenous iron group versus 18 (17%) of 106 in the oral iron group (table 2). The intravenous iron group showed no statistically significant difference in the CCI score (12·5 [SD 19] vs 17·5 [SD 24]; p=0·10) and numbers of



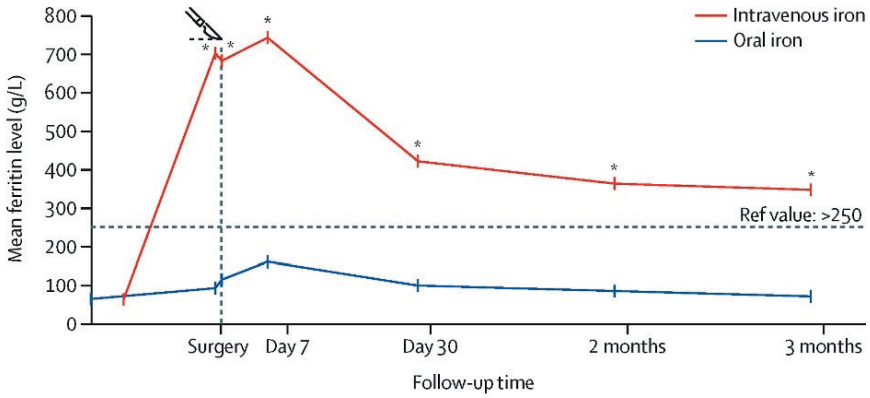
	Baseline	Admission	Day 1	Day 7	Day 30	2 months	3 months
Intravenous iron	0%	16%	2%	9%	60%	76%	77%
Oral iron	0%	15%	2%	4%	20%	46%	43%



	Baseline	Admission	Day 1	Day 7	Day 30	2 months	3 months
Intravenous iron	6·5	7·0	6·4	6·8	7·8	8·2	8·2
Oral iron	6·4	6·7	6·2	6·4	7·1	7·5	7·6

Figure 2: Haemoglobin normalisation (A) Percentage of patients with haemoglobin normalisation. (B) Haemoglobin levels (mmol/L) during follow-up. *The differences found were statistically significant.

patients who received reinterventions (8 [8%] of 96 vs 17 [16%] of 106, RR 0·52 [95% CI 0·24–1·15]; p=0·13), compared with the oral iron group. During surgery, 2 (2%) of 202 patients received a blood transfusion in the entire cohort, whereas 9 (9%) of 96 patients in the intravenous group received a blood transfusion during follow-up at 6 months compared with 15 (14%) of 106 in the oral iron group (RR 0·66 [95% CI 0·30–1·44]; p=0·39).



	Baseline	Admission	Day 1	Day 7	Day 30	2 months	3 months
Intravenous iron	63	701	681	741	420	362	346
Oral iron	64	92	114	160	99	85	71

Figure 3: Ferritin levels (µg/L) during follow-up *The differences found were statistically significant.

The proportion of patients readmitted was similar for the intravenous iron and oral iron groups (10 [10%] of 96 vs 10 [9%] of 106; RR 1·10 [95% CI 0·48–2·54]; p=0·82), and there was no difference in the total length of stay between intravenous iron and oral iron (5 days [IQR 4–9] vs 5 days [IQR 4–10]; p=0·55). Six (6%) of 96 patients in the intravenous iron group and 12 (11%) of 106 in the oral iron group were admitted to ICUs (RR 0·55 [95% CI 0·22–1·41]; p=0·23), and the mortality rate was 2 (2%) of 96 patients in the intravenous iron group and 7 (7%) of 106 in the oral iron group (RR 0·32 [95% CI 0·07–1·48]; p=0·18). No differences in treatment-emergent serious adverse events were seen (table 3). Serious adverse events reported were anastomotic leakage (n=11), aspiration pneumonia (n=5), intra-abdominal abscess (n=5), myocardial infarction (n=2), omental ischaemia (n=1), internal herniation (n=1), duodenal perforation (n=1), postoperative bleeding (n=1), cauda equina syndrome (n=1), pneumonia (n=1), fascial dehiscence (n=1), congestive heart failure (n=1), and intestinal perforation (n=1).

The as-treated analysis comprised 125 (62%) of 202 patients (appendix p 9). Patients were excluded from the as-treated analysis because they crossed between treatment groups (n=3), received the wrong or incomplete intravenous dose (n=20), reported multiple missed oral doses (n=2), or there was less than 2 weeks between the intervention beginning and surgery (n=52). In the as-treated analysis, there was both a lower overall reintervention rate in the intravenous iron group compared with the oral iron group (3 [6%] of 51 vs 13 [18%] of 74; RR

Table 2: Surgical outcomes

	Total (n=202)	Intravenous iron (n=96)	Oral iron (n=106)	Effect size (95% CI)	p value
Intraoperative complications	12 (6%)	7 (7%)	5 (5%)	1·55 (0·51–4·71)	0·55
Postoperative complications					
During admission	91 (45%)	38 (40%)	53 (50%)	0·79 (0·58–1·08)	0·14
30 days	101 (50%)	43 (45%)	58 (55%)	0·82 (0·62–1·09)	0·16
6 months	106 (52%)	46 (48%)	60 (57%)	0·85 (0·65–1·11)	0·22
Clavien-Dindo classification*					
I	46 (23%)	22 (23%)	24 (23%)	1·01 (0·61–1·68)	0·96
II	66 (33%)	26 (27%)	40 (38%)	0·72 (0·48–1·08)	0·11
IIIa	10 (5%)	4 (4%)	6 (6%)	0·74 (0·21–2·53)	0·75
IIIb	9 (4%)	3 (3%)	6 (6%)	0·55 (0·14–2·15)	0·50
IVa	3 (1%)	2 (2%)	1 (1%)	2·21 (0·20–23·97)	0·61
IVb	4 (2%)	1 (1%)	3 (3%)	0·37 (0·04–3·48)	0·62
V	7 (3%)	2 (2%)	5 (5%)	0·44 (0·09–2·22)	0·45
Clavien–Dindo score of 3 or higher*	30 (15%)	12 (13%)	18 (17%)	0·74 (0·37–1·45)	0·37
Glasgow prognostic score					
0 (good prognosis)	70/150 (47%)	36/72 (50%)	34/78 (44%)	1·15 (0·82–1·62)	0·43
1 (intermediate prognosis)	56/150 (37%)	27/72 (38%)	29/78 (37%)	1·01 (0·67–1·53)	0·97
2 (poor prognosis)	24/150 (16%)	9/72 (13%)	15/78 (19%)	0·65 (0·30–1·39)	0·26
Reintervention rate*					
During admission	16 (8%)	6 (6%)	10 (9%)	0·66 (0·25–1·75)	0·45
30 days	22 (11%)	7 (7%)	15 (14%)	0·52 (0·22–1·21)	0·17
6 months	25 (12%)	8 (8%)	17 (16%)	0·52 (0·24–1·15)	0·13
Reintervention type*					
Surgical, during admission	11 (5%)	3 (3%)	8 (8%)	0·41 (0·11–1·52)	0·22
30 days	12 (6%)	3 (3%)	9 (8%)	0·37 (0·10–1·32)	0·14
6 months	12 (6%)	3 (3%)	9 (8%)	0·37 (0·10–1·32)	0·14
Endoscopic, admission	2 (1%)	0	2 (2%)	NA	0·50
30 days	2 (1%)	0	2 (2%)	NA	0·50
6 months	3 (1%)	0	3 (3%)	NA	0·25
Radiological, admission	5 (2%)	4 (4%)	1 (1%)	4·42 (0·50–38·8)	0·19
30 days	10 (5%)	5 (5%)	5 (5%)	1·10 (0·33–3·70)	1·00
6 months	12 (6%)	6 (6%)	6 (6%)	1·10 (0·37–3·31)	1·00
Blood transfusions					
Peroperative	2 (1%)	1 (1%)	1 (1%)	1·10 (0·07–17·41)	1·00
During admission	20 (10%)	7 (7%)	13 (12%)	0·60 (0·25–1·43)	0·35
30 days	23 (11%)	8 (8%)	15 (14%)	0·59 (0·26–1·33)	0·27
6 months	24 (12%)	9 (9%)	15 (14%)	0·66 (0·30–1·44)	0·39
Adjuvant treatment	61/202 (30%)	31/96 (32%)	30/106 (28%)	1·14 (0·75–1·74)	0·54
Adjuvant chemotherapy	60/181 (33%)	31/89 (35%)	29/92 (32%)	1·11 (0·73–1·67)	0·64
Additional oncological surgery†	5/202 (3%)	0	5 (5%)	NA	0·061

Readmissions					
30 days	11 (5%)	4 (4%)	7 (7%)	0·60 (0·18–1·97)	0·54
6 months	20 (10%)	10 (10%)	10 (9%)	1·10 (0·48–2·54)	0·82
Intensive care unit admission	18 (9%)	6 (6%)	12 (11%)	0·55 (0·22–1·41)	0·23
Length of stay, days	5 (4–10); n=202	5 (4–9)	5 (4–10)	NA	0·55
Index admission	5 (4–8); n=201	5 (4–9)	5 (4–9)	NA	0·55
Readmissions	0 (0–0); n=202	0 (0–0)	0 (0–0)	NA	0·75
Stay per readmission	7 (3–20); n=20	7 (5–32)	5 (2–17)	NA	0·18
Mortality	9 (4%)	2 (2%)	7 (7%)	0·32 (0·07–1·48)	0·18
Oncological	2 (1%)	0	2 (2%)	NA	0·50
Treatment-related adverse events	31 (15%)	8 (8%)	23 (22%)	0·38 (0·18–0·82)	0·0085
Grade 3 or higher	0	0	0	NA	NA
Serious adverse events	30 (15%)	12 (13%)	18 (17%)	0·74 (0·37–1·45)	0·37
Comprehensive Complication Index score	15·1 (22); n=202	12·5 (19)	17·5 (24)	−4·98 (10·98–1·03)	0·10

Data are n (%), n/N (%), mean (SD), or median (IQR). NA=not available.
* Reintervention for further oncological treatment was not used in this analysis.
† These surgeries consisted of hyperthermic intraperitoneal chemotherapy (n=3), decompression laminectomy for vertebral metastasis (n=1), and resection for pancreatic cancer (n=1).

0·34 [95% CI 0·10–1·12]; p=0·062) and a lower surgical reintervention rate (0 [0%] of 51 vs 8 [11%] of 74; p=0·021). All other outcomes had similar results across groups, even though there was a greater absolute difference in haemoglobin levels during follow-up, with higher levels in the intravenous iron group.

Patients with a baseline haemoglobin of more than 6·2 mmol/L (10·0 g/dL) had better outcomes after treatment with intravenous iron than oral iron (appendix pp 4, 11). At 6 months, the cumulative reintervention rate was lower in the intravenous iron group (1 [2%] of 62 vs 11 [18%] of 61; RR 0·09 [95% CI 0·01–0·67]; p=0·0022), as was the surgical reintervention rate (0 [0%] of 62 vs 5 [8%] of 61; p=0·028) and the ICU admission rate (1 [2%] of 62 vs 8 [13%] of 61; RR 0·12 [95% CI 0·02–0·95]; p=0·017). Comparable numbers of complications with Clavien–Dindo score 3 and a CCI score were observed between groups. Patients with a baseline haemoglobin level of 6·2 mmol/L (10·0 g/dL) or less had similar results to the main analysis.

Male patients appeared to benefit more from intravenous iron compared with oral iron, with a lower number of Clavien–Dindo score 3 or higher complications, lower CCI score, lower reintervention rate at 6 months, and lower rate of ICU

admissions. In female patients and other subgroup analyses, results were similar to the main analysis (appendix pp 10, 12–14).

The linear mixed model revealed no differences in Brief Fatigue Inventory scores between groups (p=0·36), using time, baseline score, and randomisation results as fixed effects. Similar results were seen for the EQ5D index value (p=0·46) and EQ5D health status score (p=0·46). For the EORTC-30, improved results were observed in the oral iron group on the Role Functioning Scale (p=0·031). Similarly, for the EORTC-C29, the oral iron group had better results on three symptom scales than the intravenous iron group: weight (p=0·0040), increased stool frequency (p=0·018), and dyspareunia (p=0·020; appendix pp 15–17).

Table 3: Grading treatment-emergent adverse events.

	Intravenous iron (n=96)				Oral iron (n=106)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Discoloured faeces	0	0	0	0	14 (13%)	0	0	0
Anastomotic leakage	0	5 (5%)	0	0	0	3 (3%)	2 (2%)	1 (1%)
Aspiration pneumonia	0	0	1 (1%)	1 (1%)	0	0	0	3 (3%)
Intra-abdominal abscess	0	1 (1%)	0	0	0	4 (4%)	0	0
Omental ischemia	0	1 (1%)	0	0	0	0	0	0
Myocardial infarction	0	0	1 (1%)	0	0	1 (1%)	0	0
Postoperative bleeding	..	..	..	..	0	1 (1%)	1 (1%)	0
Internal herniation	0	0	1 (1%)	0	0	0	0	0
Duodenal perforation	0	0	0	1 (1%)	0	0	0	0
Cauda equina syndrome*	0	0	0	0	0	1 (1%)	0	0
Pneumonia	0	0	0	0	0	1 (1%)	0	0
Fascial dehiscence	0	0	0	0	0	1 (1%)	0	0
Congestive heart failure	0	0	0	0	0	0	1 (1%)	0
Intestinal perforation	0	0	0	0	0	0	0	1 (1%)

Grade 1–2 treatment-emergent adverse events occurring in more than 10% of patients and all grade 3–5 events are reported.
* One patient developed cauda equine syndrome during admission caused by a previously unknown vertebral metastasis, requiring emergency surgery.

DISCUSSION

This international RCT investigating the efficacy of intravenous versus oral iron treatment for preoperative iron deficiency anaemia in patients undergoing surgery for colorectal cancer did not reveal a superiority of intravenous over oral iron treatment with respect to haemoglobin-normalisation on the day of admission. However, intravenous iron treatment showed improved haemoglobin normalisation after surgery compared with oral iron treatment. Serum transferrin saturation, ferritin, and haematocrit levels were all significantly higher in the intravenous iron group at day of admission and most postoperative timepoints. By contrast, oral iron treatment did not restore ferritin levels at any timepoint included in this study.

To our knowledge, this is the first RCT to report findings on the efficacy of preoperative iron supplementation for patients with colorectal cancer on relevant clinical outcomes, such as complications, reinterventions, and postoperative stay, to provide evidence on whether intravenous iron or oral iron supplementation has an effect in prehabilitation for patients undergoing colorectal surgery.

This RCT showed that the proportion of patients with normalised haemoglobin on the day of surgery was small in both treatment groups. A possible explanation is that the median time from intravenous iron supplementation to surgery was too short, as over half the patients underwent surgery within 2 weeks of the first intravenous iron supplementation. Notably, surgery in this study was not postponed, as the effect of postponement was unclear and to reflect implementation in daily practice. Therefore, this short interval reflects clinical practice, because the time interval itself was no reason for exclusion from the study. Haemoglobin normalisation during follow-up were also lower than expected in our sample size calculation. The study used in our power calculation included postpartum women with iron deficiency anaemia and might not be ideally suitable, but was chosen because no other RCT comparing intravenous and oral iron was available at the time.[14]

The results from this study are in line with those from a 2020 RCT,[16] which also reported low proportions of patients with haemoglobin normalisation by the day of surgery. The study compared intravenous iron supplementation with placebo in patients undergoing major abdominal surgery for several indications, and the preoperative haemoglobin-normalisation was reportedly 21% after intravenous iron and 10% after placebo (RR 2·06 [92% CI 1·27–3·35]) after 2 weeks of treatment.[16]

Although complete haemoglobin normalisation was not reached on the day of surgery in any group, our results clearly showed differences between the treatment regimens during the convalescent phase. Almost two-thirds of patients who received intravenous iron reached haemoglobin-normalisation 6 weeks after infusion. If haemoglobin normalisation itself is considered important, then this period of delay to surgery should be considered in future. The greatest increase in the proportion of patients who reached haemoglobin-normalisation occurred at 4 weeks after surgery; thus, a postponement of surgery of this length to prepare patients could be considered. Even though surgery can usually be facilitated within 2 weeks in the Netherlands, delaying surgery for at least 4 weeks to give the patient iron treatment appears to be safe.[21] Nevertheless, even without reaching normalised haemoglobin, the restoration of iron reserves using intravenous iron treatment showed a positive effect on postoperative complications.

Oral iron supplementation was unable to restore ferritin levels at any time during follow-up. Treatment with oral iron might seem attractive due to its simplicity and low cost, but it might not be the optimal treatment for patients with colorectal cancer.[7] During inflammatory conditions, iron absorption from the gut is hampered, and iron released from cells is inhibited and hence not available for metabolisation.[22, 23] Additionally, adherence to oral iron treatment can be impaired in patients with colorectal cancer. Digestion problems and possible obstructive complaints caused by the tumour might lead to a reduced intake of oral iron below the dosage prescribed. Our data suggest that oral iron in patients with colorectal cancer is unable to restore iron storage levels. Apparently, all orally supplemented iron that was absorbed was used for erythropoiesis, as reflected by the increase in haemoglobin levels when iron reserves remained depleted.

Transferrin saturation was chosen over ferritin as an inclusion criterium in this study, because ferritin can also be elevated by inflammation by being an acute phase protein. A potential effect of inflammation causing anaemia might have been possible in this study, but we expect this effect was small. Both transferrin saturation and ferritin were low at baseline.

Patients with mild anaemia who were treated with intravenous iron showed better clinical outcomes than those treated with oral iron. This is of particular interest because this subgroup of patients often remains untreated for anaemia. Although haemoglobin levels were not different on the day of admission or on the day after surgery, fewer ICU admissions and reinterventions were reported in patients who underwent intravenous iron treatment. It is possible that the increased iron reserves (as seen in the increased ferritin levels) ameliorated metabolic reactions that rely on iron. Low ferritin levels might

be a more relevant biomarker for worse clinical outcomes than previously thought. The results from this RCT suggest that the restoration of iron reserves is more relevant than the restoration of the haemoglobin level.

No differences were seen in functional outcomes between the intravenous and oral iron treatment groups, despite the improved haemoglobin-normalisation after intravenous-iron treatment. A third of patients had adjuvant chemotherapy, which might have mitigated the effect of improved haemoglobin levels. Furthermore, it is possible that the questionnaires used in this study were unable to detect a difference reflecting the improved haemoglobin levels in the intravenous iron group. A study investigating the effects of iron treatment in patients with heart failure found a significantly greater 6 min walking distance after intravenous iron treatment compared with oral iron treatment.[24]

There were no differences observed in the proportions of patients receiving blood transfusions between patients treated with intravenous and oral iron, and they were relatively low in both groups (intravenous [9%] vs oral [14%]). We expected this to be low and inadequate as a primary endpoint, because an RCT[16] found no difference in allogeneic blood transfusion rate during follow-up when comparing intravenous iron treatment and placebo. A review of six RCTs that investigated some form of iron treatment for preoperative anaemia found no difference in blood transfusion rates when comparing iron therapy with placebo or standard care.[15] The transfusion rate in colorectal surgery is generally too low to consider the need for transfusion as a suitable primary endpoint when studying iron supplementation in these patients.

In this study we have documented the short-term outcomes of different iron treatments on patients, but the long-term oncological outcomes are still awaited. Iron treatment might impair oncological outcomes, because increased concentrations of intraluminal iron could promote the growth of pathogenic gut bacteria involved in tumour progression.[25] However, whether or not iron supplementation is associated with tumour recurrence is yet to be determined.

Over the past two decades, many improvements have been made to surgical care for patients with colorectal cancer, resulting in improved oncological outcomes. In the past 5 years, there has been greater focus on the prehabilitation of patients to ensure that they are fit for surgery, with measures including home physical therapy training plans, high protein diets, smoking cessation, and weight loss programmes.[26] Intravenous iron is a relatively straightforward intervention that requires one or two visits, can be carried out in an outpatient setting, and is not strenuous for the patient. Therefore, the intervention should be considered

as one easy intervention within a prehabilitation programme. Logistics can be optimised by administering the intravenous iron shortly after the haemoglobin and ferritin levels are known, and treatment would ideally start directly after the patient is informed about undergoing surgery. As shown in our study, intravenous iron treatment was feasible across centres, administered within 5 days following diagnosis of iron deficiency with a very low number of adverse events during supplementation. Additionally, haemoglobin could be a potential frailty marker to identify those patients that are in need of prehabilitation, because it reflects tumour progression, nutritional status, and functional status.

One of the strengths of this study was the pragmatic setup and its generalisability. It is the first study that clearly selected patients undergoing surgery for colorectal cancer with a proven preoperative iron deficiency anaemia with clinically significant endpoints. No previous studies are available with such a large number of patients with colorectal cancer receiving maximal doses of iron treatment.

One possible limitation of this study was that the sample size needed to be recalculated, because of incomplete primary endpoint data. However, this limitation appeared to affect both treatment groups similarly and was mainly due to logistical issues, such as earlier rescheduling of the resection without the study team receiving a notification. We do not believe this limitation has influenced the results between groups. A related limitation might be that some patients received an incomplete or wrong dose of intravenous iron, which was mostly caused by earlier rescheduling of surgery. Another limitation was the dosing schedule of oral iron in our study. New evidence suggests that lower dosage regimens on intermittent days, instead of daily dosage, might increase uptake of oral iron and reduce side-effects, while increasing haemoglobin levels.[27] Another possible limitation is that our study was possibly underpowered to detect statistical differences in clinical outcomes in the entire cohort, as could be seen in the lower absolute rates in complications, reinterventions, ICU admissions, and mortality after intravenous iron treatment.

Restoration of iron stores is only feasible with intravenous iron, justifying intravenous iron infusion as part of a prehabilitation programme for patients undergoing colorectal surgery to reduce postoperative negative sequelae. In selected patients, surgery might be delayed to augment the effect of intravenous iron on haemoglobin normalisation.

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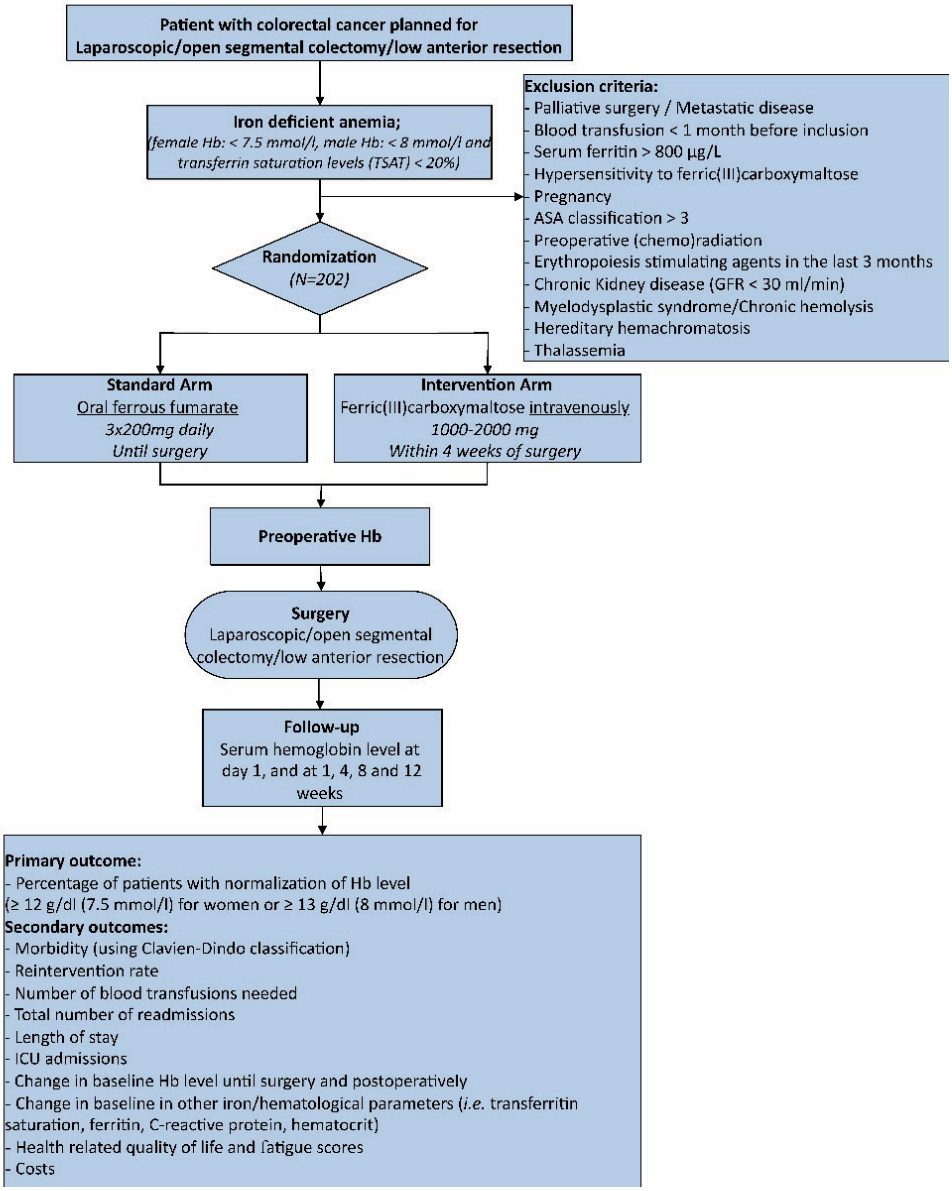
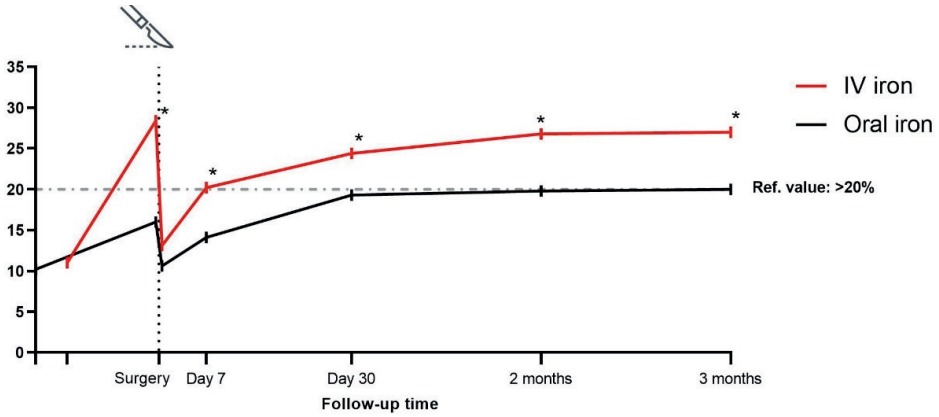
APPENDIX

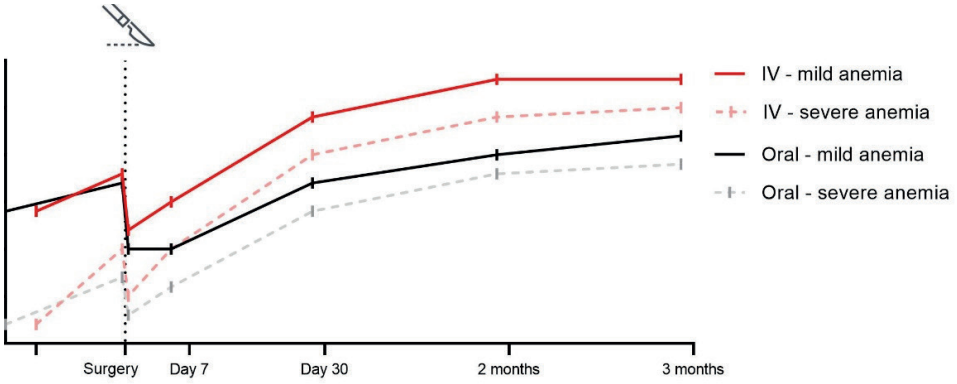


Supplementary figure 1: *Study design.*



	Baseline	Admission	Day 1	Day 7	Day 30	2 months	3 months
IV iron	11.0%	28.4%	13.1%	20.2%	24.4%	26.8%	27.0%
Oral iron	10.2%	16.0%	10.6%	14.1%	19.3%	19.8%	20.0%

Supplementary figure 2: *Transferrin saturation (TSAT) levels during follow-up.*



Supplementary figure 3: *Haemoglobin levels (mmol/l) during follow-up for patients with a mild anemia (≤ 6.2 mmol/l) and severe anemia (> 6.2 mmol/l) at baseline.*

Supplementary table 1: *Details study interventions.*

IV iron treatment	n	**IV received (n = 97)**	n	**Oral received (n = 105)**
Number of IV infusions	97		0	
One infusion		31 (32%)		NA
Two infusions		66 (68%)		NA
Incomplete infusion		2 (2%)		NA
Total dose	97		0	
1000 mg		30 (31%)		NA
1500 mg		44 (45%)		NA
2000 mg		22 (23%)		NA
Other*		1 (1%)		NA
Complication during infusion	97	0	0	NA
Dose received according to protocol	97	77 (79%)	0	NA
Side effects during infusion	97	8 (8%)	0	NA
Headache		3 (3%)		NA
Nausea		1 (1%)		NA
Dizziness		1 (1%)		NA
Fatique		1 (1%)		NA
Pain at injection site		1 (1%)		NA
Abd. and atypical chest pain		1 (1%)		NA
Oral iron treatment				
Median number of days received (IQR)	0	NA	93	23 (15–36)
Side effects during oral supplements	0	NA	105	23 (22%)
Stomach complaints		NA		7 (7%)
Obstipation		NA		4 (4%)
Nausea		NA		3 (3%)
Diarrhoea		NA		2 (2%)
Discoloured faeces		NA		14 (13%)

**One patient received a dose of 700 mg, because of a low body weight*
Data are n (%) or median (IQR). Continuous outcomes were analysed using a Mann–Whitney U test.
IV: intravenous; IQR: interquartile range; mg: milligram; abd: abdominal.

Supplementary table 2: *Intraoperative outcomes.*

	n	**Total n = 202**	**IV iron n = 96**	**Oral iron n = 106**	**p-value**
Operation time (min)	170	157 (SD 73)	151 (SD 65)	163 (SD 80)	0·29
Blood loss (cc)	83	126 (SD 193)	101 (SD 166)	147 (SD 212)	0·29
Peroperative bleeding	202	4 (2%)	2 (2%)	2 (2%)	1·00
Postoperative AB continued	199	19 (10%)	9 (10%)	10 (10%)	1·00
T-stage (pathology)	202				
T0		3 (2%)	2 (2%)	1 (1%)	0·32
T1		5 (3%)	4 (4%)	1 (1%)	
T2		32 (16%)	16 (16%)	16 (15%)	
T3		116 (58%)	57 (60%)	59 (56%)	
T4		46 (23%)	17 (18%)	29 (27%)	
N-stage (pathology)					
N0	202	132 (65%)	61 (64%)	71 (67%)	0·047
N1		51 (25%)	30 (31%)	21 (20%)	
N2		19 (9%)	5 (5%)	14 (13%)	
Iron supplementation after surgery	202	65 (32%)	5 (5%)	60 (57%)	<0·0001
During admission	202	46 (23%)	4 (4%)	42 (40%)	<0·0001
Admission - 30 days	178	44 (25%)	4 (5%)	40 (43%)	<0·0001
Admission - 6 months	179	23 (13%)	1 (1%)	22 (25%)	<0·0001
Type of iron after surgery					
Oral	48	48 (100%)	4 (100%)	44 (100%)	NA
IV		0	0	0	
Complete FU at 30 days	202	193 (96%)	94 (98%)	99 (93%)	0·18
Withdrawn		3 (2%)	1 (1%)	2 (2%)	0·27
Death during admission		6 (3%)	1 (1%)	5 (5%)	
Complete FU at 6 months	202	193 (96%)	94 (98%)	99 (93%)	0·18
Withdrawn	202	3 (2%)	1 (1%)	2 (2%)	0·27
Death within 30 days		6 (3%)	1 (1%)	5 (5%)	

**In one patient the tumor could not be resected because of in growth in surrounding tissues and a diverting stoma was created*

Data are n (%) or mean (SD). Dichotomous outcomes were analysed using a two-sided Chi-square test or Fisher's Exact test, continuous outcomes using a Student's T-test.

IV: intravenous; min: minutes; cc: millilter; AB: antibiotics; FU: follow-up.

Supplementary table 3: *Laboratory parameters*

	n	IV iron	n	Oral iron	Effect size (95%-CI)	p-value
Relative risk ratio						
Normalized Hb (%)	84	14 (17%)	97	15 (16%)	1.08 (0.55-2.10)	0.83
Day 1	*89*	2 (2%)	*101*	3 (3%)	0.76 (0.13-4.43)	0·76
Day 7	*83*	9 (11%)	*95*	4 (4%)	2.58 (0.82-8.06)	0·090
Day 30	*82*	49 (60%)	*88*	18 (21%)	2.92 (1.87-4.58)	<0·0001
2 months	*74*	56 (76%)	*83*	37 (45%)	1.69 (1.29-2.23)	<0·0001
3 months	*74*	56 (76%)	*86*	37 (43%)	1.76 (1.34-2.32)	<0·0001
Mean difference						
Hb (mmol/l)	*96*	6·5 (SD 0·7)	*106*	6·4 (SD 0·8)	0·074 (-0·13 to 0·28)	0·48
Admission	*84*	7·0 (SD 0·9)	*97*	6·7 (SD 0·8)	0·26 (0·01 to 0·51)	0·041
Day 1	*89*	6·4 (SD 0·7)	*101*	6·2 (SD 0·8)	0·24 (0·01 to 0·46)	0·042
Day 7	*83*	6·8 (SD 0·8)	*95*	6·4 (SD 0·8)	0·43 (0·19 to 0·68)	0·0006
Day 30	*82*	7·8 (SD 0·8)	*88*	7·1 (SD 0·8)	0·68 (0·43 to 0·93)	<0·0001
2 months	*74*	8·1 (SD 0·8)	*83*	7·4 (SD 0·9)	0·73 (0·46 to 0·99)	<0·0001
3 months	*74*	8·2 (SD 0·9)	*86*	7·6 (SD 0·7)	0·61 (0·35 to 0·87)	<0·0001
TSAT (%)	*92*	11·0 (SD 11·5)	*98*	10·2 (SD 9·2)	0·86 (-2·12 to 3·84)	0·57
Admission	*65*	28·4 (SD 15·2)	*81*	16·0 (SD 13·6)	12·42 (7·70 to 17·13)	<0·0001
Day 1	*65*	13·1 (SD 7·6)	*79*	10·6 (SD 10·3)	2·42 (-0·63 to 5·46)	0·12
Day 7	*53*	20·2 (SD 9·1)	*67*	14·1 (SD 11·5)	6·15 (2·34 to 9·96)	0·0018
Day 30	*70*	24·4 (SD 11·6)	*76*	19·3 (SD 14·4)	5·15 (0·85 to 9·46)	0·019
2 months	*61*	26·8 (SD 10·0)	*64*	19·8 (SD 12·9)	7·05 (2·94 to 11·2)	0·0009
3 months	*61*	27·0 (SD 12·8)	*68*	20·0 (SD 12·5)	6·98 (2·56 to 11·4)	0·0022
Ferritine (µg/l)	*89*	63 (SD 134)	*100*	60 (SD 87)	2·60 (-29·40 to 34·60)	0·87
Admission	*68*	701 (SD 389)	*80*	90 (SD 177)	610 (509 to 712)	<0·0001
Day 1	*65*	682 (SD 375)	*74*	112 (SD 177)	570 (474 to 666)	<0·0001
Day 7	*56*	729 (SD 396)	*68*	155 (SD 162)	574 (469 to 677)	<0·0001
Day 30	*76*	415 (SD 271)	*75*	98 (SD 153)	316 (246 to 388)	<0·0001
2 months	*61*	357 (SD 270)	*65*	75 (SD 95)	282 (211 to 352)	<0·0001
3 months	*63*	341 (294)	*65*	64 (SD 96)	277 (201 to 354)	<0·0001
Hematocrit (%)	*88*	34 (SD 3)	*93*	33 (SD 4)	0·70 (-0·42 to 1·81)	0·22
Admission	*78*	36 (SD 4)	*91*	35 (SD 4)	1·16 (-0·05 to 2·38)	0·060
Day 1	*88*	33 (SD 4)	*95*	32 (SD 4)	0·89 (-0·23 to 2·02)	0·12
Day 7	*81*	35 (SD 4)	*91*	33 (SD 5)	2·29 (0·93 to 3·65)	0·0011
Day 30	*80*	39 (SD 4)	*84*	37 (SD 4)	2·45 (1·16 to 3·75)	0·0003
2 months	*69*	41 (SD 9)	*78*	40 (SD 9)	3·43 (0·49 to 6·37)	0·023
3 months	*68*	37 (SD 9)	*77*	37 (SD 9)	3·77 (0·78 to 6·75)	0·014
CRP (mg/L)	*86*	15 (SD 23)	*90*	22 (SD 36)	-6·80 (-14·79 to 2·19)	0·14
Admission	*69*	17 (SD 25)	*83*	22 (SD 28)	-5·08 (-13·61 to 3·45)	0·24
Day 1	*82*	91 (SD 55)	*90*	97 (SD 55)	-5·81 (-22·3 to 10·7)	0·49
Day 7	*77*	61 (SD 65)	*90*	80 (SD 84)	-19·3 (-42·5 to 3·94)	0·10
Day 30	*65*	39 (SD 4)	*84*	37 (SD 4)	-7·40 (-18·05 to 3·25)	0·17
2 months	*63*	4 (SD 9)	*62*	10 (SD 24)	-6·34 (-12·7 to 0·01)	0·050
3 months	*65*	12 (SD 31)	*69*	6 (SD 14)	5·71 (-2·46 to 13·9)	0·17
Albumine (g/L)	*74*	38 (SD 5)	*82*	38 (SD 8)	0·69 (-1·36 to 2·73)	0·51

Data are n (%) and mean (SD). Dichotomous outcomes were analysed using a two-sided Chi-square test or Fisher's Exact test and presented with relative risk ratios and 95% confidence intervals. Continuous outcomes were analysed using a Student's T-test and presented with mean difference and 95% confidence intervals.

Hb: haemoglobin; Adm: admission; mo: months; SD: standard deviation; TSAT: transferrin saturation; CRP: C-reactive protein

Supplementary table 4: *As-treated analysis.*

	n	**Total** n = 125	**IV iron** n = 51	**Oral iron** n = 74	Effect size (95%-CI)	p-value
Postoperative complication rate						
6 months	125	60 (48%)	24 (47%)	36 (49%)	0·97 (0·67 to 1·41)	0·86
CD of 3 or higher, n patients	125	19 (15%)	6 (12%)	13 (18%)	0·67 (0·27 to 1·65)	0·45
Comprehensive Complication Index (CCI)	125	14·5 (SD 23)	11·4 (SD 18)	16·6 (SD 25)	-5·27 (-13·39 to 2·84)	0·20
Reintervention rate at 6 months	125	16 (13%)	3 (6%)	13 (18%)	0·34 (0·10 to 1·12)	0·062
Surgical reinterventions	125	8 (11%)	0	8 (11%)	NA	0·021
Blood transfusions	125	8 (6%)	2 (4%)	6 (8%)	0·48 (0·10 to 2·30)	0·47
Baseline Hb level (mmol/L)	125	6·5 (SD 0·7)	6·5 (SD 0·7)	6·4 (SD 0·8)	0·10 (-0·17 to 0·37)	0·47
Admission	111	7·0 (SD 0·9)	7·2 (SD 0·9)	6·8 (SD 0·9)	0·42 (0·08 to 0·75)	0·016
Day 1	119	6·4 (SD 0·8)	6·6 (SD 0·7)	6·3 (SD 0·8)	0·24 (-0·05 to 0·54)	0·10
Day 7	109	6·6 (SD 0·8)	7·0 (SD 0·8)	6·4 (SD 0·8)	0·53 (0·23 to 0·83)	0·00070
Day 30	106	7·4 (SD 0·8)	7·8 (SD 0·6)	7·2 (SD 0·8)	0·68 (0·39 to 0·97)	<0·0001
2 months	93	7·7 (SD 0·9)	8·2 (SD 0·6)	7·4 (0·8)	0·80 (0·48 to 1·12)	<0·0001
3 months	94	7·8 (SD 0·9)	8·2 (SD 0·9)	7·6 (0·8)	0·57 (0·22 to 0·92)	0·0017
Normalisation Hb						
Admission	111	23 (21%)	11 (26%)	12 (18%)	1·45 (0·70 to 2·99)	0·32
Day 1	119	4 (3%)	1 (2%)	3 (4%)	0·49 (0·05 to 4·60)	0·65
Day 7	109	5 (5%)	3 (7%)	2 (3%)	2·22 (0·39 to 12·72)	0·39
Day 30	106	42 (40%)	27 (61%)	15 (24%	2·54 (1·54 to 4·18)	0·0001
2 months	94	54 (58%)	29 (78%)	25 (45%)	1·76 (1·25 to 2·46)	0·0013
3 months	94	55 (59%)	28 (80%)	27 (46%)	1·75 (1·27 to 2·42)	0·0011
ICU admission	125	10 (8%)	2 (4%)	8 (11%)	0·36 (0·08 to 1·64)	0·20
Length of stay in days, total	125	5 (4-7)	5 (3-7)	5 (4-7)	NA	0·53
Mortality	125	6 (5%)	1 (2%)	5 (7%)	0·29 (0·04 to 2·41)	0·40

** Patients were excluded from as-treated analysis when patients crossed over from treatment group (n = 3), received the wrong or incomplete IV dose (n = 20), report of multiple missed oral doses (n = 2) and <2 weeks between start intervention and surgery (n = 52)*
IV: intravenous; CD: Clavien–Dindo; Hb: haemoglobin ICU: intensive care unit
Data are n (%), mean (SD) or median (IQR). Dichotomous outcomes were analysed using a two-sided Chi-square test or Fisher's Exact test and presented with relative risk ratios and 95% confidence intervals. Continuous outcomes were analysed using a Student's T-test and presented with mean difference and 95% confidence intervals.

Supplementary table 5: *Subgroup analysis for patients with age > 70 years and age ≤ 70 years.*

	Age ≤ 70	IV iron	Oral iron	Effect size		Age > 70	IV iron	Oral iron	Effect size	
	n = 100	n = 46	n = 54	(95%-CI)	p-value	n = 102	n = 50	n = 52	(95%-CI)	p-value
Postoperative complication rate										
6 months	50 (50%)	20 (44%)	30 (56%)	0·78 (0·52 to 1·18)	0·23	56 (55%)	26 (52%)	30 (58%)	0·90 (0·63 to 1·28)	0·56
CD of 3 or higher, n patients	14 (14%)	5 (11%)	9 (17%)	0·65 (0·24 to 1·81)	0·41	16 (16%)	7 (14%)	9 (17%)	0·81 (0·33 to 2·01)	0·79
Comprehensive Complication Index (CCI)	12·6 (SD 15·4)	9·7 (SD 12·9)	15·0 (SD 17·0)	-5·37 (-11·46 to 0·71)	0·083	17·6 (SD 26·3)	15·1 (SD 22·6)	20·0 (SD 29·4)	-4·90 (-15·24 to 5·40)	0·35
Reintervention rate at 6 months	14 (14%)	5 (11%)	9 (17%)	0·65 (0·24 to 1·81)	0·41	11 (11%)	3 (6%)	8 (15%)	0·39 (0·11 to 1·39)	0·20
Surgical reinterventions	5 (5%)	1 (2%)	4 (7%)	0·29 (0·03 to 2·53)	0·37	7 (7%)	2 (4%)	5 (10%)	0·42 (0·09 to 2·05)	0·44
Blood transfusions	12 (12%)	3 (7%)	9 (17%)	0·39 (0·11 to 1·36)	0·12	12 (12%)	6 (12%)	6 (12%)	1·04 (0·36 to 3·01)	1·00
Baseline Hb level (mmol/L)	6·4 (SD 0·8)	6·6 (SD 0·7)	6·4 (SD 0·8)	0·20 (-0·11 to 0·51)	0·21	6·5 (SD 0·7)	6·4 (SD 0·7)	6·5 (SD 0·7)	-0·05 (-0·32 to 0·23)	0·74
Admission	6·9 (SD 0·9)	7·2 (SD 0·9)	6·8 (SD 0·9)	0·37 (-0·003 to 0·74)	0·050	6·8 (SD 0·8)	6·9 (SD 0·8)	6·7 (SD 0·8)	0·17 (-0·17 to 0·51)	0·31
Day 1	6·3 (SD 0·8)	6·5 (SD 0·7)	6·1 (SD 0·8)	0·35 (0·03 to 0·67)	0·030	6·3 (SD 0·8)	6·4 (SD 0·8)	6·3 (SD 0·8)	0·12 (-0·21 to 0·45)	0·46
Day 7	6·6 (SD 0·8)	6·9 (SD 0·7)	6·3 (SD 0·8)	0·56 (0·25 to 0·88)	0·0006	6·6 (SD 0·9)	6·7 (SD 0·9)	6·4 (SD 0·9)	0·30 (-0·09 to 0·68)	0·13
Day 30	7·4 (SD 0·9)	7·8 (SD 0·8)	7·1 (SD 0·8)	0·72 (0·37 to 1·07)	<0·0001	7·4 (SD 0·9)	7·7 (SD 0·8)	7·0 (SD 0·8)	0·65 (0·28 to 1·02)	0·0008
2 months	7·9 (SD 0·9)	8·2 (SD 0·9)	7·6 (SD 0·8)	0·65 (0·27 to 1·03)	0·0010	7·6 (SD 0·9)	8·1 (SD 0·8)	7·2 (SD 0·9)	0·84 (0·46 to 1·22)	<0·0001
3 months	7·9 (SD 1·0)	8·3 (SD 1·0)	7·5 (SD 0·7)	0·80 (0·41 to 1·18)	<0·0001	7·9 (SD 0·8)	8·1 (SD 0·8)	7·6 (SD 0·7)	0·43 (0·08 to 0·77)	0·017
Normalisation Hb										
Admission	18 (20%)	8 (21%)	10 (20%)	1·05 (0·46 to 2·40)	1·00	11 (12%)	6 (13%)	5 (11%)	1·23 (0·40 to 3·74)	0·76
Day 1	2 (2%)	1 (2%)	1 (2%)	1·24 (0·08 to 19·21)	1·00	3 (3%)	1 (2%)	2 (4%)	0·52 (0·05 to 5·56)	1·00
Day 7	6 (6%)	5 (12%)	1 (2%)	6·19 (0·75 to 50·97)	0·086	7 (8%)	4 (10%)	3 (7%)	1·40 (0·33 to 5·87)	0·71
Day 30	47 (41%)	27 (66%)	10 (20%)	3·23 (1·78 to 5·85)	<0·0001	30 (38%)	22 (54%)	8 (21%)	2·62 (1·33 to 5·16)	0·0022
2 months	52 (65%)	29 (83%)	23 (51%)	1·62 (1·17 to 2·24)	0·0031	41 (53%)	27 (69%)	14 (37%)	1·88 (1·18 to 2·99)	0·0044
3 months	45 (55%)	28 (78%)	17 (37%)	2·11 (1·39 to 3·19)	0.0002	48 (62%)	28 (74%)	20 (50%)	1·47 (1·03 to 2·12)	0·032
ICU admission	6 (6%)	2 (4%)	4 (7%)	0·59 (0·11 to 3·06)	0·68	12 (12%)	4 (8%)	12 (12%)	0·52 (0·17 to 1·62)	0·35
Length of stay, total	5 (4-8)	5 (4-8)	6 (4-10)	NA	0·19	5 (4-11)	6 (4-10)	5 (4-12)	NA	0·66
Mortality	1 (1%)	0	1 (2%)	NA	1·00	8 (8%)	2 (4%)	6 (12%)	0·35 (0·07 to 1·64)	0·27

IV: intravenous; CD: Clavien–Dindo; Hb: haemoglobin ICU: intensive care unit
Data are n (%), mean (SD) or median (IQR). Dichotomous outcomes were analysed using a two-sided Chi-square test or Fisher's Exact test and presented with relative risk ratios and 95% confidence intervals. Continuous outcomes were analysed using a Student's T-test and presented with mean difference and 95% confidence intervals.

Supplementary table 6: *Subgroup analysis for patients with mild and severe anemia at baseline*

	Hb ≤ 6·2 n = 79	IV iron n = 34	Oral iron n = 45	Effect size (95%-CI)	p-value	Hb > 6·2 n = 123	IV iron n = 62	Oral iron n = 61	Effect size (95%-CI)	p-value
Postoperative complication rate										
6 months	40 (51%)	15 (44%)	25 (56%)	0·79 (0·50 to 1·26)	0·31	66 (54%)	31 (50%)	35 (57%)	0·87 (0·63 to 1·21)	0·41
CD of 3 or higher, n patients	13 (17%)	7 (21%)	6 (13%)	1·54 (0·57 to 4·18)	0·54	17 (14%)	5 (8%)	12 (20%)	0·41 (0·15 to 1·09)	0·062
Comprehensive Complication Index (CCI)	14·9 (SD 20·6)	13·6 (SD 21·6)	15·9 (SD 19·0)	-2·31 (11·67 to 7·04)	0·62	15·2 (SD 22·5)	11·8 (SD 17·1)	18·6 (SD 26·6)	-6·72 (-14·70 to 1·25)	0·10
Reintervention rate at 6 months	13 (17%)	7 (21%)	6 (13%)	1·54 (0·57 to 4·18)	0·39	12 (10%)	1 (2%)	11 (18%)	0·09 (0·01 to 0·67)	0·0022
Surgical reinterventions	7 (9%)	3 (9%)	4 (9%)	0·99 (0·24 to 4·14)	1·00	5 (4%)	0	5 (8%)	NA	0·028
Blood transfusions	16 (20%)	5 (15%)	11 (24%)	0·60 (0·23 to 1·57)	0·40	8 (7%)	4 (7%)	4 (7%)	0·98 (0·26 to 3·76)	1·00
Baseline Hb level (mmol/L)	5·7 (SD 0·4)	5·7 (SD 0·4)	5·7 (SD 0·4)	-0·0089 (-0·19 to0·18)	0·92	6·9 (SD 0·4)	6·9 (SD 0·4)	6·9 (SD 0·5)	-0·02 (-0·17 to 0·14)	0·85
Admission	6·3 (SD 0·8)	6·5 (SD 0·7)	6·2 (SD 0·8)	0·28 (-0·07 to 0·64)	0·11	7·2 (SD 0·7)	7·3 (SD 0·8)	7·2 (SD 0·6)	0·15 (-0·12 to 0·42)	0·28
Day 1	5·9 (SD 0·7)	6·0 (SD 0·7)	5·8 (SD 0·7)	0·25 (-0·07 to 0·56)	0·13	6·6 (SD 0·7)	6·7 (SD 0·7)	6·5 (SD 0·7)	0·14 (-0·13 to 0·41)	0·31
Day 7	6·3 (SD 0·8)	6·5 (SD 0·8)	6·1 (SD 0·8)	0·37 (-0·001 to 0·75)	0·051	6·8 (SD 0·8)	7·0 (SD 0·8)	6·5 (SD 0·8)	0·41 (0·10 to 0·72)	0·011
Day 30	7·2 (SD 1·0)	7·5 (SD 1·0)	6·9 (SD 0·8)	0·60 (0·14 to 1·05)	0·011	7·6 (SD 0·8)	7·9 (SD 0·7)	7·2 (SD 0·8)	0·67 (0·39 to 0·96)	<0·0001
2 months	7·5 (SD 1·0)	7·9 (SD 1·1)	7·3 (SD 0·9)	0·60 (0·08 to 1·11)	0·024	7·9 (SD 0·8)	8·3 (SD 0·6)	7·5 (SD 0·8)	0·73 (0·44 to 1·03)	<0·0001
3 months	7·6 (SD 0·9)	8·0 (SD 1·1)	7·4 (SD 0·8)	0·61 (0·14 to 1·07)	0·012	8·0 (SD 0·8)	8·3 (SD 0·8)	7·7 (SD 0·7)	0·55 (0·25 to 0·86)	0·0006
Normalisation Hb										
Admission	4 (5%)	3 (9%)	1 (2%)	4·03 (0·44 to 36·99)	0·31	25 (24%)	11 (21%)	14 (26%)	0·82 (0·41 to 1·63)	0·56
Day 1	1 (1%)	0	1 (2%)	NA	1·00	4 (4%)	2 (4%)	2 (4%)	1·00 (0·15 to 6·85)	1·00
Day 7	4 (6%)	2 (7%)	2 (5%)	1·45 (0·22 to 9·70)	1·00	9 (8%)	7 (13%)	2 (4%)	3·44 (0·75 to 15·79)	0·16
Day 30	21 (31%)	16 (57%)	5 (13%)	4·57 (1·90 to 11·03)	<0·0001	46 (45%)	33 (61%)	13 (27%)	2·26 (1·35 to 3·76)	0·0006
2 months	31 (51%)	15 (63%)	16 (43%)	1·45 (0·89 to 2·34)	0·14	62 (65%)	41 (82%)	21 (46%)	1·80 (1·28 to 2·53)	0·0002
3 months	30 (48%)	16 (67%)	14 (36%)	1·86 (1·12 to 3·08)	0·018	63 (65%)	40 (80%)	23 (49%)	1·64 (1·18 to 2·26)	0·0014
ICU admission	9 (11%)	5 (15%)	4 (9%)	1·65 (0·48 to 5·70)	0·49	9 (7%)	1 (2%)	8 (13%)	0·12 (0·02 to 0·95)	0·017
Length of stay, total	6 (4-10)	6 (4-12)	5 (4-9)	NA	0·40	5 (4-10)	5 (4-8)	5 (4-11)	NA	0·17
History of cardiac disease	17 (22%)	7 (21%)	10 (22%)	0·93 (0·39 to 2·18)	1·00	25 (20%)	12 (19%)	13 (21%)	0·91 (0·45 to 1·83)	0·83
Mortality	3 (4%)	1 (3%)	2 (4%)	0·66 (0·06 to 7·00)	1·00	6 (5%)	1 (2%)	5 (8%)	0·20 (0·02 to 1·63)	0·11

IV: intravenous; CD: Clavien–Dindo; Hb: haemoglobin ICU: intensive care unit

Data are n (%), mean (SD) or median (IQR). Dichotomous outcomes were analysed using a two-sided Chi-square test or Fisher's Exact test and presented with relative risk ratios and 95% confidence intervals. Continuous outcomes were analysed using a Student's T-test and presented with mean difference and 95% confidence intervals.

Supplementary table 7: *Subgroup analysis for male and female patients.*

	Female n = 97	IV iron n = 47	Oral iron n = 50	Effect size (95%-CI)	p-value	Male n = 105	IV iron n = 49	Oral iron n = 56	Effect size (95%-CI)	p-value
Postoperative complication rate										
6 months	49 (51%)	22 (47%)	27 (54%)	0·87 (0·58 to 1·29)	0·48	57 (54%)	24 (49%)	33 (59%)	0·83 (0·58 to 1·19)	0·31
CD of 3 or higher, n patients	10 (10%)	7 (15%)	3 (6%)	2·48 (0·68 to 9·04)	0·19	20 (19%)	5 (10%)	15 (27%)	0·38 (0·15 to 0·97)	0·045
Comprehensive Complication Index (CCI)	11·9 (SD 15·9)	12·8 (SD 19·0)	11·1 (SD 12·4)	1·72 (-4·72 to 8·17)	0·60	18·0 (SD 25·7)	12·2 (SD 18·6)	23·1 (SD 29·8)	-10·98 (-20·76 to 1·21)	0·028
Reintervention rate at 6 months	9 (9%)	6 (13%)	3 (6%)	2·13 (0·56 to 8·02)	0·31	16 (15%)	2 (4%)	14 (25%)	0·16 (0·04 to 0·68)	0·0029
Surgical reinterventions	3 (3%)	2 (4%)	1 (2%)	2·13 (0·20 to 22·70)	0·61	9 (9%)	1 (2%)	8 (14%)	0·14 (0·02 to 1·10)	0·035
Blood transfusions	13 (13%)	6 (14%)	7 (13%)	0·91 (0·33 to 2·52)	1·00	11 (11%)	3 (6%)	8 (14%)	0·43 (0·12 to 1·53)	0·21
Baseline Hb level (mmol/L)	6·3 (SD 0·7)	6·3 (SD 0·7)	6·3 (SD 0·7)	0·05 (-0·22 to 0·33)	0·70	6·6 (SD 0·7)	6·7 (SD 0·7)	6·6 (SD 0·8)	0·10 (-0·19 to 0·39)	0·47
Admission	6·6 (SD 0·8)	6·8 (SD 0·7)	6·5 (SD 0·8)	0·23 (-0·12 to 0·58)	0·19	7·1 (SD 0·8)	7·2 (SD 0·9)	7·0 (SD 0·7)	0·28 (-0·06 to 0·62)	0·11
Day 1	6·1 (SD 0·7)	6·3 (SD 0·7)	5·9 (SD 0·8)	0·45 (0·15 to 0·75)	0·0037	6·5 (SD 0·8)	6·5 (SD 0·7)	6·5 (SD 0·8)	0·06 (-0·26 to 0·38)	0·72
Day 7	6·5 (SD 0·8)	6·7 (SD 0·8)	6·3 (SD 0·8)	0·34 (0·01 to 0·68)	0·043	6·6 (SD 0·9)	6·9 (SD 0·9)	6·4 (SD 0·9)	0·52 (0·16 to 0·88)	0·0050
Day 30	7·3 (SD 0·9)	7·7 (SD 1·0)	6·9 (SD 0·8)	0·74 (0·36 to 1·11)	0·0002	7·5 (SD 0·8)	7·9 (SD 0·7)	7·2 (SD 0·8)	0·65 (0·31 to 0·98)	0·0002
2 months	7·6 (SD 0·9)	7·9 (SD 0·9)	7·3 (SD 0·8)	0·63 (0·23 to 1·03)	0·0023	7·9 (SD 0·9)	8·4 (SD 0·7)	7·5 (SD 0·9)	0·81 (0·45 to 1·16)	<0·0001
3 months	7·7 (SD 0·9)	7·9 (SD 0·9)	7·4 (SD 0·7)	0·49 (0·12 to 0·87)	0·011	8·1 (SD 0·9)	8·4 (SD 0·9)	7·7 (SD 0·7)	0·71 (0·36 to 1·06)	<0·0001
Normalisation Hb										
Admission	16 (18%)	6 (15%)	10 (21%)	0·71 (0·28 to 1·77)	0·58	13 (14%)	8 (18%)	5 (10%)	1·82 (0·64 to 5·15)	0·37
Day 1	2 (2%)	1 (2%)	1 (2%)	1·07 (0·07 to 15·56)	1·00	3 (3%)	1 (2%)	2 (4%)	0·60 (0·06 to 6·40)	1·00
Day 7	8 (9%)	4 (10%)	4 (9%)	1·13 (0·30 to 4·21)	1·00	5 (5%)	5 (12%)	0	NA	0·019
Day 30	39 (46%)	29 (69%)	10 (24%)	2·90 (1·63 to 5·17)	<0·0001	28 (33%)	20 (50%)	8 (17%)	2·88 (1·43 to 5·80)	0·0013
2 months	46 (61%)	27 (77%)	19 (48%)	1·62 (1·12 to 2·36)	0·0085	47 (57%)	29 (74%)	18 (42%)	1·78 (1·19 to 2·64)	0·0030
3 months	47 (61%)	26 (74%)	21 (50%)	1·49 (1·04 to 2·13)	0·030	46 (57%)	30 (77%)	16 (36%)	2·12 (1·38 to 3·24)	0·0002
ICU admission	7 (7%)	5 (11%)	2 (4%)	2·66 (0·54 to 13·05)	0·26	11 (11%)	1 (2%)	10 (18%)	0·11 (0·02 to 0·86)	0·010
Length of stay, total	5 (4-8)	5 (4-8)	5 (4-7)	NA	0·84	5 (4-10)	5 (4-10)	5·5 (4-12)	NA	0·50
History of cardiac disease	16 (17%)	9 (19%)	7 (14%)	1·37 (0·55 to 3·38)	0·59	26 (25%)	10 (20%)	16 (29%)	0·71 (0·36 to 1·43)	0·33
Mortality	2 (2%)	1 (2%)	1 (2%)	1·06 (0·07 to 16·53)	1·00	7 (7%)	1 (2%)	6 (11%)	0·19 (0·02 to 1·53)	0·12

IV: intravenous; CD: Clavien–Dindo; Hb: haemoglobin ICU: intensive care unit

Data are n (%), mean (SD) or median (IQR). Dichotomous outcomes were analysed using a two-sided Chi-square test or Fisher's Exact test and presented with relative risk ratios and 95% confidence intervals. Continuous outcomes were analysed using a Student's T-test and presented with mean difference and 95% confidence intervals.

Supplementary table 8: *Subgroup analysis for patients with high and low baseline CRP.*

	CRP ≤ 5 n = 74	IV iron n = 35	Oral iron n = 39	Effect size (95%-CI)	p-value	CRP > 5 n = 102	IV iron n = 49	Oral iron n = 56	Effect size (95%-CI)	p-value
Postoperative complication rate										
6 months	30 (41%)	12 (34%)	18 (46%)	0·74 (0·42 to 1·31)	0·30	64 (63%)	29 (57%)	35 (69%)	0·83 (0·61 to 1·12)	0·22
CD of 3 or higher, n patients	6 (8%)	3 (9%)	3 (8%)	1·11 (0·24 to 5·17)	1·00	20 (20%)	7 (14%)	13 (26%)	0·54 (0·23 to 1·24)	0·21
Comprehensive Complication Index (CCI)	10·6 (SD 19·2)	9·4 (SD 19·3)	11·7 (SD 19·3)	-2·24 (-11·21 to 6·73)	0·62	19·0 (SD 24·2)	14·3 (SD 18·9)	23·7 (SD 27·9)	-9·47 (-18·82 to -0·11)	0·047
Reintervention rate at 6 months	6 (8%)	4 (11%)	2 (5%)	2·23 (0·44 to 11·43)	0·41	16 (16%)	2 (4%)	14 (28%)	0·14 (0·03 to 0·60)	0·0011
Surgical reinterventions	4 (5%)	2 (6%)	2 (5%)	1·11 (0·17 to 7·50)	1·00	7 (7%)	1 (2%)	6 (12%)	0·17 (0·02 to 1·34)	0·11
Blood transfusions	8 (11%)	2 (6%)	6 (15%)	0·37 (0·08 to 1·72)	0·27	14 (14%)	6 (12%)	8 (16%)	0·75 (0·28 to 2·01)	0·78
Baseline Hb level (mmol/L)	6·5 (SD 0·8)	6·5 (SD 0·7)	6·5 (SD 0·8)	0·01 (-0·35 to 0·38)	0·94	6·5 (SD 0·7)	6·6 (SD 0·7)	6·4 (SD 0·7)	0·17 (-0·11 to 0·45)	0·22
Admission	7·0 (SD 0·9)	6·9 (SD 0·8)	7·1 (SD 0·9)	-0·16 (-0·58 to 0·26)	0·46	6·7 (SD 0·9)	7·1 (SD 0·9)	6·4 (SD 0·8)	0·64 (0·30 to 0·98)	0·0003
Day 1	6·3 (SD 0·8)	6·3 (SD 0·7)	6·4 (SD 0·9)	-0·01 (-0·40 to 0·38)	0·96	6·3 (SD 0·8)	6·5 (SD 0·8)	6·1 (SD 0·8)	0·40 (0·07 to 0·72)	0·016
Day 7	6·8 (SD 0·8)	6·9 (SD 0·9)	6·6 (SD 0·8)	-0·23 (-0·20 to 0·65)	0·29	6·5 (SD 0·9)	6·7 (SD 0·8)	6·2 (SD 0·8)	0·62 (0·28 to 0·95)	0·0004
Day 30	7·5 (SD 0·9)	7·7 (SD 0·8)	7·3 (SD 0·9)	0·33 (-0·11 to 0·76)	0·14	7·4 (SD 0·9)	7·9 (SD 0·8)	6·9 (SD 0·7)	1·01 (0·67 to 1·35)	<0·0001
2 months	7·7 (SD 0·9)	7·8 (SD 0·9)	7·6 (SD 0·8)	0·25 (-0·20 to 0·70)	0·28	7·8 (SD 1·0)	8·4 (SD 0·7)	7·3 (SD 0·8)	1·08 (0·72 to 1·44)	<0·0001
3 months	7·7 (SD 0·8)	7·9 (SD 0·8)	7·5 (SD 0·7)	0·35 (-0·04 to 0·75)	0·079	8·0 (SD 0·9)	8·3 (SD 1·0)	7·7 (SD 0·8)	0·66 (0·27 to 1·06)	0·0012
Normalisation Hb										
Admission	15 (23%)	4 (13%)	11 (31%)	0·44 (0·16 to 1·23)	0·14	10 (11%)	8 (17%)	2 (4%)	3·91 (0·88 to 17·43)	0·090
Day 1	1 (1%)	0	1 (3%)	NA	1·00	4 (4%)	2 (4%)	2 (4%)	1·02 (0·15 to 6·95)	1·00
Day 7	5 (8%)	4 (13%)	1 (3%)	4·53 (0·54 to 38·36)	0·18	8 (9%)	5 (11%)	3 (6%)	1·67 (0·42 to 6·58)	0·71
Day 30	28 (44%)	17 (55%)	11 (34%)	1·60 (0·90 to 2·84)	0·10	33 (39%)	28 (65%)	5 (12%)	5·47 (2·34 to 12·81)	<0·0001
2 months	33 (56%)	17 (59%)	16 (53%)	1·10 (0·70 to 1·73)	0·68	48 (63%)	32 (87%)	16 (41%)	2·11 (1·42 to 3·14)	<0·0001
3 months	30 (52%)	17 (65%)	13 (41%)	1·61 (0·97 to 2·66)	0·061	53 (66%)	32 (82%)	21 (51%)	1·60 (1·15 to 2·24)	0·0036
ICU admission	6 (8%)	3 (9%)	3 (8%)	1·11 (0·24 to 5·17)	1·00	11 (11%)	3 (6%)	8 (16%)	0·38 (0·11 to 1·33)	0·20
Length of stay, total	4 (3-6)	4 (3-6)	5 (4-7)	NA	0·44	7 (4-11)	6 (4-10)	7 (4-12)	NA	0·68
Mortality	2 (3%)	1 (3%)	1 (3%)	1·11 (0·07 to 17·15)	1·00	6 (6%)	1 (2%)	5 (10%)	0·20 (0·02 to 1·65)	0·21

IV: intravenous; CD: Clavien–Dindo; Hb: haemoglobin ICU: intensive care unit
Data are n (%), mean (SD) or median (IQR). Dichotomous outcomes were analysed using a two-sided Chi-square test or Fisher's Exact test and presented with relative risk ratios and 95% confidence intervals. Continuous outcomes were analysed using a Student's T-test and presented with mean difference and 95% confidence intervals.

Supplementary table 9: *Subgroup analysis for patients with high and low baseline ferritin.*

	Ferritin ≤ 30 n = 103	IV iron n = 52	Oral iron n = 51	Effect size (95%-CI)	p-value	Ferritin > 30 n = 86	IV iron n = 37	Oral iron n = 49	Effect size (95%-CI)	p-value
Postoperative complication rate										
6 months	47 (46%)	22 (42%)	25 (47%)	0·86 (0·57 to 1·32)	0·49	53 (62%)	20 (54%)	33 (67%)	0·80 (0·56 to 1·15)	0·21
CD of 3 or higher, n patients	13 (13%)	6 (12%)	7 (14%)	0·84 (0·30 to 2·33)	0·78	14 (16%)	5 (14%)	9 (18%)	0·74 (0·27 to 2·01)	0·55
Comprehensive Complication Index (CCI)	12·9 (SD 20·5)	11·8 (SD 21·5)	14·0 (SD 19·6)	-2·12 (-10·18 to 5·93)	0·60	17·9 (SD 23·4)	13·4 (SD 15·3)	21·3 (SD 27·7)	-7·98 (-18·04 to 2·09)	0·12
Reintervention rate at 6 months	11 (11%)	5 (10%)	6 (12%)	0·82 (0·27 to 2·51)	0·76	12 (14%)	3 (8%)	9 (18%)	0·44 (0·13 to 1·52)	0·22
Surgical reinterventions	6 (6%)	1 (2%)	5 (10%)	0·20 (0·02 to 1·62)	0·11	4 (5%)	2 (5%)	2 (4%)	1·32 (0·20 to 8·97)	1·00
Blood transfusions	13 (13%)	4 (8%)	9 (18%)	0·44 (0·14 to 1·33)	0·15	11 (13%)	5 (14%)	6 (12%)	1·10 (0·37 to 3·34)	1·00
Baseline Hb level (mmol/L)	6·4 (SD 0·7)	6·4 (SD 0·7)	6·4 (SD 0·8)	0·08 (-0·20 to 0·37)	0·55	6·6 (SD 0·7)	6·6 (SD 0·8)	6·5 (SD 0·7)	0·12 (-0·20 to 0·44)	0·46
Admission	7·0 (SD 0·8)	7·0 (SD 0·8)	6·9 (SD 0·8)	0·09 (-0·23 to 0·42)	0·55	6·7 (SD 0·9)	7·0 (SD 1·0)	6·5 (SD 0·9)	0·46 (0·04 to 0·88)	0·031
Day 1	6·3 (SD 0·8)	6·4 (SD 0·7)	6·2 (SD 0·9)	0·22 (-0·09 to 0·52)	0·16	6·3 (SD 0·8)	6·5 (SD 0·9)	6·2 (SD 0·8)	0·34 (-0·04 to 0·71)	0·077
Day 7	6·6 (SD 0·8)	6·7 (SD 0·8)	6·5 (SD 0·7)	0·25 (-0·07 to 0·57)	0·12	6·5 (SD 0·9)	6·9 (SD 0·8)	6·2 (SD 0·9)	0·68 (0·28 to 1·09)	0·0013
Day 30	7·5 (SD 0·8)	7·8 (SD 0·6)	7·2 (SD 0·8)	0·66 (0·36 to 0·96)	<0·0001	7·2 (SD 1·0)	7·6 (SD 1·1)	6·9 (SD 0·7)	0·75 (0·31 to 1·19)	0·0011
2 months	7·9 (SD 0·8)	8·2 (SD 0·7)	7·6 (SD 0·8)	0·65 (0·31 to 0·99)	0·0003	7·6 (SD 1·0)	8·1 (SD 1·0)	7·2 (SD 0·8)	0·88 (0·44 to 1·32)	0·0002
3 months	8·0 (SD 0·8)	8·3 (SD 0·7)	7·6 (SD 0·7)	0·74 (0·42 to 1·05)	<0·0001	7·8 (SD 1·0)	8·0 (SD 1·1)	7·6 (SD 0·8)	0·47 (0·01 to 0·93)	0·044
Normalisation Hb										
Admission	19 (20%)	8 (17%)	11 (24%)	0·71 (0·32 to 1·61)	0·45	7 (9%)	4 (13%)	3 (7%)	1·94 (0·47 to 8·05)	0·43
Day 1	1 (1%)	0	1 (2%)	NA	1·00	4 (5%)	2 (6%)	2 (4%)	1·29 (0·19 to 8·68)	1·00
Day 7	6 (6%)	4 (8%)	2 (4%)	1·88 (0·36 to 9·77)	0·68	6 (8%)	4 (13%)	2 (5%)	2·77 (0·54 to 14·20)	0·23
Day 30	38 (43%)	27 (61%)	11 (24%)	2·51 (1·43 to 4·42)	0·0004	24 (35%)	19 (59%)	5 (14%)	4·39 (1·85 to 10·43)	<0·0001
2 months	49 (65%)	30 (81%)	19 (49%)	1·66 (1·16 to 2·38)	0·0032	37 (54%)	22 (73%)	15 (40%)	1·86 (1·19 to 2·91)	0·0054
3 months	49 (61%)	32 (82%)	17 (41%)	1·98 (1·34 to 2·93)	0·0002	39 (57%)	20 (69%)	19 (48%)	1·45 (0·97 to 2·18)	0·076
ICU admission	9 (9%)	4 (8%)	5 (10%)	0·79 (0·22 to 2·76)	0·74	9 (11%)	2 (5%)	7 (14%)	0·38 (0·08 to 1·72)	0·29
Length of stay, total	5 (4-8)	5 (4-7)	5 (4-11)	NA	0·24	6 (4-11)	6 (4-16)	5 (4-10)	NA	0·61
History of cardiac disease	20 (19%)	9 (17%)	11 (22%)	0·80 (0·36 to 1·77)	0·63	20 (23%)	9 (24%)	11 (22%)	1·08 (0·50 to 2·34)	1·00
Mortality	4 (4%)	2 (4%)	2 (4%)	0·98 (0·14 to 6·70)	1·00	5 (6%)	0	5 (10%)	NA	0·067

IV: intravenous; CD: Clavien–Dindo; Hb: haemoglobin ICU: intensive care unit
Data are n (%), mean (SD) or median (IQR). Dichotomous outcomes were analysed using a two-sided Chi-square test or Fisher's Exact test and presented with relative risk ratios and 95% confidence intervals. Continuous outcomes were analysed using a Student's T-test and presented with mean difference and 95% confidence intervals.

Supplementary table 10: *Brief Fatique Inventory results.*

	Baseline		Admission		2 weeks		4 weeks		3 months		6 months		
	IV iron	Oral iron	IV iron	Oral iron	IV iron	Oral iron	IV iron	Oral iron	IV iron	Oral iron	IV iron	Oral iron	p-value
n available	*78*	*82*	*51*	*51*	*68*	*69*	*66*	*69*	*70*	*62*	*56*	*63*	
Brief Fatique Inventory - absolute (0 best, 10 worst)	3,76	3,18	3,45	2,89	3,6	3,8	2,84	2,98	2,96	2,8	3,1	2,22	0·53

IV: intravenous;

Supplementary table 11: *Quality-of-Life outcomes.*

	Baseline				*4 weeks*				6 months				
	n	IV iron	*n*	Oral iron	*n*	IV iron	*n*	Oral iron	*n*	IV iron	*n*	Oral iron	p-value	favoring
EQ5D (higher is better)														
Index value	*78*	0,846	*83*	0,878	*67*	0,869	*69*	0,907	*60*	0,9	*68*	0,9	0·46	
Health status score	*78*	64,2	*83*	67,1	*66*	71,2	*69*	70,9	*60*	71,6	*68*	78,3	0·46	
EORTC-C30 Global health status (Higher is better)	*78*	60,3	*82*	69,0	*67*	67,9	*68*	71,7	*59*	74,9	*68*	81,6	0·25	
EORTC-C30 -functional scales (Higher is better)														
Physical functioning	*78*	75,0	*83*	81,7	*67*	75,4	*70*	77,8	*60*	80,3	*68*	85,7	0·67	
Role functioning	*78*	70,5	*83*	75,9	*67*	61,2	*70*	69,3	*60*	75,8	*68*	85,3	0·031	oral
Emotional functioning	*78*	68,4	*83*	76,1	*67*	83,5	*69*	86,7	*60*	83,5	*68*	90,6	0·32	
Cognitive functioning	*77*	83,1	*83*	89,6	*67*	88,3	*69*	86,2	*60*	86,4	*68*	91,4	0·33	
Social functioning	*78*	78,4	*83*	84,9	*67*	76,9	*69*	83,1	*60*	84,7	*68*	89,0	0·36	
EORTC-C30 -symptom scales (higher is more complaints)														
Fatigue	*78*	40,0	*83*	30,2	*67*	31,7	*70*	32,5	*60*	29,3	*68*	19,2	0·83	
Nausea and vomiting	*78*	5,6	*83*	5,0	*67*	5,0	*70*	8,3	*60*	6,1	*68*	1,2	0·82	
Pain	*78*	19,7	*83*	12,9	*67*	19,7	*70*	14,5	*60*	11,4	*68*	8,8	0·62	
Dyspnoea	*77*	24,7	*82*	15,4	*67*	17,9	*69*	14,0	*59*	15,3	*68*	12,3	0·12	
Insomnia	*78*	25,6	*83*	21,7	*67*	19,4	*70*	19,5	*59*	20,9	*67*	17,4	0·75	
Appetite loss	*78*	22,6	*82*	16,3	*67*	17,9	*70*	17,6	*60*	11,1	*68*	4,4	0·48	
Constipation	*78*	19,2	*82*	13,0	*67*	8,5	*69*	6,8	*60*	11,7	*68*	6,4	0·58	
Diarrhoea	*78*	22,6	*83*	21,3	*66*	17,7	*69*	14,5	*60*	13,3	*68*	7,4	0·38	
Financial difficulties	*78*	6,4	*83*	3,6	*67*	7,0	*69*	6,3	*60*	3,9	*68*	3,4	0·58	
EORTC-CR29 - functional scales (higher is better)														
Body Image	*77*	89,2	*83*	93,0	*67*	88,6	*69*	93,4	*60*	88,7	*67*	95,5	0·27	
Anxiety	*77*	50,2	*83*	53,8	*67*	69,2	*69*	70,5	*60*	71,1	*67*	79,6	0·92	
Weight	*77*	81,8	*83*	80,3	*67*	80,6	*69*	86,5	*60*	81,7	*67*	93,0	0·0040	oral
Sexual interest (men)	*38*	76,3	*43*	74,4	*39*	71,8	*31*	74,2	*33*	68,7	*38*	67,5	0·62	
Sexual interest (women)	*36*	91,7	*36*	89,8	*25*	90,7	*35*	88,6	*22*	86,4	*25*	84,0	0·80	

EORTC-CR29 - Symptom scales (higher is more complaints)														
Urinary frequency	*77*	34,6	*83*	32,3	*67*	34,1	*69*	33,1	*60*	29,4	*67*	26,4	0·77	
Blood and mucus in stool	*77*	9,3	*83*	8,6	*67*	1,7	*69*	1,7	*60*	2,2	*67*	1,0	0·16	
Increased stool frequency*	*74*	15,3	*77*	12,8	*63*	22,8	*66*	17,4	*56*	14,0	*65*	11,5	0·018	oral
Urinary incontinence	*77*	8,2	*83*	7,2	*67*	5,5	*69*	6,3	*60*	9,4	*67*	9,0	0·51	
Dysuria	*77*	3,9	*83*	2,0	*67*	4,0	*69*	3,9	*60*	2,2	*67*	1,5	0·75	
Abdominal pain	*77*	24,7	*83*	18,9	*67*	16,9	*69*	17,4	*60*	12,2	*67*	6,0	0·59	
Buttock pain	*77*	6,9	*83*	5,6	*67*	10,4	*69*	9,7	*60*	7,2	*67*	5,0	0·44	
Bloating	*77*	24,2	*83*	24,1	*67*	15,9	*69*	13,0	*60*	19,4	*67*	7,0	0·050	
Dry mouth	*77*	19,9	*83*	21,7	*67*	17,4	*69*	20,8	*60*	18,3	*67*	12,4	0·95	
Hair loss	*77*	3,5	*83*	0,0	*67*	5,0	*69*	1,9	*60*	7,2	*67*	4,0	0·30	
Taste	*77*	13,0	*83*	5,6	*67*	13,9	*69*	12,6	*60*	13,9	*67*	7,5	0·61	
Flatulence	*74*	27,0	*77*	26,4	*63*	27,5	*65*	23,6	*56*	28,0	*66*	25,8	0·45	
Faecal incontinence	*74*	7,7	*76*	6,6	*64*	11,5	*66*	6,6	*56*	7,1	*66*	5,1	0·16	
Sore skin	*73*	8,7	*77*	6,1	*63*	14,8	*66*	6,6	*56*	7,7	*66*	8,1	0·63	
Embarrassment	*74*	12,6	*76*	12,3	*62*	12,9	*66*	9,6	*56*	13,1	*66*	7,1	0·18	
Stoma care problems	*0*	NA	*2*	16,7	*4*	25,0	*6*	16,7	*3*	0,0	*6*	5,6	NA	
Impotence	*37*	29,7	*40*	32,5	*38*	24,6	*28*	23,8	*29*	29,9	*36*	25,0	0·45	
Dyspareunia*	*24*	2,8	*23*	7,2	*16*	8,3	*28*	1,2	*18*	9,3	*16*	0,0	0·020	oral

**GEE model*

Supplementary table 12: *number of included patients per study site.*

Study site	Principle Investigator	Number of inclusions
Amsterdam UMC, Location AMC, Amsterdam, The Netherlands	Prof. dr. W.A. Bemelman	44
TergooiMC, Hilversum, The Netherlands	Dr. A.A.W. van Geloven	27
Isala Hospital, Zwolle, The Netherlands	Dr. H.L. van Westreenen	26
Flevo Hospital, Almere, The Netherlands	Dr. A.W.H. van de Ven	19
Meander Medical Centre, Amersfoort, The Netherlands	Prof. dr. E.C.J. Consten	15
Antonius Hospital, Sneek, The Netherlands	Dr. G.J. Veldhuis	12
Gelre Hospital, Apeldoorn, The Netherlands	Dr. E.S. van der Zaag	10
Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands	Dr. M.F. Gerhards	9
Albert Schweitzer Hospital, Dordrecht, The Netherlands	Dr. J.A.B. van der Hoeven	9
IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy	Dr. A. Spinelli	8
Spaarne Gasthuis, Hoofddorp, The Netherlands	Dr. G. Heuff	6
Amsterdam UMC, Location VUmc, Amsterdam, The Netherlands	Dr. J.B. Tuynman	5
Amstelland Hospital, Amstelveen, The Netherlands	Dr. T. Kuiper	4
Hospital Gelderse Vallei, Ede, The Netherlands	Dr. C. Sietses	4
Haaglanden Medical Centre, Den Haag, The Netherlands	Dr. M. Westerterp	4

CHAPTER 4

Highly selective diversion with pro-active leakage management after low anterior resection for rectal cancer

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ABSTRACT

Whether a diverting stoma during low anterior resection prevents anastomotic leakage and its sequela is an ongoing debate. This single institutional cohort study shows that with a policy of highly selective diversion, anastomotic leakages can be adequately managed using a proactive surveillance and treatment protocol, resulting in over 90% one-year anastomotic integrity, and 76% of patients never having a stoma.

INTRODUCTION

Routine creation of a diverting stoma after low anterior resection (LAR) for rectal cancer with primary anastomosis is standard practice in many institutions worldwide. This is based on meta-analysis, showing that a diverting stoma significantly reduces clinical anastomotic leakage and reoperation rates, although not affecting mortality.[1] However, occult and late leakages, stoma-related interventions as well as all other disadvantages of a diverting stoma are often not fully taken into account. Creation of a diverting stoma results in complications in over 50%[2], and closure of diverting stomas is associated with 17.3% morbidity and 0.4% mortality in meta-analysis[3]. Not having a stoma appears to be one of the most relevant outcomes for patients, with a similar perceived importance as not having complications or being cured of cancer[4]. Therefore, fecal diversion in LAR for rectal cancer is increasingly debated.

In our tertiary referral center in the Netherlands, we shifted from routine to highly selective fecal diversion (HSD) after LAR for rectal cancer[5]. This updated case series of HSD evaluates the postoperative course and the proportion of patients with a functional anastomosis at one-year.

METHODS

Methods are detailed in Appendix A.

RESULTS

LAR with anastomosis was performed in 99 patients. Sixty-eight percent was male , mean BMI was 25 kg/m2, mean age was 62 years, and 49% underwent neoadjuvant therapy (Appendix B). Five patients had a pre-existent double loop colostomy due to obstruction. During LAR, two loop colostomies were closed and six new loop ileostomies were created. Stoma creation was due to an ultra-low hand-sewn anastomosis (n=3), failure of the stapling device (n=1), and routinely in the early transition period (n=2). In total, after LAR, nine patients had a diverting stoma (Appendix C).

Anastomotic leakage

Anastomotic leakage occurred in 16 patients (16%) after a median interval of 6 days (IQR 3-13). Fourteen were diagnosed within 30 days (88%). Treatment of anastomotic leakage is described in Appendix D. Two patients were treated with antibiotics, of whom one had a primary stoma. A secondary stoma was

constructed in 12 patients. Ten patients were treated with endoscopic vacuum therapy (EVT), followed by transanal closure of the anastomotic defect in 9 patients. A new anastomosis was constructed after further mobilization of the afferent colon in three patients.

In 10 patients with leakage, the diverting stoma was closed within 1 year. Salvage intersphincteric resection of the anastomosis with end-colostomy and omentoplasty was performed in 4 patients because of anastomotic fistula (n=2) or large persisting leak (n=2), controlling pelvic sepsis in three patients. At end of follow-up, three patients had a chronic presacral sinus, of whom two still had a diverted anastomosis. Total median length of stay was 6 days (IQR 5-12). One patient died 184 days postoperatively because of suicide (not related to pelvic sepsis).

One-year functional anastomosis and stoma-related outcomes

The proportion of patients with a functional anastomosis at one-year was 86/94 (91%) (Table 1). A total of 75 patients (76%) never had a stoma at any time during the one year postoperative period. Four patients had a permanent colostomy related to anastomotic leakage, one for local recurrence and one patient for pain and LARS-symptoms.

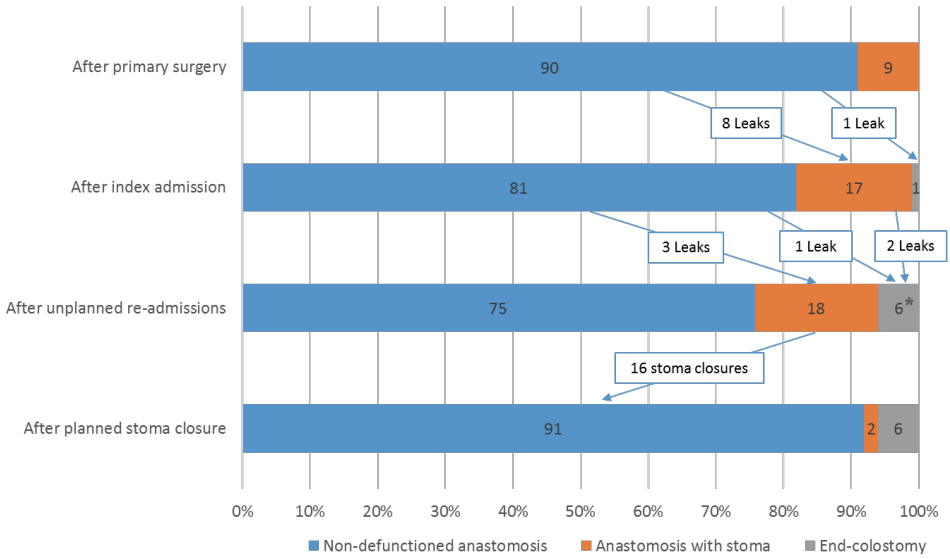

Figure 1: Patient selection, defunctioning stoma construction, stoma closure and permanent stoma.

Table 1: Surgical outcomes up to 1 year

Outcome	N patients with data	HSD
Presence of stoma, n (%)		
Never had a stoma	99	75 (76)
At 6 months	99	11 (11)
At 12 months	94	8 (9)
Anastomotic integrity, n (%)		
Functioning primary anastomosis at 6 months[a]	99	87 (88)
Functioning redo anastomosis at 6 months	99	1 (1)
Diverted primary anastomosis at 6 months	99	4 (4)
Diverted redo anastomosis at 6 months	99	2 (2)
Primary anastomosis resected until 6 months	99	5 (5)
Functioning primary anastomosis at 12 months	94	83 (88)
Functioning redo anastomosis at 12 months	94	3 (3)
Diverted primary anastomosis at 12 months	94	2 (2)
Diverted redo anastomosis at 12 months	94	0 (0)
Primary anastomosis resected until 12 months	94	6 (6)
Readmissions, n (%)		
Total number of patients	99	34 (34)
For ileostomy closure	99	17 (17)
For AL or early post-operative complications	99	15 (15)
For further oncological treatment	99	10 (10)
For high-output stoma	99	1 (1)
Reinterventions related to LAR, n (%)		
Total patients	99	24 (24)
Ileostomy closure	99	22 (22)
Other (e.g. transanal closure)	99	17 (17)
Endoscopic	99	16 (16)
Radiological	99	8 (8)
Reinterventions for further oncological treatment, n (%)	99	5 (5)
Total	99	10 (10)
Surgical	99	9 (9)
Radiological	99	1 (1)
Reintervention for LARS, n (%)	99	1 (1)
Length of stay, days		
Index admission for LAR, median (IQR)	99	6 (5-7)
During complete follow-up, median (IQR)	99	6 (5-12)
Patients admitted to ICU, n (%)	99	2 (2)
ICU stay, total no. days per patient	2	2, 2
Mortality within 90 days postoperatively, n (%)	99	1 (1)

HSD=highly selective diversion; n=number; FU=follow-up; IQR=interquartile range; LAR=low anterior resection; LARS=low anterior resection syndrome; ICU=intensive care unit; [a] Primary functioning anastomosis was defined as: the anastomosis created during TME, without fecal diversion

DISCUSSION

In this single center cohort study, we evaluated the outcomes of an institutional protocol of HSD with proactive diagnosis and management of anastomotic leakage after LAR for rectal cancer. Following our initial report that included 40 patients, the extended experience in 99 patients who received neoadjuvant radiotherapy in 48% reveals that 91% of evaluable patients at one year had a functioning anastomosis, without leakage related mortality, and with 76% of patients not having a stoma at any time. It should be emphasized that implementation of a strict anastomotic leakage surveillance and management protocol[6] is required to achieve these results.

This study confirms the safety of omitting a diverting stoma in terms of postoperative mortality as found in trials randomizing between diverting stoma or not[7]. Thirty-day mortality was even lower in Dutch hospitals with a policy of more selective diversion compared to routine diversion (1.0% vs. 2.9%; p=0.02)[8], probably explained by close postoperative observation with immediate intervention to prevent uncontrolled sepsis and failure to rescue.

Similar studies on HSD are scarce. A Swedish single center study describes an institutional shift in the opposite direction and similar overall anastomotic leakage rates were found, with longer total hospital stay after a diverting stoma (7 vs. 4 days) [9]. In a multicenter study, diverting stomas resulted in similar early leakage rates, a higher late leakage rate, much higher reintervention rates (85% vs 2%) and a higher permanent stoma rate, than no fecal diversion (22% vs 12%)[10]. One well-known RCT on the role of diverting stoma showed higher leakage rates in the omission group (28.0% vs 10.3%), but comparable long-term stoma rates (16.9% vs 13.8%) after 42 months of follow-up [11]. The long-term stoma rate of 9% in the present study is lower than mostly reported with the majority undergoing primary fecal diversion [12].

The association between anastomotic leakage and oncological recurrence has been used to promote diverting stomas[13]. However, if higher early clinical leakage rates without diversion or more late occult leakages in the presence of a diverting stoma make any difference in the risk of inflammation induced oncological recurrence remains unknown.

Creation of an ileostomy comes with high peri-operative morbidity and readmission rates, mainly due to dehydration and obstruction[14]. Furthermore, if bowel continuity is restored, presence of a diverting ileostomy has been associated with impaired bowel function[15]. A proactive policy to control pelvic

sepsis and repair of the anastomosis can preserve function of the neorectum if extrapolating similar data from ileoanal pouch surgery.[16] Another underreported but clinically relevant problem is stoma-site incisional herniation, which occurs in up to 35% of patients and requires surgical repair in up to two-thirds of patients[17]. A diverting stoma relates to increased healthcare costs, which are mainly due to higher reintervention and readmission rates. [18]

In summary, diverting stomas are not without harm and the effectiveness of a diverting stoma in preventing anastomotic leaks in the long run is uncertain. Close postoperative observation in combination with CRP-measurement and CT-scan with rectal contrast makes early treatment of leakage safe and effective[19]. Upcoming techniques for active treatment of anastomotic leakage using EVT and transanal closure of the anastomotic defect might preserve anastomotic integrity[20]. Such treatment seems to be most effective at an early stage of leakage.

There are some limitations. First, no comparison was made with a control group, but we previously reported on a historical comparison with routine diversion[5]. Patients were operated in an academic institution by experienced colorectal surgeons, for which reason this study might be subject to sampling bias and likely has restricted external validity. Finally, there is the retrospective design of the present study and the relatively small sample size

CONCLUSION

This single-center retrospective cohort study showed that LAR with HSD does not expose patients to unacceptable risks with a protocol of early diagnosis and pro-active treatment of anastomotic leakage, while three quarters of the patients benefitted from not having any stoma. A functioning anastomosis in over 90% of the patients at one year appears favorable if compared to literature.

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Supplementary material

Appendix A: Methods

METHODS

This is a retrospective single-institutional case series, using a prospectively kept registry of patients who underwent colorectal resections between December 2014 and July 2019 in the Amsterdam UMC, location AMC. The start of the inclusion period reflects the implementation of an institutional protocol of HSD, which was parallel to the introduction of transanal total mesorectal excision (TaTME). Experience was derived from a similar policy in ileoanal pouch anastomoses at our institution[1] Details of this institutional protocol and results of the first 40 patients were previously published[2]. Inclusion criteria were adult patients undergoing LAR with creation of an anastomosis for primary rectal cancer within 8 cm from the anorectal junction on MRI, or completion total mesorectal excision (TME) after local excision. Exclusion criteria were: partial mesorectal excision, surgery for recurrent rectal cancer, no creation of an anastomosis at primary surgery and follow-up less than 6 months.

Procedure

erwent a TaTME, performed by one or two out of three colorectal surgeons. Preoperatively, mechanical bowel preparation and intravenous antibiotics were given. During surgery, a full splenic flexure mobilization was routinely performed with high ligation of the inferior mesenteric vein. As a routine, the superior rectal artery was transected with preservation of the left colic artery if possible. A stapled anastomosis was created if sufficient length of the rectal cuff was available. A diverting stoma was only created on indication, as judged by the operating surgeon(s). Postoperatively, CRP was measured at day 4 in all patients. If CRP was elevated and/or in case of clinical suspicion for anastomotic leakage, a CT-scan with transanal contrast was performed. If an anastomotic leakage was diagnosed, re-laparoscopy and endoscopic inspection of the anastomosis was performed, preferably within 6 hours. In general, a diverting stoma was constructed and endoscopic vacuum therapy (EVT) therapy started as originally described by Weidenhagen[3]. Incidentally an immediate redo of the anastomosis was performed. Our unit has modified the Weidenhagen technique by performing transanal closure of the anastomotic defect as soon as EVT therapy resulted in a clean, granulating cavity, which we first described in 2011[4-6] and which is available as a video vignette [7]. Anastomotic integrity in patients that had

a diverting ileostomy at the index operation was assessed by endoscopy within 2 weeks to diagnose silent leaks and treat them accordingly.

Definition

An anastomotic Leakage was defined as "a breach in a surgical join between two hollow viscera, with or without active leak of luminal contents"[8]. Any presacral abscess, presacral fluid collections, air around anastomotic site or pelvic fistula (e.g. towards bladder, vagina, skin) was also considered an anastomotic leakage. Reoperation was defined as any reoperation related to rectal cancer within 1 year (i.e. emergency surgery for leak or liver resection for metastases). Readmission was defined as any readmission within 1 year related to rectal cancer

Data collection and outcome parameters

Data was collected on baseline characteristics, operative details, early postoperative complications and follow-up until 12 months after surgery. Primary outcome was the proportion of patients with a functional anastomosis among all patients who completed one-year follow-up. Secondary outcomes were anastomotic leakage rate (overall, <30 days, ≥30 days), time until diagnosis of leakage, diverting stoma rates (after index admission, re-admission, 1-year), 90-day mortality rate, ICU admission, 1-year end-colostomy rate, readmissions, reinterventions, reoperations, proportion of patients never having any stoma, and total length of stay until 1 year. Data were collected from electronic medical records

Statistical analysis

Data were reported as either means with standard deviation or medians with interquartile range (IQR), depending on distribution. Data are presented as 6 months follow-up or follow-up at 1 year, according to completeness of data. A curve of the presence of a stoma over time was presented as percentage of patients with a stoma at any time-point up to 1 year postoperatively. Data analysis was performed in IBM SPSS statistics version 26. Results were reported according to the STROBE-statement.

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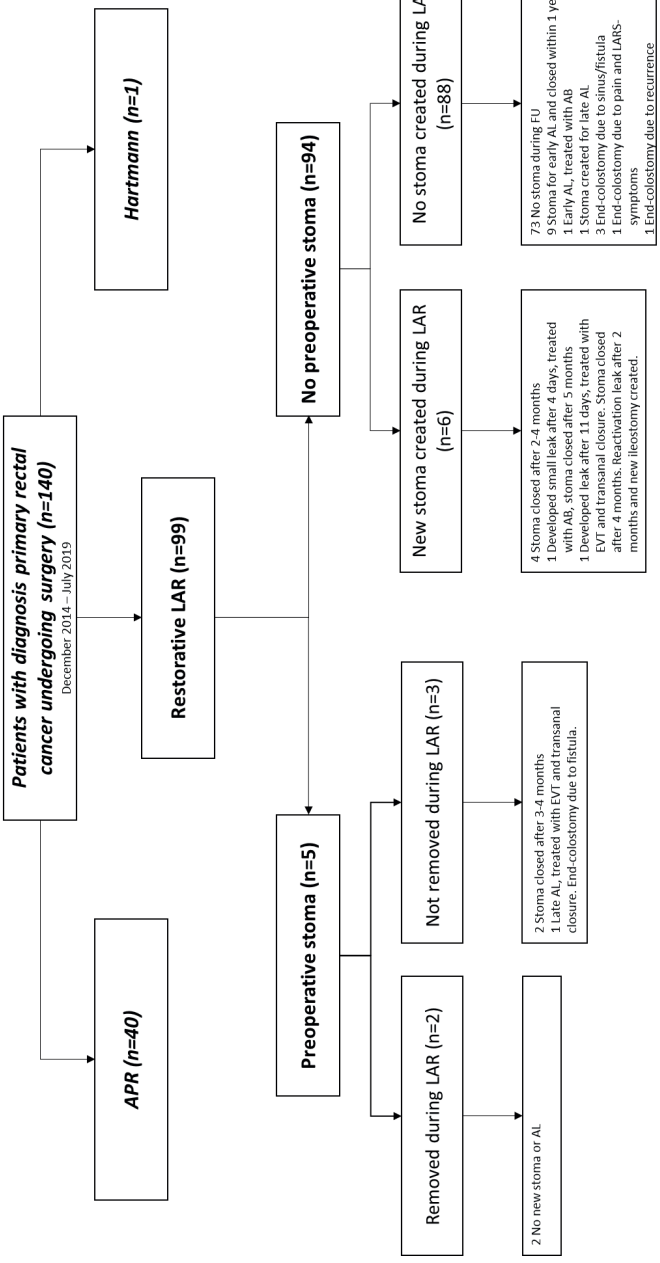
Appendix B

Supplementary table 1: *Baseline characteristics, operative details and patholo.*

Characteristic	HSD (n = 99)
Male gender, n (%)	67 (68)
Age, mean (SD), years	62 (9)
BMI, mean (SD), kg/m2	25 (3)
Current smokers, n (%)	13 (13)
ASA 3 or higher, n (%)	9 (9)
Clinical tumour staging, n (%)	
T1-2	32(32)
T3	57 (58)
T4	10 (10)
N1 or higher	46 (47)
M1	11 (11)
Prior double loop colostomy, n (%)	5 (5)
Tumour distance from ARJ on MRI in cm, mean (SD)[a]	4 (2.2)
Neoadjuvant therapy, n (%)	
Short course radiotherapy	24 (24)
Chemoradiotherapy	25 (25)
Surgical approach, n (%)	
Laparoscopic	96 (97)
Open	3 (3)
Conversion	0
Multivisceral resection, n(%)	15 (15)
Diverting stoma, n (%)	
Prior double loop colostomy kept in situ, n (%)	3 (3)
Ileostomy	6 (6)
Anastomotic technique, n (%)	
Stapled	92 (93)
Hand-sewn	7 (7)
Anastomotic configuration, n (%)	
Side-End	86 (87)
End-End	12 (12)
Coloanal-pouch	1 (1)
Pathology, n (%)	
(y)T0-2	46 (47)
(y)T3	49 (49)
(y)T4	4 (4)
(y)N1-2	35 (35)
CRM involvement (≤ 1 mm)	7 (7)
Adjuvant chemotherapy, n (%)[b]	2 (2)

HSD=highly selective diversion; n=number; SD=standard deviation; BMI=body mass index; ASA=American Society Anesthesiology; MRI=magnetic resonance imaging; ARJ=anorectal junction;
[a] Threatened MRF was defined as a distance from the tumour or malignant lymph node to the MRF of ≤ 1mm
[b] One patient received adjuvant chemotherapy because of a synchronous sigmoid tumour and one patient received adjuvant chemotherapy following curative intent local treatment of synchronous liver metastases in the CAIRO-V study.

Appendix C



Supplementary figure 1: *Patient selection, defunctioning stoma construction, stoma closure and permanent stoma.*

Appendix D

Supplementary table 2: *Incidence and management of anastomotic leakage and permanent colostomies, stratified for the presence of a diverting stoma after LAR.*

	Diverting Stoma present after LAR		
	No	**Yes**	**Total**
Number of patients	**90**	**9**	**99**
Anastomotic Leakage, no. of patients	13	3	16
Early < 30 days	12	2	14
Late > 30 days	1	1	2
Interval from LAR to diagnosis of AL, median (IQR), days	5 (3-12)	11 (4-50)	6 (3-13)
Interval from diagnosis of AL to treatment, median (IQR) ,days	0 (0-1)	0 (0-10)	0 (0-1)
Interval from diagnosis of AL to start EVT, median (IQR), days	0 (0-10)	6 (1-10)	1 (0-10)
Reactivation of leak after stoma closure[a]	0	1	1
Treatment of anastomotic leakage, no. of patients			
Antibiotics	1	1	2
EVT + secondary ileostomy + transanal closure	5	0	5
EVT + transanal closure[b]	0	1	1
EVT + secondary ileostomy + redo anastomosis	1	0	1
Secondary ileostomy + resuturing anastomosis	1	0	1
Secondary ileostomy + redo anastomosis	2	0	2
EVT + transanal closure + creation end colostomy (intersphincteric APR) + omentoplasty	0	1	1
EVT + secondary ileostomy + creation end colostomy (intersphincteric APR) + omentoplasty	1	0	1
EVT + secondary ileostomy + transanal closure + creation end colostomy[c] (intersphincteric APR) + omentoplasty	1	0	1
Creation end colostomy[c] (intersphincteric APR) + omentoplasty	1	0	1
End colostomy at end of follow-up, no. of patients	5	1	6
Chronic sinus/fistula	3	1	4
Recurrent cancer	1	0	1
Pain and LARS-symptoms	1	0	1

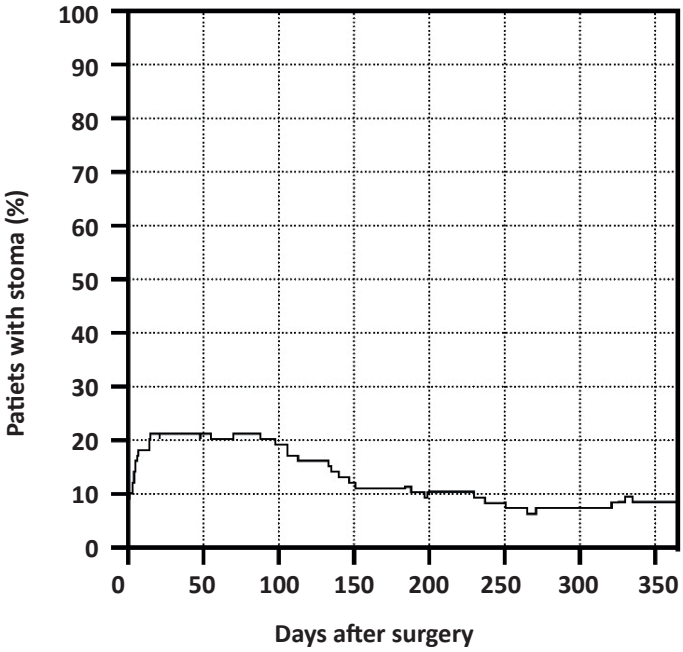
LAR=low anterior resection; IQR=interquartile range; EVT= endoscopic vacuum therapy; APR=abdominoperineal resection; LARS=low anterior resection syndrome

[a] A leak was defined as reactivated, when a leak was diagnosed after a diverting stoma was closed

[b] After closure of the primary stoma, there was a reactivation of the leak. Secondary treatment comprised of EVT + secondary ileostomy + transanal closure

[c] Colostomy was preceded by secondary ileostomy (n=2), EVT treatment (n=3), transanal closure of anastomotic defect (n=2)

Appendix E



Supplementary figure 2: *Percentage of patient with a stoma during FU*

CHAPTER 5

Usefulness of CT scan as part of an institutional protocol for proactive leakage management after low anterior resection for rectal cancer

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ABSTRACT

Purose: Highly selective fecal diversion after low anterior resection (LAR) for rectal cancer requires a strict postoperative protocol for early detection of anastomotic leakage (AL). The purpose of this study was to evaluate C-reactive protein (CRP) based CT imaging in diagnosis and subsequent management of AL.

Methods: All patients that underwent a CT scan for suspicion of AL after transanal Total Mesorectal Excision for rectal cancer in a university centre (2015-2020) were included. Outcome parameters were diagnostic yield of CT and timing of CT and subsequent intervention.

Results: Forty-four out of 125 patients underwent CT (35%) with an overall median interval of 5 hours (IQR 3-6) from CRP measurement. The anastomosis was diverted in 7/44 (16%). CT was conclusive or highly suspicious for AL in 23, with confirmed AL in all those patients (yield 52%), and was false-negative in one patient (sensitivity 96%). CT initiated subsequent intervention after median 6 hours (IQR 3-25). There was no or minor suspicion of AL on imaging in all 20 patients without definitive diagnosis of AL. After CT imaging on day 2, AL was confirmed in 0/1, and these proportions were 6/6 for day 3, 7/10 for day 4, 2/4 for day 5, and 9/23 beyond day 5.

Conclusion: In the setting of an institutional policy of highly selective fecal diversion and pro-active leakage management, the yield of selective CT imaging using predefined CRP cut-off values was 52% with a sensitivity of 96%, enabling timely and tailored intervention after a median of 6 hours from imaging.

INTRODUCTION

Anastomotic leakage (AL) after low anterior resection (LAR) for rectal cancer is a severe complication with frequent need for reinterventions and readmissions, and is associated with worse oncological outcome, increased health care costs and decreased quality of life.[1-4] Conventional treatment of AL consists of fecal diversion and drainage of the abscess and a subsequent period of secondary healing, while dismantling of the anastomosis might be performed in more severe cases. More recently, pro-active approaches have been developed using endoscopic vacuum therapy (EVT) and early closure of the anastomotic defect[5, 6]. Early initiation of EVT appears to be more effective, when the presacral cavity is still pliable and unaffected by chronic inflammation, thereby increasing the chance of eventual restoration of bowel continuity.

Timely detection seems important to limit the consequences of AL, but consensus on diagnostic protocols with clear implications for subsequent management is lacking. Clinical parameters indicative of AL include pelvic pain, nausea, tachycardia, tachypnea, hypotension and fever.[7, 8] Serum C-reactive protein (CRP)-levels can be indicative of infectious complications with discriminative power on day 3 and 4[9]. Both clinical parameters and CRP can result in false-negative and false-positive findings that hamper their use for proper selection of patients who require subsequent invasive diagnostics (e.g. endoscopy, laparoscopy) or immediate surgical treatment. CT imaging can add diagnostic accuracy, but not all radiological features associated with AL are highly sensitive.[10, 11]

Fecal diversion might mask the presence of an AL, which results in delayed diagnosis, thereby losing the window of opportunity for early intervention.[12] This was one of the reasons, besides the associated morbidity and need for reinterventions related to a stoma, to implement a policy of highly selective diversion after LAR at our institute. This policy appeared to be safe and did not lead to more complicated leaks, while having low permanent stoma-rates.[13] CT imaging with rectal contrast is one of the corner stones of our institutional protocol for early detection of AL with subsequent tailored intervention.

The primary aim of this study was to evaluate the usefulness of CT imaging within an institutional protocol for early detection of AL in patients after transanal Total Mesorectal Excision (TaTME)for rectal cancer with highly selective fecal diversion. The secondary aims of this study were to analyze the yield of CT depending on time interval from index surgery, CRP values at time of imaging relative to predefined cut-off values, sensitivity of the individual radiological features, and timing of initial postoperative CT imaging and subsequent reinterventions.

METHODS

Study population

A retrospective cohort study was performed, including all patients that underwent CT imaging for suspicion of AL after TaTME for primary mid or distal rectal cancer, with or without temporary diverting stoma operated between April 2015 and December 2020, in the Amsterdam UMC, location AMC. Exclusion criteria were partial mesorectal excision and surgery for recurrent rectal cancer.

Surgery and perioperative management

All patients underwent TaTME without routine diverting stoma. A policy of highly selective fecal diversion was introduced in our centre in 2014 as previously described.[14] All patients received preoperative mechanical bowel preparation and intravenous preoperative antibiotics. Postoperatively, CRP was routinely measured at day 4 until 2019, and on day 3 since then, related to the design of the IMARI study[15]. If CRP levels were elevated above predefined cut-off values and/or there was a clinical suspicion of AL, patients underwent a CT scan with iv contrast and preferably also water-soluble oral and rectal contrast. Cut-off values for CRP were based on a previous review (CRP > 172 mg/L on day 3, > 124 mg/L on day 4 and > 144 mg/L on day 5).[9] If AL was suspected or clearly visible on CT, subsequent management consisted of endoscopic assessment of the anastomosis and surgical reintervention whenever indicated (e.g. construction of a diverting ileostomy, abdominal lavage for peritonitis). If endoscopy revealed an abscess cavity, EVT-treatment was initiated by placing a vacuum sponge. When the cavity appeared clean with granulation tissue after a few exchanges, the defect was closed with transanal sutures. Details of this technique were published earlier[6]

Data collection and outcome parameters

Electronic medical files were used for data collection. Data was collected on baseline characteristics, index operation, serum CRP-levels, postoperative imaging, clinical parameters, postoperative complications, and reinterventions. All radiological characteristics, including timing and individual features were collected from the radiology reports. Clinical parameters potentially associated with AL were collected at time of diagnosis of AL or 24 hours prior to diagnosis of AL. The primary outcome was the diagnostic yield of CT. Secondary outcomes included individual radiological features indicative for diagnosing AL, mean CRP levels at the time of CT on different postoperative days, proportion of CT with preceding CRP above predefined cut-off levels on different postoperative days,

timing of CT imaging, and timing and type of reinterventions for confirmed AL. Eventually confirmed diagnosis of AL was defined as an anastomotic defect found during endoscopy and/or surgery followed by treatment for AL.

Statistical analysis

for suspicion of AL, and for the subgroups with or without confirmed AL. The data was analyzed using IBM SPSS statistics, version 26.0, Armonk, NY. Chi-square test was used for categorical and dichotomous variables, presented as absolute numbers with percentages. For continuous variables with a normal distribution, an independent sample T test was used and outcomes were reported as mean with standard deviation. In case of a non-normal distribution, a Mann-Whitney U test was used to calculate the median with interquartile range. Sensitivity and specificity rates were calculated for anastomotic leakage, using the outcome of the CT scan as testing modality and confirmation of diagnosis by either endoscopy or surgical intervention. Median time intervals in hours were calculated between index operation and first CRP, index operation and first CT scan, index operation and first reintervention, first CRP and CT imaging and CT imaging and first reintervention. Two sided p-values were calculated and considered statistically significant if $p<0.05$.

RESULTS

Study population

Out of 125 patients that underwent TaTME for rectal cancer during the study period, 44 patients (35%) underwent a diagnostic CT scan for suspicion of AL (figure 1). The mean age was 61 years, mean BMI was 26 kg/m2 and 34 (77%) were male. Preoperative radiotherapy was given in 22 patients (50%) and 7 patients had a diverted anastomosis (16%) (table 1).

CT imaging and radiological features

combination of elevated CRP and clinical signs in 18 patients, and clinical signs of AL in 16 patients. CT imaging was performed after median 148 hours (IQR 94-335) from index surgery and after median 5 hours (IQR 3-6) from last CRP measurement preceding CT imaging. Of all patients, 40 (91%) received at least rectal contrast (Table 2). No complications of contrast administration were registered.

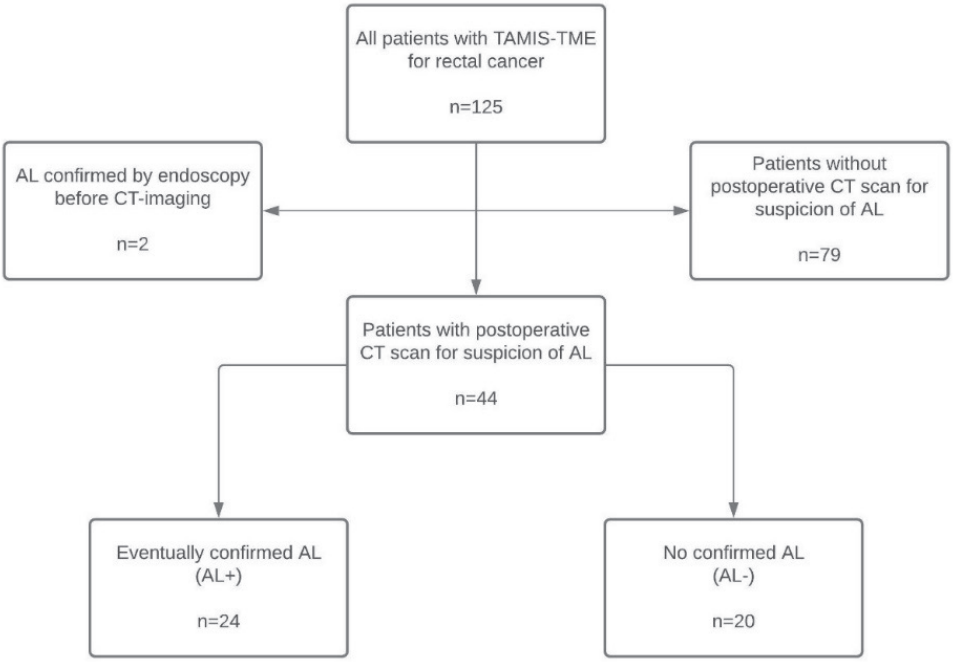

Figure 1: Flowchart of included patients.

AL was eventually confirmed in 24 of 44 patients with CT imaging for suspected AL (55%). CT scan was conclusive or highly suspicious of AL in 23 of those 24 cases, resulting in a yield of 23/44 (52%). The only false-negative finding (sensitivity 96%) was in a patient with a diverting ileostomy who had an initial negative CT scan for AL on POD 3. During routine follow-up at 2 weeks, a leak was found by endoscopy and subsequently treated. In another patient with an eventually confirmed AL, the first CT scan could not be adequately assessed due to artefacts caused by a total hip prostheses. This patient underwent a second CT scan the next day, which was conclusive for AL. In a third patient, explorative laparoscopy for suspected AL revealed peritonitis without a defect of the anastomosis and abdominal washout with formation of an ileostomy was performed. During repeat endoscopy 4 days later, an anastomotic defect was seen and endosponge treatment started.

In the 20 patients without confirmed AL, the radiology reports indicated no (n=16) or minor (n=4) suspicion for AL (specificity of 100%). Based on CT findings in the AL- group, no endoscopies or surgical explorations with negative findings were performed. There were two patients with eventually confirmed AL who

Table 1: Demographics of 44 patients who underwent CT scan for suspected anastomotic leakage after TME for rectal cancer, stratified for confirmed leakage (AL+) by surgery and/or endoscopy or no leakage (AL-).

	Total (n=44)	**AL + (n=24)**	**AL - (n=20)**	**p-value**
Mean Age in years [SD]	61 ± 9	60 ± 9	61 ± 9	0.859
Gender (male)	34 (77%)	19 (79%)	15 (75%)	0.743
Mean BMI (kg/m2) [SD]	26 ± 4	25 ± 4	26 ± 4	0.835
Smoker	5 (11%)	1 (4%)	4 (20%)	0.099
ASA score				
I	10 (23%)	7 (29%)	3 (15%)	0.319
II	33 (75%)	17 (71%)	16 (80%)	
III + IV	1 (2%)	0	1 (5%)	
Neoadjuvant radiotherapy	22 (50%)	10 (42%)	12 (60%)	0.226
Stoma after LAR	7 (16%)	5 (21%)	2 (10%)	0.328
Preoperative colostomy	1 (2%)	1 (4%)	0	
No stoma	37 (84%)	19 (79%)	18 (90%)	0.328
Anastomotic technique				
Stapled	40 (91%)	20 (83%)	20 (100%)	0.056
Hand-sewn	4 (9%)	4 (17%)	0	
Anastomotic configuration				
Side-to-end	29 (66%)	14 (58%)	15 (75%)	0.895
End-to-end	15 (34%)	10 (42%)	5 (25%)	

AL anastomotic leakage, SD standard deviation, BMI Body Mass Index in kilograms (kg) per square meter (m2), ASA-score American Society of Anesthesiologists physical status

did not initially undergo CT imaging, because diagnosis of AL was confirmed by endoscopy before CT imaging was performed. These two patients were not included in the present analysis.

Four radiological features were significantly more often seen in the AL+ group: contrast extravasation in 78% vs 0% (p=0.000), air around the anastomosis in 63% vs 25% (p=0.013), intra-abdominal free air in 71% vs 40% (p=0.040) and extraluminal air in 71% vs 30% (p=0.007). A vaginal fistula was seen in two patients with confirmed AL. The presence of radiological features stratified for confirmed diagnosis of AL are summarized in *Table 2.*

Postoperative vital and clinical parameters at time of CT imaging

The presence of vital and other clinical parameters at the time of CT imaging are shown in Table 3. Most of the parameters were not discriminative for AL, except for need for oxygen (17% vs 0%, p=0.05) and abnormal temperature (48% vs. 15%, p=0.022

Timing of CT scan and corresponding CRP-levels

CT imaging was performed on day 2 after a CRP of 336 mg/L, and on day 3 in 6 patients after a mean CRP of 300 mg/L, which was the only CRP measurement in 3 patients and CRP was measured more than once in the other 3 patients. Ten patients had a CT scan on day 4 after a mean CRP of 283 mg/L, which was the only or repeated CRP measurement in 4 and 6 patients, respectively. A total of 4 CT scans were performed on day 5 after repeated CRP measurement with a mean of 189 mg/L of the CRPs preceding CT imaging. The remaining 23 patients underwent CT imaging for suspected AL later on, and CRP was not measured within 24 hours from imaging in 7 of those patients. All CRPs preceding imaging on day 3, 4 or 5 were above the predefined cut-off levels for suspected AL. The proportions of patients with confirmed AL for the different postoperative days of CT imaging were 0/1 (0%) on day 2, 6/6 (100%) on day 3, 7/10 (70%) on day 4, 2/4 (50%) on day 5, and 9/23 (39%) beyond day 5. Table 4 summarizes these data with stratification between confirmed AL or not.

Reintervention for AL

Reintervention for AL consisted of conservative treatment with antibiotics in 2 patients (8%). Ten patients (42%) received a diverting ileostomy and started EVT, 4 patients (17%) underwent a diverting ileostomy with EVT and suturing of the defect, 5 patients (21%) started with EVT alone, 2 patients (8%) underwent a redo-procedure with ileostomy and 1 patient (2%) underwent an intersphincteric resection of the anastomosis with end-colostomy. No mortality due to AL occurred.

Timing of CRP-measurement, imaging and reinterventions

Median time interval between index surgery and initial CRP measurement was 71 hours (64-91) for patients in the AL+ group versus 92 hours (78-94) in the AL- group (p=0.009). Time interval between index surgery and the first postoperative CT scan in the AL+ group was 82 hours (77-258) compared to 250 hours (118-598) in the AL- group (p=0.020). Time between last CRP and CT imaging in the AL + group was 5 hours (3-6) versus 3 hours (1-6) in the AL- group (p=0.413). Time

Table 2: Characteristics of CT-imaging for the total cohort of 44 patients with suspected leakage after low anterior resection, and for those with (AL+) or without (AL-) confirmed leakage.

	Total (n=44)	AL + (n=24)	AL - (n=20)	p-value
Contrast				
IV + oral + rectal	17 (39%)	11 (46%)	6 (30%)	0.455
IV + rectal	22 (50%)	12 (50%)	10 (50%)	
IV + oral	3 (7%)	1 (4%)	2 (10%)	
Oral + rectal	1 (2%)	0	1 (5%)	
IV only	1 (2%)	0	1 (5%)	
Radiological feature				
Abscess near anastomosis	2 (5%)	2 (8%)	0	0.186
Abscess not near anastomosis	13 (30%)	8 (33%)	5 (25%)	0.546
Contrast extravasation*	18 (45%)	18 (78%)	0	0.000
Fluid around anastomosis	12 (27%)	8 (33%)	4 (20%)	0.323
Free fluid intra-abdominally	14 (32%)	5 (21%)	9 (45%)	0.087
Air around anastomosis#	20 (46%)	15 (63%)	5 (25%)	0.013
Free air intra-abdominally	25 (57%)	17 (71%)	8 (40%)	0.040
Extraluminal air#	23 (52%)	17 (71%)	6 (30%)	0.007
Fat infiltration	13 (29%)	6 (25%)	7 (35%)	0.469
Presacral collection	12 (28%)	8 (35%)	4 (20%)	0.281
Vaginal fistula	2 (5%)	2 (8%)	0	0.186
Other CT findings				
Paralytic ileus	9 (21%)	5 (21%)	4 (20%)	0.946
Bladder wall thickening	2 (5%)	1 (4%)	1 (5%)	0.895
Pancreatitis	3 (7%)	1 (4%)	2 (10%)	0.445
Sigmoid perforation	1 (2%)	0	1 (5%)	0.268
Air around vaginal top	1 (2%)	0	1 (5%)	0.268
Strangulation ileus	1 (2%)	0	1 (5%)	0.268
Retention bladder	1 (2%)	0	1 (5%)	0.268
Wound infection	1 (2%)	0	1 (5%)	0.268
Perihepatic fluid collection	1 (2%)	0	1 (5%)	0.268

CT computed tomography, AL anastomotic leakage, IV intravenous
* Percentage corresponds with total number of patients that received rectal contrast (n=40), of which 23 in the AL+ group and 17 in the AL- group # Extraluminal air and air around anastomosis are reported separately based on radiological reports

from CT imaging to first reintervention in the AL+ group was 6 hours (3-25). See also *table 5* and *figure 2.*

Table 3: Vital and clinical parameters on the day of the first postoperative CT scan for suspected anastomotic leakage after low anterior resection, displayed for the total cohort and depending on whether or not the leakage was confirmed by surgery and/or endoscopy.

	Total (n= 43/44)	AL + (n=23/24)*	AL - (n=20)	p-value
Vital parameters				
Hypotension, (syst. BP <100mmHg)	6 (14%)	3 (13%)	3 (15%)	0.853
Tachycardia, (>100BPM)	13 (30%)	9 (39%)	4 (20%)	0.173
Abnormal temperature[1]	14 (33%)	11 (48%)	3 (15%)	0.022
Fever (T>38°C)	10 (23%)	8 (35%)	2 (10%)	0.055
Hypothermia (T<36°C)	4 (9%)	3 (13%)	1 (5%)	0.365
Tachypnea (resp.rate >20/min)	6 (14%)	4 (17%)	2 (10%)	0.485
Clinical parameters				
Need for oxygen	4 (9%)	4 (17%)	0	0.050
Pelvic pain	35 (81%)	20 (87%)	15 (75%)	0.315
Nausea	27 (63%)	15 (65%)	12 (60%)	0.724
Vomiting	22 (51%)	14 (61%)	8 (40%)	0.172
Nasogastric tube	15 (35%)	7 (30%)	8 (40%)	0.512
Abdominal distention	12 (28%)	5 (22%)	7 (35%)	0.334

*Vital and clinical parameters of one patient with AL could not be retrieved AL anastomotic leakage, Syst. BP Systolic blood pressure, mmHg millimeters of mercury, BPM beats per minute, T Temperature, min minutes, resp. respiratory 1Disturbances in temperature defined by either hypo- (T<36°C) or hyperthermia (T>38°C)

DISCUSSION

In this retrospective cohort study, the added value of CRP guided CT imaging was evaluated for the diagnosis and subsequent management of AL after TME for rectal cancer in a cohort with highly selective diversion. CT imaging was performed in 35% of the initial cohort, which was based on CRP levels above predefined cut-off values on day 3-5 in 45% of those patients. CT imaging in the remaining patients was performed on other postoperative days for different reasons. The overall yield of CT imaging was 52%, with a sensitivity of 96% and

a specificity of 100%. CT imaging was performed after median 148 hours from TME and 5 hours from last CRP. The yield of CT imaging seemed to decrease with increasing interval from TME. Subsequent first reintervention for AL after CT imaging followed after a median of 6 hours and no endoscopic or surgical interventions with negative findings were performed after a negative CT scan, indicating the added valued of CT in timely and tailored re-intervention using this institutional protocol.

Compared to literature, the present study reveals a relatively high rate of positive CT scans (55%) and low rate of false-negative (2%) and false-positive (0%) findings.[11, 16] A recent study including patients that underwent CT imaging for AL-suspicion after colorectal surgery found 24.8% of scans positive for AL with a 32% false-negative and 7% false-positive rate[17]. A possible explanation for the high yield of CT imaging is the use of a postoperative protocol with routine CRP measurement, which increases the a priori likelihood of AL in the tested population. This protocol might also increase diagnostic accuracy, besides the close collaboration and joined effort by clinicians and radiologists in our unit to interpret the images and to take all available clinical, laboratory and radiological signs of AL into account for a definitive diagnosis.

It is also important to emphasize the specific setting of this study with highly selective diversion. The diagnosis of AL is often more clear in the absence of a diverting stoma and this might have also contributed to the high diagnostic accuracy. Especially in those patients with early clinical signs of AL, there is a high yield of CT imaging: 15 confirmed ALs out of 20 CT scans performed on postoperative day 3-5 (75%). Diagnosing AL might be more difficult in case of routine diversion because of masked clinical signs of AL or even asymptomatic leaks.

Timing of CT scanning is essential for adequate detection of AL, because it might take some time before an abscess cavity behind the anastomosis becomes visible. In defunctioned cohorts, it has been suggested that CT-imaging should be performed at least 7 days postoperatively[16, 18]. The present study suggests that CRP measurements can facilitate timely CT imaging with a high yield early on in the postoperative period, although this cannot be extrapolated to studies with routine fecal diversion. Rectal contrast is another valuable element of CT imaging for this purpose, although a fluid collection in contact with the anastomosis not containing contrast is also highly suspicious. A retrospective cohort study with 108 patients that received a CT scan within 16 days after colorectal surgery found that fluid near the anastomosis, air near the anastomosis, intra-abdominal air and

Table 4: Timing of CT imaging with corresponding CRP levels and elevated CRP according to predetermined cut-off values for each postoperative day, with subgroup analysis whether or not anastomotic leakage was eventually confirmed.

	Total	AL +	AL -	p-value
CT on day 2	**1/44**	**0/24**	**1/20**	
Mean CRP	336 ± NA	NA	336 ± NA	NA
CT on Day 3	**6/44**	**6/24**	**0/20**	
Mean CRP*	300 ± 72	300 ± 72	NA	NA
CRP > 172	6 (100%)	6 (100%)	0	NA
CT on Day 4	**10/44**	**7/24**	**3/20**	
Mean CRP*	283 ± 76	293 ± 62	260 ± 115	0.554
CRP > 124	10 (100%)	7 (100%)	3 (100%)	NA
CT on Day 5	**4/44**	**2/24**	**2/20**	
Mean CRP*	189 ± 44	193 ± 59	185 ± 47	0.897
CRP > 144	4 (100%)	2 (100%)	2 (100%)	NA
CT beyond day 5	**23/44**	**9/24**	**14/20**	
CRP measured preceding CT	16/44	7/24	9/20	
Mean CRP*	83 ± 61	106 ± 50	66 ± 67	0.209

AL Anastomotic leakage, *CRP* C-reactive protein, *=last CRP preceding CT scan in case of multiple measurements. Cut-off values for CRP to predict AL were previously calculated in a review by Singh et al: CRP > 172 on day 3, CRP >124 on day 4 and CRP> 144 on day 5.

Table 5: Timing of CRP-measurement, imaging and reinterventions.

	Total cohort			AL +			AL -			
	n	*median*	*IQR*	*n*	*median*	*IQR*	*n*	*median*	*IQR*	*p-value*
TME - initial CRP, (hours)	*42*	87	69-94	22	71	64-91	20	92	78-94	0.009
TME - first CT imaging, (hours)	*44*	148	94-335	24	82	77-258	20	250	118-598	0.020
Initial CRP - last CRP[1], (hours)	*35*	25	12-144	22	22	6-124	13	68	18-229	0.123
CRP preceding CT[1] – CT, (hours)	*35*	5	3-6	22	5	3-6	13	3	1-6	0.413
CT - first reintervention, (hours)	*24*	6	3-25	24	6	3-25	NA	NA	NA	NA

AL Anastomotic leakage, *TME* total mesorectal excision, *CRP* C-reactive protein, *CT* Computed tomography, *IQR* Interquartile range
[1] Last CRP before CT imaging (in case of multiple CRP measurements), only included for patients with serum CRP-levels that were measured within 24 hours of the CT scan

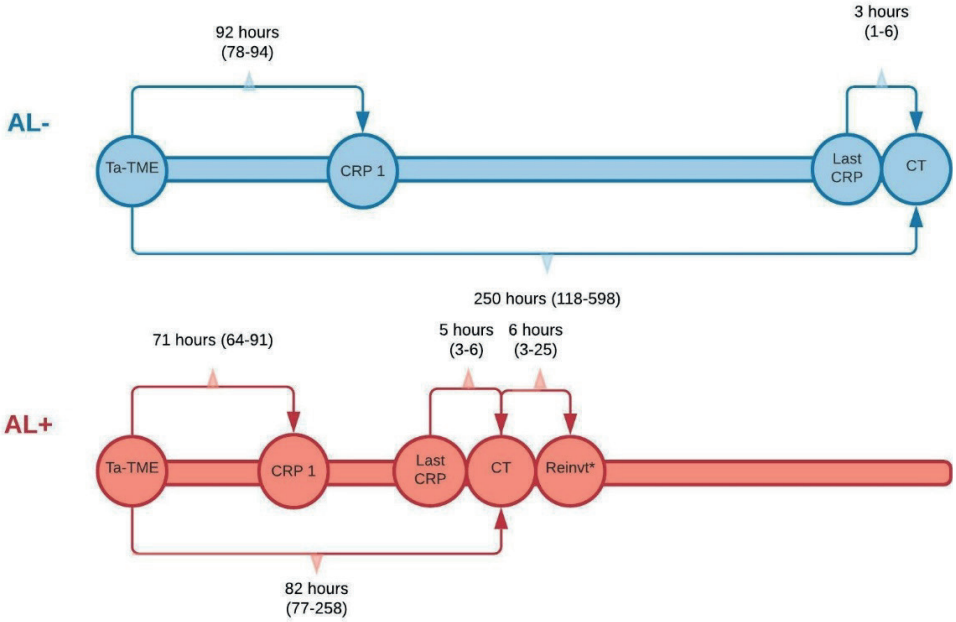

Figure 2: Median time interval in hours between index surgery, CRP measurements, CT imaging and subsequent reintervention.

contrast leakage to be highly associated with AL[10]. Another study showed similar results; of the patients with an AL, 32/33 (97%) had contrast extravasation on their CT and 97/114 (85%) had a perianastomotic fluid collection[11]. We found a presacral collection in 20% of patients without confirmed leakage, which reveals that this should be interpreted with caution. Size of the collection and increase in size over time might be more specific for AL[19]. There are also pitfalls related to the rectal contrast. At an early stage, the defect could be too small to permit extraluminal flow of contrast. By overinflating the balloon, a (small) defect in a low anastomosis could have been sealed during imaging. Finally, inadequate contrast administration might lower the sensitivity in detecting AL[17]. Subsequently false negative imaging may lead to delay in reintervention and increased mortality[20].

Singh et al. calculated the predictive value of serum CRP levels on postoperative day 3, 4, and 5[9]. In this review, patient groups were heterogenous, both segmental colon and rectal resections were included, and diversion rates were unclear. Diversion is less common after segmental colon resections, which probably increases the validity of these data for our cohort of highly selective diversion. All confirmed leaks had a CRP level above the published cut-off levels by Singh

et al. However, once CT imaging has been performed based on these CRP cut-off values, CRP is no longer predictive for AL given the similar CRP levels in those patients without confirmed AL. Delay in elevation of CRP is possible and may be normal due to surgical stress[21, 22]. Repeat measurements might be necessary as some patients in this cohort had normal CRP levels on day 3, but showed increased CRP-levels on day 4 or day 5.

All patients in this study cohort were operated on in an academic teaching hospital with a proactive treatment approach to AL. Endoscopy was often part of subsequent interventions following CT imaging. Endoscopy is able to confirm suspected AL based on CT, but this requires specific expertise. A small area of granulation tissue without visible defect might hide the leak. If there is presacral collection on CT, probing of such an area with a forceps or guide wire should then be performed to prove the diagnosis of AL. Furthermore, endoscopic inspection of the anastomosis can be valuable to determine the exact size of the defect and whether there is retraction or ischemia of the afferent loop. More research may be needed to investigate the accuracy and additional value of endoscopy versus CT in detecting AL as a single or combined diagnostic modality.

Our AL rate of 19% (24/125) seems higher than often reported. Clinical AL rates might be lower in case of routine diversion in combination with a relatively limited follow-up, mostly 30 to 90 days postoperatively. If patients are diverted, diagnosis of AL might occur only following closure of the diverting stoma after several months. In addition, asymptomatic leaks in diverted patients are often not reported. In a Dutch national cross-sectional study, the initially reported 30-day AL rate of 8.2% in the national audit appeared to be actually 13.4% when reviewing patient files in detail, and at 1 year this increased to 20%.[4] We also investigated our own transition from standard to selective diversion and found similar AL-rates, similar end-colostomy rates, but much higher long-term ileostomy rates after routine diversion, because many temporary ileostomies are never closed unintentionally.[14, 23]

Limitations of this study are the relatively small study population and retrospective design. Initial CRP levels were not measured on the same day for all patients due to changes in protocol, as was stated before. In the review by Sing et al., as referred to in the methods [9], the negative predictive values on day 3 and 4 were similar and should not influence the results in a significant way. The original radiological reports were used in the analysis, without interpretation of the features. Experience of the radiologist and explicit reporting of relevant features could have influenced results. However, we aimed to determine the value of CT

based on routine daily practice, for which reason we decided not to revise the images by expert radiologists or second readers.

In conclusion, this study showed a high yield of CT imaging in an academic center with a policy of highly selective fecal diversion after TME for rectal cancer and a pro-active leakage management. CT imaging can be performed in an early postoperative setting based on elevated CRP levels above published cut-off values for postoperative day 3-5, together with other clinical signs of AL. This allows for timely and tailored subsequent reintervention for AL within a few hours, and prevents overtreatment with negative explorative interventions at the same time.

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Appendix

Supplementary table 1: *Tumor Characteristics.*

	Total (n=44)	AL + (n=24)	AL - (n=20)	p-value
T-stage				
T1	3 (7%)	1 (4%)	2 (10%)	0.135
T2	13 (30%)	7 (29%)	6 (30%)	
T3a	10 (22%)	5 (21%)	5 (25%)	
T3b	7 (16%)	7 (29%)	0	
T3c	7 (16%)	2 (8%)	5 (25%)	
T4	4 (9%)	2 (8%)	2 (10%)	
N-stage				
N0	21 (48%)	14 (58%)	7 (35%)	0.132
N1 + N2	23 (52%)	10 (42%)	13 (65%)	
M- Stage				
Lung	2 (5%)	1 (4%)	1 (5%)	0.447
Liver	4 (9%)	3 (13%)	1 (5%)	
Other	2 (5%)	2 (8%)	0	

TNM-stage Tumor Nodus Metastasis stage (as preoperatively determined by MRI-scanning), MRI magnetic resonance imaging

CHAPTER 6

TreatmENT of AnastomotiC LeakagE after rectal cancer resection (TENTACLE – Rectum)

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ABSTRACT

Background: Anastomotic Leakage is a severe complication after Low Anterior Resection (LAR) for rectal cancer and occurs in up to 20% of patients. Most research focusses on reducing incidence and predictive factors of anastomotic leakage. There are no robust data on severity and treatment strategies with associated outcomes.

Objectives: The objective of the TENTACLE – Rectum study is 1) to investigate which factors contribute to anastomotic leakage severity and to compose an anastomotic leakage severity score and 2) to evaluate the effects of different treatment approaches on pre-specified outcome parameters, stratified for severity score and other leakages characteristics.

Methods: The TENTACLE-Rectum is an international multicenter retrospective cohort study. Patients who developed anastomotic leakage after LAR for primary rectal cancer between Jan 1st 2014 and Dec 31st 2018 will be included by each center. We aim to include 1246 patients in this study. The primary outcome is 1-year stoma-free survival (i.e. patients alive at 1 year without a stoma). Secondary outcomes include number of reinterventions and unplanned readmissions within one year, total hospital stay within one year, total time of having a stoma until one year, type of stoma present at one year (defunctioning, permanent), secondary leakage related complications, mortality and hospital related costs. For objective 1, regression models are used to create an anastomotic leakage severity score. For objective 2, effectiveness of different treatment strategies for leakage is tested after correction for severity score and leakage characteristics, in addition to other potential patient and primary treatment related confounders.

Conclusion: The TENTACLE-Rectum will be the first large international collaborative study on severity and treatment of anastomotic leakage after LAR for rectal cancer, which entails an important step towards evidence-based recommendations and improving outcome of patients who experience severe treatment related morbidity.

INTRODUCTION

Anastomotic leakage occurs in up to 20% after low anterior resection (LAR) for rectal cancer[1-3]. It comprises a wide range of clinical entities at first presentation, from occult leakage below a defunctioning stoma to fecal peritonitis with multiple organ failure. Initially silent leaks can develop into chronic pelvic sepsis. In general, it is a severe complication associated with high morbidity, ICU admission, prolonged hospital stay and need for reinterventions and readmissions. Permanent stoma rates of around 20% have been reported and this is associated with a significant impact on quality of life [4]. In addition, anastomotic leakage is reported to be independently associated with an increased risk of local recurrence and reduced long term survival[5].

Conventional treatment of anastomotic leakage after LAR consists of fecal diversion, achieved by a primary or secondary defunctioning stoma, and less frequently breakdown of the anastomosis with end colostomy. Additionally, antibiotics are given and the pelvic abscess is often drained. However, up to 50% of the leaks do not heal with such passive management, especially not in an irradiated field[1]. Pelvic sepsis might even persist after constructing an end colostomy. A competent sphincter, impeding adequate drainage of a presacral abscess, likely contributes to non-healing of a leak. For this reason, management of leakage is shifting towards more active treatment strategies in most recent years [6-9].

Remarkably, there is no robust evidence comparing different treatments of anastomotic leakage after LAR and there are no evidence-based treatment algorithms. An important reason for this lack of good quality evidence is the clinical heterogeneity of patients with anastomotic leakage after LAR, which complicates performing meaningful studies. In addition, there is no generally accepted pre-treatment anastomotic leakage classification and leakage severity is currently graded according to how it is treated[10]. Although scoring anastomotic leakage by how it is treated is useful for reporting the consequences of anastomotic leakage, it is by definition unsuitable for research comparing different treatment strategies for anastomotic leakage. Moreover, it cannot be used to guide decision making when anastomotic leakage is diagnosed in a clinical setting.

Therefore, the aims of this study are 1) To investigate which factors contribute to anastomotic leakage severity and use these data to compose an anastomotic leakage severity score, and 2) to evaluate the effectiveness of different treatment approaches on different pre-specified outcome parameters, stratified by severity score, anatomical characteristics of the leak and timing of diagnosis.

METHODS

Study design

TENTACLE - Rectum study is an international multicenter retrospective cohort study in which all consecutive patients who underwent LAR for rectal cancer between January 1st 2014 and December 31st 2018 and subsequently developed anastomotic leakage after low anterior resection for rectal cancer will be included from each participating center. Follow-up of included patients will be at least 1 year. The study opened in April 2020 and will recruit until Dec 2020. Possibly, the inclusion period will be extended 3-6 months because of the COVID-19 pandemic. The study timeline is presented in Figure 1.

The TENTACLE-Rectum is open to participate for all centers that perform rectal cancer surgery. All centers are asked to fill out a questionnaire about their practice. This includes questions on hospital type, rectal cancer case-load, LAR case-load and available diagnostic and treatment modalities. International research networks will be asked to support this study in order to increase inclusion of patients and optimize the chance of obtaining robust results. The TENTACLE – Rectum study is an investigator initiated study which receives financial support from Medtronic Inc. The company is not involved in the conduct of the study or analysis and interpretation of the data.

Study population

Inclusion criteria are: (1) Aged 18 years or older; (2) primary tumor with the lower border below the level of the sigmoid take-off according to the international consensus definition of the rectum [11]; (3) LAR with primary anastomosis with or without defunctioning loop ileostomy for either (a) primary cancer, (b) completion total mesorectal excision after local excision or (c) salvage resection for regrowth after watch & wait or (d) salvage resection after local excision; (4) anastomotic leakage according to the following definition: “a breach in a surgical join between two hollow viscera, with or without active leak of luminal contents”, being diagnosed at any time point during the first postoperative year[12]

Exclusion criteria are: (1) Rectal resection for benign disease; (2) Rectal resection for recurrent rectal cancer after previous low anterior resection or other primary malignancies; (3) Emergency resection;

Collaborators from the participating centers are provided with instructions on patient selection and data entry to ensure homogeneity in the inclusion process and data entry, and to ensure that any anastomotic leakage occurring within

one year postoperative will be captured during screening of the medical files, including occult leaks and late leaks developing after ileostomy closure.

Study parameters

Hospital characteristics

The following hospital characteristics will be collected through a questionnaire that is sent to the coordinating investigator of all sites: hospital type (academic, non-academic teaching, categorical); annual volume of rectal cancer resections, annual volume of restorative LAR, and number of restorative LAR for rectal cancer with the lower border below the sigmoid take-off on sagittal MRI during the period 2014-2018; number of hospital beds; diagnosis and treatment strategy depending on surgeon-on-call (general or colorectal surgeon); ward facilities (e.g. dedicated colorectal nurse / physician assistant); types of diagnostic and treatment modalities that are available in the hospital.

Patient, cancer treatment and index operation characteristics

Collected patient characteristics are sex, age, height, weight, ASA classification, Charlson comorbidity index, tumor location (distance from anorectal junction to the lower border of the tumor on sagittal MRI), preoperative T-stage, preoperative N-stage, preoperative M-stage and year of surgery. Cancer treatment characteristics include type of neoadjuvant therapy, surgical approach (e.g. minimally invasive versus open), extent of resection, level of vascular ligation and splenic flexure mobilization, type of anastomosis (e.g. configuration, hand sewn versus (single/double) stapled) and distance from the anal verge, and primary defunctioning stoma.

Anastomotic leakage characteristics

The following characteristics regarding anastomotic leakage diagnosis will be recorded: time from surgery to diagnosis of the leakage (days) and modality performed to diagnose anastomotic leakage. At the time of diagnoses, vital signs, leukocyte count, CRP, serum albumin and creatinine will be recorded (parameters within 24 hours from the test that first diagnosed the leak are used). Anastomotic leakage characteristics are: location of the leak (e.g. dorsal versus ventral, blind loop versus anastomosis), fistulation (e.g. vagina, perineum), estimated proportion of the circumference, presence of ischemia and retraction of the afferent colon, contaminated spaces and degree of contamination, and drains in place at diagnosis with corresponding location.

Anastomotic leakage treatment characteristics

Anastomotic leakage treatment characteristics include admission to intensive care or high care, need for emergency surgery, reoperation approach (e.g. minimally invasive or open), type of reoperation (e.g. secondary defunctioning stoma, drainage, suturing of the anastomosis, breakdown of the anastomosis), endoscopic vacuum assisted drainage, percutaneous drainage, and transanal drainage.

Outcome parameters

The primary outcome parameter is the 1-year stoma free survival. Secondary outcomes includes: ICU length of stay, mortality, comprehensive complications index [13], total number of reinterventions (surgical, radiological, endoscopic) within one year, total number of unplanned readmissions within one year, total hospital stay during one year, total time of having a stoma until one year, stoma present at one year, type of stoma present at one year (defunctioning, permanent), secondary leakage related complications (extrapelvic abscess, cutaneous fistula, vaginal fistula, bladder fistula, small bowel fistula, ureteric fibrosis with hydronephrosis), hospital related costs.

Sample size calculation

For study objective 1, creation of a risk score with 20 candidate predictors with a one year stoma-free survival rate of 70% and a Nagelkerke R^2 of 0.15 requires a total of 1097 patients with anastomotic leakage. For comparing the effectiveness of different treatment strategies (study objective 2), a relative difference of 25% in 1-year stoma-free survival is considered clinically significant, which corresponds to an absolute difference of 7% based on an expected 1-year stoma-free survival of 70%. With a power of 0.80 and a significance level of 0.05, a total of 1246 patients are needed to detect this difference.

Pilot study

After the study protocol and online CRF were developed, we invited a panel of international experts on anastomotic leakage and rectal cancer surgery from seven countries to participate in a pilot (table 1). The international steering committee was asked to contribute 5 patients to the online CRF and provide feedback on the protocol and CRF. The feedback was used to refine the protocol and CRF before finalizing these, to ensure international consensus and clarity on the use of the CRF and definitions. The feedback was evaluated by the study group and implemented if deemed relevant. The pilot was performed from January 2020 – April 2020.

Data handling and regulatory considerations

Data will be collected in an online CRF, using the Castor database system (www.castoredc.com). This online medical research database system is certified to meet international security standards and is compliant with all relevant regulations, amongst which are ICH-GCP, GDPR, HIPAA, FDA 21 CFR part 11, ISO 27001 and ISO 9001.

All pseudo-anonymized patient data will be entered by or under supervision of the treating physician(s). Each patient will be coded with a unique patient number, before being entered into the database. Surgeons who participate in the TENTACLE – Rectum study keep a password coded file that can identify individual patients, which will be locked away in their practice. This file can be accessed by the local investigators if needed, for example in case a relevant new research question requires entering of additional data into the database. Up to 4 users per participating center will receive a Castor-account and can enter data into the database.

Data verification and data validation

After the inclusion of new cases closes, data verification aims to increase the quality and completeness of the data. Data verification includes checking the data for inconsistencies and flagging parameters with substantial missing data that is deemed likely to be recorded in the medical files by the study team. This is fed back to the local investigators and they will have the opportunity to complete or adjust their data. After data verification, we aim to validate a core parameter set for 10-20% of the inclusions using local data validators who are recruited independently of the original study team.

Statistical Analysis

Main study objective 1

First, univariable analysis is performed on variables that are considered to be potentially relevant for the anastomotic leakage severity score, i.e. parameters that are available at the time of diagnosis. Anastomotic leakage characteristics and patient characteristics are of particular interest for this objective. Second, factors that are considered to be clinically relevant based on literature and/or expert opinion are selected for multivariable analysis. Backwards selection is used to exclude values of $p \geq 0.05$ from the competing risks model. Results are presented as odds ratio (OR) with 95% confidence intervals (CI). Third, the multivariable competing risks model will be internally validated by bootstrapping,

using 5000 bootstrap resamples. Finally, a nomogram is constructed based on the final bootstrapped multivariable regression analysis.

If casemix is found to be very strongly associated with outcome relative to the severity score (to the extent that the severity score is of limited additional value in the regression model), latent class analysis is used [14]. The parameters included in the anastomotic leakage severity score are used to create casemix corrected classes of anastomotic leakage severity.

Main study objective 2
In this analysis, the different treatment modalities are the exposures. The association between anastomotic index operation characteristics, leakage characteristics and outcome parameters will be evaluated for the exposures in regression analysis. Correction for patient characteristics, tumor characteristics and anastomotic leakage severity score is performed.

Based on the results of this first analysis, subgroups of patients are created based on individual index operation and leakage characteristics or based on a combination of characteristics. The effectiveness of anastomotic leakage treatment strategies is assessed in regression models for the different outcome parameters and corrected for patient characteristics, tumor characteristics and anastomotic leakage severity score, if appropriate. Comparison of the primary outcome parameter and secondary outcome parameters will be expressed in terms of a odds ratio and corresponding 95% confidence intervals.

Ethical considerations
This study will be conducted in compliance with the principles of the declaration of Helsinki. The study protocol and relevant documents have been approved by the medical ethical committee of the Radboud University Medical Center, Nijmegen, the Netherlands. All participating centers are provided with the study protocol and relevant documents. Because of the international study design, local ethical approval is left at the discretion of the participating center. The TENTACLE-Rectum has been registered on Clinicaltrials.gov (NCT 04127734). The full study protocol can be accessed on www.tentaclestudy.com.

Publications
We aim to publish two main manuscripts that cover the results of our main study objectives. These will be submitted to peer-reviewed journals. The TENTACLE – Rectum study embraces corporate authorship and a

maximum of 4 collaborators per center that contribute to this study will form the TENTACLE – Rectum collaborative study group. This group will be part of all publications in which TENTACLE – Rectum study data is used. The protocol writing committee is fully involved in conducting this study and will be included as authors in the main publications in which the TENTACLE – Rectum study data is used.

DISCUSSION

Anastomotic leakage remains a frequent and severe complication after rectal cancer surgery. Although previous research mainly focused on incidence and has established (amendable) risk factors for anastomotic leakage[15-17], the optimal treatment of an anastomotic leakage after LAR is unknown. There are several explanations for this observation. Treatment of anastomotic leakage often takes place in the emergency setting, is chosen on a case by case basis depending on several patient and surgical factors and is influenced by preferences and expertise of the surgeon involved. In addition, the numbers of patients per center is relatively small, despite the fact that anastomotic leakage is one of the most frequent complications. Actually, anastomotic leakage is a low-volume heterogeneous disease entity with high complexity. This has likely hampered the initiation of standardized institutional treatment protocols and design of prospective studies. The clinical heterogeneity of patients with anastomotic leakage and the wide variety in treatment approaches results in several clinically relevant subgroups, and this complicates interpretation and generalizability of the small underpowered individual studies. Finally, some misperceptions might have contributed to the paucity of available evidence in this field. These misperceptions include overestimation of spontaneous healing of an anastomotic leakage, and underestimation of late anastomotic problems as a consequence of a longstanding sealed abscess.

Anastomotic leakage is currently classified based on how it is treated [10, 18], but this classification can by definition not be used for research on what treatments are most effective. Therefore, a classification of severity of leakage should be based on pre-treatment characteristics, like the anastomotic leakage severity score we aim to create. Such a score is needed to enable meaningful research on the effectiveness of anastomotic leakage treatment strategies and support clinicians in decisions on how to treat individual patients with anastomotic leakage.

The main strengths of the present study are the high level of detail of the collected data and the large number of patients we aim to include. This large number of

patients is needed to perform regression analysis with a high number of factors, and this facilitates subgroup analyses for distinct clinical entities that we might identify. If more patients are included, even more detailed statistical models can be built to accommodate clinical heterogeneity. The inclusion of a high number of patients is made possible by the international collaborative nature of this study, which at the same time contributes to generalizability of results to other populations. The pilot study that was performed together with core collaborators from different continents ensured that the CRF also includes parameters that are important to other geographical regions and that definitions are clear for all collaborators worldwide.

Perhaps the most important limitation is the retrospective nature of the study. Because of the large number of patients that is needed to achieve our main aims, a prospective study was considered to be unfeasible. The data that is generated in this study can be used to inform what factors are important to incorporate into future prospective studies, preferably also including quality of life endpoints. Another limitation is that confounding by indication (*i.e.* patients who receive a type of treatment are inherently different from other patients) may occur. However, the absence of quality data on the effectiveness of anastomotic leakage treatment has led to a wide variety of treatment options that can be used for any given patient. In this case, regression analysis of detailed parameters in a large cohort of patients is expected to accommodate most of this possible bias. Although we recognize that this study will not answer all questions regarding anastomotic leakage treatment, we believe it will generate valuable data from a unique dataset and hope it will serve as a solid basis for future studies.

An important aspect of this study is investigating whether clinical leakage entities can be found for which some types of treatments are generally more effective than others. These hypothesis generating analyses could lead to a more personalized approach to anastomotic leakage treatment. As an example, a type of anastomotic leakage which was specifically addressed when designing this study is the occult or minimal symptomatic leakage below a defunctioning stoma that was constructed at index surgery. Such a leak often appears to be healed during assessment of the anastomosis a few months later, but might subsequently reactivate after restoring continuity. These leakages, of which the incidence is likely to be underreported [19-21], can ultimately have severe consequences (e.g. chronic pelvic sepsis, fistulation) despite initially presenting as a 'silent' leak. This probably needs a more pro-active management from the beginning, and likely needs a different type of treatment strategy in case of persistent non-healing later on. Conducting an international

multicenter cohort study of the intended size may therefore also provide an opportunity to study several clinically rare, but important subgroups.

CONCLUSION

The TENTACLE-Rectum study is a large international collaborative study, which will investigate which factors contribute to anastomotic leakage severity and evaluate treatment efficacy for different relevant subgroups, different clinical settings, and different treatment modalities.

Table 1: TENTACLE-Rectum international steering committee.

Principal Investigator	Hospital	City	Country
Albert Wolthuis	UZ Leuven	Leuven	Belgium
F Borja de Lacy	Hospital Clinic de Barcelona	Barcelona	Spain
Hans de Wilt	Radboudumc	Nijmegen	The Netherlands
Jeremy Lefevre	Hopitaux de Paris	Paris	France
Michael Solomon	University of Sydney central clinical school	Sydney	Australia
Matteo Frasson	Valencia university hospital La Fe	Valencia	Spain
Nicolas Rotholtz	Hospital Alemán, Buenos Aires	Buenos Aires	Argentina
Pieter Tanis	Amsterdam UMC	Amsterdam	The Netherlands
Quentin Denost	Bordeaux university hospital	Bordeaux	France
Rodrigo Perez	University of Sao Paulo	Sao Paolo	Brazil
Tsuyoshi Konishi	Cancer institute hospital Tokyo	Tokyo	Japan

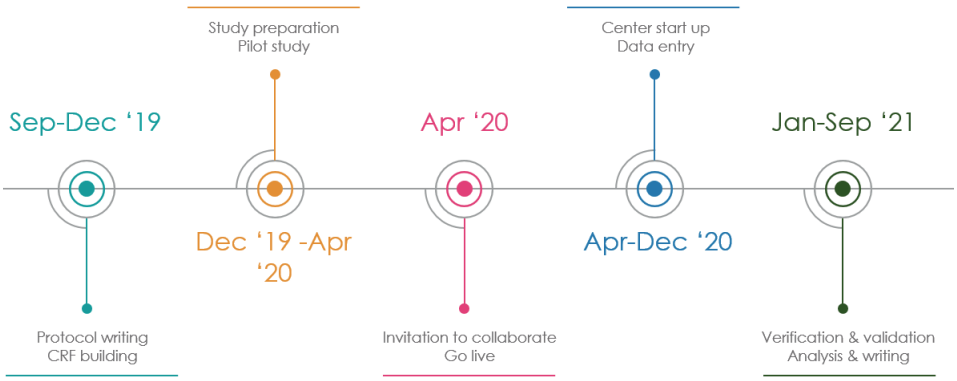

Figure 1: Study timeline.

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CHAPTER 7

International expert opinion on optimal treatment of anastomotic leakage after rectal cancer resection: a case-vignette study

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ABSTRACT

Purpose: Little is known about optimal treatment of anastomotic leakage after low anterior resection (LAR) for rectal cancer and whether treatment strategy depends on leakage features and patient characteristics. The objective of this study was to determine which treatment principles are used by expert colorectal surgeons worldwide.

Methods: In this international case vignette study, participants completed a survey on their preferred treatment for 11 clinical cases with varying leakage features and two patient scenarios depending on surgical risk (total of 22 cases).

Results: In total, 42 of 64 invited surgeons completed the survey from 18 countries worldwide. The majority worked at a university training hospital (62%) and had more than 15 years of experience performing LAR for rectal cancer (52%). Early leaks in septic patients were preferably treated by major salvage surgery, to some extent depending on patient scenario. In early leaks in non-septic patients, drainage and fecal diversion were the cornerstone of proposed treatment. Endoscopic vacuum therapy was more often proposed than percutaneous drainage. A minority proposed anastomotic reconstruction, more often for larger defects. Treatment of late leaks ranged from watchful waiting, drainage or transanal repair to major (non-)restorative salvage surgery, with minimal influence of degree of symptoms on proposed strategy. Leaks of the blind loop and rectovaginal fistulae showed high variability in proposed treatment strategy.

Conclusion: This TENTACLE-Rectum case vignette study demonstrates tailored treatment strategies depending on clinical type of leak and patient characteristics, with variable degrees of consensus and knowledge gaps which should be addressed in future studies.

INTRODUCTION

Anastomotic leakage (AL) after low anterior resection (LAR) for rectal cancer remains a highly prevalent complication with serious consequences and leads to increased morbidity, increased risk of reinterventions, increased 90-day mortality in elderly patients, increased permanent stoma rates and decreased quality of life. [1-6] In contrast to numerous studies on risk factors and prevention of anastomotic leakage, little is known about how to effectively treat AL after LAR.

Conventionally, AL after LAR is treated by dismantling the anastomosis or creating a diverting stoma (if not already present) and radiological or manual drainage of presacral collections[1]. More recently, new techniques have emerged such as endoscopic vacuum therapy (EVT), where a negative-pressure sponge is placed endoscopically into the presacral cavity.[7] EVT can be combined with transanal closure of the defect (endoscopic vacuum assisted surgical closure (EVASC)).[8] For certain types of leaks, such as a rectovaginal fistula or an ischaemic afferent colon, major reconstructive surgery can be considered: immediate redo anastomosis, delayed redo (Turnbull-Cutait), or intersphincteric proctectomy with complete debridement and pelvic cavity filling (e.g. omentoplasty).

The wide variety in applied treatment approaches is likely related to the clinical heterogeneity of AL after LAR. Different clinical entities can be defined depending on the time-interval until diagnosis, concomitant abdominal sepsis, presence of ischaemia, degree of dehiscence, leakage-related symptoms such as sacral pain, and other leakage features such as the presence of a fistula (e.g. to the vagina).

Scarcely available studies on the treatment of AL after LAR focus on the efficacy of a single modality in unspecified leaks. In clinical practice, one should probably define the treatment goal and select a corresponding treatment principle first, and then choose the most-suited modality to achieve this. Key principles in the treatment of AL can be identified in addition to general supportive interventions (e.g. feeding, antibiotics): abscess drainage, fecal diversion, temporary takedown of the anastomosis, reconstruction of the anastomosis, watchful waiting (WW) and definitive salvage surgery. Focusing on treatment principles instead of individual modalities may give more insight into the question how AL should be approached based on relevant clinical parameters.

The aim of this case vignette study was to gain more insight into how an international group of expert colorectal surgeons approach AL after LAR for rectal cancer in general, and to investigate how these surgeons might tailor their approach to different subtypes of AL based on several leakage and patient characteristics.

METHODS

Study design

This was an international case vignette study in which a group of international experts were invited to participate by completing an online survey about the treatment of AL after LAR for rectal cancer. Invited experts were either part of the steering committee of the TENTACLE - Rectum study, or the international TaTME Guidance collaborative. [9, 10] Invited experts are all experienced colorectal surgeons performing TME surgery and being actively involved in relevant scientific projects and/or colorectal societies. This survey consisted of a short general questionnaire and case discussions. The latter part included 11 clinical cases with different leakage features, and each case was presented for two different scenarios reflecting patients with low and high surgical risk, respectively (total 22 cases). The survey can be found in Table 1 and 2, and a summary of the clinical cases is presented in Table 3. The survey was collected through the online platform Pluvo (www.pluvo.com) and all answers were analyzed and reported anonymously.

Table 3: Summary clinical cases.

Case	Day	Diversion	Symptoms	Summary presentation AL
1	3	Yes	Septic	Ischaemia afferent colon
2	3	Yes	Septic	Complete dehiscence anastomosis (3cm retraction)
3	5	No	Mild	Presacral collection (2x2cm) + 1/3 defect on endoscopy
4	5	Yes	None	Presacral collection and contrast extravasation, no defect on endoscopy
5	5	No	Mild	Presacral collection and contrast extravasation, defect blind loop (2x2cm)
6	5	Yes	Mild	Presacral collection and contrast extravasation, large defect (>50%) without ischaemia
7	50	Yes	None	Contrast extravasation and a small presacral collection
8	50	Yes	None	Contrast extravasation, but no presacral collection
9	50	Yes	Mild	Pus and air discharge through the vagina, no other clinical symptoms
10	250	No	Pain and LARS	Day 80 after closure of diverting ileostomy. Sacral pain and severe LARS. Presacral collection, 25% defect on posterior side
11	250	No	Mild	Mild pain, flatulence and mucus per anum. Presacral collection of air, 25% defect posterior side

Questionnaire

The general questionnaire contained questions about the participants and their institutional setting (country, type of hospital, experience, annual caseload), therapeutic modalities used for AL, available techniques for transanal surgery, general treatment principles (fecal diversion, preferred approach to drain a pelvic abscess or to treat abdominal free fluid and fecal/purulent peritonitis) and experience with anastomotic reconstruction.

Clinical cases

Eleven clinical cases were formulated by the TENTACLE - Rectum study team, with the aim to provide a broad range of leakage features that were expected to influence treatment strategy. These features included time interval to diagnosis of AL (e.g. early leak on day 5, late diagnosed leaks on day 50 and 250), degree of dehiscence, location of the leak, retraction of the afferent loop, vascularization, size of presacral collections, presence of contrast extravasation on imaging, clinical symptoms (e.g. pain or low anterior resection syndrome (LARS)), hemodynamic instability (septic patient) and presence of a diverting ileostomy. All cases were presented for two clinical risk scenarios, which were a fit young patient and an elderly frail patient with comorbidities. Participants were able to select multiple answers for each clinical case to ensure that choosing a combination of modalities was possible.

Treatment principles

For each clinical case, participants were asked to choose the most suitable treatment principle(s):

a) *Drainage*: interventions aimed to drain presacral collections, e.g. intermittent transanal drainage (i.e. endoscopic wash-out), percutaneous radiological drainage, EVT

b) *Reconstruction*: procedures to transanally close the defect (open surgical approach (just Lonestar), transanal minimally invasive surgery (TAMIS) approach, endoscopic clipping (e.g. OVESCO)) or redo anastomosis after resection of the leaking anastomosis (i.e. immediate or delayed (Turnball-Cutait)).

c) *Fecal diversion*: temporary diversion (defunctioning ileostomy or colostomy)

d) *Anastomotic take-down with possibility of secondary reconstruction:* end-c*olostomy without removing rectal stump, leaving the original anastomosis in place.*

e) *Watchful waiting:* awaiting secondary healing.

f) *Definitive salvage surgery without possibility of secondary reconstruction:* intersphincteric resection of the rectal stump/anastomosis with debridement of the pelvic cavity and presacral filling (omentoplasty, flaps

Analysis

Descriptive statistics were used for this explorative study to gain insight into different treatment strategies for AL after LAR. Proportions of selected treatment modalities by participants were presented for each clinical case and clinical risk scenario. Analyses were carried out with IBM SPSS statistics, version 26.0 (IBM, Corp Armonk, New York, United States of America).

RESULTS

Part 1: Questionnaire

Out of 64 invited participants, 42 experts filled out the survey from 18 countries worldwide (66%). Most respondents originated from Europe (n=25), of which 4 from the United Kingdom and 4 from the Netherlands. The majority worked at an academic teaching hospital (62%) and had more than 15 years of experience performing LAR for rectal cancer (52%). In 62% of the participants, the annual number of LAR performed was more than 50 procedures (Table 1).

Amongst available treatment modalities for AL in the respondent's hospital (Table 1), CT guided transgluteal drainage was most frequently reported (93%). EVT was also commonly available (74%), as well as some type of transanal platform (TAMIS 86%, transanal endoscopic microsurgery (TEM) 48%, open transanal approach with retractor 88%).

Personal preferences of the participants regarding treatment of AL are displayed in Table 2. Ninety-one percent of respondents diverted the leaking anastomosis always, or almost always with a few exceptions (small leak or EVT). The preferred approach(es) to drain a pelvic (presacral) abscess was/were transgluteal percutaneous drainage in 62%, EVT in 50%, laparoscopic transabdominal drainage in 33% and transabdominal percutaneous drainage in 26%.

Of the participants, 6 (14%) had no experience with anastomotic reconstruction, 30 (71%) had experience with transanal closure and 30 (71%) had experience with redo procedures during which a new anastomosis is constructed. Abdominal free fluids were preferably approached by laparoscopy (57%), followed by percutaneous drainage (26%). The preferred approach for fecal or purulent peritonitis was most often laparoscopic (69%).

Part 2: Clinical cases

Results from the clinical cases can be found for early leaks in Table 4 and for late leaks in Table 5.

Early leakage with sepsis (case 1,2)

In a septic patient with an ischemic afferent colon (case 1), surgical modalities were preferred. Anastomotic take-down with possibility of secondary reconstruction was chosen most often (69%). Definitive salvage surgery was chosen more often in the elderly frail patient compared to the young fit patient (52% vs 24%) and take-down with possibility of secondary reconstruction was chosen less often in elderly frail patients (52% vs 69%).

In a septic patient with a completely dehiscent anastomosis (case 2), takedown with possibility of secondary reconstruction was performed less often compared to case 1, with similar proportions for the two patient scenario's (38% in the young fit patient vs 43% in the elderly frail patient). Restorative treatment with anastomotic reconstruction was chosen in the young fit patient in 45% and definitive salvage surgery was the main treatment approach in the elderly frail patient in 41%.

Early leakage without sepsis (case 3-6)

In a non-diverted patient with mild symptoms, a presacral collection and a defect (1/3 circumference) on endoscopy (case 3), proposed treatment approach seemed to be independent from age and comorbidities, except from a higher proportion watchful waiting in young fit patients (21% vs 5%). Most chose drainage (83% in the young fit patient and 88% in the elderly frail patient) combined with fecal diversion (76% and 81%, resp.). Preferred drainage modality was EVT (48% in the young fit patient and 55% in the elderly frail patient). The anastomosis would have been reconstructed by a minority of respondents (29% in the young fit patient and 26% in the elderly frail patient). In a diverted patient with an asymptomatic presacral collection without visible defect on endoscopy (case 4), most participants also chose drainage (81% in the young fit patient and 83% in the elderly frail patient), preferably by percutaneous drainage. EVT as well as reconstruction were less often proposed in case 4 as compared to case 3, with higher proportions of watchful waiting.

In case of a non-diverted defect in the blind loop of a side-to-end anastomosis with mild symptoms (case 5), preferred treatment was comparable to case 3, although a diverting stoma was slightly less often proposed in the elderly

Table 1: Surgeon details

Question:	Total cohort (n=42)
1. Country of origin	
Europe	25 (60%)
North-America	7 (17%)
South-America	5 (12%)
Oceania	3 (7%)
Asia	2 (5%)
2. Type of Hospital	
Academic training hospital	26 (62%)
General teaching hospital	10 (24%)
Cancer center	5 (12%)
General (non-teaching) hospital	1 (2%)
3. Years of experience	
0-5 years	4 (10%)
6-10 years	8 (19%)
11-15 years	8 (19%)
>15 years	22 (52%)
4. Anual LAR caseload hospital	
0-49	16 (38%)
50-99	18 (43%)
100 or more	8 (19%)
5. Therapeutic modalities used for treatment of anastomotic leakage	
Ultrasound guided percutaneous drainage	27 (64%)
CT-guided transgluteal drainage	39 (93%)
Laparoscopic absess drainage with placement abd. drain	36 (86%)
Transanal drainage under general anesthesia and placement of catheter for further drainage and irrigation of cavity	33 (79%)
Endoscopic washout of the abscess cavity	25 (60%)
EVT	31 (74%)
Endoscopic vacuum assisted closure system (EVT + surgical closure defect)	19 (45%)
Endoscopic clipping (i.e. OVESCO)	4 (9%)
Examination/transanal drainage under anesthesia	25 (60%)
Other	5 (12%)
6. Available transanal approaches?	
TAMIS	36 (86%)
TEM	20 (48%)
Open transanal approach with retractor	37 (88%)
TEO	10 (24%)

LAR: low anterior resection; CT: computed tomography; EVT: endoscopic vaccuum therapy; TAMIS: transanal minimally invasive surgery; TEM: transanal endoscopic microsurgery; TEO: Transanal endoscopic operation;

Table 2: preferences

Question	Total cohort (n=42)
7. Do you always obtain fecal diversion (if not already present) in case of AL?	
Yes, always	12 (29%)
Almost always, except small leak	24 (57%)
Almost always, except EVT patients	2 (5%)
Other	2 (5%)
8. How are you preferably approaching a pelvic (presacral) abscess?	
Manual transanal drainage on the ward	5 (12%)
Transgluteal percutaneous drainage	26 (62%)
Laparoscopic transabdominal drainage	14 (33%)
Endoscopic drainage without vacuum therapy	6 (14%)
EVT	21 (50%)
Transabdominal percutaneous drainage	11 (26%)
EUA + transanal tube drainage	21 (50%)
9. Do you have any experience with anastomotic reconstruction?	
No	6 (14%)
Yes, transanal closure	30 (71%)
Yes, redo	30 (71%)
10. How would you approach a substantial amount of abdominal free fluids on CT in a patient with an ileostomy and non-ischemic leaking anastomosis?	
Radiological	11 (26%)
Laparoscopy	24 (57%)
Laparotomy	2 (5%)
11. What is your preferred approach for fecal or purulent peritonitis?	
Laparoscopy	29 (69%)
Laparotomy	12 (29%)

AL: anastomotic leakage; EVT: endoscopic vaccuum therapy; EUA: examination under anesthesia.

frail patient. Reconstruction was less often preferred for defects of the blind loop in younger patients, compared to the elderly frail patient (14% vs 29%). Independent of patient scenario, less often EVT and more often percutaneous drainage was preferred for a blind loop defect as compared to a defect of the circular anastomosis.

If a mild symptomatic large defect is seen on endoscopy (>50% of circumference) with primary defunctioning stoma in situ (case 6), temporary take-down of the anastomosis was more often chosen compared to case 3, especially in the elderly frail patient (26% vs 0%). Also more often transanal surgical closure was considered than for case 3 (38% in the young fit patient and 29% in the elderly frail patient). Mainstay of treatment remained drainage (88% in the young fit patient and 76% in the elderly frail patient).

Late leakage (case 7-11)

Cases 7 and 8 are patients with a late radiological diagnosis of a diverted asymptomatic leakage based on contrast extravasation (postoperative day 50), with (case 7) or without (case 8) presacral collection. In contrast to early leaks, watchful waiting was most often proposed for both the young fit and elderly frail patient, especially in the absence of a presacral collection: 69% and 62% for case 7 and 88% and 83% for case 8, respectively. Drainage of a presacral collection in such occult leaks would not have been performed by the majority of respondents, with even lower proportions of reconstruction.

In a patient with a diverted rectovaginal fistula (case 9), surgical intervention would be performed more often when compared to the asymptomatic late leaks (case 7, 8). Preferred surgical strategy in the young fit patient was any type of reconstruction (50%) with less often anastomotic take-down with possibility of secondary reconstruction (12%) and definitive salvage surgery without restoration of continuity (10%). Corresponding proportions in the elderly frail patient were 38%, 19% and 29%. Some would wait for the fistula to heal by itself. Many respondents asked for further information on the location and size of the defect.

In a patient with a secondary leak after stoma closure presenting with sacral pain and severe LARS (case 10), treatment approach included drainage in two-third of respondents (67% in the young fit patients and 69% in the elderly frail patient) and less frequently fecal diversion (48% and 31%). Also many surgeons would perform any surgical intervention to treat the leak itself, consisting of reconstruction (41% and 26%), anastomotic take down with possibility of secondary reconstruction (5% and 7%), and definitive salvage surgery without restoration of continuity (12% and 26%). A minority of participants chose watchful waiting in such a patient with sacral pain and severe LARS (12%). Case 11 represents an almost chronic leak with bowel continuity and mild symptoms. Proposed treatment strategies were comparable with those for case 10.

Preferred type of treatment

Regarding drainage of presacral collections, EVT was the preferred strategy among the participants, with small differences depending on the indication. Percutaneous radiological drainage and intermittent transanal irrigation were second and third choice, with comparable proportions in most of the cases. If fecal diversion was chosen, predominantly a diverting ileostomy would be created instead of a colostomy (e.g. case 3 (69% vs 7%) or case 10 (38% vs 5%)). If transanal surgical closure was proposed, this would have been performed either by an open technique or by TAMIS in similar proportions.

Table 4: Cases with early anastomotic leakage

	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6	
	Young	Old	Young	Old	Young	Old	Young	Old	Young	Old	Young	Old
Drainage	10 (24%)	8 (19%)	18 (43%)	13 (31%)	35 (83%)	37 (88%)	34 (81%)	35 (83%)	35 (83%)	34 (81%)	37 (88%)	32 (76%)
Intermittent transanal drainage	6 (14%)	4 (10%)	7 (17%)	4 (10%)	11 (26%)	10 (24%)	5 (12%)	3 (7%)	11 (26%)	5 (12%)	10 (24%)	7 (17%)
Percutaneous radiological drainage	5 (12%)	5 (12%)	5 (12%)	8 (19%)	11 (26%)	11 (26%)	24 (57%)	24 (57%)	18 (43%)	17 (41%)	11 (26%)	13 (31%)
Endoscopic vacuum therapy (EVT)	0	2 (5%)	8 (19%)	6 (14%)	20 (48%)	23 (55%)	7 (17%)	7 (17%)	14 (33%)	17 (41%)	24 (57%)	19 (45%)
Reconstruction	4 (10%)	2 (5%)	19 (45%)	6 (14%)	12 (29%)	11 (26%)	3 (7%)	4 (10%)	6 (14%)	12 (29%)	16 (38%)	12 (29%)
Transanal surgical closure–open approach	0	0	5 (12%)	2 (5%)	7 (17%)	8 (19%)	3 (7%)	4 (10%)	1 (2%)	7 (17%)	11 (26%)	7 (17%)
Transanal surgical closure–TAMIS	1 (2%)	0	9 (21%)	3 (7%)	12 (29%)	10 (24%)	3 (7%)	4 (10%)	5 (12%)	11 (26%)	14 (33%)	9 (21%)
Transanal closure–endoscopic clipping	0	0	0	0	0	1 (2%)	0	0	0	2 (5%)	0	0
Immediate redo-anastomosis	4 (10%)	1 (2%)	6 (14%)	1 (2%)	1 (2%)	0	0	0	2 (5%)	2 (5%)	3 (7%)	2 (5%)
Delayed redo-anastomosis	3 (7%)	1 (2%)	8 (19%)	2 (5%)	0	0	0	0	0	0	1 (2%)	1 (2%)
Fecal diversion	NA	NA	NA	NA	32 (76%)	34 (81%)	NA	NA	33 (79%)	29 (69%)	NA	NA
Defunctioning ileostomy					29 (69%)	25 (60%)			30 (71%)	22 (52%)		
Defunctioning colostomy					3 (7%)	7 (17%)			2 (5%)	6 (14%)		
Anastomotic take-down with possibility of secondary reconstruction	29 (69%)	22 (52%)	16 (38%)	18 (43%)	2 (5%)	0	0	0	0	1 (2%)	5 (12%)	11 (26%)
Watchful waiting	1 (2%)	1 (2%)	4 (10%)	0	9 (21%)	2 (5%)	16 (38%)	12 (29%)	6 (14%)	1 (2%)	6 (14%)	2 (5%)
Definitive salvage surgery without restoration of continuity	10 (24%)	22 (52%)	7 (17%)	17 (41%)	0	0	0	0	0	4 (10%)	1 (2%)	4 (10%)
Intersphyncteric resection rectal stump/anastomosis	5 (12%)	16 (38%)	3 (7%)	13 (31%)	0	0	0	0	0	4 (10%)	0	4 (10%)
Debridement pelvic cavity	9 (21%)	17 (41%)	5 (12%)	13 (31%)	0	0	0	0	0	3 (7%)	1 (2%)	4 (10%)
Presacral filing with omentoplasty/flaps	1 (2%)	8 (19%)	1 (2%)	9 (21%)	0	0	0	0	0	3 (7%)	0	3 (7%)
Other	2 (5%)	0	1 (2%)	0	0	0	0	4 (10%)	0	0	1 (2%)	3 (7%)
Combined modalities												
Drainage and reconstruction	1 (2%)	0	10 (24%)	4 (10%)	12 (29%)	11 (26%)	3 (7%)	4 (10%)	4 (10%)	11 (26%)	15 (36%)	12 (29%)
EVASC (EVT with some form of transanal surgical closure)	0	0	3 (10%)	2 (5%)	8 (19%)	9 (21%)	1 (2%)	4 (10%)	2 (5%)	7 (17%)	11 (26%)	7 (17%)

EVT endoscopic vaccuum therapy, *TAMIS* transanal minimally invasive surgery.

Table 5: Cases with late anastomotic leakage.

	Case 7		Case 8		Case 9		Case 10		Case 11	
	Young	Old	Young	Old	Young	Old	Young	Old	Young	Old
Drainage	15 (36%)	20 (48%)	3 (7%)	5 (12%)	20 (48%)	16 (38%)	28 (67%)	29 (69%)	31 (74%)	27 (64%)
Intermittent transanal drainage	4 (10%)	6 (14%)	0	2 (5%)	8 (19%)	6 (14%)	6 (14%)	10 (24%)	8 (19%)	9 (21%)
Percutaneous radiological drainage	2 (5%)	5 (12%)	0	1 (2%)	5 (12%)	6 (14%)	10 (24%)	9 (21%)	6 (14%)	6 (14%)
Endoscopic vacuum therapy (EVT)	11 (26%)	11 (26%)	2 (5%)	4 (10%)	8 (19%)	7 (17%)	18 (43%)	16 (38%)	22 (52%)	22 (52%)
Reconstruction	7 (17%)	7 (17%)	8 (19%)	7 (17%)	21 (50%)	16 (38%)	17 (41%)	11 (26%)	15 (36%)	9 (21%)
Transanal surgical closure–open approach	5 (12%)	5 (12%)	5 (12%)	5 (12%)	8 (19%)	7 (17%)	6 (14%)	4 (10%)	8 (19%)	5 (12%)
Transanal surgical closure–TAMIS	5 (12%)	7 (17%)	8 (19%)	7 (17%)	8 (19%)	8 (19%)	7 (17%)	5 (12%)	8 (19%)	6 (14%)
Transanal closure–endoscopic clipping	0	0	1 (2%)	1 (2%)	1 (2%)	0	0	0	0	0
Immediate redo-anastomosis	2 (5%)	0	2 (5%)	0	7 (17%)	4 (10%)	10 (24%)	5 (12%)	6 (14%)	3 (7%)
Delayed redo-anastomosis	0	0	0	0	6 (14%)	4 (10%)	3 (7%)	3 (7%)	1 (2%)	2 (5%)
Fecal diversion	NA	NA	NA	NA	NA	NA	20 (48%)	13 (31%)	17 (41%)	18 (43%)
Defunctioning ileostomy							16 (38%)	10 (24%)	15 (35%)	13 (31%)
Defunctioning colostomy							2 (5%)	1 (2%)	1 (2%)	4 (10%)
Anastomotic take-down with possibility of secondary reconstruction	2 (5%)	0	0	0	5 (12%)	8 (19%)	2 (5%)	3 (7%)	3 (7%)	4 (10%)
Watchful waiting	29 (69%)	26 (62%)	37 (88%)	35 (83%)	8 (19%)	5 (12%)	5 (12%)	3 (7%)	6 (14%)	8 (19%)
Definitive salvage surgery without restoration of continuity	0	0	0	0	4 (10%)	12 (29%)	5 (12%)	11 (26%)	2 (5%)	7 (17%)
Intersphyncteric resection rectal stump/anastomosis					4 (10%)	12 (29%)	5 (12%)	10 (24%)	2 (5%)	7 (17%)
Debridement pelvic cavity					3 (7%)	7 (17%)	4 (10%)	10 (24%)	2 (5%)	7 (17%)
Presacral filing with omentoplasty/flaps					3 (7%)	6 (14%)	1 (2%)	9 (21%)	1 (2%)	6 (14%)
Other	1 (2%)	2 (5%)	0	0	5 (12%)	4 (10%)	1 (2%)	3 (7%)	1 (2%)	2 (5%)
Combined modalities										
Drainage + reconstruction	5 (12%)	7 (17%)	1 (2%)	4 (10%)	9 (21%)	8 (19%)	12 (29%)	9 (21%)	12 (29%)	8 (19%)
EVASC (EVT with TAMIS or open surgical closure)	3 (7%)	7 (17%)	1 (2%)	3 (7%)	3 (7%)	4 (10%)	4 (10%)	4 (10%)	8 (19%)	6 (14%)

EVT endoscopic vaccuum therapy, *TAMIS* transanal minimally invasive surgery.

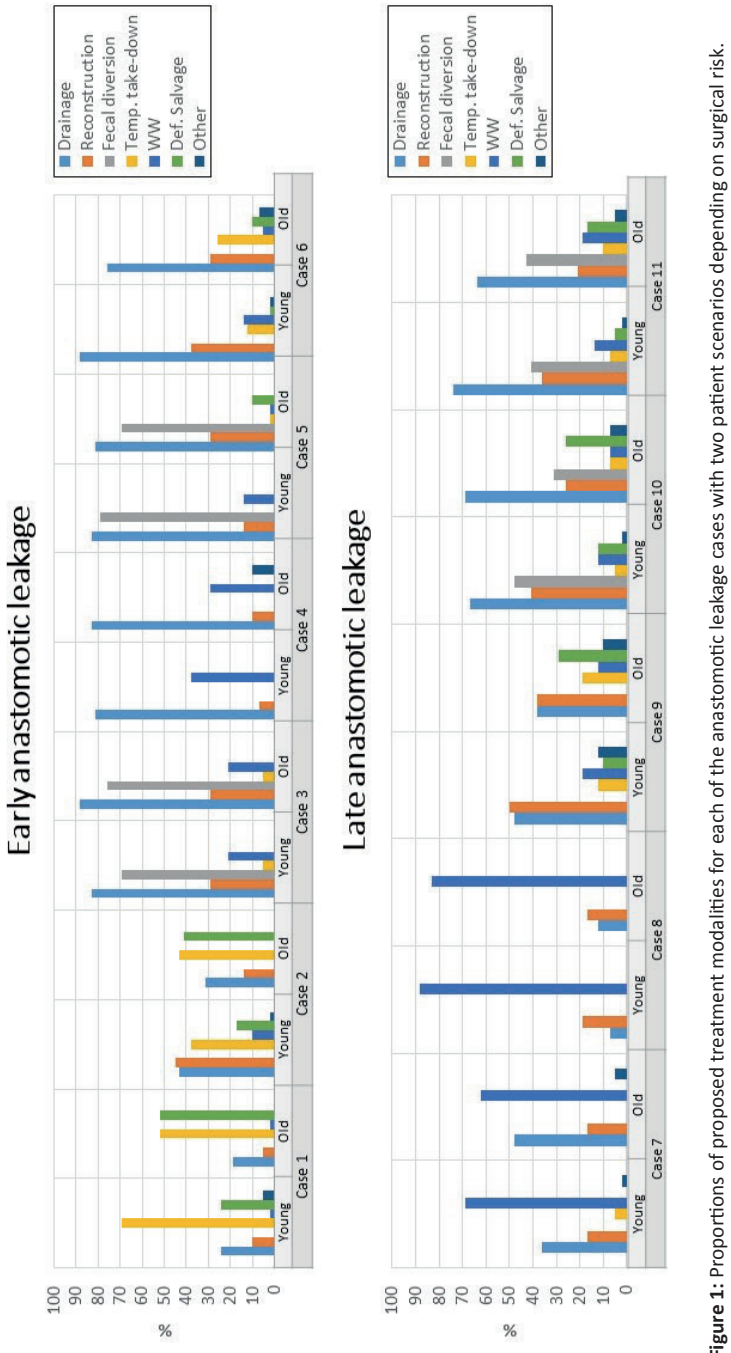

Figure 1: Proportions of proposed treatment modalities for each of the anastomotic leakage cases with two patient scenarios depending on surgical risk.

DISCUSSION

This case vignette study shows that proposed treatment strategies for AL after LAR for rectal cancer differed substantially depending on clinical presentation, leakage features and patient characteristics. A variable degree of consensus among the experts was observed. In addition to supportive care, drainage and fecal diversion are still considered to be the two main modalities of treatment, with a preference for active drainage using EVT among the participating surgeons. Among the minority who proposed surgical interventions, a wide variety in preferences for transanal repairs, dismantling of the anastomosis and definitive salvage surgery was found. The results of this survey point towards several knowledge gaps.

The proposed treatment strategies with tailoring to the different clinical cases revealed some general principles as reflected by high consensus among the participating surgeons. Surgical treatment of the leakage was generally reserved for patients with a severe acute leakage in accordance with a published Delphi consensus [11]. Transanal repair of the anastomosis or complete redo-anastomosis were infrequently used.

Besides these common practices, there were remarkable differences in surgeon preference in some cases. Some surgeons still relied on drainage in a septic patient with ischemic or completely retracted afferent colon. One might question whether this results in adequate control of sepsis, especially since passive drainage was the proposed modality (e.g. intermittent transanal or percutaneous drainage). Probably, pelvic drainage in such a patient can be used as a bridge to major salvage surgery, but active drainage with EVT might then be more effective on theoretical grounds. However, EVT is not available in every hospital, which might be the reason to use other drainage modalities. Optimal timing of salvage surgery and the role of bridging strategies with EVT to reduce morbidity of major acute surgery are interesting fields of research to explore.

In patients with an early leakage, no sepsis and a small sized defect, drainage and fecal diversion (if applicable) was the preferred strategy of the respondents. Direct reconstruction was attempted in 7-39%, often combined with a drainage procedure. Interestingly, for similar patients with a larger defect (>50%), a greater proportion of respondents would have attempted a direct closure method. Although a greater defect size might reduce the probability of leak healing without interventions aimed at repairing the defect, larger defects are also more difficult to close. In addition, traction on the anastomosis is more likely

to be an explanatory component in larger leakages, which could hamper defect closure. A redo anastomosis, which has the potential to keep continuity without the drawbacks of defect closure may be an alternative and was indeed chosen by a limited number of respondents.

Leakage of the blind loop seems to be a distinct leakage entity after LAR, although seldom described in literature. Blind loop leakage can be more difficult to drain effectively, and attempts of transanal or transabdominal closure are likely to fail based on personal experiences. These leaks appear to be prognostically worse with a lower chance of successful secondary healing. Hypothetically, intraluminal pressure within the blind loop can become high with peristaltic contractions in the presence of a competent internal sphincter, which probably explains low chance of healing by any modality. This theory would argue in favour of major salvage surgery, but this is not confirmed by the present survey. Performing focus groups discussions on leakage of the blind loop or collecting such cases in large multicenter collaborative research enabling pooled analyses, would likely provide more insight into this entity.

For an acute leak with a collection but no defect visible on endoscopy (case 4), most respondents chose percutaneous drainage and less frequently EVT or intermittent transanal drainage. The latter options require trans-anastomotic access. If there is an acute leak with a collection, one might be able to identify a small area of granulation tissue with an underlying small defect. Endoscopic probing of the anastomosis using a guide wire or biopsy forceps can help in identifying occult defects, which can subsequently be dilated. Expanding such a tiny defect often feels like aggravating the problem, which probably explains the clear preference of the participating surgeons for percutaneous drainage. Which strategy results in the highest chance of anastomotic integrity in the end is another interesting knowledge gap.

It is remarkable that drainage was still proposed by a substantial number of participants in late leaks. A pelvic abscess will generally induce extensive fibrosis around it. Collections diagnosed beyond the first few weeks are less likely to collapse by drainage as a result of this fibrosis formation with less pliability of surrounding tissues as a result. Even active drainage using EVT seems less successful in case of late initiation of treatment.[8] The GRECCAR group, which looked at EVT without transanal closure for AL, found a much higher restored continuity rate if treatment was initiated in the first 15 days after surgery (72% vs 28%).[12] The value of drainage procedures in late leaks as either a single modality or as a bridge to surgical interventions has still to be defined. Regarding the

minority of participants proposing transanal closure of a late leak, the chance of success might be low when attempting to approximate the fibrotic edges of the two bowel ends together with stitches.

In a patient with a rectovaginal fistula (case 9), there was a large variety in chosen modalities and many participants indicated that they would like to know more details on the size and location of the defect. The preference for surgical interventions of the participants is likely explained by the presumed low chance of spontaneous healing, because the fistula becomes the route of least resistance. Drainage is often difficult, because generally no collections build up. Whether specific details of the rectovaginal fistula should guide (type of) surgical intervention is unclear. In general, this less common presentation of AL is associated with many interventions, a significant impact on quality of life and a high rate of definitive salvage surgery, and available literature remains scarce [13, 14].

Symptoms of late leaks often consist of major LARS and sacral pain. Symptoms of frequent defecation will logically improve with fecal diversion, but chronic pelvic sepsis likely persists and can even worsen over time. Therefore, fecal diversion is not expected to reduce sacral pain. In case of severe symptoms, major salvage surgery might be the best option, but this was only chosen by a minority of participants. A reserved attitude towards major salvage surgery can be explained by the surgical complexity as well as the high risk of complications and need for reinterventions, with poor functional outcome in case of redo anastomosis. [15, 16] Remarkably, an almost asymptomatic leak (case 11) was similarly treated as a very symptomatic leak (case 10).

The two different patient scenarios (the young fit or the elderly frail patient) did not appear to have much impact on decision making in general, which is an interesting finding. Nevertheless, some exceptions were found. For example, participants were more likely to wait for secondary healing in young fit patients with early leaks, with slightly more definitive salvage surgery in elderly frail patients. In the absence of any evidence, one might also propose a more proactive surgical strategy in a young and fit patient to maximize chances of preserving the anastomosis. Whether age and clinical condition should guide treatment strategy also deserve attention in future studies.

This study has several limitations. Patient preference and shared decision making are not included. Some patients may opt for a definitive stoma to prevent an extended treatment period and if patients are unmotivated or unfit, this can alter the decision for a treatment option. We also did not focus on possible delay of treatment. Some participants commented that in some cases they would first

wait several months, before attempting major reconstructive surgery. There is also a potential bias in how some treatment options were described with unclarity of the used terms. For example, “delayed re-do anastomosis” was defined as a two-step redo (Turnbull-Cutait procedure), but might have been interpreted as a redo-anastomosis several weeks or months after diagnosis of the leak. We were not able to find clear differences in treatment approaches between countries or continents, but the participants might not have been representative for their countries. Finally, the exact location of the leak was not taken into account and some treatment modalities might be more suitable for certain locations. For example, EVT is easier to apply for posterior leaks, because there is more space compared to the anterior side. Location might be another variable to explore in future studies.

CONCLUSION

This case-vignette study showed that proposed treatment modalities and principles for AL after rectal cancer are influenced by clinical leak presentation and patient characteristics. The heterogeneity of strategies to treat different cases of AL underlines the need for more clinical data on what strategies work for which patients with particular leakage characteristics.

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Supplementary table 1: Country or origin participants

Country of ori-gin	**n**	**%**
USA	5	12%
Australia	4	10%
Netherlands	4	10%
UK	4	10%
Italy	3	7%
Spain	3	7%
Switzerland	3	7%
Austria	2	5%
Belgium	2	5%
Brasil	2	5%
Canada	2	5%
France	2	5%
Argentina	1	2%
Japan	1	2%
New Zealand	1	2%
NL	1	2%
South Korea	1	2%
Sweden	1	2%

CHAPTER 8

Dealing with complications of colorectal surgery using the transanal approach – When and how?

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ABSTRACT

The transanal approach is a new and exciting addition to the surgeons repertoire to deal with complications after colorectal surgery. Improved exposure, accessibility and visibility greatly facilitates adequate dissection of the affected area with potential increase in effectiveness and reduced morbidity. An essential component in salvaging anastomotic leaks of low colorectal, coloanal or ileoanal anastomoses is early diagnosis and early treatment, especially when starting with endoscopic vacuum therapy (EVT), followed by early surgical closure (EVASC). Redo surgery using a Transanal Minimally Invasive Surgery (TAMIS) platform for chronic leaks after TME surgery or surgical causes of pouch failure successfully mitigates limited visibility and exposure by using a bottom-up approach.

INTRODUCTION

Resectional surgery of the rectum for various diseases is associated with a certain risk of pelvic complications that might result in presacral abscess and fistula formation. Most common underlying diseases are rectal cancer, inflammatory bowel disease (IBD), polyposis syndromes, and other pelvic malignancies. Both restorative and non-restorative sphincter sparing rectal resections are performed in the treatment of these diseases. These procedures can lead to anastomotic leakage or pelvic abscess on top of a rectal stump, respectively.

The transanal approach can be used for early treatment of infectious pelvic complications, as well as for salvage surgery for chronic septic complications. It should be emphasized that there is a paucity of literature on this topic, with mostly small cohort studies. There are no good quality comparative studies, neither randomized nor non-randomized, for which reason we do not know the optimal treatment of leakage of low pelvic anastomoses. This article is largely based on the experiences of a national referral centre for anastomotic failure, and most of the recommendations are based on expert opinions.

Leakage of colo-rectal, colo-anal and ileo-anal anastomoses

Anastomotic leakage (AL) remains one of the most feared complications. It leads to significant impairment of quality of life and functional outcomes, additional reinterventions and reoperations, worse oncological outcomes, increased health care costs and permanent stomas. [1-3]

Reported AL-rates after rectal cancer surgery are highly variable. The German, Swedish and TaTME registries found leakage rates of 10.8%, 11.9% and 15.7%.[4-6] A substantial amount of false-negative (29%) and false-positive (1.3%) diagnosis were found after chart review in the Swedish registry. Retrospective chart review in the Dutch national cross-sectional SNAPSHOT study revealed a much higher leakage rate within 30 days than initially reported in the national audit (13.4% vs 8.2%), and this increased to 20% after 4 years of follow-up, due to late detection of leakage and chronic sinus. [7] The main contributing factor to late leakages is the silent course, due to the presence of a diverting stoma, and even if a diverted anastomosis appears intact, an occult leakage can become symptomatic once the stoma is reversed.

Despite the high prevalence of AL after rectal cancer surgery, there is very little literature available how to manage this complication. It is generally accepted, that as first step the leak should be defunctioned if not done so before. However,

there is no consensus how to drain and manage the septic cavity. Options are surgical drainage, radiological drainage (either transabdominal, transgluteal or transperineal), and transanal drainage with passive drains or vacuum systems. [7-9] In the previously mentioned Dutch SNAPSHOT study with long-term follow-up, the management of the leak showed to be very dissatisfactory, because a chronic sinus remained in half of patients. [7] The pelvis has often been irradiated before surgery, producing a scarred and fibrotic surgical field with reduced pliabilty of the neorectum and healing capacity of the chronic sinus.

The treatment of AL itself might also lead to secondary complications. After removal of a transgluteal drain, fistulae can develop along the old drain tract. These fistulae can subsequently lead to the formation of new abscesses and even to life-threatening complications such as necrotizing fasciitis.[10]

Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is one of the main treatment modalities in therapy refractory patients with ulcerative colitis and familiarly adenomatous polyposis (FAP), as well as selected patients with Crohn's disease and some rare other diseases. Reported anastomotic leakage rates after pouch surgery are also highly variable [11-13]. One of the explanations is, again, the unrecognized asymptomatic leak, especially in the presence of a diverting stoma. Similar to low colonic anastomoses, occult ileo-anal anastomotic leaks might become clinically apparent later on, and late anastomotic failures can be misdiagnosed as Crohn's disease in the pouch or refractory pouchitis.[14] It is quite obvious that these leaks are not accounted for in the 30 day or in hospital leak rates.

Proactive approach of anastomotic leakage

Traditionally, a passive approach is used in the treatment of AL. A diverting stoma is created, if not created primarily, and abscesses are drained either transanal or radiologically. From here, watchfull waiting is applied in the hope that the anastomosis will heal in time. Taking down a low pelvic anastomosis is not recommended because of future difficulties to reconnect, and should therefore only be performed in a specific cases, mostly because of ischemia, major dehiscence or uncontrollable pelvic sepsis.

In the last decade, the paradigm of treating a pelvic anastomosis has shifted towards a pro-active approach with early treatment after early diagnosis. Several reviews showed that postoperative CRP-measurement can effectively indicate the presence of infectious complications including anastomotic leakage as early as day 3[15]. When CRP is elevated above a certain threshold (e.g. >172 on day

three), a CT-scan with rectal contrast can be made to determine if an anastomosis is leaking. Also, clinical signs of leakage and/or repeated CRP measurements showing a certain trend can help in guiding the need for additional imaging or endoscopy to check the integrity of the anastomosis. Such diagnostic strategies are all intended to detect any leaking anastomosis as early as possible, no matter whether it is symptomatic or not, in order to immediately start treatment that aims for preservation of anastomotic integrity.

The omission of a diverting stoma during primary surgery is critical in early diagnosis of AL, because a non-diverted leak is rarely asymptomatic. Traditionally, a stoma is created to allow the anastomosis to heal before the fecal stream is restored. However, long-term leakage rates are similar irrespective of fecal diversion. Omission of a diverting stoma at primary surgery appears safe, under the condition that there is a strict institutional protocol for early diagnosis of AL, and routine diversion leads to many unintended permanent stomas, besides other disadvantages. [16, 1718]

Early and active treatment appears to be vital in the management of anastomotic leakage. First, this prevents clinical deterioration of the patient's condition, which is especially important in the absence of fecal diversion. Second, early treatment might preserve the integrity of the bowel preventing that the bowel at the anastomotic site becomes fibrotic resulting in a chronic leak. Without any or only limited abdominal contamination and in the absence of ileus, a laparoscopic reintervention is still possible for creating the diverting ileostomy if not present. A minimally invasive reintervention has shown to be beneficial for the patient as compared to an open approach[19]. Secondly, it allows for early interference with cascades that rapidly worsen the local pelvic conditions. The resting tone of the anal sphincters prevents effective drainage of the bowel and the adjacent septic cavity. Accumulation of gas, feces and mucous in the neorectum and presacral septic cavity cannot be prevented, thereby hampering healing of the leak.

Transanal surgery for acute Leaks

When an AL has been diagnosed, the first priority is to control pelvic sepsis by creating a diverting stoma (if not created primarily) and washout of the colon in case of a colorectal anastomosis. If the afferent bowel is vital, it is advised not to explore an ileo-anal or colo-anal anastomosis from the abdominal side, because visibility is very limited and inadvertent traction on the afferent bowel loop might enlarge the anastomotic defect. Transanal or endoscopic inspection can ascertain the viability of the bowel (ischaemic or not), the location of an anastomotic

defect (circular anastomosis, top of a blind loop), the size of the defect (partial, complete dehiscence), whether a sinus/cavity is visible and the size and content of the cavity. In women, the vagina has occasionally been incorporated into the stapled anastomosis, or a leak is decompressed via a weak spot in the vagina. Under these circumstances, air or stool evacuates per vaginam.

One of the important modalities in transanal management of acute leaks is the Endoscopic Vacuum Therapy (EVT), in which a poly-urethane sponge is placed in the abscess cavity, and subsequently connected to a negative pressure suction device (Endo-SPONGE®, B.Braun Medical B.V., Melsungen, Germany).[20] This allows for active and continuous drainage and the sponge itself allows for uniform contact with the cavity wall, producing a healthy granulating cavity over time. The sponges are changed in an outpatient setting every 3-4 days in the endoscopy room. EVT works best in combination with diversion although it has been applied successfully without a diverting stoma in selected cases. In the absence of a diverting stoma, it is quite likely that the vacuum system loses its vacuum due to the intact transit of stool and feces being sucked into the vacuum system. [21, 22]

The indication for starting EVT depends on the first visual inspection of the anastomosis. In our opinion, starting EVT is always a good option as initial step in the management of a leak, especially if the leak has been diagnosed early. In non-diverted patients with early diagnosed leakage of a colo-anal or ileo-anal anastomosis, EVT can start within 4-6 days after the index operation. In case of diversion, routine endoscopic evaluation should be done within 10-14 days, enabling immediate start of EVT after diagnosis of the leak. Early initiation of EVT showed to be more effective in anastomotic salvage [9 23 24] Even if there is a very small defect, this should be dilatated endoscopically to facilitate the tube for EVT. This might feel counter intuitive, but further dehiscence does not worsen the outcome in such cases later on, because the alignment of the bowel ends will be preserved. In case of an abdominal drain, it is sometimes necessary to withdraw the drain to allow for collapse of the top of the cavity during EVT, by which the presacral cavity will be sealed off at the pelvic inlet and separated from the abdominal cavity.

The EVT therapy with the Endosponge system was first described by Weidenhagen in 2008, and he used this as a single treatment modality with tapering of the sponge during each exchange [20]. This resulted in gradual collapse of the cavity behind the anastomotic defect, and EVT was stopped when only a small sinus remained. At the Amsterdam UMC, location AMC, we modified this active

treatment approach and introduced the Endoscopic Vacuum Assisted Surgical Closure (EVASC) of the anastomotic defect[25]. The reasons were that complete healing of the anastomosis by EVT alone required numerous exchanges during an intensive treatment period for both patients and doctors. Furthermore, there is a chance of retraction of the afferent bowel with increasing dehiscence. The neorectum can become rigid because of the secondary healing process with fibrosis, especially during lengthy EVT treatments. Finally, a small remaining sinus can become the route of least resistance with reactivation of the leak once bowel continuity has been restored. Therefore, we hypothesized that primary closure of the anastomotic defect, as soon as a granulating aspect of the cavity behind is found, can speed up the process of healing, thereby also preserving alignment of bowel ends and compliance of the neorectum. For this reason, we introduced the combined treatment modality of EVT with early surgical closure (EVASC).

In our experience, it usually takes 2-4 sponge exchanges to obtain a clean cavity and allow for endoscopic vacuum assisted early surgical closure (EVASC) of the remaining defect (Figure 1). In case of prior radiotherapy and large abscess cavities with abundant necrotic tissue and debris, another 2-4 sponge exchanges might be necessary. The cavity should be carefully irrigated and debrided during endoscopic inspection before placing a new sponge. Endoscopic graspers or snares can be used to remove debris and necrosis. Partial closure might be considered during initial assessment of the leakage, when there is a more than 180 degrees dehiscence. Partial reconstruction of the anastomosis might prevent progressive dehiscence and retraction, and the remaining defect can be used for subsequent EVASC. Leaks with very small cavities behind it (e.g. anteriorly located leaks) are often too small to facilitate the smallest sized Endosponge. Then, simple resuturing without EVT might be considered.

Transanal closure of an anastomotic defect is performed in the lithotomy position under general anesthesia with intravenous antibiotics. The Endosponge is removed and the neorectum or pouch as well as the cavity are irrigated with a betadine solution. For low colo-anal anastomoses or ileo-anal pouches, sufficient exposure can be obtained by just using a Lone Star retractor and some specula (e.g. Langenbeck retractor). When the defect is located more proximal, a transanal platform (e.g. GelPOINT Path Transanal Acces Platform) can be installed. One should ideally visualize the cavity, because sometimes pieces of sponge can remain behind. A gauze can be placed in the afferent colon loop or pouch to prevent accidental closure when placing the sutures. A suction drain (6-8 Fr.) is placed through the wall of the rectal stump or anal canal into the

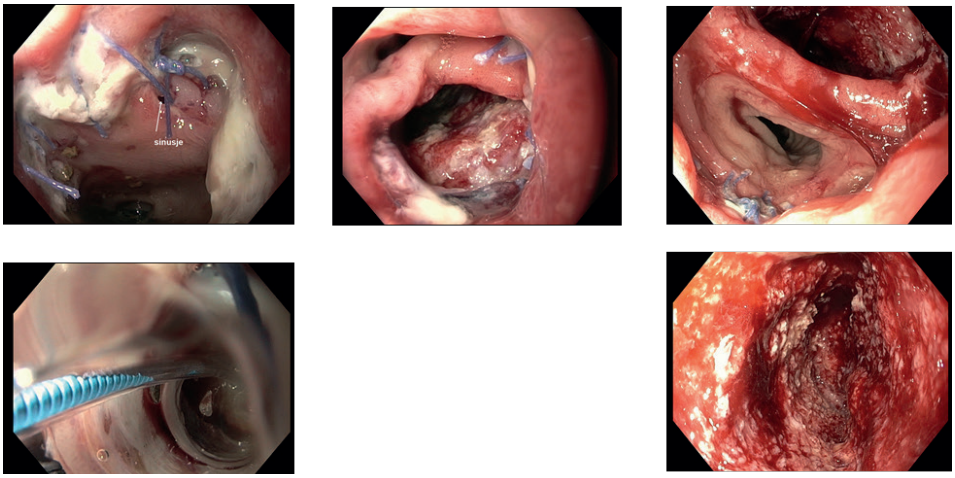

Figure 1: EVT treatment for AL. After two Endosponge exchanges, the cavity appeared clean with granulation tissue and suitable for early surgical closure (EVASC).

abscess cavity and fixated with sutures at the level of the anoderm. The drain can be placed using the small redon needle in an antegrade direction or retrograde direction, the latter being performed by bringing the needle into the cavity, and then moving the needle with the point in the direction of the dentate line with a needle holder. This might be a challenging part of the procedure. Appropriate drain placement seems to be an essential component of EVASC, because this will result in collapse of the cavity behind the reconstructed anastomosis by suctioning the wall of the neorectum or pouch to the sacrum. For the highest chance of obtaining complete vacuum in the cavity, a drain tract of sufficient length is chosen through normal tissue with an exit point distal from the anastomosis, and not through the anastomotic defect.

Mobilization of the proximal or distal rectal cuff can provide additional length to approximate the defect. Then, the defect is closed with interrupted full-thickness 2-0 Vicryl sutures with a 5/8 circle needle. We do not recommend the use of a running V-lock suture based on our experience. If there is a bit of traction, it is helpful to first place all the sutures, and subsequently relieve the tension of the Lone Star during knotting. If an endoscopic platform is used, it is still advised to bring the endings of every single suture out of the transanal platform with temporary fixation of the stitches on the Lone Star retractor, although this requires the installation of the pneumorectum every time again. Subsequently

the port is removed with handed knot tying. Finally, the afferent loop is inspected for patency. Details on the procedure and a video vignette on the procedure were published earlier by our group and another example can be seen in Figure 2. [23, 25, 26]

Postoperative protocol entails drain removal on day 5-7 in the outpatient clinic and oral antibiotics for 7-10 days. Endoscopic inspection after 2 weeks is essential to evaluate if the procedure has been successful. In case of failure, one might consider to restart EVASC and to perform a second attempt of closure within 2 weeks. When endoscopic inspection reveals an intact anastomosis, CT-scan with rectal contrast is performed to exclude any remaining fluid collection behind the reconstructed anastomosis. If such a collection is seen on CT, but without contrast extravasation or substantial amount of air, transgluteal percutaneous drainage might be considered. But if there is any suspicion of recurrent leakage, restart of EVASC is advised.

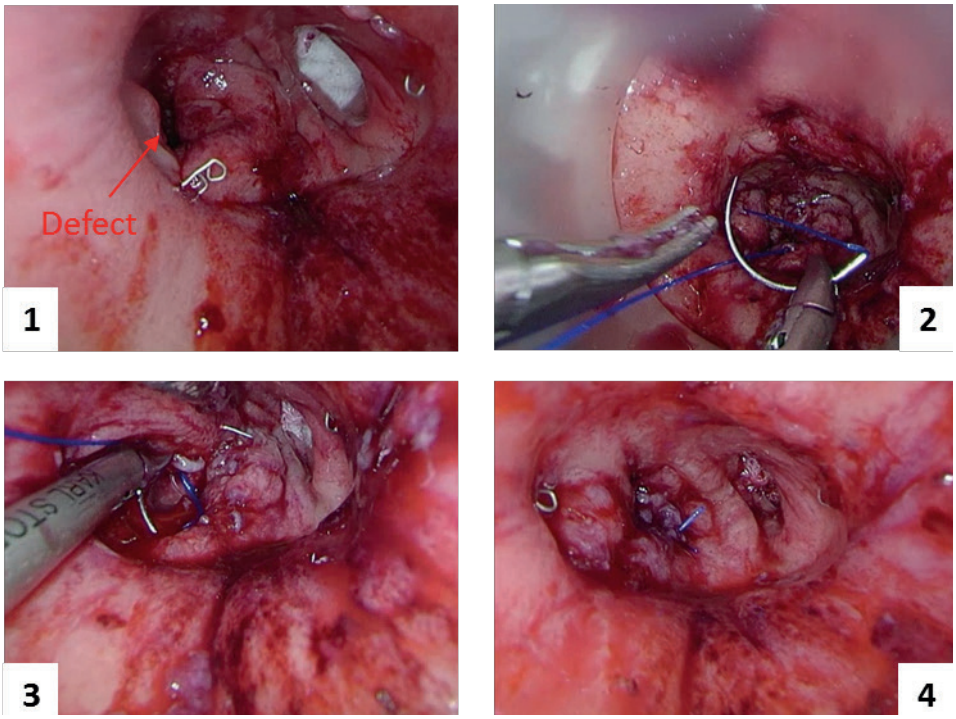

Figure 2: Transanal closure of a defect in the blind loop of a side-to-end anastomosis. Image 1 shows the anastomotic defect after prior EVT-treatment. In Image 2 and 3 transanal sutures are placed closing the defect. In Image 4 the defect is closed

The exceptions in which EVASC might not be the best treatment is when early inspection (until 7-10 days postoperative) reveals a vaginal fistula or ischemia of the afferent loop in a patient that is not septic and does not have abdominal contamination. Then, there is a possibility to perform an acute redo anastomosis. This entails transanal resection of the insufficient anastomosis with laparoscopic mobilization of the colon to gain additional length. Subsequently, an immediate or delayed (Turnball-Cutait) hand-sewn colo-anal anastomosis can be performed [27, 28].

A recent systematic review, including 276 patients treated with EVT for anastomotic leakage found a healed anastomosis rate of 85.3% and a stoma reversal rate of 75.9%.[29] Critical appraisal showed a wide variety in patients (rectal cancer, IBD, FAP etc.) and treatment (mostly EVT alone, some EVASC or fibrin glue). A retrospective study compared patients that underwent EVT with patients that underwent conventional treatment and found higher restored continuity rates after EVT-treatment (86.7% vs 65.9%).[30] This study might be subject to selection bias, because the conventional group consisted of significantly more cancer patients and related neoadjuvant therapy.

In the multicenter CLEAN study coordinated by our centre, EVASC for low colorectal/coloanal anastomotic leaks in 30 patients with a 73% neo-adjuvant radiotherapy rate, resulted in a healed anastomosis in 70% and restored continuity in 67%. [24] Patients that were treated within 21 days after index operation (n=15 in both cohorts), showed more healed anastomoses (73% vs 67%) and more restored continuity (73% vs 60%). We recently updated our institutional results with EVASC, which revealed a healed anastomosis rate of more than 90% since the introduction of the transanal platform in 2014 (unpublished data).

A retrospective study investigating EVT in 20 patients (including 3 patients with EVASC), found a restored continuity rate of 70% and a healed anastomosis rate of 85% [31].

Most effective use of EVASC has been reported for patients with leakage of an ileo-pouch anal anastomosis [32]. A retrospective cohort study from our group compared EVASC with conventional treatment and found higher anastomotic healing rates (100% vs 52%) after EVASC at six months. [25] Another retrospective study from our center found that conventional treatment showed worse pouch function and higher pouch failure rate, if compared to EVASC. [33] Because of the high efficacy of early diagnosis and pro-active treatment strategy found in the treatment for pouch leakage, we have adapted our protocol for colo-rectal and colo-anal leaks. Our current success rates are significantly higher than were published in the CLEAN-study and we hope to present these soon.[24]

A pro-active AL management algorithm is displayed in figure 3, and represents the institutional. protocol as we use at the Amsterdam UMC. After diagnosis, a diverting stoma is created, if not created primarily to control pelvic sepsis. EVASC is preferred treatment and preferably starts within 4 - 14 days after index surgery, and within 48 hours of diagnosis of AL. When the leak has healed based on endoscopic and imaging assessment, the stoma is reversed. When the leak has not healed based on endoscopic assessment, a second attempt of EVASC can be started. Sometimes only a small remaining sinus is found, and further healing is awaited during the next few months.

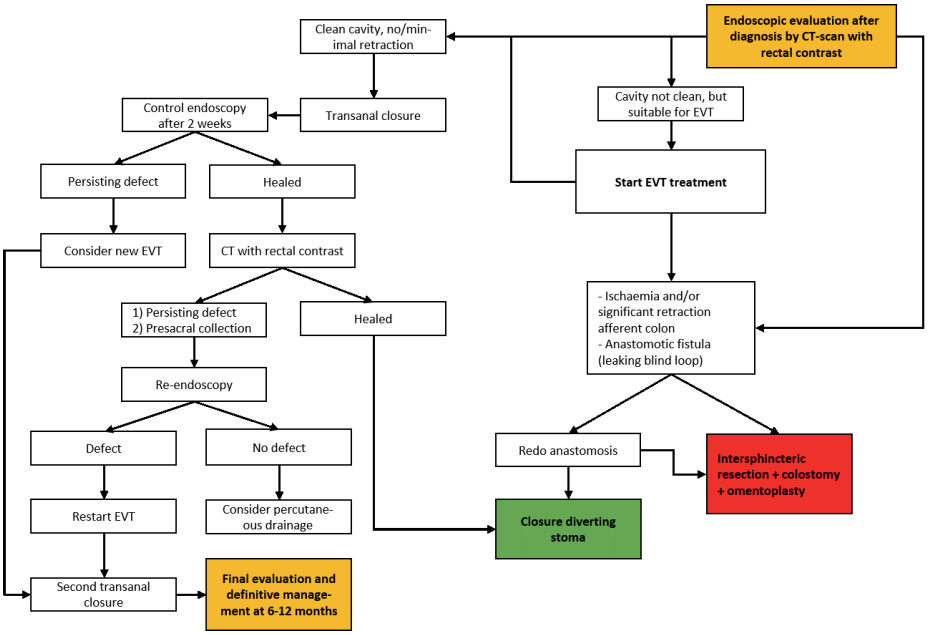

Figure 3: Pro-active management EVASC algorithm

Transanal surgery for chronic leaks

A chronic presacral sinus is the result of non-healing of a pelvic anastomosis. Most sinuses are asymptomatic for a certain period of time varying from months to numerous years. But in the presence of a competent sphincter, the longstanding retention is likely to result in progressive pelvic infection with secondary fistula formation. This is an important clinical problem and its incidence may be underestimated, because long-term follow-up is required. Complaints can be limited to pain or increased defecation, but some patients might develop sepsis

with severe conditions such as necrotizing fasciitis, pelvic fistula, hydronephrosis, coxarthritis etc [10].

When an acute leak does not heal or if a patient presents with a chronic sinus, it is important to discuss the natural course of this condition and treatment options with the patient. In a shared decision fashion the patient can decide what to do. Options are wait and see, endoscopic or local attempts to treat the sinus or major redo surgery with or without restoration of the continuity. It is important to notice that the presence of a diverting stoma does not prevent potential worsening of the pelvic condition during the subsequent years, because mucus, pus and air can accumulate in the sinus due to the inability for adequate drainage in the presence of a closed anal sphincter. Marsupialisation of the sinus by using an endoscopic surgical stapler or by simple electrocautery has been advocated as a treatment option, but this only optimizes drainage of the cavity into the neo-rectum. The intra-luminal retention and absence of a bowel wall at the level of the sinus is still a risk for progressive pelvic inflammation with abscess and fistula formation, particularly in the irradiated patients. Chronic sinuses have also been treated with an injection of fibrin glue after curettage of the cavity. [34, 35] High success rates have been reported of both marsupialization and fibrin glue, but these treatments are likely to fail with extended follow-up in our experience. Promising results have been published when using endoscopic sinusotomy for a chronic ileal pouch sinus and might prevent major redo surgery. [36]

When a patient doesn't experience symptoms from the presacral sinus and is not motivated for major salvage surgery after being fully informed, a wait and see approach can be employed. This might consist of yearly pelvic imaging with CT or MRI. The patient should know that referred leg pain is one of the warning signs of fistula formation along the piriformis muscle, with the need for urgent intervention.

Definitive treatment of a chronic presacral sinus can only be achieved by major salvage surgery, in which a few basic treatment principles have to be followed. EVT prior to salvage surgery for a few days can be beneficial to clean the abscess cavity. The first component of salvage surgery is resection of the old anastomosis or remaining rectal stump, with complete debridement and excision of all fibrotic tissue and cleaning of fistula tracts. Technically, this is the most demanding step, irrespective of the intention to preserve the continuity.

A redo of the anastomosis can be the last chance to preserve bowel continuity before creation of a permanent stoma. If this is the goal of salvage surgery, a rectotomy below the anastomosis is performed, followed by close bowel dissection and excision of the leaking anastomosis until *rendez-vous* with the

top down transabdominal mobilization of the afferent bowel loop is achieved. Subsequently, extensive debridement is performed.

When bowel continuity is chosen not be restored, salvage surgery is performed by intersphincteric dissection of the rectal stump and close bowel dissection along the leaking anastomosis until *rendez-vous* with the top-down dissection is achieved. Presacral veins are generally thrombosed during the period of chronic inflammation. Presacral fibrosis can be removed with sharp dissection without the risk of significant bleeding. However, debridement should be more carefully performed at the level of the pelvic side walls with preservation of the ureters.

The second component of major salvage surgery is filling of the created pelvic cavity with well-vascularized tissue. This might either consist of the neorectum (afferent colon or ileoanal pouch), or autologous tissue when restoration of bowel continuity is not intended anymore, e.g. omentoplasty. Restoring the continuity with neorectum or pouch or filling the cavity with omentoplasty is less demanding than the preceding step. It is obvious that in case of restoration of the continuity, the new anastomosis can once again leak, and if healed, the function of the redo low anastomosis has to be awaited. [37, 38] Redo anastomosis is therefore a valuable option in selected patients that have a strong wish against a permanent stoma and can accept uncertain functional outcomes and morbidity. For obliteration of the cavity with well-vascularised tissue, first choice is an omentoplasty, but filling can also be obtained by creating a myocutaneous flap (e.g. rectus abdominis muscle flap). [10, 39, 40] Omentum is well-vascularised and improves immunological response and angiogenesis.[41, 42] Filling of the presacral cavity also prevents descent of small intestines, decreasing the chance of obstruction and formation of enteroperineal fistulas. When combining an intersphincteric resection with filling of the anorectal cavity with omentum, wound healing can be achieved in 78%, which improves to 88% when performed in a single setting [40].

A bottom-up approach enables greater exposure and visibility during major salvage surgery for chronic leaks. It is sometimes almost impossible to reach the chronic sinus top down from the abdomen, especially because the posterior bladder wall and internal genital organs have shifted dorsally to some degree, and have become more rigid due to fibrosis, particularly after a low Hartmann procedure. The top down dissection starts to become extremely tedious at the level of the vesicels where the rectum is curving anteriorly. This limits the exposure from the abdominal side, without the possibility to retract the anterior pelvic compartment because of rigidity of the tissues. Therefore, a transanal approach is very helpful overcoming this technical difficulty.

Traditionally, a transanal appraoch was performed in an open manner, either in the supine or prone position. With the help of a Lonestar retractor and other retractors, the bottom up dissection was carried out. An intersphincteric dissection or rectotomy at the level of the dentate line was performed depending on intended preservation of continuity, and further dissection of the anastomosis and afferent colon loop was performed as far as the exposure allowed for. Applying an open transanal approach is disadvantageous, because the upper border of the prostate can rarely be reached due to lack of exposure.

With help of the Transanal Minimal Invasive Surgery (TAMIS) platform, the procedure is greatly facilitated by superior exposure, adequate illumination, a magnified view, and completing the bottom up dissection beyond the vesicels and upper border of the prostate is rarely a problem anymore. Combining the abdominal top down dissection and the TAMIS bottom up dissection with *rendez-vous* at the level of the vesicels generally ensures a very controlled and safe operation. [43] The use of a TAMIS platform significantly contributes to the quality of the debridement, and facilitates the dissection of the distal rectal cuff for constructing a redo anastomosis, even with the possibility of a stapled redo anastomosis in patients with a relatively high primary anastomosis.

Salvage surgery can be performed as a simultaneous transanal and transabdominal laparoscopic two-team approach, which is especially helpful when making the *rendez-vous*. The abdominal phase includes full mobilization of the splenic flexure to obtain additional length and meticulous dissection of the afferent colon towards the level of the pelvic inlet. Ureteric stents might be used, but the value seems limited in the presence of extensive fibrosis. The same holds true for ileo-anal pouch redo surgery, where the abdominal approach is necessary to obtain sufficient length of the mesentery to make the pouch reach.

In case of redo anastomosis, the transanal phase can start with a purse-string of the afferent colon. However, creating a purse-string is less important in redo surgery compared to low anterior resection for rectal cancer, because the surgical field is already contaminated and a purse-string won't prevent infection. The rectal cuff is incised distal of the anastomosis and the anastomosis is mobilized. It is important to stay close to the bowel wall, because there is no mesorectum and surrounding structures along the ventral and lateral dissection planes (e.g. autonomic nerves, urethra) can easily be damaged. When the neorectum is fully mobilized and rendez-vous with the abdominal dissection plane is achieved, the colon is exteriorised either via the anal canal or via a Pfannenstiel incision. The level of colonic transection is determined after assessing the perfusion and

pliability of the tissue. Subsequently a new anastomosis can be created, either hand-sewn or by a circular stapler, depending on the available length of the rectal cuff. Alternatively, a Turnball-Cutait procedure can be performed with delayed anastomosis, particulary in the presence of urethral or vaginal fistula. In a Turnbull-Cutait delayed redo anastomosis, temporary sutures are placed, the colon is exteriorized through the anal canal, and after 7-10 days, the redundant colon is resected and the anastomosis is completed. Delayed anastomosis might also be beneficial for a redo anastomosis after ultralow anterior resections. However, immediate coloanal anastomosis has better functional outcomes, when compared to delayed [28].

A recent review on redo anastomosis for complicated colorectal or coloanal anastomoses showed a pooled 79% anastomotic integrity rate during follow-up with a 16% major complication rate. [44]

The major complication rate appears low, when compared to the individual cohort studies including only redo anastomosis for chronic pelvic sepsis (41% AL rate [38], 40.6% morbidity rate[37]) and might be explained by the heterogeneity in indication for redo surgery. Patients with an anastomotic leakage after redo surgery have a decreased chance of bowel continuity (OR 0.022).[38]

A minimally invasive transanal approach in redo surgery can provide better access to the surgical field and debridement of the presacral space can be performed more complete. Transanal minimally invasive redo surgery compared to conventional treatment showed a restored continuity rate of 72% vs 61% and it was possible to make a stapled anastomosis more often (62% vs 0%)[43]. In addition, the transabdominal part of the operation could be done more often minimally invasive.

The transanal approach can also be used for many various surgical causes of pouch failure, because of the superior accessibility. Considerations to perform a redo pouch or pouch excision are largely similar to treating a chronic sinus after rectal cancer surgery. However, patients receiving an IPAA for ulcerative colitis, FAP or Crohn's disease are often younger, more fit for major salvage surgery and might have a stronger wish to preserve the anastomosis and prevent a permanent stoma.

When performing a sleeve advancement of the pouch (e.g. for cuffitis), first the mucosa is incised at the level of dentate line. Then the dissection is continued proximally, until the affected area is incorporated and the sleeve can be advanced without tension. The sleeve is then trimmed to excise the affected tissue and

the new cuff is than sutured to the anoderm. When a sleeve advancement is likely to result in tension at the anastomotic site (e.g. larger defect than expected or chronic sinus), the pouch can be fully mobilized transabdominally and transanally. If possible, the pouch can be remodeled or a new pouch can be created and anastomosed to the anus. A combined abdominal and transanal approach enables optimal preservation of the pouch and surrounding structures due to the superior exposure and operative view, thereby preventing damage to the nerves and ureters.

CONCLUDING REMARKS

Early transanal closure of anastomotic defects after a short period of endoscopic vacuum therapy (EVASC) proved to be very successful in early salvage of anastomotic leaks of low colo-anal, colo-rectal, and ileo-anal anastomoses. Early diagnosis and initiation of vacuum therapy is crucial. Redo surgery for chronic pelvic sepsis after TME surgery and for surgical causes of pouch failure is greatly facilitated by TAMIS enabling precise bottom up dissection beyond the upper border of the prostate and the vesicels.

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CHAPTER 9

Endoscopic Vacuum-assisted Surgical Closure (EVASC) of anastomotic defects after low anterior resection for rectal cancer; lessons learned

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ABSTRACT

Background: Endoscopic vacuum assisted surgical closure (EVASC) is an emerging treatment for AL, and early initiation of treatment seems to be crucial. The objective of this study was to report on the efficacy of EVASC for anastomotic leakage (AL) after rectal cancer resection and determine factors for success.

Methods: This retrospective cohort study included all rectal cancer patients treated with EVASC for a leaking primary anastomosis after LAR at a tertiary referral centre (July 2012 - April 2020). Early initiation (≤21 days) or late initiation of the EVASC protocol was compared. Primary outcomes were healed and functional anastomosis at end of follow-up.

Result: Sixty-two patients were included, of whom 38 were referred. Median follow-up was 25 months (IQR 14-38). Early initiation of EVASC (≤21 days) resulted in a higher rate of healed anastomosis (87% vs 59%, OR 4.43 [1.25-15.9]) and functional anastomosis (80% vs 56%, OR 3.11 [1.00-9.71]) if compared to late initiation. Median interval from AL diagnosis to initiation of EVASC was significantly shorter in the early group (11 days (IQR 6-15) vs 70 days (IQR 39-322), p<0.001). A permanent end-colostomy was created in 7% and 28%, respectively (OR 0.18 [0.04-0.93]). In 17 patients with a non-defunctioned anastomosis, and AL diagnosis within 2 weeks, EVASC resulted in 100% healed and functional anastomosis.

Conclusion: Early initiation of EVASC for anastomotic leakage after rectal cancer resection yields high rates of healed and functional anastomosis. EVASC showed to be progressively more successful with the implementation of highly selective diversion and early diagnosis of the leak.

INTRODUCTION

Anastomotic leakage (AL) is still one of the most feared complications after low anterior resection (LAR) for rectal cancer, and is associated with increased morbidity, impaired functional outcomes and reduced cancer free survival.[1, 2] Additionally, the economic burden to health care systems is high, with increased post-operative reinterventions, need for intensive care, lengthened hospital stay and readmissions.[3, 4] Despite high reported incidences of AL of up to 30% [5-7], there is very little literature on effective treatment of AL after LAR.

Conventional management of AL usually consists of faecal diversion (if not diverted primarily) and control of pelvic sepsis with transgluteal, percutaneous

or transanal drainage. Rarely, dismantling of the anastomosis is required.[8] Faecal diversion and passive drainage alone do not always lead to adequate and long-term control of pelvic sepsis.[9] The internal sphincter acts as a functional barrier which causes retention, with retrograde filling of the abscess cavity behind the anastomotic defect with pus, faecal material and debris. Even if sepsis is controlled, this mechanism often prevents complete healing of the anastomosis, especially in an irradiated field.[5, 9] Failure to achieve mucosal approximation can eventually result in severe problems related to a chronic presacral sinus.[10]

Endoscopic vacuum therapy (EVT) is a relatively new approach, in which vacuum-sponges are placed via the anastomotic defect into the abscess cavity. [11, 12] With negative pressure and continuous drainage, active healing of the abscess cavity is stimulated by reducing oedema, decreasing bacterial colonization and simultaneously increasing local blood perfusion that results in granulation of the perianastomotic cavity. Originally, the size of the sponge was gradually reduced during each exchange, until only a small sinus remains. [13] We adapted the technique by adding transanal closure of the anastomotic defect over a small suction drain as soon as the cavity is clean and granulating, which is named the endoscopic vacuum assisted surgical closure (EVASC) protocol. [14, 15] This reduces the number of required sponge exchanges, aims for rapid restoration of mucosal alignment, and minimizes fibrotic changes with preservation of compliance of the neorectum.

Early detection and initiation of treatment of AL is pivotal, when the neorectum is still pliable and unaffected by chronic inflammation.[16] Preliminary results from the multicentre CLEAN-study and GRECCAR group suggest that early start of EVT (<3 weeks CLEAN and < 2 weeks GRECCAR) might increase the chance of restored continuity, but patient numbers in both studies were small.[14] This study describes the extended experience with EVASC in rectal cancer patients at the initiating center of the CLEAN-study, with the aim to evaluate efficacy of EVASC and factors impacting success.

MATERIALS AND METHODS

Study design and patients

This is a retrospective cohort study of patients who underwent EVASC at a tertiary referral centre (Amsterdam UMC, location AMC) between July 2012 and April 2020. Patients were eligible for inclusion if aged ≥18 years, diagnosed with AL after TME for rectal cancer at the AMC or a referring hospital, and were managed with EVASC. Patients with a chronic sinus (a leak present > 1 year after index surgery) were excluded. Patients undergoing a redo-anastomosis were included if performed after failed EVASC, but were excluded if only preceded by a few days of EVT to clean the abscess to ensure only patients with at least one full EVASC cycle were included. The local medical ethical committee approved no written informed consent was necessary because of the retrospective nature of this study and that only a letter of no objection was sent to all eligible patients. If no objection was filed after 4 weeks, participants were included in this study.

Diagnosis and therapeutic interventions

In our unit, TaTME was introduced at the end of 2014, and routine diversion was stopped in the beginning of 2015 with a postoperative protocol of CRP based CT imaging of the anastomosis.[17] Referred patients were in general diverted and had conventional (either open or laparoscopic) TME surgery.

After AL diagnosis, intravenous antibiotics were started and relaparoscopy performed for ileostomy formation, if no primary ileostomy was present. In parallel, endoscopic inspection of the anastomosis and placement of the first Endo-SPONGE® (B.Braun Medical B.V., Melsungen, Germany) was carried out. If the access to the cavity was too small for the smallest insertion tube (10mm), the leak was dilated endoscopically to facilitate the smallest calibre insertion tube of the Endo-Sponge kit. Diagnosis and initial management for AL of referred patients was according to local protocol, and EVT was started as early as possible after initial outpatient consultation at our institution.

After initial Endo-SPONGE® placement, subsequent exchanges were performed under conscious sedation every 3 to 4 days, in an outpatient setting if possible. One or more sponges were placed depending on the size of the abscess cavity. After placement, the sponge was connected to a vacuum bottle with constant negative pressure (*Redyrob® TRANS PLUS suction device, Melsungen, Germany).* The anastomotic defect was closed surgically once sepsis was controlled and the abscess cavity was clean, showing healthy granulation tissue (figure 1). Details

of the technique were described earlier [12, 14] and a video vignette is available online[15]. After TaTME, mostly the use of the Lonestar retractor sufficed to expose the leaking anastomosis and close the defect, while the TAMIS platform was used to close the defect for higher anastomoses after conventional TME. A drain was placed perianastomotic in the cavity through the rectal wall just below the defect. It was placed during the transanal closure procedure to ensure collaps of the presacral cavity after the procedure by negative pressure from the drain and was removed after 5-7 days.[15]

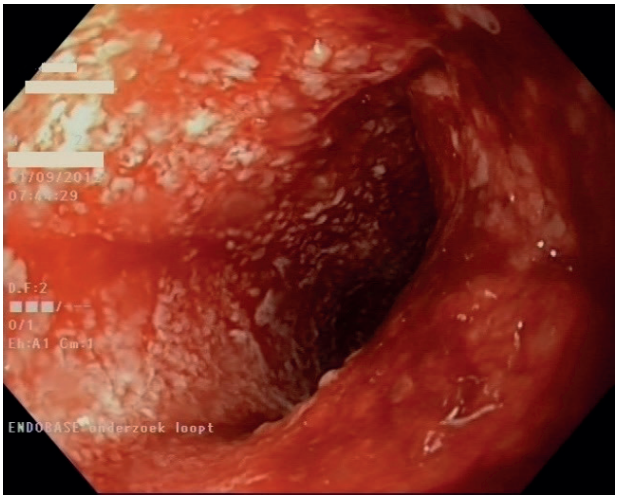


Figure 1: Healthy granulating tissue covering a presacral cavity after successful treatment with EVT.

Integrity of the anastomosis was checked two weeks after surgical closure by endoscopy followed by CT scan with rectal contrast. In case of failed EVASC (persisting leak), repeat EVASC was attempted if considered potentially successful. In case of persisting leakage, redo anastomosis was offered to patients highly motivated for preserving bowel continuity. Alternatively, intersphincteric resection of the anastomosis, omentoplasty and end-colostomy was performed to treat the chronic sinus.

Outcomes and data collection

Baseline, preoperative, intraoperative and postoperative data of the index surgery was collected until end of follow-up from electronic records and by contacting the referring hospitals to optimize completeness. Main outcome parameters were the proportions of healed and functional anastomosis at end of follow-up

or at time of death. Secondary outcomes included, total number of EVT cycles and sponge exchanges, number of transanal closure attempts, anastomotic redo surgery, type of healed or functional anastomosis (primary or redo), and end-colostomy rate at end of follow-up

Definitions

A healed anastomosis was defined as no contrast extravasation visible on CT-scan and/or an intact anastomosis during endoscopy, independent of the presence of a diverting stoma. A functional anastomosis was defined as a healed anastomosis with restored bowel continuity.

An EVT cycle was calculated from (re)start of EVT treatment until any other reintervention, such as transanal closure, or period of observation. Individual number of sponge exchanges were also calculated separately.

Patient groups

Patients were subdivided based on the time to initiation of the EVASC protocol (date of first intervention): within 21 days of the index surgery, or later than 21 days, based on the results of the CLEAN-study.[14] Subgroup analysis was performed for 1) patients that underwent TaTME; 2) Patients with an anastomotic fistula towards the vagina, bladder or perineum, 3) patients that received a diverting stoma during index surgery; 4) Patients with leak diagnosis within 2 weeks after primary surgery 5) Referred patients with index operation elsewhere.

Statistical analysis

Data was either presented as mean with standard deviation or median with interquartile range, depending on the distribution, which was checked by visual inspection of the frequency distribution. Categorical outcomes were analysed using a Chi-square test and continuous outcomes using a student's T-test. Kruskal-Wallis test was used for non-parametrical continuous data. Significance was set at a p-value of less than 0.05. Odds ratios with 95% confidence intervals were calculated for the primary binary outcomes (healed and functional anastomosis rates) and the end-colostomy rate. All statistical analyses were carried out with IBM SPSS statistics, version 26.0 (IBM, Corp Armonk, New York, United States of America). Results were reported adherent to the STROBE-statement.[18]

RESULTS

During the study period, a total of 126 patients were treated with EVASC for leakage of a low pelvic anastomosis, of which 62 patients met the inclusion criteria and were included in the present analysis (Figure 2). Of these 62 patients, 22 were included in the CLEAN study[14]. Thirty-eight patients (61%) were referred after index surgery at another hospital. Patients were male in 71% and the mean BMI was 26 kg/m2 (table 1). Some form of neoadjuvant radiotherapy was given in 73%. A total of 5 patients were diagnosed with an anastomotic fistula at time of AL-diagnosis, which was a vaginal fistula in four patients and a fistula towards the gluteal region in one patient. Two patients had a preoperative diverting colostomy due to obstruction and 37 (61%) received a diverting ileostomy at the index operation. Median follow-up was 25 months (IQR 14 - 38).

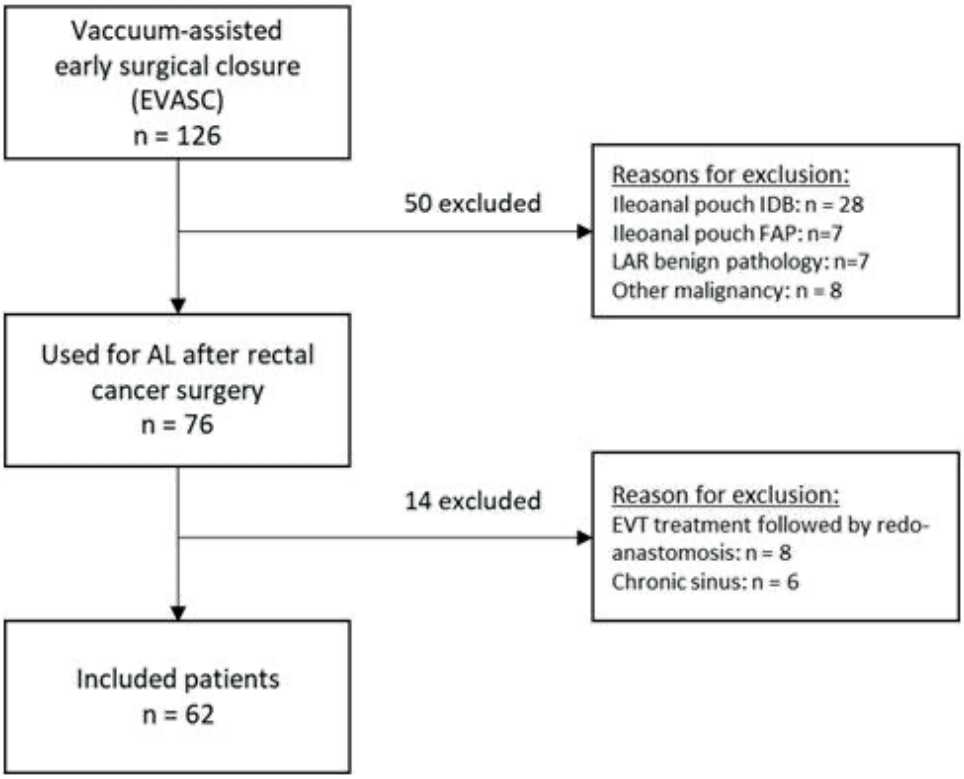


Figure 2: Patient flow diagram.

Table 1: Baseline characteristics.

	Total (n=62)	LAR to EVASC ≤ 21 days (n=30)	LAR to EVASC >21 days (n=32)	p-value
Gender (male), n (%)	44 (71%)	22 (73%)	22 (69%)	0.691
Age in years	61 ± 9	52 ± 10	60 ± 9	0.460
BMI (kg/m2)	26 ± 4	26 ± 3	26 ± 4	0.738
Current smokers, n (%)	9 (15%)	5 (17%)	4 (13%)	0.642
ASA				
ASA 1	23 (37%)	9 (30%)	14 (44%)	0.406
ASA 2	36 (58%)	20 (67%)	16 (50%)	
ASA 3 or higher	3 (5%)	1 (3%)	2 (6%)	
Neoadjuvant therapy, n (%)				
SCRT	22 (36%)	5 (17%)	17 (53%)	0.003
Chemoradiotherapy	23 (37%)	10 (33%)	13 (41%)	0.553
Location of index operation, n (%)				
AMC	24 (39%)	19 (63%)	5 (16%)	0.000
Elsewhere	38 (100%)	11 (37%)	27 (84%)	
Surgical technique, n (%)				
TaTME	12 (19%)	10 (33%)	2 (6%)	0.007
Conventional TME	50 (81%)	20 (67%)	30 (94%)	
Type of anastomosis, n (%)				
Stapled	58 (94%)	27 (90%)	31 (97%)	0.271
Hand-sewn	4 (7%)	3 (10%)	1 (3%)	
Diverting stoma after LAR, n (%)				
None	23 (37%)	16 (53%)	7 (22%)	0.034
Ileostomy	37 (61%)	13 (43%)	24 (75%)	
Pre-existing colostomy	2 (2%)	1 (3%)	1 (3%)	

LAR=low anterior resection; EVASC= endoscopic vacuum assisted surgical closure; BMI= body mass index; ASA=American Society Anesthesiology; SCRT= short course radiotherapy; AMC = Amsterdam Medical Center; TaTME = transanal total mesorectal excision; TME = total mesorectal excision;

EVASC and other reinterventions

The EVASC protocol was started early (≤ 21 days) in 30 patients and late (>21 days) in 32 patients after the index operation. Median interval from TME to start of the EVASC protocol was shortest in the early group (11 vs. 70 days). Interventions for AL are summarized in Table 2. Median number of sponge exchanges until transanal closure was similar in both groups (4 vs 4). Median number of EVT cycles appeared lower in the early group (1), compared to the late group (2), although not statistically significant. The majority of patients (77%), underwent only one attempt of transanal closure of the anastomotic defect.

Table 2: Details of EVASC and surgical interventions for anastomotic leakage.

	Total (n=62)	LAR to EVASC ≤ 21 days (n=30)	LAR to EVASC >21 days (n=32)	p-value
Median interval from TME to AL in days (IQR)	13 (5-28)	7 (4-13)	27 (14-46)	0.000
Median interval from TME to first reintervention* in days (IQR)	17 (8-43)	9 (4-14)	42 (24 -77)	0.000
Median interval from TME to start EVASC in days (IQR)	23 (11-78)	11 (6-15)	70 (39-322)	0.000
EVT				
Median Endosponge exchanges (IQR)	4 (2-10)	4 (2-11)	4 (2-10)	0.831
Median cycles of EVT**, (IQR)	1 (1-2)	1 (1-2)	2 (1-2)	0.052
1 cycle	37 (60%)	22 (73%)	15 (47%)	
2 cycles	16 (26%)	5 (17%)	11 (34%)	
3 cycles	6 (10%)	1 (3%)	5 (16%)	
4 cycles	3 (5%)	2 (7%)	1 (3%)	
Retractor system used for transanal closure, n (%)				
Lonestar retractor	34 (55%)	18 (60%)	16 (50%)	0.429
Transanal platform	28 (45%)	12 (40%)	16 (50%)	
Median no. of transanal closure procedures (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	0.832
One	48 (77%)	23 (77%)	25 (78%)	
Two	11 (18%)	5 (17%)	6 (19%)	
Three	2 (3%)	1 (3%)	1 (3%)	
Four	1 (2%)	1 (3%)	-	
Redo anastomosis after failed EVASC treatment, n (%)	11 (18%)	4 (13%)	7 (22%)	0.379
Median FU in months (IQR)	25 (14-38)	22 (13-50)	27 (18-37)	0.190
Died during FU, n (%)	11 (18%)	8 (27%)	3 (9%)	0.075
Recurrence/metastatic disease	8 (13%)	7 (23%)	1 (3%)	0.072
Other/unknown	3 (5%)	1 (3%)	2 (6%)	

LAR=low anterior resection; EVASC=endoscopic vacuum assisted surgical closure; EVT=endoscopic vacuum therapy; TME=total mesorectal excision; AL=anastomotic leakage; IQR=interquartile range
** reintervention could be stoma formation, EVT, combination of stoma and EVT or other interventions*
*** Cycle of EVT: one series is from start until stop of EVT therapy or until a surgical intervention (e.g. transanal closure.)*

Surgical outcomes

Surgical outcomes are summarized in Table 3. Anastomotic healing rate was 73% in the total cohort, which was higher in the early group (87%), compared to the late group (59%, OR 4.43 [1.25-15.9]). The proportion of patients with a functional anastomosis at time of death or end of follow-up was also highest in the early group (80% vs 56%, OR 3.11 [1.00-9.71]). Intersphincteric resection of the anastomosis with creation of end-colostomy was performed in 11 patients (18%) of which 2 patients in the early group, compared to 9 in the late group (OR 0.18 [0.04-0.93]). A redo-procedure of the anastomosis after at least one EVASC treatment was performed in 11 patients (18%), which occurred most frequent in the late group (7 patients (22%)). Causes for non-continuity in the total cohort were metastatic disease (6%), a persisting leak (6%), anastomotic fistula (15%), local recurrence (2%), patient preference (2%) and functional complaints (2%).

Table 3: Surgical outcomes.

	Total cohort (n=62)	LAR to EVASC ≤ 21 days (n=30)	LAR to EVASC >21 days (n=32)	OR (95%-CI)
Anastomosis healed (with or without diversion), n (%)	45 (73%)	26 (87%)	19 (59%)	4.43 [1.25-15.9]
Anastomosis functional (healed with restored continuity), n (%)	42 (68%)	24 (80%)	18 (56%)	3.11 [1.00-9.71]
Outcome related to type of anastomosis and presence of a stoma, n (%)				
Primary anastomosis healed, diverted	3 (5%)	2 (7%)	1 (3%)	2.21 [0.19-25.6]
Primary anastomosis healed, non-diverted (functional)	37 (60%)	21 (70%)	16 (50%)	2.33 [0.82-6.62]
Primary anastomosis non-healed, diverted	4 (7%)	2 (7%)	2 (6%)	1.07 [0.14-8.13
Redo-anastomosis healed, non-diverted (functional)	5 (8%)	3 (10%)	2 (6%)	1.66 [0.26-10.8]
Redo-anastomosis, non-healed, diverted	2 (3%)	-	2 (6%)	0.94 [0.86-1.03]
End-colostomy	11 (18%)	2 (7%)	9 (28%)	0.18 [0.04-0.93]
Reasons for non-continuity, n (%)				
Metastatic disease	4 (6%)	3 (10%)	1 (3%)	-
Persisting leak/chronic sinus	4 (6%)	-	4 (13%)	-
Anastomotic fistula*	9 (15%)	2 (7%)	7 (22%)	-
Local recurrence	1 (2%)	1 (3%)	-	-
Patient preference	1 (2%)	-	1 (3%)	-
Functional complaints	1 (2%)	-	1 (3%)	-

LAR=low anterior resection; EVASC; endoscopic vacuum assisted surgical closure; FU=follow-up; IQR=interquartile range
*including both persisting anastomotic fistula or newly developed fistula after EVASC-treatment was completed.

Subgroup analysis

Patients with an anastomotic fistula had a significantly worse healing (20% vs 77%, OR 0.074 [0.01-0.72]) and functionality rate (20% vs 72%, OR 0.098 [0.01-0.94]), compared to patients without a fistula, respectively. Patients with a primary diverted anastomosis had worse healing (62% vs 91%, OR 0.15 [0.03-0.75]) and functionality (54% vs 91%, OR 0.11 [0.02-0.54]) rates, while the end-colostomy rate (26% vs 4%, OR 7.58 [0.90-62.5]) was higher if compared to patients without a primary diverted anastomosis. Diagnosis of AL within 2 weeks showed higher healed (79% vs 63%, OR 2.25 [0.72-7.01]) and functional anastomosis rates (74% vs 58%, OR 2.00 [0.68-5.93]), although not significant (table 4). No differences were found between patients who underwent index surgery at the AMC versus referred patients, or conventional TME vs TaTME (supplementary table 1). In 17 patients without anastomotic fistula, without primary diverting stoma and leak diagnosis <2 weeks, healed and functional anastomosis rate were both 100%. Details are presented in table 4.

Table 4: Surgical outcomes – subgroup analysis.

Anastomotic fistula*	**Fistula (n=5)**	**No fistula (n=57)**	**OR (95%-CI)**
Anastomosis healed (with or without diversion), n (%)	1 (20%)	44 (77%)	0.074 [0.01-0.72]
Anastomosis functional (healed with restored continuity), n (%)	1 (20%)	41 (72%)	0.098 [0.01-0.94]
End-colostomy, n (%)	2 (40%)	9 (16%)	3.56 [0.52-24.4]
Start EVASC ≤ 21 days, n (%)	2 (40%)	28 (49%)	-
Initial diverting stoma at index surgery	**Stoma (n=39)**	**No stoma (n=23)**	**OR (95%-CI)**
Anastomosis healed (with or without diversion), n (%)	24 (62%)	21 (91%)	0.15 [0.03-0.75]
Anastomosis functional (healed with restored continuity), n (%)	21 (54%)	21 (91%)	0.11 [0.02-0.54]
End-colostomy, n (%)	10 (26%)	1 (4%)	7.58 [0.90-62.5]
Start EVASC ≤ 21 days, n (%)	14 (36%)	16 (70%)	-
Leak diagnosis ≤ 2 weeks	**AL ≤ 2 wks (n=38)**	**AL > 2 wks (n=24)**	**OR (95%-CI)**
Anastomosis healed (with or without diversion), n (%)	30 (79%)	15 (63%)	2.25 [0.72-7.01]
Anastomosis functional (healed with restored continuity), n (%)	28 (74%)	14 (58%)	2.00 [0.68-5.93]
End-colostomy, n (%)	6 (25%)	5 (13%)	2.20 [0.59-8.20]
Start EVASC ≤ 21 days, n (%)	30 (79%)	-	-

*=five patients initially presented with an anastomotic fistula towards the vagina (n=4) or gluteal region (n=1) and were treated with EVASC. Patients who developed an anastomotic fistula after completing EVASC were not included for this analysis. EVASC= endoscopic vacuum assisted surgical closure; AL= anastomotic leakage;

DISCUSSION

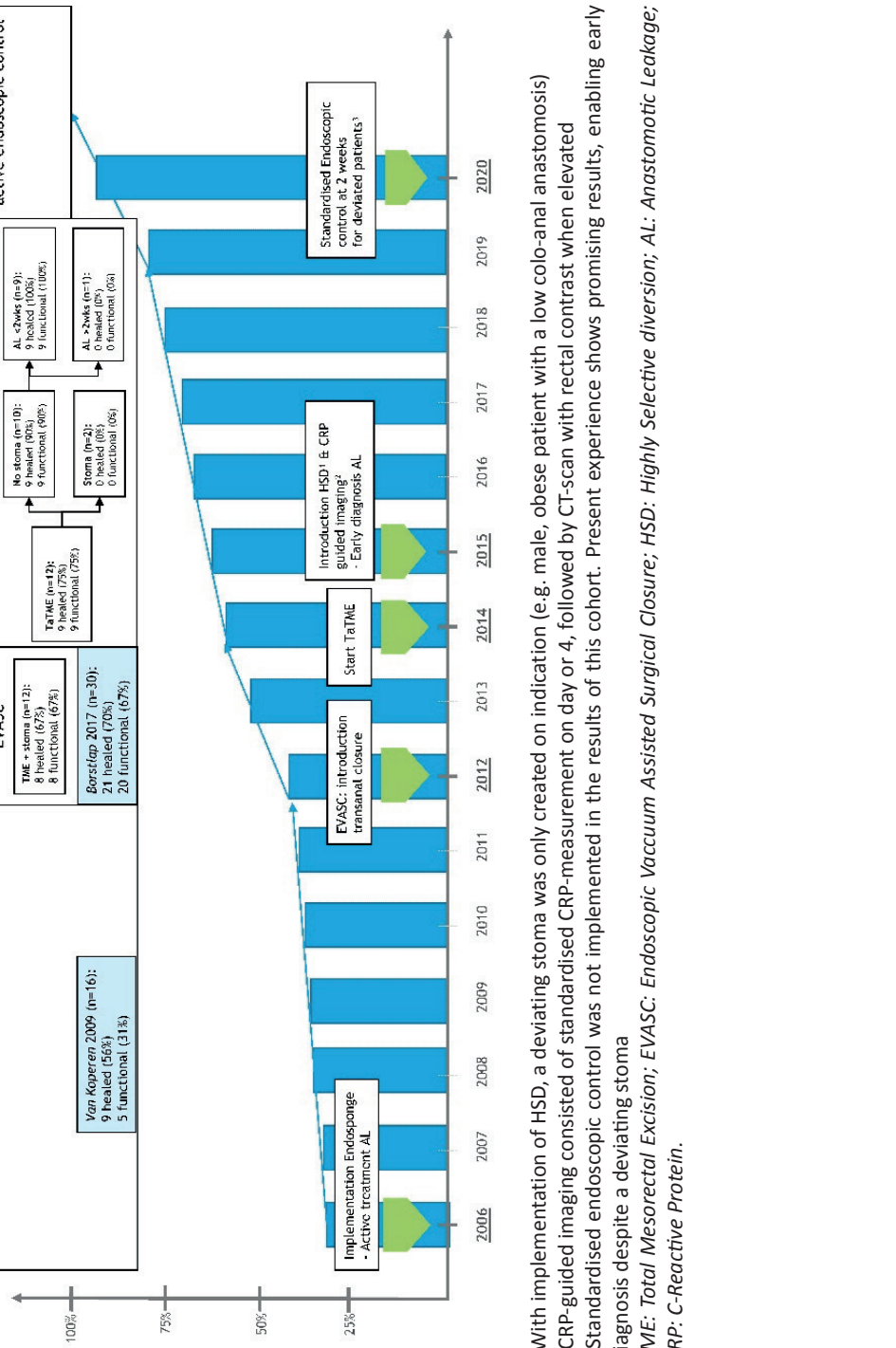
EVT of leaking low anastomoses is applied in our unit since 2006.[12] Over time we moved away from the original EVT technique as described by Weidenhagen with tapering of the sponge during subsequent exchanges, and started to close the anastomotic defect as soon as the cavity was clean and granulating (the EVASC protocol). This retrospective cohort study analysed 62 rectal cancer patients who underwent EVASC, of whom the majority was referred from other institutions with delayed start of treatment. The overall proportion of healed anastomosis was 73% and 68% had a functional anastomosis at end of follow-up. Early initiation of EVASC within 21 days after index surgery resulted in significantly higher proportion of healed and functional anastomosis. In a subgroup of 17 patients without primary diversion, without anastomotic fistula and leak diagnosis within 2 weeks, a functional anastomosis at end of follow-up was achieved in all patients.

The increasing success rate of salvaging the leaking anastomosis reflects the evolution of the EVASC protocol. Highly selective diversion, use of a transanal platform, proactive diagnosis of anastomotic leaks using CT guided imaging, and early endoscopic assessment of anastomotic integrity increased the healing and functionality rates of the leaking anastomoses to 100% in the most recent patients. The developments in treatment over the last 15 years since the implementation of Endosponge treatment in 2006 can be seen in figure 3.

A recent review based on 17 studies, which included 276 patients treated with EVT for AL, found an anastomotic healing rate of 85.3%.[19] However, this review might be difficult to compare with the present study given the heterogeneity in treatment (e.g. EVT with or without transanal closure) and indication for primary surgery (e.g. rectal cancer or IBD). The GRECCAR group reported on a multicentre experience of EVT without transanal closure in 62 patients treated between 2012 and 2017.[16] Despite exclusion of patients with an anastomotic fistula, a lower functional anastomosis rate of 55% was found after median 37 months of follow-up if compared to the present study. Similarly, they showed a higher restored continuity rate when EVT was started within 15 days (72.4% vs 27.8%). These data are in line with published results of EVT without transanal closure from our group, revealing anastomotic healing rates of 75% versus 38% using a 6 weeks cut-off.[12] However, another retrospective cohort study compared early start (≤21 days after LAR) with late start (>21 days after LAR) of EVT in a small cohort of 20 patients, and found an identical anastomotic healing rate of 70% in both groups.[20]

Passive treatment with local drainage and faecal diversion is often insufficient as presented in data from the Dutch SNAPSHOT collaboration.[5] One year after LAR,

Figure 3: Developments in treatment over the last 15 years for anastomotic leakage after LAR since implementation of Endosponge in 2006.



[1] With implementation of HSD, a deviating stoma was only created on indication (e.g. male, obese patient with a low colo-anal anastomosis)

[2] CRP-guided imaging consisted of standardised CRP-measurement on day or 4, followed by CT-scan with rectal contrast when elevated

[3] Standardised endoscopic control was not implemented in the results of this cohort. Present experience shows promising results, enabling early diagnosis despite a deviating stoma

TME: Total Mesorectal Excision; EVASC: Endoscopic Vaccuum Assisted Surgical Closure; HSD: Highly Selective diversion; AL: Anastomotic Leakage; CRP: C-Reactive Protein.

conservative treatment for AL resulted in a chronic sinus in half of all patients with AL. Transanal or radiological drainage of the pelvic abscess to treat AL was described in a retrospective study in 54 patients with AL after rectal cancer surgery.[9] Continuity was restored in 50% after drainage alone and if drainage failed, a redo-anastomosis was performed in 21 patients (39%). Continuity was restored in 80% at end of follow-up and 20% had received an end-colostomy. Although many patients had their continuity restored, major salvage surgery was required more often and many lost their initial anastomosis.

Early initiation of the vacuum therapy is crucial to avoid fibrotic scarring and retraction of the anastomotic edges. Significant retraction and fibrosis of the anastomotic defect makes surgical closure technically difficult, reducing the success rate of the technique. The ability to close the defect can be assessed during each subsequent sponge exchanges. After removal of the sponge, slight suction with the endoscope will make the neorectum collapse. This enables judgement whether the two anastomotic edges reach sufficiently to make surgical closure technically possible. If the anastomotic edges are scarred and fibrotic as in late diagnosed and chronic leaks, the edges remain separated during endoscopic suction.

Early diagnosis of the leak depends on a proactive assessment of anastomotic healing using CRP guided imaging in the non-diverted patients, and early endoscopic assessment in the diverted patients within 10-14 days after the index operation. In more recent years, we have been able to generally start the EVASC protocol within 5 days in the non-diverted patients, resulting in a high success rate.

The second factor for technical success of the EVASC protocol depends on the ease of surgical closure and therefore level of the anastomosis. Low colorectal and coloanal anastomosis done via the TaTME technique are relatively easy to close, mostly using only a Lonestar retractor.

Based on our experience, anastomotic defects can be classified according to the size of the leak and the extent of retraction present (Supplementary table 2). Significant retraction precludes surgical closure. Large defects with significant retraction or complete dehiscence due to necrosis of the afferent loop are not suitable for EVASC. The EVT can then be used for optimal sepsis control and cleansing as preparation for (an early) redo of the complete anastomosis (Supplementary figure 1).

Patients often received neoadjuvant radiotherapy in our cohort (73%). Radiotherapy is a known risk factor for AL and impairs wound healing due

to fibrosis and reduced oxygenation of the surgical field.[21] Neo-adjuvant chemoradiotherapy is also associated with larger abscess cavities, longer duration of EVT, more sponge exchanges and longer time to closure of the leak.[22]

In the referred group, a longer interval to AL diagnosis, first intervention and start of the EVASC protocol was observed. This might be a reflection of the absence of a proactive protocol to assess the anastomotic integrity and the time-consuming referral process to a tertiary centre. Others were referred after failed attempts to salvage the anastomosis at the referral site.

The presence of an anastomotic fistula, for example to the vagina, can compromise successful EVASC treatment. One of the reasons for less successful EVASC in those patients might be related to the limited capacity of acquiring an appropriate vacuum seal. But fistulas to the vagina are difficult to treat anyway, and almost always require major salvage surgery.[23]

In some patients, anastomotic redo surgery was performed after one or more failed EVASC attempts. Although not significant, more redo-procedures were performed in the late group (7 versus 4, p=0.379). When a first attempt of EVASC has not been successful, one can decide to continue vacuum therapy in the way Weidenhagen described it originally, tapering the size of the sponge every exchange, thereby making the cavity gradually reduce in size until a small sinus remains

Effective implementation of an EVASC protocol depends on two important factors. First, the Endo-Sponge® kit must be available. In a number of countries, the kit is not available (eg. the US), although there are off-label possibilities.[24] Second, EVASC requires a protocolised infrastructure in the surgical unit with a 24/7 availability of skilled personnel, operating theatre and endoscopic facilities.

This study has several limitations. First, all data was extracted retrospectively and missing data had to be requested from referring hospitals. However, all required data for analysing the primary and secondary outcomes were complete. Second, referral bias might have underestimated success rates. Besides, the fact that this is a single centre experience limits the external validity of the study. Third, this study did not take the location and degree of anastomotic dehiscence into account, which is difficult to analyze retrospectively. These factors might influence the effectiveness of EVASC. Finally, although the current series is probably the largest in literature, the numbers are still small. Further research in larger cohorts (e.g. TENTACLE study[25]) can provide more definitive evidence on the most effective management of anastomotic leakage.

CONCLUSION

This comparative cohort study reveals that initiation of EVASC within 3 weeks is important for successful restoration of bowel continuity after anastomotic leakage following rectal cancer resection. EVASC appeared to be progressively successful with the implementation of highly selective diversion and early diagnosis of the leaks within 2 weeks, resulting in a healed and functional anastomosis rate nearing 100%.

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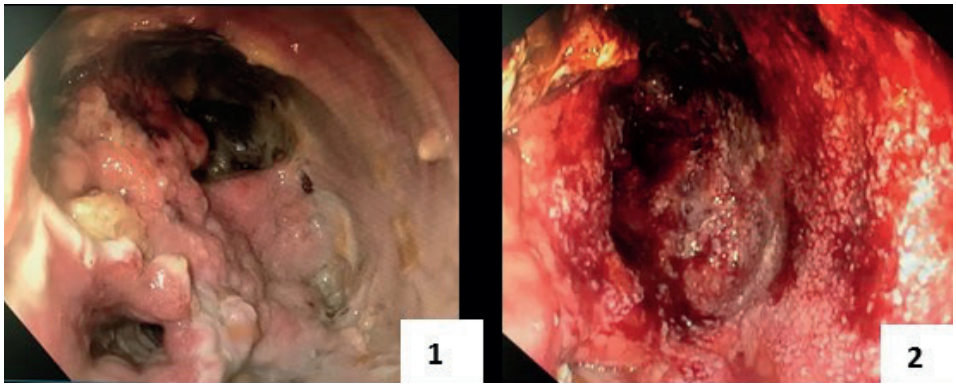
Supplementary table 1: Surgical outcomes - subgroup analysis for AMC vs referred and TaTME vs. conventional TME.

	AMC (n=24)	Referred (n=38)	p-value
Anastomosis healed (with or without diversion), n (%)	17 (71%)	28 (74%)	0.806
Anastomosis functional (healed with restored continuity), n (%)	17 (71%)	25 (66%)	0.679
End-colostomy, n (%)	4 (17%)	7 (18%)	0.860
	TaTME (n=12)	**TME (n=50)**	**p-value**
Anastomosis healed (with or without diversion), n (%)	9 (75%)	36 (72%)	0.834
Anastomosis functional (healed with restored continuity), n (%)	9 (75%)	33 (66%)	0.549
End-colostomy, n (%)	2 (17%)	9 (18%)	0.914

AMC= Amsterdam medical center; TaTME=transanal total mesorectal excision.

Supplementary table 2: Classification and treatment strategy of anastomotic leakage.

Anastomosis	Treatment
Defect < 1/3 + no retraction	EVASC
Defect > 1/3 + no retraction	Partial closure followed by EVASC
Defect > 1/3 + significant retraction	EVT assisted early redo anastomosis



Supplementary figure 1: Endoscopic images showing an anastomotic defect > 1/3 of the circumference with significant retraction after TaTME. Image 1 is on first endoscopic inspection after index operation. Image 2 shows a clean granulating cavity after EVT-treatment at 10 days postoperative, after which the patient underwent a successful redo-procedure of the anastomosis.

CHAPTER 10

Comparison of proactive and conventional treatment of anastomotic leakage in rectal cancer surgery; a multicentre retrospective cohort series

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ABSTRACT

Purpose: Comparative studies on efficacy of treatment strategies for anastomotic leakage (AL) after low anterior resection (LAR) are almost non-existing. This study aimed to compare different proactive and conservative treatment approaches for AL after LAR.

Methods: This retrospective cohort study included all patients with AL after LAR in three university hospitals. Different treatment approaches were compared, including a pair-wise comparison of conventional treatment and endoscopic vacuum assisted surgical closure (EVASC). Primary outcomes were healed and functional anastomosis rates at end of follow-up.

Results: Overall, 103 patients were included, of which 59 underwent conventional treatment and 23 EVASC. Median number of reinterventions was 1 after conventional treatment, compared to 7 after EVASC ($p<0.01$). Median follow-up was 39 and 25 months, respectively. Healed anastomosis rate was 61% after conventional treatment, compared to 78% after EVASC ($p=0.139$). Functional anastomosis rate was higher after EVASC, compared to conventional treatment (78% vs 54%, $p=0.045$). Early initiation of EVASC in the first week after primary surgery, resulted in better functional anastomosis rate compared to later initiation (100% vs 55%, $p=0.008$).

Conclusion: Pro-active treatment of AL consisting of EVASC resulted in improved healed and functional anastomosis rates for AL after LAR for rectal cancer, compared to conventional treatment. If EVASC was initiated within the first week after index surgery, a 100% functional anastomosis rate was achievable.

INTRODUCTION

Anastomotic leakage (AL) is one of the most dreaded complications after low anterior resection (LAR) for rectal cancer and is associated with increased rates of morbidity and mortality, higher rates of permanent stomas, worse oncological outcomes and additional healthcare costs. [1-3] The incidence of AL remains high with rates up to 20% during the first year after index surgery[4] and there is still limited evidence on most effective treatment strategies for AL after LAR.

Conventional treatment of AL consists of the creation of a diverting ileostomy, if not created primarily, and surgical or radiological drainage of any present abscess collections. In selected patients dismantling of the anastomosis might be indicated. If initial treatment fails, an intersphincteric resection of the

anastomosis with creation of an end-colostomy may be required to gain control of pelvic sepsis. More recently, pro-active treatment strategies have emerged, such as endoscopic vacuum therapy (EVT). In EVT, an open-pored polyurethane sponge is placed into the presacral cavity and connected to a controlled negative pressure system, which increases local blood flow, reduces bacterial load and stimulates formation of granulation tissue. These actions lead to the gradual collaps of the abscess cavity. [5, 6]

This labor-intensive protocol was first described by Weidenhagen et al. (2008) and adapted in Amsterdam, whereby vacuum therapy was only used to clean the cavity enabling surgical closure of the anastomotic dehiscence within 2 weeks; endoscopic vacuum assisted surgical closure (EVASC). [7-9] Previous studies showed that EVT and EVASC are effective treatments for AL, especially when it is initiated early after AL diagnosis in the first few weeks after the index operation.[8, 10] Other pro-active treatment strategies include endoscopic clipping or transanal suturing of the defect. [11]

Comparative studies on efficacy of different treatment strategies are almost non-existing in current literature. This comparative cohort study aimed to compare the efficacy of different pro-active and conventional treatment strategies for AL with healed and functional anastomosis rates as primary outcomes.

METHODS

Study population

AL after LAR for rectal cancer who were operated between February 2009 and April 2020 at three university centres. Patients were excluded if they underwent surgical resection for benign disease, a partial mesorectal excision, resection without formation of a anastomosis or if they were diagnosed with a chronic sinus (leak diagnosis > 1 year after LAR). The local medical ethical committees approved no written informed consent was necessary because of the retrospective nature of this study.

Surgery and treatment for AL at the different centres

Amsterdam

In Amsterdam UMC, location AMC (AMS), patients underwent conventional TME with routine diversion until an institutional shift at the end of 2014 towards transanal TME (TaTME) with highly selective diversion.[12] All patients received

preoperative mechanical bowel preparation and intravenous antibiotics. Throughout the entire study period, an early diagnosis and pro-active treatment strategy was attained. A CRP-based imaging protocol consisting of a computed tomography (CT) scan with rectal contrast was used to diagnose AL.[13] After AL-diagnosis, a diverting ileostomy was created (if not created primarily) to control pelvic sepsis and when the cavity appeared suitable, EVT was started immediately. When the cavity seemed clean with granulation tissue, it was closed with transanal sutures and two weeks after surgical closure, the anastomosis was evaluated endoscopically. If a healed anastomosis was observed during endoscopy and confirmed by a CT-scan with rectal contrast, the diverting ileostomy was closed. A more detailed description was published earlier and a video is available on transanal closure. [8, 14]

Oxford

In the Oxford University Hospitals (OXF), patients underwent a conventional TME or TaTME based on the operating surgeons' preference with standard deviation. All patients received mechanical bowel preparation and intravenous antibiotics preoperatively. When there was a clinical suspicion of AL, a CT-scan with rectal contrast was made. After detecting AL, the abscess cavity was drained either surgically or endoscopically, with incidental use of transanal closure and/or EVT in more recent years, based on the surgeons' preference. If secondary healing of the presacral cavity was achieved, and confirmed by CT scan with rectal contrast, the diverting ileostomy was closed.

Barcelona

In the Hospital Clinic of Barcelona (BAR), patients underwent either conventional TME or TaTME based on the operating surgeons' preference with selective diversion. All patients received preoperative mechanical bowel preparation and intravenous antibiotics. A CT-scan with rectal contrast or direct surgical intervention was performed if AL was suspected. A diverting stoma was created (if not present after LAR) and abdominal or presacral collections were drained either surgically or radiologically. After secondary healing of the presacral cavity, confirmed by CT scan with rectal contrast, the diverting stoma was closed.

Data collection and outcome parameters

All data was retrieved from electronic medical files from the three individual hospitals and included baseline characteristics, index operation, AL diagnosis, reinterventions, readmissions and length of follow-up. Primary outcomes were healed and functional anastomosis rate. Secondary outcomes were interval from

LAR to AL-diagnosis, number and type of reintervention, number and reason for readmission, length of stay during index admission and related to index surgery until end of follow-up, interval from LAR to healed and functional anastomosis, type of stoma at end of follow up and number of end colostomies.
A healed anastomosis was defined as having no active leak or chronic sinus, confirmed clinically, by endoscopy and/or by CT-imaging. A functional anastomosis was defined as a healed anastomosis with restored continuity. Readmissions were counted as at least one overnight admission in the hospital. Out-patient treatment with one-day admission (e.g., sponge exchange) was not counted as a readmission. One sponge series was defined as the period from initial placement and exchanges (including the last exchange) until any other type of intervention was performed (e.g., surgical closure) or a watch-and-wait strategy was adopted.

Conventional treatment was defined as conservative treatment with creation of a diverting stoma, if not primarily present, and drainage of present collections (either radiologically, manually or surgically) awaiting secondary healing. EVASC was defined as described above (a few rounds of EVT, followed by surgical closure of the defect), regardless of drainage or stoma creation. EVT was defined as multiple rounds of EVT without surgical closure, regardless of drainage or stoma creation. Transanal suturing was defined if only surgical closure of the defect was performed (no EVT), regardless of drainage or stoma creation. Redo-anastomosis was defined as complete dismantlement of the primary anastomosis and creation of a new secondary anastomosis. 'Mucosal approximation strategy' was defined as having a pro-active treatment strategy in which approximation of the mucosal edges was obtained, and this included EVASC, transanal closure and redo-anastomosis.

Statistical analysis

Results were presented separately for the different treatment strategies; conventional treatment, EVASC, EVT without surgical closure, transanal suturing and re-do anastomosis. Comparative subgroup analysis was performed for conventional vs. EVASC, early initiation of EVASC (≤ 7 days) vs. late initiation (> 7 days) and treatment including mucosal approximation vs. other treatment. Continuous data was presented as mean with standard deviation (SD) or median with interquartile range (IQR), depending on their distribution. Categorical data was presented as absolute numbers with percentages. Student's t-test was used for continuous and normally distributed variables. For non-normal distributed continuous variables, a Mann-Whitney U test was used to calculate median and IQR. Median interval in days was calculated between index operation and AL-diagnosis and between index operation and first reintervention for AL. Chi-square

was used to for dichotomous and categorical data. Two sides p values <0.05 were considered statistically significant. All analyses were performed with IBM SPSS statistics, version 26.0.0 (IBM Corp. Armonk, NY, United States).

RESULTS

Study population

A total of 103 patients were included, of whom 33 from AMS, 36 from OXF and 58 from BAR. Conventional treatment was performed in 59 patients, EVASC in 23, EVT in 12, transanal suturing in 6 and redo anastomosis in 3. More patients had received no neoadjuvant therapy after conventional treatment (61%) and EVT (58%), compared to EVASC (39%) and transanal suturing (33%). The proportion of diverting stoma after primary resection was similar after conventional treatment (59%) and EVASC (48%), but was higher after EVT (75%) and transanal suturing (83%), see also figure 1. For all baseline characteristics, see Table 1.

AL-diagnosis

Timing of AL diagnosis is displayed in Table 2. AL was diagnosed within 14 days after index operation in 68% in the conventional group, compared to 78% in the EVASC group, 83% in EVT- no closure and 67% in the transanal suturing group. Differences in median interval from LAR to initiation of treatment were similar to time to diagnosis.

Reinterventions

Reintervention rate excluding stoma creation/closure was only 53% in the conventional group, compared to 100% in the other groups. The median number of reinterventions was highest in the EVT-group (8, IQR 4-15), followed by EVASC (7, IQR 5-10), transanal suturing (1.5, IQR 1-4) and conventional treatment (1, IQR 0-1). Resection of the anastomosis with creation of end-colostomy was performed most often in the EVT-group (33%), followed by conventional treatment (24%), transanal suturing (17%) and EVASC (17%).

Readmissions

Readmissions excluding stoma creation/closure was highest in transanal suturing (83%), followed by EVT (75%), EVASC (70%) and conventional treatment (54%). Median number of readmissions was higher in EVT and transanal suturing (2, IQR 0-3 and 2, IQR 1-3), compared to conventional and EVASC (1, IQR 0-1 and 1, IQR 0-3)) Reason for readmissions were mainly for treatment of AL. Median total

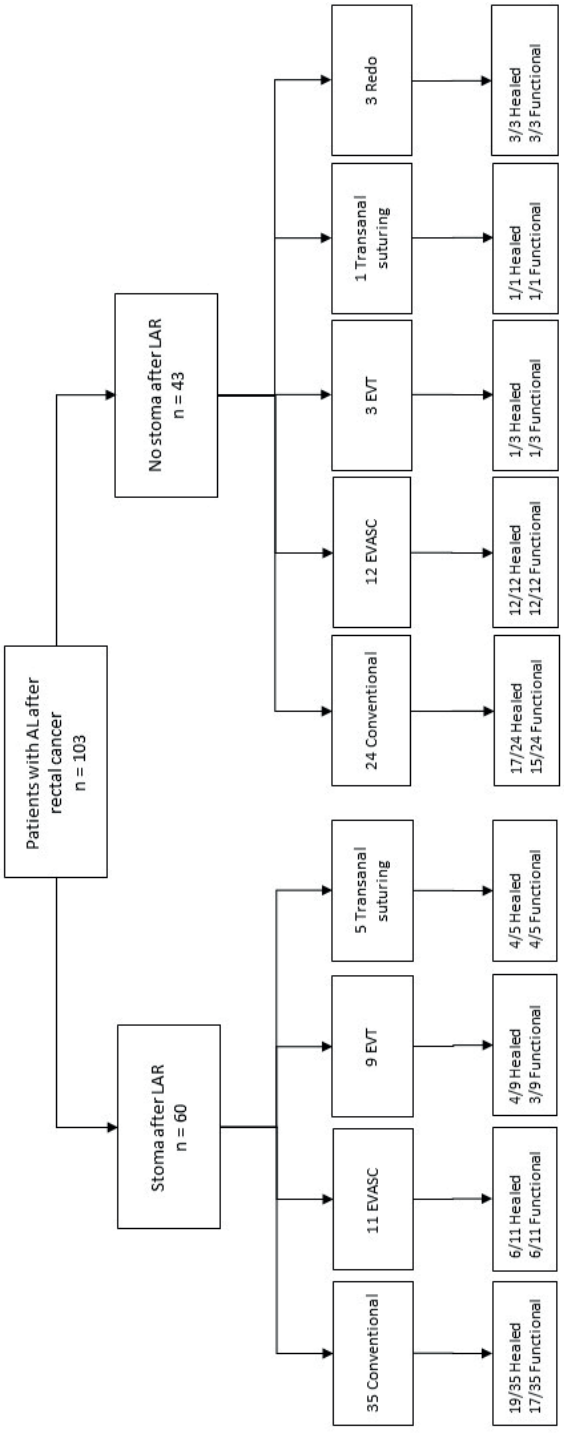

***Figure 1:** Flow diagram.*

AL: anastomotic leakage; LAR: low anterior resection; EVASC: endoscopic vacuum assisted surgical closure; EVT: endoscopic vacuum therapy;

Table 1: Baseline characteristics.

	Conventional (n=59)	EVASC (n=23)	EVT (n=12)	Transanal suturing (n=6)	Redo (n=3)
Gender (male)	45 (76%)	20 (87%)	11 (92%)	5 (83%)	2 (67%)
Mean Age in years [SD]	65 (SD 3)	64 (SD 7)	64 (SD 12)	59 (SD 5)	58 (SD 1)
Mean BMI (kg/m2) [SD]	26 (SD 3)	27 (SD 4)	26 (SD 4)	25 (SD 4)	25 (SD 1)
Smoker	15 (29%)	4 (19%)	1 (14%)	1 (20%)	1 (33%)
ASA					
ASA 1	11 (19%)	4 (17%)	2 (17%)	4 (67%)	0
ASA 2	37 (63%)	13 (57%)	7 (58%)	2 (33%)	3 (100%)
ASA 3 or higher	11 (19%)	6 (26%)	3 (25%)	0	0
Neoadjuvant treatment					
None	36 (61%)	9 (39%)	7 (58%)	2 (33%)	3 (100%)
Short-course radiotherapy	3 (5%)	5 (22%)	0	1 (17%)	0
Chemoradiotherapy	19 (32%)	8 (35%)	4 (33%)	3 (50%)	0
Chemotherapy only	1 (2%)	1 (4%)	1 (8%)	0	0
Previous abdominal surgery	9 (16%)	3 (13%)	0	1 (17%)	0
Surgical approach index rectal cancer resection					
Open	1 (2%)	2 (9%)	2 (17%)	0	0
Laparoscopic	58 (98%)	21 (91%)	10 (83%)	5 (100%)	3 (100%)
Surgical technique					
LAR	30 (51%)	11 (48%)	7 (58%)	1 (17%)	0
TaTME	29 (49%)	12 (52%)	5 (42%)	5 (83%)	3 (100%)
Type of anastomosis					
Stapled	51 (93%)	21 (91%)	11 (92%)	3 (50%)	3 (100%)
Configuration					
SE	41 (70%)	15 (65%)	9 (75%)	5 (83%)	2 (67%)
EE	17 (29%)	7 (30%)	3 (25%)	1 (17%)	1 (33%)
Other	1 (2%)	1 (4%)	0	0	0
Diverting stoma after LAR					
None	24 (41%)	12 (52%)	3 (25%)	1 (17%)	3 (100%)
Created during LAR	32 (54%)	10 (44%)	8 (67%)	5 (83%)	0
Preoperative ileostomy	3 (5%)	0	0	0	0
Preoperative colostomy	0	1 (4%)	1 (4%)	0	0
Institute					
AMC	7 (12%)	19 (83%)	2 (17%)	1 (83%)	3 (100%)
OXF	18 (31%)	4 (17%)	9 (75%)	5 (83%)	0
BAR	34 (58%)	0	1 (8%)	0	0

EVASC: endoscopic vacuum assisted surgical closure; EVT: endoscopic vacuum therapy; SD: standard deviation; BMI: Body Mass Index; ASA: American Society of Anesthesiologists; LAR: low anterior resection; TaTME: transanal total mesorectal excision; SE: side-to-end; EE: end-to-end; AMS: Amsterdam; OXF: Oxford; BAR: Barcelona;.

Table 2. Timing of leakage diagnosis and subsequent treatment with detailed description of reinterventions and readmissions.

	Conventional (n=59)	EVASC (n=23)	EVT (n=12)	Transanal suturing (n=6)	Redo (n=3)
Interval from LAR to AL diagnosis in days (IQR)	5 (3-27)	7 (4-14)	6 (2-12)	8.5 (4-19)	4 (NA)
< 14 days	40 (68%)	18 (78%)	10 (83%)	4 (67%)	3 (100%)
< 30 days	46 (78%)	20 (87%)	11 (92%)	6 (100%)	3 (100%)
< 90 days	54 (92%)	23 (100%)	11 (92%)	6 (100%)	3 (100%)
Interval from LAR to first reintervention for AL in days (IQR)	7 (4-20)	7 (4-16)	8 (3-20)	11 (4-55)	5 (NA)
Reinterventions – all					
Median (IQR)	2 (1-3)	8 (6-12)	9 (5-16)	2.5 (2-5)	2 (NA)
Reinterventions – excluding stoma creation/closure	31 (53%)	23 (100%)	12 (100%)	6 (100%)	3 (100%)
Median (IQR)	1 (0-1)	7 (5-10)	8 (4-15)	1.5 (1-4)	2 (NA)
Radiological reintervention	7 (12%)	6 (26%)	3 (25%)	0	0
Median (IQR)	0 (0-0)	0 (0-1)	0 (0-1)	NA	NA
Endoscopic reinterventions	3 (5%)	23 (100%)	12 (100%)	1 (17%)	1 (33%)
Median (IQR)	0 (0-0)	4 (3-6)	6 (3-9)	0 (0-0)	0 (NA)
Endoscopic vacuum therapy	1 (2%)	23 (100%)	12 (100%)	0	1 (33%)
Sponge series (IQR)	0 (0-0)	1 (1-1)	1 (1-1)	NA	0 (NA)
*Sponge exchanges (IQR)**	4 (NA)	3 (2-8)	5 (3-8)	NA	3 (NA)
Surgical reinterventions - all	53 (90%)	23 (100%)	12 (100%)	6 (100%)	3 (100%)
Median (IQR)	2 (1-2)	3 (3-4)	3 (2-4)	2.5 (2-4)	2 (NA)
Surgical reinterventions - excluding stoma creation/closure	26 (44%)	23 (100%)	11 (92%)	6 (100%)	3 (100%)
Median (IQR)	0 (0-1)	1 (1-3)	2 (2-3)	1.5 (1-3)	1 (NA)
Surgical drainage	26 (44%)	5 (22%)	6 (50%)	3 (50%)	0
Median (IQR)	0 (0-1)	0 (0-0)	1 (0-1)	0.5 (0-1)	0 (0-0)
Washout	6 (10%)	7 (30%)	7 (58%)	3 (50%)	0
Median (IQR)	0 (0-0)	0 (0-1)	1 (0-2)	0.5 (0-1)	0 (0-0)
Other (e.g., rectal catheter. debridement fistula etc.)	14 (24%)	5 (22%)	10 (83%)	3 (50%)	1 (33%)
Median (IQR)	0 (0-0)	0 (0-0)	1 (1-1)	0.5 (0-2)	0 (NA)
Transanal closure	5 (9%)	23 (100%)	3 (25%)#	6 (100%)	0
Median (IQR)	0 (0-0)	1 (1-2)	0 (0-1)	1 (1-1)	0 (0-0)
Redo-anastomosis	-	-	-	-	3 (100%)
Median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1 (1-1)
Resection anastomosis with end colostomy	14 (24%)	4 (17%)	4 (33%)	1 (17%)	0
Median (IQR)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-0)
Stoma-related surgical reinterventions					
Creation/correction of stoma	19 (31%)	14 (71%)	4 (33%)	1 (17%)	3 (100%)
Median (IQR)	0 (0-1)	1 (0-1)	0 (0-1)	0 (0-0)	1 (1-1)
Ileostomy reversal	38 (64%)	22 (96%)	5 (42%)	6 (100%)	3 (100%)
Median (IQR)	1 (0-1)	1 (1-1)	0 (0-1)	1 (1-1)	1 (1-1)

Readmissions	50 (85%)	23 (100%)	9 (75%)	6 (100%)	3 (100%)
Median (IQR)	1 (1-2)	2 (1-4)	2 (0-3)	3 (2-4)	2 (NA)
Readmissions – excluding stoma creation/closure	32 (54%)	16 (70%)	9 (75%)	5 (83%)	2 (56%)
Median (IQR)	1 (0-1)	1 (0-3)	2 (0-3)	2 (1-3)	1 (NA)
Treatment for AL	17 (29%)	14 (61%)	8 (67%)	3 (50%)	1 (33%)
Median (IQR)	0 (0-1)	1 (0-2)	1 (0-1)	1 (0-2)	0 (NA)
Ileus	5 (9%)	1 (4%)	2 (33%)	2 (33%)	0
Median (IQR)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-0)
Other	9 (15%)	3 (13%)	2 (17%)	2 (33%)	1 (33%)
Median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0 (NA)
Stoma-related readmissions					
Stoma closure	35 (59%)	20 (87%)	2 (17%)	56 (100%)	3 (100%)
Median (IQR)	1 (0-1)	1 (1-1)	0 (0-0)	1 (1-1)	1 (1-1)
Stoma-related problems	6 (10%)	4 (17%)	0	2 (33%)	0
Median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-0)
Length of stay					
Index admission for LAR in days (IQR)	12 (7-20)	15 (5-25)	30 (18-58)	10 (5-31)	10 (NA)
During complete FU in days (IQR)	19 (12-31)	30 (23-43)	52 (33-88)	22 (13-49)	13 (NA)
Total – without stoma closure in days (IQR)	16 (9-28)	25 (19-34)	52 (33-84)	18 (10-37)	11 (NA)

EVASC: endoscopic vacuum assisted surgical closure; EVT: endoscopic vacuum therapy; LAR: low anterior resection; AL: anastomotic leakage; IQR: inter-quartile range; FU: follow-up
**Only patients who underwent Endoscopic vacuum therapy were included in this analysis*
[#] A total of three patients underwent surgical closure before start of endoscopic vacuum therapy.

Table 3: Surgical outcomes.

	Conventional (n=59)	**EVASC (n=23)**	**EVT (n=12)**	**Transanal suturing (n=6)**	**Redo (n=3)**
Median follow up in months (IQR)	39 (24-62)	25 (12-59)	30 (21-61)	37 (32-45)	19 (NA)
Healed anastomosis at EFU	36 (61%)	18 (78%)	5 (42%)	5 (83%)	3 (100%)
Median interval from LAR to healed anastomosis in days (IQR)	141 (77-216)	114 (48-210)	304 (197-567)	104 (60-252)	153 (NA)
Functional anastomosis at EFU	32 (54%)	18 (78%)	4 (33%)	5 (83%)	3 (100%)
Median interval from LAR to functional anastomosis in days (IQR)	267 (142-368)	185 (146-292)	364 (325-676)	296 (207-353)	188 (NA)
Stoma at EFU					
Pre-LAR ileostomy	2 (3%)	0	0	0	0
Primary ileostomy (created during LAR)	4 (7%)	1 (4%)	4 (33%)	0	0
Secondary ileostomy (after LAR)	2 (3%)	0	0	0	0
Tertiary ileostomy (stoma after stoma closure)	1 (2%)	0	1 (8%)	0	0
End-colostomy	14 (24%)	4 (17%)	3 (25%)	1 (17%)	0
No stoma. not healed at EFU	4 (7%)	0	0	0	0

EVASC: endoscopic vacuum assisted surgical closure; EVT: endoscopic vacuum therapy; LAR: low anterior resection; AL: anastomotic leakage; IQR: inter-quartile range; EFU: end of follow-up.

Table 4: Pair-wise comparison and subgroup analysis.

	Conventional (n=59)	EVASC (n=23)	p-value
Median follow up in months (IQR)	39 (24-62)	25 (12-19)	0.124
Interval LAR-AL diagnosis	5 (3-27)	7 (4-14)	0.921
Interval LAR-first reintervention for AL	7 (4-20)	7 (4-16)	0.918
Healed anastomosis at EFU	36 (61%)	18 (78%)	0.139
Median interval from LAR to healed anastomosis in days (IQR)	141 (77-216)	114 (48-210)	0.271
Functional anastomosis at EFU	32 (54%)	18 (78%)	0.045
Median interval from LAR to functional anastomosis in days (IQR)	267 (142-368)	185 (146-292)	0.245
Median number of reinterventions	2 (1-3)	8 (6-12)	<0.001
Median number of surgical reinterventions	2 (1-2)	3 (3-4)	<0.001
Median number of readmissions	1 (1-2)	2 (1-4)	<0.001
Planned readmissions	1 (0-1)	2 (1-2)	<0.001
Unplanned readmissions	0 (0-1)	0 (0-1)	0.479
Total length of stay	19 (12-31)	30 (23-43)	0.004
	EVASC (n=23)		
	Early (≤7days) (n=12)	**Late (>7 days) (n=11)**	**P=value**
Healed anastomosis at EFU	12 (100%)	6 (55%)	0.008
Median interval from LAR to healed anastomosis in days (IQR)	107 (44-185)	123 (90-357)	0.291
Functional anastomosis at EFU	12 (100%)	6 (55%)	0.008
Median interval from LAR to functional anastomosis in days (IQR)	185 (128-258)	233 (152-393)	0.250
Median number of reinterventions	9 (6-12)	8 (6-13)	0.880
Median number of readmissions	1 (1-2)	4 (2-7)	<0.001
Total length of stay	29 (23-39)	30 (18-60)	0.566
	Mucosal approximation[1] (n=32)	**Passive/other (n=71)**	**p-value**
Healed anastomosis at EFU	26 (81%)	41 (58%)	0.021
Median interval from LAR to healed anastomosis in days (IQR)	114 (64-204)	163 (80-248)	0.080
Functional anastomosis at EFU	26 (81%)	36 (51%)	0.003
Median interval from LAR to functional anastomosis in days (IQR)	207 (151-298)	291 (148-371)	0.138
Median number of reinterventions	8 (3-10)	2 (1-3)	<0.001
Median number of readmissions	2 (1-3)	1 (1-2)	<0.001
Total length of stay	29 (18-42)	23 (15-46)	0.237

EVASC: endoscopic vacuum assisted surgical closure; IQR: inter-quartile range; LAR: low anterior resection; AL: anastomotic leakage; EFU: end of follow-up
[1] Mucosal approximation was defined as having a pro-active treatment strategy in which approximation of the mucosal edges was obtained, and this included EVASC, transanal closure and redo-anastomosis.

length of stay excluding stoma closure/creation was highest after EVT (52 days, IQR 33-84), followed by EVASC (25 days, IQR 19-34), transanal suturing (18 days, IQR 10-37) and conventional treatment (16 days, IQR 9-28)

Surgical outcomes

The outcomes regarding anastomotic healing and bowel continuity after a median follow-up of 25-39 months are displayed in Table 3. The percentage of healed anastomosis at the end of follow-up was 61% after conventional treatment, 78% after EVASC, 42% after EVT and 83% after transanal suturing.

Median interval from LAR to healed anastomosis was shortest after transanal suturing (104 days, IQR 60-252), followed by EVASC (114 days, IQR 48-210), conventional treatment (141 days, IQR 77-216), and EVT (304 days, 197-567). The highest proportion of patients with a functional anastomosis was found for transanal suturing (83%), followed by EVASC (78%), conventional treatment (54%) and EVT (33%). Median interval from LAR to functional anastomosis was shortest in EVASC (185 days, IQR 146-292), compared to conventional (267 days, IQR 142 – 368), transanal suturing (296 days, IQR 207-353) and EVT (364 days, IQR 325-676).

Pair-wise comparison and subgroup analysis

Pair-wise comparison showed a higher healed anastomosis rate after EVASC compared to conventional treatment (78% vs 61%), although this was not statistically significant (p=0.139). The functional anastomosis rate was significantly higher after EVASC, when compared to conventional treatment (78% vs 54%, p=0.045). In the EVASC group more surgical reinterventions were performed (median 3 vs 2, p<0.001), more readmissions (median 2 vs 1 p<0.001) and a longer length of stay (median 30 days vs 19 days, p=0.004) were seen, compared to conventional treatment. More planned readmissions were seen after EVASC (median 1 vs 2, p<0.001), but no difference in unplanned readmissions was seen (median 0 vs 0, p=0.479).

If EVASC was started in the first 7 days after surgery, the healed anastomosis rate was higher (100% vs 55%, p=0.008), compared to late initiation (>7 days). Similarly, the functional anastomosis rate was higher (100% vs 55%), with similar median number of reinterventions (9 vs 8 p=0.880) and length of stay (29 days vs 30 days p=0.566), but less readmissions (1 vs 4, p<0.001)

If mucosal approximation was obtained this led to higher healed anastomosis rate (81% vs 58%, p=0.021) and higher functional anastomosis rates (81% vs 51%, p=0.003), when compared to passive closure or other treatments. Median number of reinterventions (8 vs 2, p<0.001) and readmissions (2 vs 1, p<0.001) were higher after mucosal approximation, compared to passive closure or other treatments.

DISCUSSION

This three-centre international comparative cohort study shows that pro-active treatment of AL that aims to achieve mucosal approximation, leads to a better healed and functional anastomosis rates. These improved outcomes of a pro-active strategy however require the highest number of reinterventions and readmissions. Subgroup-analysis showed that EVASC leads to better results than conventional treatment and that a 100% success rate in achievable if EVASC is started in the first week after surgery. These findings warrant further explorative studies to define the most optimal treatment strategy for AL.

A systematic review on EVT for AL reported a stoma reversal rate of 75.9%, which is comparable to the results seen after EVASC.[6] However, AL is a heterogeneous disease entity and successful treatment depends on multiple factors. This complicates direct comparisons between published series. A recent prospective cohort study from the GRECCAR-group showed an overall success rate of 55%, and this was 72% if treatment was started within 15 days after index operation and 28% beyond 15 days.[10] A Dutch population based study showed that applied treatments for AL after LAR in routine daily practice in 2011 were successful in 52%, resulting in a chronic sinus rate of 9.5% for the total cohort of patients who underwent resection for rectal cancer.[8] A French monocentre study that investigated the efficacy of radiological or transanal drainage, showed success in 50% of patients after initial treatment.[15] At end of follow-up, 80% of patients were stoma-free, but many patients required major salvage surgery by performing a redo-anastomosis (39%). Studies that compare pro-active with conventional treatment strategies for AL after LAR are scarce. Kühn et al. compared EVT-treatment with a historical cohort that underwent conventional treatment, and found higher restored continuity rates after EVT-treatment (86.7% vs 37.5%, p=0.001).[16] Similar to our results, they found a shorter length of stay after conventional treatment (31 days vs 42 days), but time to stoma closure was not different.

One of controversial topics is the creation of a primary diverting stoma after LAR. More selective diversion (AMS and BAR) has all the advantages of not having a stoma in the majority of patients who will never develop AL, but does requires construction of secondary diverting stoma in case of AL. Opponents of a selective approach emphasize the risk of losing anastomotic integrity in the end, but the present data actually shows that routine diversion does not increase the chance of bowel continuity in case of AL. Furthermore, although a diverting ileostomy

is created with a temporary intention, up to 28% of them eventually become a permanent stoma. [17] Interestingly, permanent stomas consisted of colostomies in the vast majority of patients after selective diversion (AMS and BAR), while these were often the initial ileostomy after routine diversion (OXF).

Although EVASC required more planned readmissions and a longer length of stay, compared to conventional treatment, we believe the impact for the patient was less severe than the results suggest. Most reinterventions and readmissions for sponge replacement, transanal closure or stoma closure could be planned and performed in a controlled setting. No differences in unplanned readmissions was seen and the acute moment were AL was diagnosed often occurred during the primary admission, saving a visit to the emergency ward.

Functional outcomes were not measured in this cohort series because of the retrospective study design, but could have been more favourable in the pro-active treatment group. The development of LARS is multifactorial, including postoperative changes of the pelvic floor and sphincter function, height of the anastomosis, neoadjuvant treatment and alterations in colonic microbiota[18, 19]. Another factor has been analysed in a recent meta-analysis, which showed an increased risk of majors LARS in patients with an ileostomy (OR 2.84 (95%CI 1.70-4.75)) and in patients with a longer time to stoma closure (mean difference 2.39 months (OR 1.28 -3.51)).[20] Pro-active treatment of AL resulted in restored continuity almost 5 months earlier in AMS compared to the other two centres.

This study has a number of limitations. First, there are several methodological issues related to the retrospective study design and relatively small sample size. Although the retrospective nature could lead to potential loss of data, all data regarding the primary outcomes was complete in this study. Second, the definition of a healed anastomosis is debatable. Regular endoscopic control of the anastomosis was performed in AMS, but not in the other centres. Because of restricted accuracy of endoscopy and imaging, a 'healed' anastomosis might still hide a small sinus behind it, that might become active if restoring bowel continuity. Therefore, these results should be interpreted with caution. It should be noted that the functional anastomosis rate might be more valuable as an outcome compared to the healed anastomosis rate, because it represents a more reliable and relevant outcome. Third, there might be performance bias by including patients from different hospitals. However, this seems to be the only feasible way to compare pro-active and conventional treatment for AL at present because of the practical implications. Fourth, no details on leak size were available. It is possible that the high success rate in transanal closure group might

be because the defect at time of diagnosis was limited and direct surgical closure was feasible. Fifth, difference in rates of neoadjuvant treatment and diverting stoma after primary surgery were seen between groups, which may influence success rates. Finally, larger cohort series are needed to confirm present findings and to increase insight into the most effective treatment modalities (e.g., TENTACLE study [21]).

CONCLUSION

A pro-active treatment strategy consisting of EVASC resulted in a higher healed and functional anastomosis rate, compared to conventional treatment and a 100% success rate is achievable if EVASC is initiated within the first week after primary surgery. This could justify the need for a higher number of reinterventions if applying a pro-active treatment.

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Supplementary table 1: Oncological staging.

	Conventional (n=59)	EVASC (n=23)	EVT (n=12)	Transanal suturing (n=6)	Redo (n=3)
Pathological stage					
T-stage					
T0	1 (2%)	1 (4%)	0	1 (17%)	0
T1	6 (10%)	4 (17%)	2 (17%)	1 (17%)	0
T2	20 (34%)	8 (35%)	1 (8%)	1 (17%)	0
T3	30 (51%)	8 (35%)	8 (67%)	3 (50%)	3 (100%)
T4	2 (3%)	2 (9%)	1 (8%)	0	0
N-stage					
N1 or higher	19 (32%)	8 (35%)	4 (33%)	2 (33%)	0
M-stage					
M1	3 (5%)	5 (22%)	0	2 (33%)	0

Supplementary table 2: Primary outcomes compared between centers.

	AMS vs OXF		AMS vs BAR		BAR vs OXF	
	Absolute diff.	P-value	Absolute diff.	P-value	Absolute diff.	P-value
Healed anastomosis	+8%	0.482	+11.9%	0.307	-3.9%	0.736
Median Interval from LAR to healed anastomosis	-102 days	0.000	-56 days	0.023	-46 days	0.118
Functional anastomosis	+13.6%	0.243	+20.5%	0.086	-6.9%	0.559
Median Interval from LAR to functional anastomosis	-144 days	0.000	-164 days	0.008	+20 days	0.899

AMS: Amsterdam; OXF: Oxford; BAR: Barcelona; diff: difference; LAR: low anterior resection;.

CHAPTER 11

Endoscopic vacuum therapy and early surgical closure after pelvic anastomotic leak: meta-analysis of bowel continuity rates

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ABSTRACT

Background: Endoscopic vacuum therapy (EVT) with or without early surgical closure (ESC) is considered an effective option in the management of pelvic anastomotic leakage (AL). This meta-analysis was conducted to analyze the effectiveness of EVT in terms of stoma reversal rate and the added value of ESC.

Methods: A systematic search in PubMed, Medline and the Cochrane Library was conducted in November 2021 to identify articles on EVT in adult patients with pelvic AL. The primary outcome was restored continuity rate. Following PRISMA guidelines, a meta-analysis was performed using a random-effects model.

Results: Twenty-nine studies were included, accounting for 827 patients with leakage who underwent EVT. There was a large heterogeneity between studies in design and reported outcomes and a high risk of bias. The overall weighted mean restored continuity rate was 66.8% (95% CI, 58.8-73.9). In patients undergoing EVT with ESC, the calculated restored continuity rate was 82.0% (95% CI, 50.1-95.4) as compared to 64.7% (95% CI, 55.7-72.7) after EVT without ESC. The mean number of sponges exchanges was 3.6 (95% CI, 2.7 – 4.6) and 9.8 (95% CI, 7.3 – 12.3), respectively. Sensitivity analysis showed a restored continuity rate of 81.0% [95%CI, 55.8-99.5] for benign disease, 69.0% [95% CI, 57.3-78.7] for colorectal cancer and 65.5% [95% CI, 48.8-79.1] if neoadjuvant radiotherapy was given.

Conclusion: Available literature suggests that EVT is associated with a satisfactory stoma reversal rate, especially if combined with ESC. However, there is substantial heterogeneity and high risk of bias in current data sets.

INTRODUCTION

Anastomotic leakage (AL) is the most feared complication in colorectal surgery. This adverse event has significant consequences, including high morbidity and mortality, increased healthcare costs, and a decrease in health-related quality of life indexes, and may even carry an increased risk of locoregional recurrence[1-4]. Despite many advances and newly-developed preventive strategies [5-10], low anterior resection is still associated with incidence rates of AL of about 10-15% [1, 11].

A significant number of pelvic leakages do not heal or may develop into a chronic sinus [12, 13]. This late complication has a substantial impact on the patient's quality of life, with symptoms such as pelvic pain, purulent discharge, or even septicemia [14, 15]. Borstlap et al. reported absence of long-term healing in 48% of leakages[13]

and in half of all patients suffering from AL, the stoma can never be closed [16]. These data emphasize the need for more effective treatment strategies.

In 2008, a new treatment modality was introduced, which consisted of endoscopic placement of a vacuum sponge into the abscess cavity, connected to a negative pressure device, referred to as endoscopic vacuum therapy (EVT) [17]. The effectiveness of EVT has been explored in several cohort studies, with an increasing interest in this technique in most recent years[18-20]. Early surgical closure (ESC) by transanal suturing of the defect after a few sponge exchanges may improve outcomes further if technically feasible [21, 22]. However, complete anastomotic healing might still be difficult to achieve with a risk of recurrent sinus after an apparent healing.

The reported incidence of anastomotic healing after EVT varies between 56% to 100%, which in part reflects the lack of consensus on the definition of anastomotic healing [18, 23]. In fact, current studies have considered both complete and partial anastomotic healing as a primary outcome for therapeutic success due to this heterogeneity [20]. A more objective endpoint that better reflects the success of the therapy from a patient perspective is the rate of functional anastomosis. Therefore, this systematic review and meta-analysis was designed to evaluate the effectiveness of EVT for treating patients with pelvic AL based on stoma closure rate, and to assess whether the outcomes improve with ESC.

MATERIAL AND METHODS

Study design and registration

This work was conducted in accordance with Preferred Reporting Items for Systematic Reviews Statement for Meta-analyses (PRISMA) guidelines [24]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration no. CRD42019118088).

Search strategy and study selection

An expert librarian assisted with a systematic search conducted in PubMed, Medline, and the Cochrane Library for relevant articles between inception and February 2019, with an update in November 2021. The search strategy and information resources are detailed in the Appendix. Randomized controlled trials and observational studies of patients with pelvic intestinal AL treated with EVT were included. Only manuscripts written in English and of which the full-text was available, were included. Case reports and case series with fewer than five cases were excluded, as were animal studies. If the same group published

different articles in the same period, only the largest study was included. The literature search was performed independently by two authors: F.B.L. and S.X.R. in March 2019 and F.B.L and K.T. in November 2021. Disagreements were settled in discussion between both reviewers, and reasons for exclusion were recorded during the screening processes. References in relevant publications were manually searched seeking for additional potentially eligible studies.

Procedures and definitions

Treatment with EVT consisted of endoscopic placement of an open-pored polyurethane sponge into the abscess cavity. The procedure was performed as described in previous articles [17, 21, 25]. Sponges were replaced every three to four days, allowing for continuous monitoring of development of granulation tissue and preventing ingrowth of the sponge. The sponge was connected to a low-vacuum suction bottle to generate a negative pressure and continuous evacuation of pus. Although EVT without fecal diversion has been described, the anastomosis was generally defunctioned.

ESC is a transanal surgical procedure under general anesthesia in which the anastomotic defect is closed. This can be considered when the abscess cavity is covered with granulation tissue and the rectal cuff can be re-approximated[21, 22, 26]. ESC is performed in the Lloyd-Davies position. Depending on the height of the anastomosis, an anal retractor (e.g. Lonestar, Cooper Surgical, Trumbull, CT, USA) or an endoscopic transanal platform such as the flexible Gelpoint Path (Applied Medical, Rancho Santa Margarita, CA, USA) are used. A suction drain is placed in the cavity behind the reconstructed anastomosis, which results in obliteration of the cavity after which the neo-rectum will stick to the sacrum (Figure 1).

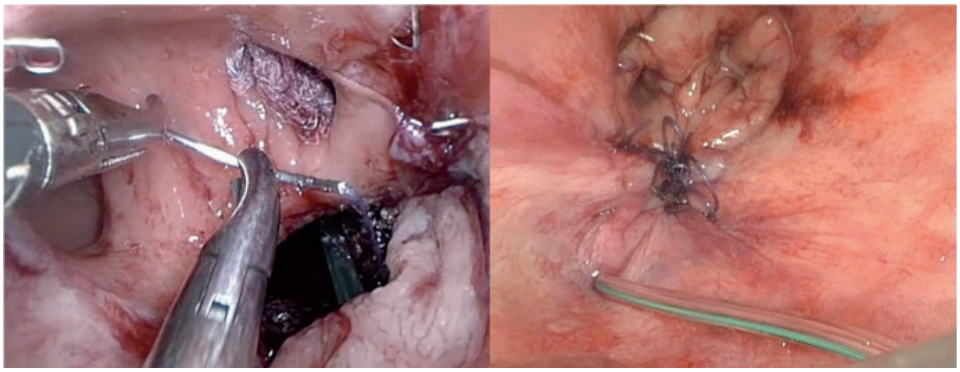

Figure 1: Early surgical closure.

Outcome measures and data collection

The primary outcome was restored continuity at the end of follow-up. Secondary outcomes included time from index surgery to start of EVT, number of sponge exchanges, time to restored continuity, and short-term and long-term complication rates.

The following data were extracted for each selected study: title, first author, year of publication, country, journal name, study design, strength of evidence, inclusion and exclusion criteria, sample size, patient characteristics (mean age, gender, body mass index (BMI), neoadjuvant radiotherapy, American Society of Anesthesiologists (ASA) classification, indication for index surgery), primary operative and postoperative outcomes (type of surgery, primary diverting stoma, time to AL diagnosis), and EVT outcomes (technical details, time to initiation of EVT, number of sponge exchanges, need for secondary stoma, drain placement and removal, adjunct treatments, procedure-related events, and late complications).

Quality assessment

Two authors (F.B.L and K.T.) independently assessed methodological quality using the Newcastle Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). A maximum of 4 points can be awarded for selection, 2 points for comparability and 3 for outcome.

Statistical analysis

Study and baseline characteristics were reported using descriptive statistics. A meta-analysis was performed for single proportions (restored continuity rate, and procedure-related and late complication rates) using a pooled random effect analysis with inverse variance weighting. I^2 was calculated to assess statistical heterogeneity. A meta-analysis was performed for single means (time from surgery to AL-diagnosis, time from surgery to start EVT, number of sponge exchanges and time to stoma reversal) from reported means and standard deviations in the included studies. When data were missing, these were calculated from other data if possible (e.g. median or IQR) using methods from Wan et al. [27]. Both fixed effect and random effects analysis were performed using an inverse variance method and statistical heterogeneity was assessed by calculating the I^2. Sensitivity analyses for restored continuity rates were conducted for EVT with or without ESC, benign disease (or >90% benign disease of included patients) versus colorectal cancer (or >90% CRC of included patients), CRC with radiotherapy versus any type of disease without radiotherapy, and primary diverting stoma

(or >80% of included patients) versus no primary diverting stoma (or <20% of included patients). Publication bias was investigated using a visual inspection of the funnel plot of restored continuity and using the Peters' test to assess linear regression of funnel plot asymmetry (based on sample size).[28]

No comparative meta-analysis between EVT with or without ESC was performed because only single cohort studies were found, and results are presented separately for both subgroups. A meta-analysis on healed anastomosis rate was not performed due to the high level of heterogeneity in definition of what constitutes a healed anastomosis. Meta-analysis was performed using RStudio version 1.2.1335 (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA, *http://www.rstudio.com/).*

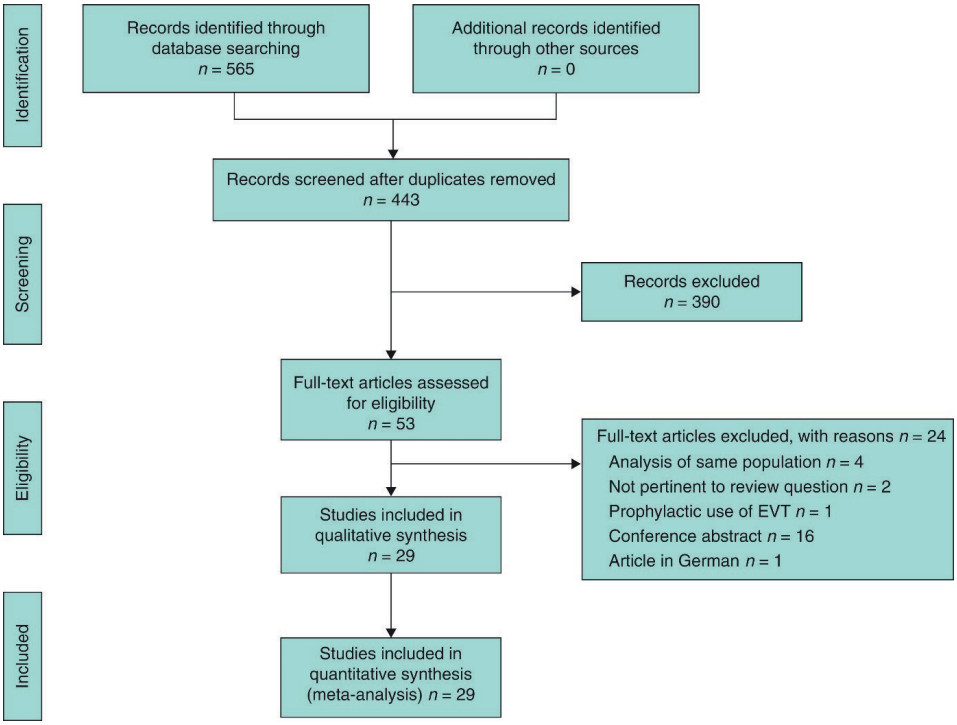

Figure 2: PRISMA flow diagram.

RESULTS

The literature search yielded 442 records. After screening for titles and abstracts, 53 articles were eligible for full-text review. Of these, 28 studies were finally included.[18, 19, 21-23, 25, 29-51] Reasons for exclusion were different articles with overlap of cohorts (n=4), articles not relevant to the review question (n=2), conference abstracts (n=16), and German language (n=1). The study flow diagram is outlined in Figure 2. No randomized controlled trial was found. Six studies were cohort studies, including one that used matching to handle allocation bias [22, 29, 31, 45, 47, 50]. The rest of studies were case series from institutional databases [18, 19, 21, 23, 25, 30, 32-44, 46, 48, 49, 51]. Four studies used ESC as an adjunct to EVT [21, 22, 25, 45]. However, the study by Huisman et al. was excluded from the subgroup analysis due to the impossibility of extracting the specific information for the ESC cohort (3 patients, 15% of the whole group)[45]. Quality assessment of the included studies are reported in Supplementary Table 2. The funnel plot appeared potentially asymmetrical, but the Peters' linear regression indicated no asymmetry in the funnel plot, indicating a low likelihood of publication bias (p = 0.356) (Supplementary Figure 1).

Table 1 shows the characteristics of the included studies, accounting for a total of 827 patients. Based on the studies reporting the indications for EVT, 613/817 patients (75.0%) underwent primary surgery for colorectal cancer[18, 19, 21-23, 25, 29-39, 41-51]. Sixty-six patients (8.1%) were treated for inflammatory bowel disease and 134 patients (16.4%) had various underlying diseases [18, 19, 21-23, 25, 29-39, 41-51].

Baseline characteristics

The pooled mean age for all patients was 62.9 years and the overall male to female ratio calculated on the basis of the studies reporting gender was 2.5: 1. Patients' weighted mean BMI was 25.4 Kg/m^2. The weighted mean time interval between index surgery and leakage diagnosis was 20.2 days (95% CI, 15.9 – 24.6).

Out of 776, 577 patients (74.4%) had a diverting stoma after primary surgery and 119/687 (17.3%) received a secondary stoma after the primary resection following diagnosis of anastomotic leakage. The pooled mean follow-up for all patients was 19.4 months. In patients undergoing EVT without ESC, 553/722 patients had fecal diversion with primary stoma (73.6%), 86/613 had a secondary stoma (14.0%) and the mean follow-up was 17.5 months. In patients undergoing EVT with ESC, 24/54 patients had fecal diversion (44%) with primary stoma, 30/54 had fecal diversion with a secondary stoma (55.6%) and the mean follow-up was 29.8 months. For details see also table 2.

Table 1: Characteristics of the included studies of endoscopic vacuum therapy (EVT) for pelvic anastomotic leakage (AL)

Author	Study design	Inclusion criteria	Indication	n	Sex, male	Age	Primary stoma	NA RT	Adjunct treatment (%)
Mees, 2008 [29]	Prospective matched cohort	Symptomatic leak after AR or IPAA	Rectal cancer and UC	5	4/5	47	NA	0/5 (0%)	None
Glitsch, 2008 [30]	Prospective case series	Symptomatic leak after AR or colectomy with extraperitoneal anastomosis	Rectal cancer	17	14/17	61	8/17 (47,1%)	9/17 (52,9%)	15 Fibrin glue (88%)
van Koperen, 2009 [18]	Prospective case series	Symptomatic leak after AR or IPAA	Rectal cancer and UC	16	9/16	64	8/16 (50,0%)	11/16 (68,8%)	None
von Bernstorff, 2009 [19]	Prospective case series	Symptomatic leak after AR	Rectal cancer	26	21/26	58	14/26 (53,8%)	14/26 (53,8%)	None
Chopra, 2009 [31]	Retrospective cohort	Symptomatic leak after AR	Rectal cancer	5	NA	NA	NA	5/5 (100%)	2 Fibrin glue (40%)
Riss, 2010 [32]	Retrospective case series	Symptomatic leak after AR or Hartmann insufficiency	Rectal cancer	9	5/9	64	4/9 (44,4%)	4/9 (44,4%)	None
Verlaan, 2011 [25]	Prospective case series	Symptomatic leak after AR or IPAA	Rectal cancer and UC or FAP	6	5/6	50	0	1/6 (16,7%)	4 ESC (66,7%), 1 Clip (16,7%)
Srinivasamurthy, 2013 [33]	Retrospective case series	Extraperitoneal anastomosis and symptomatic leak after AR or IPAA	Rectal cancer and UC	8	7/8	67	NA	7/8 (87,5%)	None
Nerup, 2013 [23]	Retrospective case series	Symptomatic leak after AR	Rectal cancer	13	11/13	64	13/13 (100%)	6/13 (46,2%)	None
Keskin, 2015 [34]	Retrospective case series	Symptomatic leak after AR, IPAA or IRA	Rectal cancer, FAP and diverticular disease	15	7/15	55	14/15 (93,3%)	6/15 (40,0%)	None
Arezzo, 2015 [35]	Retrospective case series	Symptomatic leak after AR, TEM or STARR	Rectal cancer, rectal adenoma, RV fistula	14	7/14	68	8/14 (57,1%)	7/14 (50%)	Glue and clip (33.3%)

Strangio, 2015 [36]	Prospective case series	Symptomatic leak after AR, IPAA or left colectomy	Rectal cancer, endometriotic nodule, UC, colon cancer, diverticulitis	25	18/25	67	13/25 (52%)	8/25 (32%)	None
Kuehn, 2016 [37]	Retrospective case series	Symptomatic leak after AR, Hartmann insufficiency, IPAA, TEM or STARR	Rectal cancer, diverticulitis, UC, rectal perforation, UC, fistula	41	31/41	70	19/19 (100%)	12/41 (29,3%)	None
Mussetto, 2017 [38]	Retrospective case series	Symptomatic leak after AR	Rectal cancer	11	6/11	71	NA	5/11 (45,5%)	None
Milito, 2017 [39]	Prospective case series	AL of a low rectal anastomosis	Rectal cancer	14	10/14	65	14/14 (100%)	14/14 (100%)	None
Mencio, 2018 [40]	Retrospective case series	Patients with different GI leaks	NA	10	5/10	55	7/10 (70%)	NA	None
Jimenez-Rodriguez, 2018 [41]	Prospective case series	Symptomatic leak after AR or Hartmann insufficiency	Rectal cancer	22	18/22	65	13/22 (59,1%)	17/22 (77,3%)	10 Fibrin glue (45.4%)
Borstlap, 2018 [21]	Prospective case series	Symptomatic leak after AR	Rectal cancer	30	19/30	66	23/30 (76,7%)	22/30 (73,3%)	30 ESC (100%)
Rottoli, 2018 [42]	Prospective case series	Symptomatic leak after IPAA	UC and FAP	8	NA	37	8/8 (100%)	0/8 (0%)	None
Katz, 2018 [43]	Retrospective case series	Symptomatic leak after AR, IPAA	Rectal cancer, Hirschprung, FAP, ovarian cancer with rectal involvement	6	5/6	54	3/6 (50%)	NA	None
Wasmann, 2018 [22]	Retrospective cohort	Symptomatic leak after IPAA	UC	18	12/18	41	1/18 (5,6%)	0/18 (0%)	18 ESC (100%)
Boschetti, 2018 [44]	Retrospective case series	Symptomatic leakage	Colonic cancer, rectal cancer, sigmoiditis	29	22/29	68	12/29 (41,4%)	19/29 (65,5%)	None
Huisman, 2019 [45]	Retrospective cohort	Symptomatic leakage after rectal surgery	Rectal cancer, IBD	20	14/20	64	14/20 (70%)	14/20 (70%)	3 ESC (15%)
Kantowski [46]	Retrospective case series	Anastomotic leakage after colorectal resection	Rectal cancer, diverticular disease, IBD, ischemia	89	68/89	58	87/89 (98%)	27/89 (30%)	58 transanal rinsing therapy after EVT (65%)

Abdalla, 2020 [47]	Prospective case series	Leakage after elective proctectomy	Rectal cancer, IBD	47	36/47	65	40/47 (85,1%)	27/47 (57,4%)	None
Wereen, 2020 [48]	Retrospective cohort study	Symptomatic leakage after AR	Rectal cancer	14	9/14	64	12/14 (85,7%)	13/14 (92,9%)	None
Kuhn, 2020 [49]	Prospective case series	Colorectal defects	Rectal cancer, IBD, diverticular disease, other malignancies, perforation	281	186/281	65	224/281 (79,7%)	95/281 (33,8%)	None
Jagielski, 2021 [50]	Prospective cohort study	AL after rectal cancer surgery	Rectal cancer	18	18/18	61	8/18 (44,4%)	16/18 (88,9%)	None
Keshvari, 2021 [51]	Prospective case series	AL after LAR	Rectal cancer	10	6/10	56	10/10 (100%)	10/10 (100%)	None

NA: neoadjuvant; RT: radiotherapy; ESC: early surgical closure; NL: Netherlands; UK: United Kingdom; USA: United States of America; AR: anterior resection; IPAA: ileal pouch-anal anastomosis; IRA: ileorectal anastomosis; TEM, transanal endoscopic microsurgery; STARR, stapled transanal rectal resection; AL: anastomotic leak; GI: gastro-intestinal; UC: ulcerative colitis; FAP: familial adenomatous polyposis; RV: rectovaginal; NA: not available; EVT: endoscopic vacuum therapy.

Outcomes of EVT

Table 3 shows the general outcomes of EVT including all studies independent of adjunct ESC. Random-effects meta-analysis showed that the weighted mean of restored continuity after stoma formation (either primary or secondary) was 66.8% (95% CI 58.8 – 73.9) (I^2 = 55%) (Figure 3) [18, 21-23, 25, 29, 33, 34, 36-38, 41-51]. The calculated mean of procedure-related complications was 6.7% (95% CI, 4.7 – 9.6) [18, 19, 21-23, 29-39, 41-47, 50, 51]. Healed anastomosis rates and definitions are presented separately for the included studies (Supplementary Table 1).

From the available information, EVT could be continued in an outpatient setting in 216 patients (representing 51.1% of the total of 423 patients from those studies reporting this information)[19, 29, 30, 34, 35, 41, 44, 48, 49]. The documented late complication rate was 10.8% among 21 studies comprising 440 patients (95% CI, 6.8 – 16.7) [18, 19, 21-23, 29, 30, 32, 33, 35-39, 41, 42, 44, 45, 47, 51].

Table 2: baseline characteristics of included studies.

		Total		No ESC		ESC	
	Studies	n	Pooled	n	Pooled	n	Pooled
Patient characteristics							
Gender (male), %	27	573/814	70.4%	537/760	70.7%	36/54	67%
Age in years, mean	27	804	62.9	750	63.4	54	55.9
BMI (kg/m^2), mean	10	197	25.4	149	25.5	48	25.2
Neoadjuvant radiotherapy, %	27	369/811	45.5%	346/757	45.7%	23/54	42.6%
Indication primary surgery, %							
Colorectal cancer	28	613/817	75.0%	582/763	76.3%	31/54	57.4%
IBD	28	66/817	8.1%	43/763	5%	23/54	42.6%
Other	28	134/817	16.4%	134/763	17.6%	0/54	-
Primary stoma (created during index surgery), %	24	577/776	74.4%	553/722	73.6%	24/54	44.4%
Secondary stoma (created after index surgery), %	23	119/687	17.3%	86/613	14.0%	30/54	55.6%
EVT in outpatient setting, %	9	216/423	51.1%	216/423	51.1%	0	-
Follow-up in months, mean	13	246	19.4	170	17.5	54	29.8

ESC: early surgical closure; n: number of patients; BMI: body mass index; IBS: inflammatory bowel disease; EVT: endoscopic vacuum therapy.

Time to EVT onset

Several authors have suggested that the timing of EVT may influence treatment outcomes. However, these analyses usually focus on anastomotic healing, and only three studies reported data on stoma reversal rate at the end of follow-up: Borstlap et al. found that starting EVT within the first 21 days was associated with a nonsignificant increase in the stoma reversal rate (73% vs. 60%, median

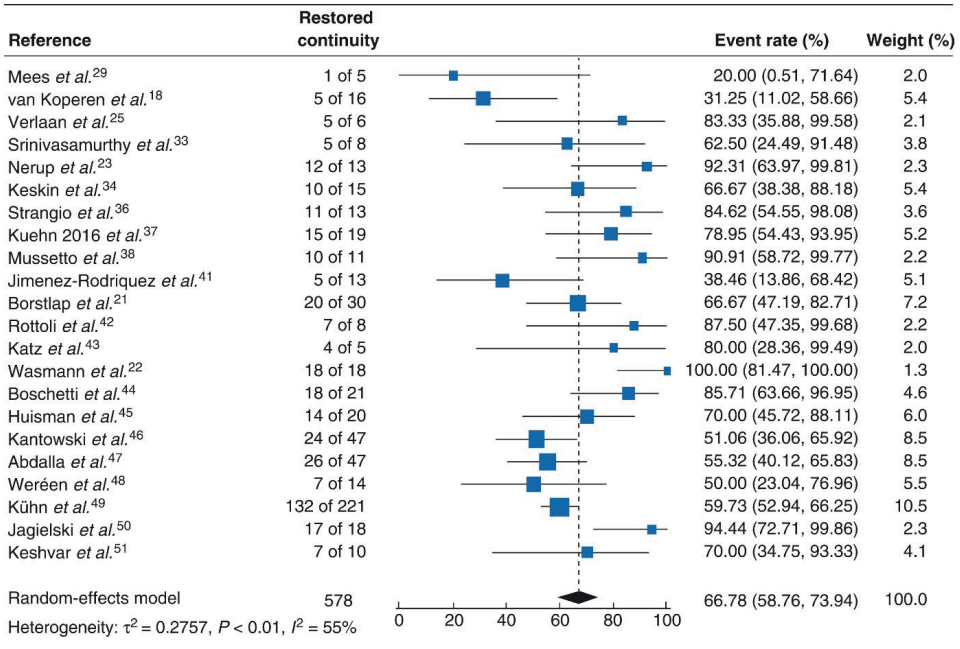

Figure 3: Forest plot showing restored continuity rates after EVT.

follow-up of 14 months) [21]. With a median follow-up of 10 months, Huisman et al reported a cumulative probability of stoma removal of 77% (95% CI, 22 – 93) when starting EVT within the first 21 days, compared to 70% (95% CI, 23 – 88) in the "late onset" group (p=0.31).[45] Abdalla et al. found higher stoma reversal rate in EVT was started 15 days after AL-diagnosis, compared to later initiation (72.4% vs 27.8%, p=0.003).[47]

EVT with or without early surgical closure

Fifty-four patients underwent EVT with ESC, of whom 23 underwent ileal pouch-anal anastomosis (IPAA). Regarding baseline characteristics, primary resection for colorectal cancer was performed in 31/54 patients who underwent EVT with ESC (57.4%) and in 582/763 (76.3%) without ESC. Corresponding proportions neoadjuvant radiotherapy were 23/54 (42.6%) and 346/757 (45.7%), respectively. Random-effects meta-analysis showed that the weighted mean of restoration of continuity in the ESC group was 82.0% (95% CI, 50.1 – 95.4) [21, 22, 25], which was 64.7% (95% CI, 55.7 – 72.7) in the group without ESC (Table 3 and Figure 4). The mean number of sponge exchanges was 3.6 (95% CI, 2.7 – 4.6) in the EVT with ESC group, compared to a mean of 9.8 (95% CI, 7.3 – 12.3) in the EVT-only group.

Sensitivity analysis

Sensitivity analysis showed a restored continuity rate of 81.0% [95%CI, 55.8-99.5] for benign disease, 69.0% [95% CI, 57.3-78.7] for colorectal cancer and 65.5% [95% CI, 48.8-79.1] if neoadjuvant radiotherapy was given (table 4). The restored continuity rate was 61.9% [95% CI, 53.4-69.7] In patients that received a primary diverting stoma and 83.1% [95% CI, 66.2-92.5] in patients without a primary stoma.

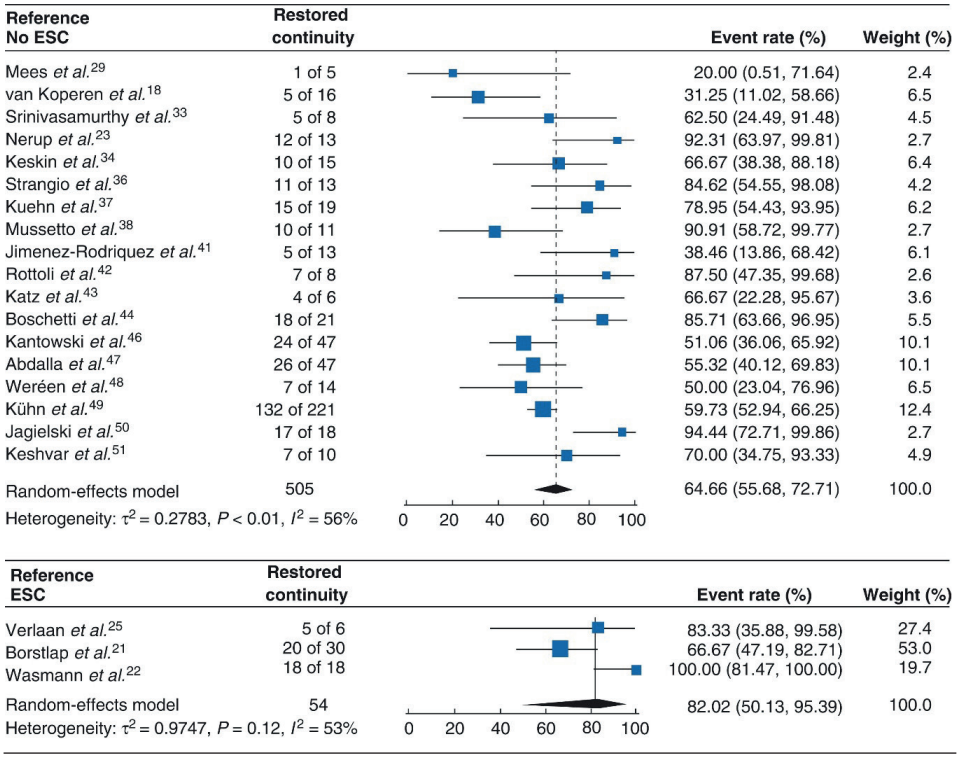

Figure 4: Forest plot showing restored continuity rates after EVT with or without ESC.

Table 3: Pooled outcomes after endoscopic vacuum therapy (EVT) in patients with pelvic anastomotic leakage (AL).

	Total			No ESC			ESC		
	Studies	**n**	**Pooled [95%-CI]**	**Studies**	**n**	**Pooled [95%-CI]**	**Studies**	**n**	**Pooled [95%-CI]**
Time from surgery to AL-diagnosis in days, mean	16	272	20.2 [15.9-24.6]	12	198	23.5 [17.2-29.9]	3	54	15.4 [8.3-22.5]
Time from surgery to EVT in days, mean	15	265	35.9 [27.8-44.0]	11	191	38.3 [28.8-47.8]	3	54	23 [9.1-37.0]
Sponges used, mean	26	710	9.1 [7.0-11.3]	22	636	9.8 [7.3-12.3]	3	54	3.6 [2.7-4.6]
Anastomotic function									
Restored continuity, %	22	578	66.8% [58.8-73.9]	18	505	64.7% [55.7-72.7]	3	54	82.0% [50.1-95.4]
Time to restored continuity in months*, mean	7	114	5.1 [3.3-6.9]	3	51	3.7 [2.5-4.9]	3	43	2.4 [0.9-4.0]
Complications									
Procedure-related, %	25	516	6.7% [4.7-9.6]	22	461	10.2% [6.7-15.1]	2	48	2.1% [0.00-0.13]
During follow-up (late), %	21	440	10.8% [6.8-16.7]	18	372	9.7% [6.0-15.3]	2	48	13.9% [1.0-72.3]

*after AL was diagnosed

ESC: early surgical closure; n: number of patients; AL: anastomotic leakage; EVT: endoscopic vacuum therapy

Table 4: Sensitivity analysis for restored continuity of different subgroups of patients undergoing EVT for pelvic AL.

	Studies	**n**	**Restored continuity [95%-CI]**
Benign disease (or >90%)	5	39	81.0% [55.8-99.5]
CRC (or at least 90%)	11	201	69.0% [57.3-78.7]
CRC with radiotherapy	5	76	65.5% [48.8-79.1]
Any type of disease, no radiotherapy	6	57	70.1% [38.8-89.7]
Primary diverting stoma (or at least 80%)	11	420	61.9% [53.4-69.7]
No primary stoma (or at most 20%)	3	81	83.1% [66.2-92.5]

EVT: endoscopic vacuum therapy; AL: anastomotic leakage; n: number of patients; CRC: colorectal cance.

DISCUSSION

successful restoration of continuity with functional anastomosis in almost two-thirds of patients. The stoma reversal rate at the end of follow-up seemed to be higher for patients treated with combined EVT plus ESC, compared to EVT alone. Most studies were retrospective cohort studies, with a large difference in cohort size ranging from 5 to 281 and a large variety in underlying disease as well as primary treatment modalities (colonic anastomosis or IPAA, with or without neoadjuvant radiotherapy. This resulted in a high risk of bias. Therefore, current findings should be carefully interpreted for the different subgroups and indications. Nevertheless, these results justify further investigation in larger prospective series and international registries with extended follow-up given the ethical and other practical and methodological issues related to controlled randomized conditions in this specific population.

EVT was developed with the aim of controlling pelvic sepsis and gradually reducing the size of the sinus. In the original publication, the Weidenhagen group reported definitive anastomotic healing in more than 96% of cases [17]. Since then, several observational studies have been published, with variable success rates in heterogeneous patient populations [17-19, 23, 29-31, 35-39, 41]. A meta-analysis based on a literature review until July 2017 included 17 studies with 276 patients, and reported a complete/partial healing rate of 85% and a stoma reversal rate of 76% [20]. Another meta-analysis with a search until December 2018 included 16 studies with 266 patients, showing a pooled treatment effect of 88%, but a stoma reversal rate of only 51%.[52] A third review until January 2019 selected 19 series with 295 patients, with a weighted success rate of EVT of 85% and a stoma closure rate of 73%.[53] Finally, the most recent review selected 20 studies from a search until June 2018 without performing meta-analysis, with the main finding of only 11 studies who reported stoma closure with a proportion ranging from 31% to 100%.[54] The present review is a valuable update with a substantially higher number of studies and patients, which also enabled sensitivity analyses of clinically relevant subgroups. Furthermore, the additional value of ESC has not been analyzed in the previously published reviews.

There is a lack of consensus on how to classify anastomotic healing after leakage. Across the included studies, we found a wide range of different definitions for this outcome. Imaging and/or endoscopic confirmation was included in some of those definitions, while others did not describe any specific criteria at all. This hinders the ability to compare results and, more importantly, underlines the need

for consensus on an objective and reproducible universal definition. For future research, objective measures for anastomotic healing should be used, such as the absence of any extraluminal air of fluid on CT scan with rectal contrast and absence of symptoms indicative of reactivation of the leakage following stoma closure.

Among the currently used definitions, a healed anastomosis may refer to true healing but also pelvic symptom containment. However, restored continuity (without the need for any major salvage surgery) is a hard endpoint that reflects the rate of functional anastomoses. Several studies have reported permanent stoma rates after conventional AL management: Maggiori et al., with a median follow-up of three years, reported a 36% rate in patients with symptomatic AL treated with secondary stoma [55]. In the 2011 Dutch Surgical Colorectal Audit, Borstlap et al. analyzed 998 patients who underwent low anterior resection and reported a 13.4% early AL rate[13]. The rate of unintentional permanent stoma after AL was 46% after median 43 months, which is similar to the 51% rate in the Dutch TME trial with seven years of follow-up [16]. The findings of the present meta-analysis show that, with a median follow-up of less than two years, EVT is associated with a long-term stoma rate of 33%, which is somewhere in between the 24% to 49% permanent stoma rate as found in the previously published meta-analyses.[20, 52, 53] This 33% stoma rate seems acceptable, but at the same time, it does not convincingly show better stoma-free survival than conventional leakage management. There might be a selection of more severe cases that are treated with EVT, with probably more asymptomatic radiological leakages in the series describing conventional leakage management.

The addition of ESC was associated with better outcomes, with a long-term stoma rate of 18%. However, it should be noted that the proportion of IPAA was relatively high in the ESC group as compared to the EVT alone group, and these results cannot be extrapolated to rectal cancer populations with neoadjuvant radiotherapy. Anastomotic leakage severity scores have to be developed for the purpose of better comparison between treatment strategies.[56]

Establishing the cost-effectiveness of a new therapy is indispensable before its use becomes widespread in reimbursed healthcare systems. The financial impact when treating a patient with AL is already high, with additional costs of more than $20,000 compared to patients with no leak[57]. The cost-effectiveness of EVT with ESC was suggested by Borstlap et al., who reported that five patients must be treated with this therapy in order to save one extra anastomosis, compared to the standard passive AL management[21]. Besides, endoscopic examinations

to place the vacuum sponge were one of the most expensive procedures. The present study found that EVT with ESC required five fewer endoscopies for sponge replacement than EVT alone. This implies a direct reduction in resources but also in the duration for treatment completion. Moreover, the suggested improved clinical outcomes observed with the addition of ESC indicates potential cost-effectiveness, but this has to be confirmed in properly designed studies The development of a pelvic AL may lead to significant postoperative bowel dysfunction. For this reason, in addition to studying how these leaks are treated with hard end-points such as stoma closure, it is important to include functional and quality of life outcomes. The ability to control pelvic sepsis and close a defect earlier with EVT and ESC, with less sponge replacements, may also have a beneficial impact on these functional complaints. This was recently shown by our group in a cohort study of patients undergoing IPAA that found that EVT with ESC, in contrast to conventional leak management, was associated with preservation of pouch function and preclusion of pouch failure.[22] Unfortunately, very few studies report on function after EVT with or without ESC, and this represents an important knowledge gap that should also be addressed in future studies.

Of all the factors that may increase the effectiveness of EVT, it seems that early diagnosis and treatment initiation are crucial.[52] A causal inference has yet to be established, but a late onset of EVT might be ineffective due to the retraction of the anastomotic edges and less pliability of the neo-rectum. A group of patients with special susceptibility are those with primary diversion and an asymptomatic AL, in whom dehiscence may be diagnosed only after stoma reversal. Therefore, in order to detect occult leakages and with the aim of initiating EVT as soon as possible, the authors recommend highly selective diversion with early C-Reactive Protein (CRP) measurement in all patients receiving a pelvic anastomosis, followed by computed tomography (CT) scan or endoscopy when necessary.[58] The sensitivity analysis also hints in a similar direction, with a higher rate of restored continuity in patients without a primary stoma, 83.1% vs 61.9%.

This study has several limitations. Firstly, the sample sizes of the included studies were mostly small and there was considerable heterogeneity among the inclusion criteria. Moreover, the studies had methodological limitations, mostly based on imperfect designs and reporting. Secondly, the primary outcome – stoma reversal rate – was considered to be at the end of the follow-up; nevertheless, additional stomas might have been created after manuscript publication, for example for a small persistent sinus or fecal incontinence. Thirdly, the majority of articles included patients with AL, but a slight proportion also involved patients with

rectal stump insufficiency following low Hartmann's procedure. These data could not be analyzed separately and may be a source of bias. To confirm the potential advantage of EVT and ESC besides other preventive and therapeutic interventions to improve anastomotic integrity rates, a large multicenter prospective clinical effectiveness trial was set up in the Netherlands and is currently underway[59].

In conclusion, this systematic review showed that EVT may be an effective therapy for pelvic AL, which is associated with a satisfactory stoma reversal rate. ESC is a relatively simple and safe procedure, with acceptable tolerance, which may play a role in further improving outcomes and decreasing resource utilization. Nevertheless, although the available outcomes are promising, further high-quality studies of appropriate size are required.

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Appendix 1: search strategy

Search strategy and information resources

MEDLINE and Cochrane Central Register of Controlled Trials databases, from database inception to November 2021 for published articles with relevant evidence regarding the EVT with or without ESC for colorectal AL. The combined terms used for the search were: ("Colorectal Surgery" OR "Colorectal Neoplasms" OR "Intestine, Large" OR "Rectal Diseases" OR "Colitis, Ulcerative" OR colo* OR rectal* OR rectum* OR anal OR ulcerative colitis OR colitis ulcer*) AND ("Anastomotic Leak" OR leak* OR insufficiency OR anastomo*) AND ("Negative-Pressure Wound Therapy" OR "Vacuum" OR vacuum OR EVAC OR transanal closure* OR trans-anal closure* OR early surgical closure OR endosponge* OR endo-sponge* OR negative pressure*).

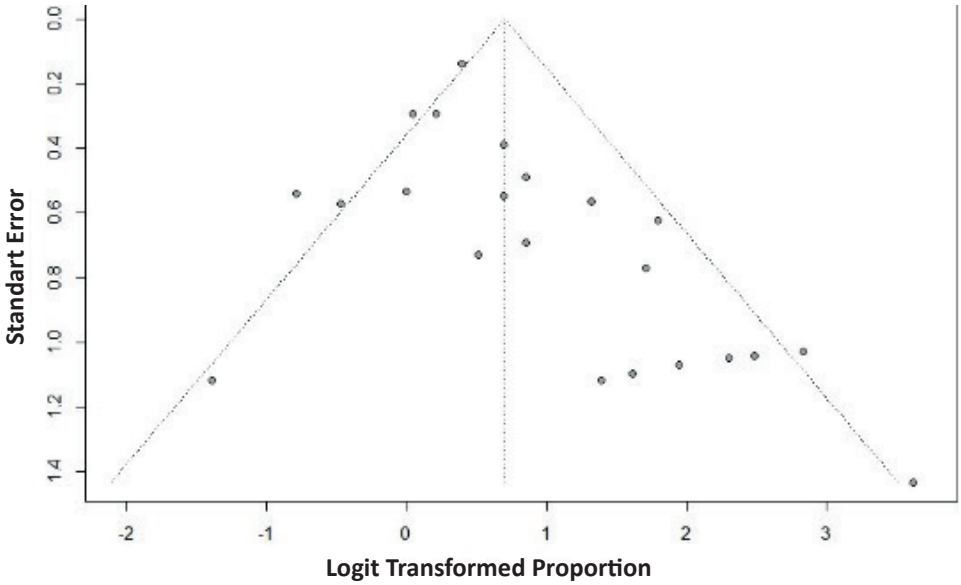
Supplementary Table 1: Definitions used for anastomotic healing/tre

Author	Definition healed/success	Follow-up modality	Healed anastomosis (%)	Days to healing	Follow-up
Mees [29]	Endoscopically proven closure of the insufficiency cavity with achievement of the normal mucosa level.	Endoscopy	5/5 (100%)	45 (32-68)[a]	-
Glitsch [30]	Complete closure of the cavity.	Endoscopy	16/17 (94%)	53 (10-221)[c]	-
van Koperen [18]	Definitive resolution of the sinus	Endoscopy	9/16 (56%)	40 (28-90)[a]	-
von Bernstorff [19]	Complete closure of the cavity	Endoscopy	23/26 (88%)	50 (10-221)[a]	-
Chopra [31]	Complete healing of the anastomotic defect with intact mucosal covering	Endoscopy	NR	NR	-
Riss [32]	A cavity that is nearly closed and totally covered by granulation tissue.	Endoscopy	6/9 (67%)	NR	-
Verlaan [25]	Closure of defect	Endoscopy + CT with enteral contrast	6/6 (100%)	13 (3-29)[a]	-
Srinivasamurthy [33]	Complete closure or a reduction in the size of the abscess cavity	Endoscopy	6/8 (75%)	NR	41 months
Nerup [23]	Closure of the perianastomotic abscess	Endoscopy	13/13 (100%)	NR	-
Keskin [34]	None	Endoscopy	12/15 (80%)	NR	-
Arezzo [35]	Complete restoration of the wall epithelium, confirmed by endoscopic examination with contrast injection during endoscopy	Endoscopy	11/14 (89%)	41 (8-114)[a]	-
Strangio [36]	Cavity less than 1 cm in diameter	Endoscopy	22/25 (88%)	28 (7-128)[a]	9 months
Kuehn 2016 [37]	None	Endoscopy	34/41 (83%)	NR	36 months
Mussetto [38]	A decreased cavity covered with granulation tissue that did not allow the insertion of a new sponge.	Endoscopy, contrast barium enema	10/11 (91%)	37 (18-65)[c]	29 months
Milito [39]	Endoscopically proven closure of the insufficiency cavity with a normal mucosa.	Endoscopy	NR	37 (19-55)[a]	-
Mencio [40]	Resolution of the leak or perforation with restoration of GI continuity and the initiation of an oral diet.	Endoscopy	6/10 (60%)	23 (NR)[c]	-
Jimenez-Rodriguez [41]	None	Endoscopy	20/22 (91%)	22 (15)[b]	12 months
Borstlap [21]	No signs of contrast extravasation during abdominal CT or contrast enema and an intact anastomosis during endoscopy	Endoscopy + CT with rectal contrast	21/30 (70%)	127 (14-722)[a]	14 months
Rottoli [42]	Closure of the defect after a progressive reduction in size of the cavity without signs of infection or complications, not requiring any other intervention than the follow-up pouchoscopy	Endoscopy	8/8 (100%)	60 (24-90)[d]	12 months
Katz [43]	None	CT with enema contrast + endoscopy	NR	NR	28 months
Wasmann [22]	Anastomotic integrity was assessed endoscopically 2 weeks after surgical closure. subsequently, CT with intraluminal contrast was used to exclude presacral fluid collections.	Endoscopy + CT with intraluminal contrast	18/18 (100%)	30 (17-40)[d]	48 months
Boschetti [44]	Cavity too small to introduce a new sponge	Endoscopy	27/29 (93%)	63 (NR)[a]	6 months
Huisman [45]	A cavity reduced in size and covered with granulation tissue that was too small to allow placement of a new endosponge	Endoscopy	17/20 (85%)	25 (3-115)[a]	10 months

Kantowski [46]	None	Endoscopy	67/89 (75%)	NR	-
Abdalla [47]	No residual leak on the control contrast-enhanced enema	Contrast-enhanced enema	NR	NR	35 months
Wereen [48]	*Not included as outcome*	NR	NR	NR	-
Kuhn 2020 [49]	Granulating closure of the cavity, more than 90% clean and granulating tissue, decreasing wound secretion, reduction of fibrinous tissue, and no interventional or surgical procedure required in the further course due to local wound healing and successful sepsis control (monitored clinically and by laboratory parameters).	Endoscopy	256/281 (91%)	NR	-
Jagielski [50]	Resolution of clinical signs and complete resolution of an abscess with leak closure by granular tissue or as the resolution of clinical signs and reduction in the size of the abscess to a diameter below 30 mm (confirmed by imaging) with filling of an abscess with granulation tissue (confirmed by endoscopy), which allowed EVT to be completed.	Endoscopy + CT with intraluminal contrast	17/18 (94%)	NR	12 months
Keshvari [51]	Closure of the cavity as observed in the flexible rectoscopy examinations	Endoscopy	8/10 (80%)	118 (68)[b]	-

Supplementary Table 2: Quality Assessment through Newcastle Ottawa Scale (NOS).

Author, year	Study design	Selection (NOS)	Comparability (NOS)	Outcome (NOS)
Mees, 2008 [29]	Prospective	⋆ ⋆ ⋆	⋆	⋆ ⋆
Glitsch, 2008 [30]	Prospective	⋆ ⋆	⋆	⋆ ⋆
Van Koperen, 2009 [18]	Prospective	⋆ ⋆ ⋆	⋆ ⋆	⋆ ⋆
Von Bernstorff, 2009 [19]	Prospective	⋆ ⋆ ⋆	⋆ ⋆	⋆ ⋆
Chopra, 2009 [31]	Retrospective	⋆ ⋆	⋆	⋆ ⋆
Riss, 2010 [32]	Retrospective	⋆ ⋆	⋆	⋆ ⋆
Verlaan, 2011 [25]	Prospective	⋆ ⋆ ⋆	⋆	⋆ ⋆ ⋆
Srinivasamurthy, 2013 [33]	Retrospective	⋆ ⋆	⋆	⋆ ⋆ ⋆
Nerup, 2013 [23]	Retrospective	⋆ ⋆ ⋆	⋆	⋆ ⋆
Keskin, 2015 [34]	Retrospective	⋆ ⋆	⋆	⋆ ⋆
Arezzo, 2015 [35]	Retrospective	⋆ ⋆ ⋆	⋆	⋆ ⋆
Strangio, 2015 [36]	Prospective	⋆ ⋆ ⋆ ⋆	⋆	⋆ ⋆
Kuehn, 2016 [37]	Retrospective	⋆ ⋆	⋆	⋆ ⋆ ⋆
Mussetto, 2017 [38]	Retrospective	⋆ ⋆ ⋆	⋆	⋆ ⋆
Milito, 2017 [39]	Prospective	⋆ ⋆	⋆	⋆ ⋆
Mencio, 2018 [40]	Retrospective	⋆ ⋆	⋆	⋆
Jimenez-Rodriquez, 2018 [41]	Prospective	⋆ ⋆ ⋆	⋆ ⋆	⋆ ⋆ ⋆
Borstlap, 2018 [21]	Prospective	⋆ ⋆ ⋆ ⋆	⋆ ⋆	⋆ ⋆ ⋆
Rottoli, 2018 [42]	Prospective	⋆ ⋆ ⋆	⋆	⋆ ⋆ ⋆
Katz, 2018 [43]	Retrospective	⋆ ⋆	⋆	⋆ ⋆ ⋆
Wasmann, 2018 [22]	Retrospective	⋆ ⋆ ⋆ ⋆	⋆ ⋆	⋆ ⋆
Boschetti, 2018 [44]	Retrospective	⋆ ⋆	⋆	⋆ ⋆ ⋆
Huisman, 2019 [45]	Retrospective	⋆ ⋆ ⋆ ⋆	⋆	⋆ ⋆ ⋆
Kantowski, 2020 [46]	Retrospective	⋆ ⋆ ⋆	⋆ ⋆	⋆ ⋆ ⋆
Abdalla, 2020 [47]	Prospective	⋆ ⋆ ⋆ ⋆	⋆ ⋆	⋆ ⋆ ⋆
Wereen, 2020 [48]	Retrospective	⋆ ⋆ ⋆	⋆ ⋆	⋆ ⋆ ⋆
Kuhn, 2020 [49]	Prospective	⋆ ⋆ ⋆	⋆ ⋆	⋆ ⋆ ⋆
Jagielski, 2020 [50]	Prospective	⋆ ⋆ ⋆	⋆ ⋆	⋆ ⋆
Keshvari, 2020 [51]	Prospective	⋆ ⋆	⋆	⋆ ⋆



Supplementary Figure 1: Funnel plot for assessment of publication bia.

CHAPTER 12

General discussion and future perspectives

GENERAL DISCUSSION

This thesis focused on different aspects of complications after surgery for colorectal cancer, with a particular interest in anastomotic leakage. Because of the multimodal aetiology of anastomotic leakage, a design for a multi-interventional program was presented in **chapter 2**, which ran like a thread through this entire thesis, because it entails all the different components: prevention, early diagnosis and prevention. In **part 1,** different strategies were investigated involved in prevention and early diagnosis of complications in colorectal surgery.

In **part 2**, different treatment strategies for anastomotic leakage were evaluated and surprisingly there is a paucity of relevant literature available for such a prevalent complication, especially for different clinical presentations of AL.

Prevention and early diagnosis

Prehabilitation in colorectal surgery is a hot topic, and in current practice more focus is placed on ensuring that patients are fit for surgery, by using physical therapy training plans, high protein diets, smoking cessation and weight loss programs.[1] Most of these programs are intensive and difficult for patients to adhere to, but restoring iron stores using IV-iron is relatively easy to implement and should be considered as low hanging fruit. Only one or two interventions are required, that can be performed in an outpatient setting and should not be too strenuous for the patient.

In **chapter 3**, we observed that IV-iron led to better Hb-normalisation from 4 weeks after surgery and was more effective at correcting haemoglobin, ferritin and TSAT levels in the perioperative phase, compared to oral iron. In mild anemic patient we also saw an improvement in the reintervention rate and ICU admission rate after IV-iron treatment, compared to oral iron. Therefore, IV-iron appeared to be more effective than oral iron in the prehabilitation phase for colorectal cancer surgery. Oral iron substitution even showed to be surprisingly ineffective, particularly in restoring iron stores and should therefore not be used to prehabilitate.

The normalisation of haemoglobin levels before surgery was low in both groups, which could possibly be explained by the short interval between iron treatment and surgery (14 days for IV-iron vs. 19 days for oral iron). The largest increase in Hb-normalisation was seen 4 weeks after surgery and delay of surgery should be considered if the patient requires prehabilitation. The severity of the anemia, can be used as a predictive value to influence the choice for longer delay.

During the trial, we experienced some logistical issues surrounding IV-iron supplementation, due to local healthcare policies. First, there is a delay of a few days between endoscopy and referral to the surgeon for discussing surgery. Second, there is a delay of a few days, when the patient has to be referred back to the gastro-enterologist to receive outpatient IV-iron treatment. If IV-iron would be added to an in institutionalized prehabilitation program, this could save 1-2 weeks before surgery and a planned delay of surgery required for Hb-normalization might even be very limited.

More evidence is accumulating indicating that the microbiome plays a role in development of AL.[2, 3] Preoperative oral antibiotics and mechanical bowel preparation could be used to alter the microbiome before surgery and might lower the risk of developing AL.[4] In the IMARI-trial (**chapter 2**) a protocol was presented for a study that will collect samples before, during and after surgery. Hopefully this will not only give insight in how the microbiome changes during surgery, but also how oral preoperative antibiotics and mechanical bowel preparation influences the microbiome.

Omission of a diverting stoma after rectal cancer surgery remains a controversial topic. The conventional idea of diversion is to temporarily bypass the anastomosis and give it opportunity to heal after surgery, without interference from the faecal stream. General believe amongst colorectal surgeons is that leaks that do occur would be less severe and a diverting ostomy would not only prevent morbidity and mortality, but also preserve the anastomosis and optimise chances of long-term continuity. However, selective diversion appears to be safe as shown **in chapter 4,** and increasing evidence suggests that having a diverting stoma by itself is a risk factor for a permanent stoma.[5] Furthermore, a diverting stoma is associated with worse functional outcomes, higher readmission rates, higher morbidity rates related to high output stoma and increased health care costs.[6-9]

It appears that an open dialogue on complications and especially anastomotic leakage is difficult. When looking at reported leakage rates in series on rectal cancer treatment, leakage rates are often below 10 percent. Studies double-checking data from patients included in large cross-sectional studies on rectal cancer surgery, have found as much as one third of leaks unreported and actual leakage rates are around 20% [10, 11]. Perhaps this also explains in part the limited evidence on effective treatment of AL.

In chapter 5, we found a high rate of positive CT-scans for AL, with a low rate of false negative (2%) and false-positive (0%) findings, compared to literature.[12-14] A possible explanation for this high diagnostic yield is the postoperative protocol

with routine CRP-measurement, which increased the likelihood of finding AL. The specific setting within a high volume institution with highly selective diversion, enabled early diagnosis, because clinical and biochemical symptoms of AL are often more clear in the absence of a diverting stoma. To confirm AL suspected on cross-sectional imaging, endoscopy can be effective and was used often in our study, but this does require specific expertise. Sometimes there is no defect visible, despite a collection on imaging and probing with an endoscopic biopsy forceps might be necessary to confirm the presence and location of the leak. All of the above did allow for timely and tailored subsequent treatment for AL within 6 hours after cross-sectional imaging for a clinical suspicion of AL, without overtreatment with negative explorative interventions.

Treatment

In the review included in this thesis (**chapter 11**), we found major heterogeneity between studies investigating EVT for AL, but also satisfactory restored continuity rates (66.8%, 95% CI, 58.8-73.9). In patients undergoing EVT with ESC results were even better; calculated restored continuity rate was 82.0% (95% CI, 50.1-95.4) as compared to 64.7% (95% CI, 55.7-72.7) after EVT without ESC. An additional benefit is that it also appears to lower the number of sponge exchanges when performing EVT with ESC (3.6 (95% CI, 2.7 – 4.6) vs 9.8 (95% CI, 7.3 – 12.3), resp.). The high rate of restored continuity after EVASC was confirmed in **chapter 10** (78%). When EVASC was initiated in the first week after primary surgery, the functional anastomosis rate was higher compared to later initiation (100% vs 55%, p=0.008).

Timing of treatment seems to influence success rates of EVT and EVASC. In **chapter 9,** the functional anastomosis rate was 80% when EVASC was started within 21 days after index surgery, compared to 56% if started later (p=0.046). Preliminary results from the multicentre CLEAN-study were similar.[15] The GRECCAR group also found improved restored continuity rates if treatment was started within 15 days (72.4% vs 27.8%, p=0.003).[16] However, one small retrospective cohort study with 20 patients comparing early and late start (>21 days after LAR) found similar healing rates of 70%. [17]

In a previous review on EVT without ESC by Shalaby et al, the restored continuity rate was higher compared to our results (75.9% vs. 64.7%).[18] A possible explanation could be that in earlier trials less difficult leaks were treated to prove the concept works. Probably more patients with high rectal cancers (or low sigmoid tumors according to the new definition[19]) requiring a partial mesorectal excision (PME) was performed instead of a TME. After a PME, the deepest part of the pelvic cavity is still filled with mesorectum facilitating healing of the leak. Another

important factor is the lower rate of neoadjuvant radiotherapy in patients with high rectal tumors. After radiotherapy, EVT treatment is less successful and requires more sponges to obtain the same results.[20] If EVASC is used for leakage of low anastomosis in benign disease, the highest success rates are seen.[21]

In the CLEAN-study a cost-effectiveness analysis was performed, showing that the direct medical costs for EVASC were €8933 per patient, which was mainly contributed by repeated need for endoscopy.[15] When comparing to their previous experience with conventional treatment, they estimated that 5 patients have to be treated with EVASC to save one additional anastomosis.[10, 15] An extensive high-quality cost-effectiveness study incorporating long-term absence from work and daily activities is yet to be undertaken and could interrogate the additional burden of having a chronic presacral sinus after conventional treatment.

FUTURE PERSPECTIVES

Clinical presentation of AL and impact on treatment

The clinical heterogeneity of AL makes it difficult to define AL. The most common definition used in current literature comes from the ISREC-group. They define AL as "a defect of the intestinal wall integrity at the colorectal or colo-anal anastomotic site leading to a communication between the intra- and extraluminal compartments" with a classification that focused on how AL is treated (A: no intervention, B: reintervention; C: surgical reintervention).[22] This classification might be useful as an outcome in reporting consequences of leakage, but does not adequately indicate the severity or how to treat different subtypes. As an example, highly selective diversion will result in more Grade C leaks, because a diverting ileostomy has to be created when a leak occurs. This approach leads to better results with less chronic leaks and permanent stoma's as seen in **chapter 4**, even though the grading might appear worse. The TENTACLE-Rectum study (**chapter 6)** is currently conducted, which aims to compose an AL severity score and subsequent optimal treatment strategies.[23]

In **chapter 7**, we observed the relevance for daily practice of identifying and describing different entities of AL. Preferred treatment was tailored to differences in clinical presentation, AL features and patient characteristics. However, in most published studies to date, no subdivision is made between different subgroups of AL which could affect treatment results. For example, rectovaginal fistulae are unlikely to heal after EVT, because it is more difficult to acquire a vacuum seal and clean the cavity. Patients with sacral pain might not be relieved of their symptoms by reconstruction, but could require major salvage surgery with radical debridement of the deep pelvic septic focus with or without a redo-anastomosis.

The location of the leak is also often overlooked and can influence treatment options and success. For example, an anterior leak is often less suitable for EVT, because there is no natural occurring cavity, compared to posterior leaks. Similarly, a leakage of the blind loop after construction of a side-to-end anastomosis is less suited for EVASC, because of a possible connection to the free abdominal space which compromises chances of healing and the location causes technical difficulties closing the defect.[24] However, no clear evidence is available on how to treat these different entities.

For some leaks it might always remain difficult to choose the appropriate approach. Late leaks appear to have less success when treated with any type of local treatment,[10, 16] and if previous treatment has already failed, the decision to finally resect the anastomosis and create an end-colostomy can be difficult. It is unknown if relatively asymptomatic patients should be treated extensively or if a subgroup might achieve passive healing over time. There is still a risk that a chronic leak can cause severe sepsis of the buttock and upper leg, even years after the index operation.[25] For such chronic cases, patient preference and shared decision making should play a central role.

Defining relevant outcomes for AL also remains an issue, as described in **chapter 11** and there remains a lot of heterogeneity between studies. Although a healed anastomosis is often used as a primary outcome, some will define this as having a clean presacral cavity, some if the cavity is closed, some if no collection is seen on imaging or defect on endoscopy and some if the patient has no more complaints. To effectively compare treatment strategies, there should either be a clearly defined and relevant definition of a healed anastomosis, or use a very concrete outcome such as a functioning anastomosis. Using this outcome assures that the leak is definitively healed after stoma closure and not simply asymptomatic after treatment. The added benefit is that not having a stoma is also one of the most important outcomes to patients, on a similar level as oncological success.[26] In addition, the moment for leak assessment should be standardised. Thirty day and in hospital leak rates are low (particularly in the defunctioned anastomosis), but increase up to over 20% after one year. For a realistic leakage rate, the ideal outcome is probably the one year anastomotic integrity rate.

Multidisciplinary multimodal approach

Anastomotic leakage remains a complicated problem and with numerous risk factors and peri-operative treatment considerations, a one-fits-all solution is unfortunately not available. A truly important aspect to guarantee treatment success is a multidisciplinary multimodal approach to AL, which starts with prehabilitation of the patient to get the patient fit to the OR. Preoperative IV-iron supplementation to improve Hb-levels and iron storage levels in patients with a preoperative iron-deficiency anemia could lead to lower morbidity rates. Iron is an important elements in multiple fysiological processes, and sufficient storage might reduce complications and enhance recovery. The effects of iron supplementation on Hb-normalisation are seen only after 2-4 weeks and delaying surgery for a few weeks to optimize preoperatively can be considered, as delay appears to be safe. In the non-defunctioned patient, early leak diagnosis is possible through CRP-guided imaging and immediate start of the EVASC-protocol when the leak is diagnosed, appears to lead to the highest long term continuity rates. This asks for an institutionalised protocol for anastomotic leakage on the surgical ward, where 24/7 access to imaging, endoscopy, OR-facilities and a dedicated surgical team is available.

Currently the TENTACLE-Rectum study described in **chapter 6** is underway and will be the first study large enough to investigate optimal treatment strategies for AL. The study has finished accrual and has included over 2500 patients from more than 200 centres worldwide. Hopefully treatment strategies for different subtypes of AL can be generated, which is currently difficult because of the low incidence in already small series.

The next step would be to investigate the effectiveness of all the different modalities of AL in a prospective setting. The IMARI-trial as described in **chapter 2** is currently underway in the Netherlands and is in the experimental phase of the study. Hopefully we will see improved long-term continuity rates after LAR with the multi-interventional program and the results from the biobank can give further insight into the influence of the microbiome on developing and possibly preventing AL.

CONCLUSION

There is a large need for standardisation in treatment of AL for rectal cancer and the multifactorial etiology and complexity of AL make it difficult to improve results by addressing one component, while so many influence each other. This warrants a multimodal approach within institutionalized protocols to effectively prevent, diagnose and treat complications after colorectal surgery.

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APPENDICES

SUMMARY

Colorectal surgery has developed over recent decades, but improvements in complication management are still to be made. In **part 1** of this thesis we investigated if complications, and specifically anastomotic leakage (AL), can be prevented and when they do occur, if they can be diagnosed early. In **part 2**, we investigated different treatment strategies for anastomotic leakage, in particular endoscopic vacuum therapy (EVT), combined with early surgical closure (ESC) and found improved restored continuity rates after endoscopic treatment of AL.

Part 1: prevention and early diagnosis

In **chapter 2**, a study protocol for a multi-interventional program to prevent, early diagnose and treat anastomotic leakage with the goal to improve intact anastomosis rates at 1 year was proposed (the IMARI-trial). This study is currently underway and entails 5 different interventions: 1. Mechanical bowel preparation with oral antibiotics; 2. Splenic flexure mobilization; 3. Fluorescence angiography; 4. CRP-guided imaging on day 3; 5. Endoscopic vacuum-assisted surgical closure (EVASC). In this study, microbiome samples will also collected for the anastomotic leakage biobank, in which we hope to find pathogenic species predictive for AL.

In **chapter 3**, we evaluated the efficacy of IV versus oral iron for patients with iron-deficiency anemia undergoing surgery for colorectal cancer to correct anemia before surgery. In this study we found that successful normalisation of Hemoglobin (Hb) levels before surgery was low 2 weeks after treatment, but was significantly more improved after IV-iron from 30 days after surgery. In patients with a mild anemia (baseline Hb >6.2 mmol/l) treated with IV-iron, there was a benefit in clinical outcomes (lower reintervention rate, less ICU admissions), compared to oral iron. Therefor it appears that IV-iron is more effective for prehabilitation, and might be ideally given at least 4 weeks before surgery.

In **chapter 4**, the effect of highly selective diversion after low anterior for rectal cancer was investigated. Omitting a diverting stoma during index operation led to an acceptable AL-rate (16%), without severe AL-related morbidity or mortality and the proportion of patients with a functional anastomosis at 1 year was high (91%). The major benefit is that 76% never had a stoma during follow-up, which saves patients an additional operation for stoma closure and prevents possible stoma-related complications.

In **chapter 5**, the efficacy of CRP-guided imaging was evaluated after LAR for rectal cancer. Within an institution that performs highly selective fecal diversion and early CRP-measurement on day 3 or 4, followed by CT-scan with rectal contrast, it is possible to detect AL with a diagnostic yield of 52%, and a sensitivity of 96%. This enabled tailored intervention for AL after 6 hours from imaging.

Part 2: treatment

In chapter 6, we proposed a protocol for an international multicentre retrospective cohort study on the treatment of AL after rectal cancer resection (the TENTACLE-Rectum study). This study aims to develop an AL severity score and investigate effective treatment strategies for different subgroups of AL. Currently this study has finished accrual of over 2500 patients from more than 200 centres worldwide and results are expected in 2023.

In chapter 7, we performed an international case-vignette study in which we asked colorectal surgery experts about preferred treatment of AL for different clinical cases and two types of patients depending on surgical risk. We found that participants tailored their approach based on leakage and patient characteristics. They would choose more often for an aggressive approach (more drainage, reconstruction, fecal diversion and temporary take-down of the anastomosis) in (septic) patients with early leaks. In late leaks, watchful waiting was the preferred approach with less diversion. More definitive salvage surgery, less watchful waiting and less reconstruction/drainage would be performed for elderly, frail patients, compared to younger patients. Results from this study will be used to guide analyses of the TENTACLE-Rectum study in **chapter 6.**

In chapter 8, we described different ways to deal with complications after colorectal surgery using the transanal approach. A bottom-up approach offers improved exposure, accessibility and visibility which greatly facilitates treatment of AL in the narrow bony pelvis. Early transanal closure of defects after a short period of endoscopic vacuum therapy proves to be successful, especially when diagnosed and treated early.

In **chapter 9**, we evaluated our own experience with EVASC for AL after LAR over the last decade and described lessons learned. Early initiation of EVASC within 21 days after LAR yielded high rates of healed and functional anastomosis and reached almost 100% within a protocol of highly selective diversion and early leak diagnosis. Late initiation of EVASC (>21 days after LAR), anastomotic fistula, diverting stoma at index operation and late diagnosis of the leak (>2 weeks after LAR) impaired success rates of EVASC.

In **chapter 10,** we compared different treatment strategies for AL and found that conventional treatment performed much worse than the EVASC-protocol. More reinterventions and readmissions were seen when patients underwent the EVASC-protocol. Proactive treatment without muscosal approximation appeared to be less effective, as could be seen in the low success rates after EVT without transanal closure.

In **chapter 11,** current literature on EVT with or without early surgical closure (ESC) for pelvic AL was evaluated. There was a large heterogeneity between studies in design and reported outcomes, leaving a high risk of bias. However, EVT showed to be an effective treatment option for pelvic AL as can be seen in a satisfactory stoma reversal rate, especially if combined with ESC.

NEDERLANDSE SAMENVATTING (Dutch summary)

De colorectale chirurgie heeft zich de afgelopen decennia ontwikkeld, maar de behandeling van complicaties kan nog steeds worden verbeterd. In **deel 1** van dit proefschrift hebben we onderzocht of complicaties, en in het bijzonder naadlekkage, kunnen worden voorkomen en als ze wel optreden, of ze vroeg kunnen worden gediagnosticeerd. In **deel 2** onderzochten we verschillende behandelstrategieën voor naadlekkage, in het bijzonder endoscopische vacuümtherapie (EVT), gecombineerd met vroege chirurgische sluiting (ESC) en vonden we een hoger percentage continuïteitsherstel na endoscopische behandeling van naadlekkage.

Deel 1: preventie en vroege diagnose

In **hoofdstuk 2** werd een onderzoeksprotocol gepresenteerd voor een multi-interventioneel programma om naadlekkage te voorkomen, vroegtijdig te diagnosticeren en te behandelen met als doel het aantal intacte anastomose 1 jaar na de operatie te verbeteren (de IMARI-studie). Dit onderzoek wordt op dit moment uitgevoerd en omvat 5 verschillende interventies: 1. Mechanische darmvoorbereiding met orale antibiotica 2. Milthoekmobilisatie 3. Fluorescentie-angiografie 4. CRP-geleide beeldvorming op dag 3; 5. Endoscopische vacuümtherapie, gecombineerd met chirurgische sluiting (EVASC). In deze studie worden ook microbioom-monsters verzameld voor de biobank naadlekkage, waarin we hopen pathogene soorten te vinden die voorspellend zijn voor naadlekkage.

In **hoofdstuk 3** evalueerden we de werkzaamheid van intraveneus (IV) versus oraal ijzer voor patiënten met een ijzergebreksanemie die een operatie ondergingen voor darmkanker. In deze studie vonden we dat dat het aantal patiënten met een succesvol genormaliseerd hemoglobine (Hb) voor de operatie laag was 2 weken na de behandeling, maar significant hoger was na IV-ijzer vanaf 30 dagen na de operatie. Bij patiënten met een milde anemie (baseline Hb >6,2 mmol/l) die werden behandeld met IV-ijzer, was er een voordeel in klinische uitkomsten (lager aantal reïnterventies, minder IC-opnames), in vergelijking met oraal ijzer. Daarom lijkt het dat IV-ijzer effectiever zou zijn voor prehabilitatie en idealiter minstens 4 weken voor de operatie gegeven wordt.

In **hoofdstuk 4** werd het effect van selectief aanleggen van een stoma tijdens een lage anterieure resectie (LAR) voor endeldarmkanker onderzocht. Het weglaten van een ontlastend stoma tijdens indexoperatie leidde tot een acceptabel percentage naadlekkages (16%), zonder ernstige naadlekkage-gerelateerde morbiditeit of mortaliteit en het percentage patiënten met een

functionele anastomose na 1 jaar was hoog (91%). Het grote voordeel is dat 76% tijdens de follow-up nooit een stoma heeft gehad, wat patiënten een nieuwe operatie bespaart om het stoma op te heffen en mogelijke stoma-gerelateerde complicaties voorkomt.

In **hoofdstuk 5** werd de effectiviteit van CRP-geleide beeldvorming geëvalueerd na LAR voor endeldarmkanker. Binnen een instelling waar zeer selectieve een ontlastend stoma wordt aangelegd en vroege CRP-meting op dag 3 of 4 uitvoert, gevolgd door CT-scan met rectaal contrast, is het mogelijk om naadlekkage te detecteren met een sensitiviteit van 96% en werd in 52% van alle gemaakte CT-scans een naadlekkage gezien. Dit maakte gepersonaliseerde behandeling voor naadlekkage 6 uur na beeldvorming mogelijk.

Deel 2: behandeling

In **hoofdstuk 6** hebben we een protocol gepresenteerd voor een internationale multicenter retrospectieve cohortstudie naar de behandeling van naadlekkage na resectie voor een rectumcarcinoom (de TENTACLE-Rectum studie). Deze studie heeft tot doel een score te ontwikkelen om de ernst van een naadlekkage aan te geven en effectieve behandelstrategieën te onderzoeken voor verschillende subgroepen van naadlekkage. Momenteel heeft deze studie de inclusie van meer dan 2500 patiënten uit meer dan 200 centra over de hele wereld afgerond en worden de resultaten in 2023 verwacht.

In **hoofdstuk 7** hebben we een internationale case-vignette studie uitgevoerd, waarin we experts op het gebied van colorectale chirurgie vroegen naar de voorkeursbehandeling van verschillende soorten naadlekkages aan de hand van klinische voorbeeldcasussen in twee soorten patiënten (fitte, jongere patiënt en een oudere, kwetsbare patiënt). We vonden dat deelnemers hun keuzes afstemden op verschillende lekkage- en patiëntkenmerken. Bij (septische) patiënten met vroege naadlekkage zouden zij vaker kiezen voor een agressieve aanpak (meer drainage, reconstructie, aanleggen van een stoma en tijdelijk ontkoppelen van de anastomose). Bij late lekken was watchful waiting de voorkeursaanpak, met minder vaak aanleggen van een stoma. Meer definitieve salvage chirurgie, minder watchful waiting en minder reconstructie/drainage zouden worden uitgevoerd voor oudere, kwetsbare patiënten, in vergelijking met jongere patiënten. De resultaten van dit onderzoek zullen worden gebruikt als leidraad voor analyses van de TENTACLE-rectum studie in **hoofdstuk 6**.

In **hoofdstuk 8** beschrijven we verschillende manieren om met complicaties na colorectale chirurgie om te gaan met behulp van de transanale benadering.

Een bottom-up benadering biedt betere blootstelling, toegankelijkheid en zichtbaarheid, wat de behandeling van naadlekkage in het smalle benige bekken aanzienlijk vergemakkelijkt. ESC van defecten na een korte periode van EVT blijkt succesvol te zijn, vooral bij vroege diagnose en behandeling.

In **hoofdstuk 9** evalueerden we onze eigen ervaring met EVASC voor naadlekkage na LAR in het afgelopen decennium en beschreven we de 'lessons learned'. Vroege start van EVASC binnen 21 dagen na LAR leverde hoge percentages genezen en functionele anastomoses op en was bijna 100% binnen een protocol van zeer selectief aanleggen van stoma's en vroege lekdiagnose. Late start van EVASC (> 21 dagen na LAR), een fistel van de anastomose, een ontlastend stoma bij indexoperatie en late diagnose van het lek (> 2 weken na LAR) verlaagden de succespercentages van EVASC.

In **hoofdstuk 10** vergeleken we verschillende behandelstrategieën voor naadlekkage en ontdekten dat conventionele behandelingen veel slechter presteerden dan het EVASC-protocol. Er werden meer herinterventies en heropnames gezien in patiënten die het EVASC-protocol ondergingen. Proactieve behandeling zonder approximeren van de mucosa bleek minder effectief, zoals te zien was in de lage succespercentages na EVT zonder transanale sluiting.

In **hoofdstuk 11** werd de huidige literatuur over EVT met of zonder vroege chirurgische sluiting (ESC) voor naadlekkage in het bekken geëvalueerd. Er was een grote heterogeniteit tussen studies in opzet en in gerapporteerde uitkomsten, waardoor een hoog risico op bias bestaat. EVT bleek echter een effectieve behandeloptie te zijn voor naadlekkage in het bekken, zoals te zien was in het redelijk hoge percentage patiënten waarin het stoma kon worden opgeheven, vooral in combinatie met ESC.

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LIST OF PUBLICATIONS

1. K. **Talboom**, I. Vogel, R.D. Blok, S.X. Roodbeen, C.Y. Ponsioen, W.A. Bemelman, R. Hompes, P.J. Tanis. Highly selective diversion with proactive leakage management after low anterior resection for rectal cancer. *Br J Surg.* 2021 Jun 22;108(6):609-612. doi: 10.1093/bjs/znab018. PMID: 33793724.

2. Y. An, S.X. Roodbeen, **K. Talboom**, P.J. Tanis, W.A. Bemelman, H. Yao, Z. Zhang, R. Hompes. A systematic review and meta-analysis on complications of Transanal Total Mesorectal Excision for rectal cancer. *Colorectal Dis.* 2021 Oct;23(10):2527-2538. doi: 10.1111/codi.15792. PMID: 34174138.

3. **K. Talboom**, M.D. Slooter, S. Sharabiany, C.P.M. van Helsdingen, S. van Dieren, C.Y. Ponsioen, C.Y. Nio, E.C.J. Consten, J.H. Wijsman, M.A. Boermeester, J.P.M. Derikx, G.D. Musters, W.A. Bemelman, P.J. Tanis, R. Hompes, IMARI-study group. IMARI: multi-Interventional program for prevention and early Management of Anastomotic leakage after low anterior resection in Rectal cancer patIents: rationale and study protocol. *BMC Surg.* 2020 Oct 15;20(1):240. doi: 10.1186/s12893-020-00890-w. PMID: 33059647.

4. **K. Talboom**, F. van Workum, G. Hannink, A. Wolthuis, B. de Lacy, J. Lefevre, M. Solomon, M. Frasson, N. Rotholtz, Q. Denost, R. Perez, T. Konishi, Y. Panis, C. Rosman, R. Hompes, P Tanis, H. de Wilt. Treatment of anastomotic leakage after rectal cancer resection: The TENTACLE-Rectum study *Colorectal Dis.* 2021 Apr;23(4):982-988. doi: 10.1111/codi.15435. Epub 2020 Dec 26. PMID: 33169512.

5. **K. Talboom**, J. van Kesteren, D.J..A. Sonneveld, P.J. Tanis, W.A. Bemelman R. Hompes. Early transanal closure after endosponge treatment for anastomotic leakage in rectal cancer surgery – a video vignette. *Colorectal Dis*. 2020 Aug;22(8):973-974. doi: 10.1111/codi.15032. Epub 2020 Apr 1. PMID: 32150763.

6. **K. Talboom**, P.J. Tanis, W.A. Bemelman, R. Hompes. Dealing with complications of colorectal surgery using the transanal approach – When and how? *Clin Colon Rectal Surg.* 2022 Feb 28;35(2):155-164. doi: 10.1055/s-0041-1742117. eCollection 2022 Mar. PMID: 35237112.

7. D.B. Keller, **K. Talboom**, C.P.M. van Helsdingen, R. Hompes. Treatment Modalities for Anastomotic Leakage in Rectal Cancer Surgery. *Clin Colon Rectal Surg.* 2021 Nov 23;34(6):431-438. doi: 10.1055/s-0041-1736465. eCollection 2021 Nov. PMID: 34853566.

8. **K. Talboom**, N.G. Greijdanus, C.Y. Ponsioen, P. J. Tanis, W.A. Bemelman, R. Hompes. Endoscopic Vacuum-assisted Surgical Closure (EVASC) of anastomotic defects after low anterior resection for rectal cancer; lessons learned. *Surg Endosc.* 2022 Nov;36(11):8280-8289. doi: 10.1007/s00464-022-09274-y. Epub 2022 May 9. PMID: 35534735.

9. **K. Talboom**, C.P.M. van Helsdingen, S. Abdelrahman, J.P.M. Derikx, P.J. Tanis, R. Hompes. Usefulness of CT scan as part of an institutional protocol for proactive leakage management after low anterior resection for rectal cancer. *Langenbecks Arch Surg.* 2022 Dec;407(8):3567-3575. doi: 10.1007/s00423-022-02652-z. Epub 2022 Aug 25. PMID: 36002771.

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Lancet Haematol. 2023 Apr;10(4):e250-e260. doi: 10.1016/S2352-3026(22)00402-1. Epub 2023 Feb 27. PMID: 36863386

11. **K. Talboom,** N.G. Greijdanus, F. van Workum, S. Ubels, C. Rosman, R. Hompes, J.H.W. de Wilt, P.J. Tanis, on behalf of the TENTACLE – Rectum working group. International expert opinion on optimal treatment of anastomotic leakage after rectal cancer resection: a case-vignette study. *Int J Colorectal Dis.* 2022 Sep;37(9):2049-2059. doi: 10.1007/s00384-022-04240-5. Epub 2022 Aug 24. PMID: 36002748

12. **K. Talboom,** F.B. de Lacy, S.X. Roodbeen, R. Blok, A. Curell, P.J. Tanis, W.A. Bemelman, R. Hompes. Endoscopic vacuum therapy and early surgical closure after pelvic anastomotic leak: meta-analysis of bowel continuity rates. *Br J Surg.* 2022 Aug 16;109(9):822-831. doi: 10.1093/bjs/znac158. PMID: 35640282.

13. **K. Talboom**, N.G. Greijdanus, N. Brinkman, R.D. Blok, S.X. Roodbeen, C.Y. Ponsioen, P.J. Tanis, W.A. Bemelman, C. Cunningham, F.B. de Lacy, Roel Hompes. Comparison of pro-active and conservative treatment of anastomotic leakage in rectal cancer surgery; a multicenter retrospective cohort series. *Techniques in Coloproctology* 2023, *in press.*

14. N.G. Greijdanus, K.R. Wienholts, S. Ubels, **K. Talboom**, G. Hannink, A. Wolthuis, F.B. de Lacy MD, J.H. Lefevre, M. Solomon, M. Frasson, N. Rotholtz, Q. Denost, R.O. Perez, T. Konishi, Y. Panis, M. Rutegård, R. Hompes, C. Rosman, F. van Workum, P.J. Tanis, J.H.W. de Wilt, TENTACLE-Rectum Collaborative Group. Stoma-free survival after rectal cancer resection with anastomotic leakage: development and validation of a prediction model in a large international cohort. *Submitted.*

15. S. Sharabiany, J.J. Joosten, **K. Talboom**, G.D. Musters, P.J. Tanis, W.A. Bemelman, R. Hompes. Management of pelvic sepsis after total mesorectal excision for rectal cancer – A 10-year experience of a national referral centre. *Submitted.*

PHD PORTFOLIO

Name PhD student:	K. Talboom
PhD period:	01-09-2019 – 31-12-2021
Name PhD supervisor:	Prof. dr. W.A. Bemelman
Name PhD co-supervisors:	Dr. R. Hompes / Dr. J.P.M. Derikx

1. PhD training

	Year	Workload (ECTS)
General courses		
- Practical Biostatistics	2019	1.4
- Clinical Epidemiology: Observational Epidemiology	2019	0.6
- Clinical Epidemiology: Evaluation of Medical Tests	2019	0.9
- Clinical Epidemiology: Systematic Reviews	2019	0.7
- Clinical Epidemiology: Randomized Clinical Trials	2020	0.6
- Entrepreneurship in Health and Life Sciences	2020	1.5
- BROK, basic course Legislation and Organisation for Clinical Researchers	2020	1.5
- Project management	2020	0.6
- English scientific writing	2020	1.5
- Computing in R	2021	0.7
- Advanced Biostatistics	2021	1.4
Specific courses		
- Sigmoid Take-off	2021	1.0
Seminars, workshops and master classes		
- Monthly Journal Club Surgery	2019-2021	2.0
- Colorectal surgery research meetings	2019-2021	1.0
- Weekly department seminars	2019-2021	2.0
Presentations		
- Presentation, European Society of Coloproctology 2020, virtual	2020	0.5
- 3x Presentation, Researchbespreking	2020, 2021	1.5
- Presentation, Chirurgendagen 2021, Den Haag	2021	0.5
- Presentation, Wetenschapsdag Regio 1 2021, Amsterdam	2021	0.5
- Presentation, Digestive Disease Days 2021, virtual	2021	0.5
- Presentation, United European Gastroenterology week 2021, virtual	2021	0.5

- Presentation, European Society of Coloproctology 2021, virtual	2021	0.5
- 2x Poster, European Society of Coloproctology 2021, virtual	2021	1.0
- Presentation, Digestive Disease Days 2022, virtual	2022	0.5
- Presentation, European Society of Coloproctology 2022, Dublin	2022	0.5
- 2x poster, European Society of Coloproctology 2022, Dublin	2022	1.0
(Inter)national conferences		
- ESCP 2019, Vienna	2019	0.5
- Wetenschapsdag 2019, Amsterdam	2019	0.5
- WCP conference 2020, virtual	2020	0.5
- ESCP 2020, virtual	2020	0.5
- Wetenschapsdag 2021, Amsterdam	2021	0.5
- Digestive Disease Days 2021, virtual	2021	0.5
- UEG week 2021, virtual	2021	0.5
- ESCP 2021, virtual	2021	0.5
- WCP conference 2021, Utrecht	2021	0.5
- Digestive Disease Days 2022, virtual	2022	0.5
- ESCP 2022, Dublin	2022	0.5

2. Teaching

	Year	Workload (ECTS)
Supervising		
- Master thesis medical student: N.G. Greijdanus	2018	2.0
- Bachelor thesis medical student: S. Abdelrahman	2019	1.0
- Bachelor students (2x)	2019	2.0

3. Parameters of Esteem

	Year
Grants	
- Additional funding KWF Research project (nr. 12314), IMARI-trial, written under guidance of prof. dr. P.J. Tanis and dr. R. Hompes.	2020
Awards and Prizes	
- Best Abstract Prize 2021, UEG Week, digital	2021

DANKWOORD

Aan elke promotie komt een einde, en zo ook deze. Een promotietijd komt bij iedereen met ups en down, maar het is uiteindelijk toch gelukt om het proefschrift af te krijgen, na jaren mezelf uit de 'naad' te hebben gewerkt voor de naadlekkages. En ondanks dat ik me soms meer een fietskoerier dan een promovendus voelde, door alle fietstochten door Amsterdam met ontlasting, darm of buikvocht in de rugzak, is het toch een fantastische tijd geweest waar ik ontzettend veel van heb geleerd. Hieronder wil ik graag een aantal mensen bedanken zonder wie dit proefschrift er niet was gekomen. Ongetwijfeld ontbreken hier een aantal mensen, maar ook veel dank aan jullie!

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Beste G4 onderzoekers, zonder jullie was er niet zoveel lol tijdens de promotietijd geweest. De koffierondes, colarondjes, vrijdaglunch, vrijdagmiddagborrels bij het rode keukentje, de laserlamp van de fluorescentiekamer (die mysterieus is verdwenen), laatste keer los bij Jos voor de pandemie, het gouden pistool, fietsrondjes en meer.

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CURRICULUM VITAE

Kevin Talboom was born in Alkmaar on July 29th 1992 and grew up in Warmenhuizen with his parents and little brother. He completed secondary school in 2010 at the Murmellius Gymnasium, after which he started medical training at the Vrije Universiteit and VUmc. After obtaining his medical degree in 2018, he went with his girlfriend Lara van Woensel to Suriname to work as a surgery resident in the Academisch Ziekenhuis Paramaribo. After returning to the Netherlands in 2019, he started as a PhD-candidate in the Amsterdam UMC, location AMC to conduct research on colorectal surgery. Under guidance of his supervisors, Kevin Talboom initiated the IMARI-trial in 2020 and was involved in setting up the Biobank Anastomotic Leakage. Additional funding was obtained from the Dutch Cancer Foundation for the IMARI-trial. Furthermore, he was responsible for coordinating the TENTACLE-Rectum study and coordinating and completing the FIT-trial. After his time as a full-time researcher, Kevin worked as a surgery resident in Tergooi Hospital in Hilversum. He will start training to become a general practitioner in September 2023. Kevin lives together with his girlfriend Lara in Amsterdam.