Defunctioning stoma in low anterior resection of the rectum for cancer: Aspects of stoma reversal, anastomotic leakage, anorectal function, and cost-effectiveness
Für Carl

Doctors must be very careful
When they take the knife!
Underneath their fine incisions
Stirs the Culprit - Life!

Emily Dickinson, ca. 1859
Defunctioning stoma in low anterior resection of the rectum for cancer: Aspects of stoma reversal, anastomotic leakage, anorectal function, and cost-effectiveness
Abstract


Rectal cancer is a common malignancy treated with surgical resection and curative intent in the majority of cases. One treatment option is low anterior resection (LAR) with preserved bowel continuity, often involving the formation of a temporary defunctioning stoma (DS).

The general aim of this thesis was to improve understanding of the role of DS in rectal cancer surgery with regard to timing of stoma reversal and development of anastomotic leakage (AL), impact on long-term anorectal function (AF), as well as aspects of cost-effectiveness.

Study I addressed the timing of stoma reversal following LAR. We found that 19% of reversed patients were reversed within 4 months of LAR, while 81% of reversals were delayed. In 58% of delayed reversals the delay was due to low priority on surgical waiting lists.

Studies II-IV were based on 234 patients randomized to receive a DS or no DS following LAR. Study II compared patients with AL following LAR diagnosed during the initial hospital stay (early leakage, EL) with patients diagnosed after hospital discharge (late leakage, LL). LL was more common in females, and originated more frequently from the transverse stapler line. EL was more common in males, and originated more frequently from the circular stapler line. Study III assessed AF 5 years after LAR with regard to whether patients initially had a DS or no DS. We found no difference in AF between the two randomized groups. When comparing with a 1-year follow-up in the same patient cohort, there were no further changes in AF over time. Study III assessed necessary healthcare resources and cost within 5 years of LAR, depending on whether patients initially had a DS or no DS. The overall cost analysis revealed a higher cost for patients randomized to DS, regardless of the cost-savings associated with a reduced frequency of anastomotic leakage.

Keywords: rectal cancer, low anterior resection, defunctioning stoma, stoma reversal, anastomotic leakage, anorectal function, costs, resources

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This thesis is based on the following four papers, which will be referred to in the text by their roman numerals:

I When are defunctioning stomas in rectal cancer surgery really reversed? Results from a population-based single center experience.
Floodeen H, Lindgren R, Matthiessen P

II Early and late symptomatic anastomotic leakage following low anterior resection of the rectum for cancer: are they different entities?
Floodeen H, Hallböök O, Rutegård J, Sjödahl R, Matthiessen P

III Evaluation of long-term anorectal function after low anterior resection: A 5-year follow-up of a randomized multicenter trial.
Floodeen H, Lindgren R, Hallböök O, Matthiessen P
Dis Colon Rectum 2014 Oct;57(10):1162-8

IV Costs and resource use following defunctioning stoma in low anterior resection: A long-term analysis of a randomized multicenter trial.
Floodeen H, Hallböök O, Hagberg L, Matthiessen P
manuscript

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ABBREVIATIONS

AL  Anastomotic Leakage
APR  Abdomino-Perineal Resection
AR  Anterior Resection
ASA  American Society of Anesthesiologists
BMI  Body Mass Index
CEA  Carcinoembryonic Antigen
CRC  Colorectal Cancer
CRP  C-reactive Protein
CT  Computed Tomography
EL  Early Leakage
DS  Defunctioning Stoma
LAR  Low Anterior Resection
LARS  Low Anterior Resection Syndrome
LL  Late Leakage
NL  No Leakage
OR  Odds Ratio
POD  Post-Operative Day
QALY  Quality-Adjusted Life Year
QoL  Quality of Life
SCFA  Short Chain Fatty Acid
SRCR  Swedish Rectal Cancer Registry
TEM  Transanal Endoscopic Microsurgery
TME  Total Mesorectal Excision
TNM  Tumor, Node, Metastasis
UICC  Union International Contre le Cancer
INTRODUCTION

Background

Colorectal cancer (CRC) is a common malignancy with an estimated 1.4 million new cases and 700,000 deaths worldwide every year (Statistics for 2012, Globocan Database). (1) An estimated $8.4 billion is spent annually on CRC care, and numbers are expected to rise with a worldwide increasing incidence and prevalence, partly due to population growth and ageing. (2) (3) Smoking, physical inactivity, excess body weight, excess alcohol consumption, and a diet high in red and processed meats are known risk factors contributing to the development of CRC, which can be altered by changes in lifestyle and behavior. (2) (4) Further known risk factors include a family history of CRC, colorectal polyps, chronic inflammatory bowel disease, as well as less common genetic disorders, such as familial adenomatous polyposis, and hereditary nonpolyposis CRC (Lynch syndrome). (5) (6)

Detection of CRC has improved with the implementation of widespread screening programs, using fecal immunochemical testing (FIT) or fecal occult blood test (FOBT), flexible sigmoidoscopy, colonoscopy, and more recently computed tomographic colonography for earlier diagnosis of CRC. (7)

Despite a slight increase in CRC incidence in recent years in Sweden, there has been a steady decrease in CRC mortality, probably due to advances in treatment strategies and perioperative care, but even reduction in risk factors (smoking) in the general population. (8) (9) (10) This trend holds true even for most European countries, with the exception of some countries in Eastern Europe. Overall, great variations remain in CRC incidence and mortality between different countries and regions. Mortality in Sweden is estimated to be around 14 per 100,000 male inhabitants, with somewhat lower numbers for females, which amounts to approximately 2600 deaths due to CRC in Sweden every year. (8) (10)

In Sweden, there are approximately 6000 new cases of CRC each year, of which one third are located in the rectum. In this thesis, rectal cancer is defined as a cancer that is partly or completely situated within 15 cm of the anal verge as measured with a rigid rectoscope, although this definition does not account for all patient variability. (11) (12) (13)
Rectal cancer is more common in men than in women. The current incidence is 24.6 per 100,000 male inhabitants and 17.3 per 100,000 female inhabitants. Overall relative 5-year survival for all rectal cancer patients in Sweden has improved over the last decade and is currently estimated to be around 62% for men and 64% for women. (10) (14) Survival rates are higher for patients undergoing surgery with curative intent and are estimated to be above 70% for patients undergoing anterior resection (AR). (15) (16)

**Low Anterior Resection**

The first resection of a part of the rectum with the construction of an anastomosis was described by Kraske in 1885 and coined “posterior resection”, as it was performed through a posterior incision including the removal of the coccyx. (17) Postoperative morbidity and mortality were high, and oncological results poor due to the lack of understanding of the mechanisms of tumor spread. Based on the pathological studies by Miles in 1908, the abdomino-perineal resection (APR) was introduced, which resulted in lower postoperative mortality and local recurrence rates. (18) In 1921, Hartmann introduced a two-step procedure for the removal of a rectal tumor, leaving a rectal stump and fashioning a permanent colostomy. This procedure, called Hartmann’s procedure, is still in use today as a one-step procedure. (19)

Dixon and Best reintroduced the sphincter saving approach in the 1940s called “anterior resection”. (20) The term “anterior resection” (AR) refers to a procedure through an abdominal incision, as opposed to the posterior resection through a perineal incision described by Kraske.

Sphincter saving procedures became more common, and based on the better understanding of tumor spread, (21) the concept of total mesorectal excision (TME) was introduced by Heald in 1982. (22) The principles of TME surgery include the sharp dissection under direct vision in the embryological avascular planes between the visceral and parietal pelvic fascia, removing the rectum with an intact mesorectum. With TME surgery, Heald reported 5-year recurrence rates lower than 5% without additional treatment. (23) TME principles are applied today in sphincter preserving procedures, as well as in APR and Hartmann’s procedure with good oncological results. (24)
Low anterior resection (LAR) refers to an AR with dissection down to the pelvic floor according to TME principles. All patients in this thesis were treated with LAR for low rectal cancer. Median height of the anastomosis in patients included in the RECTODES trial was 5 cm above the anal verge.

**Patient flow and necessary healthcare resources in rectal cancer care**

A newly diagnosed rectal cancer is treated with a surgical approach in the majority of cases. A typical patient might present with changed defecation habits or rectal bleeding, and will be referred to a surgical department handling rectal cancer care. (25) Patient history and a physical examination are guidance in the evaluation of the suspected diagnosis. A rectal exam is performed, both by digital rectal examination and rigid rectoscopy, which give information about the macroscopic aspects and local properties of the findings. Tissue samples are taken to ascertain tumor diagnosis. Additional blood tests examine general health status and quantify the tumor-specific bio-marker carcinoembryonic antigen (CEA). (26) Diagnostic imaging is obtained to verify the clinical findings, and to investigate local extent of disease as well as possible distant metastasis.

Once the diagnosis of rectal cancer is confirmed and diagnostic work-up completed, the patient is discussed at a multi-disciplinary team-conference including surgeon, radiologist, oncologist, pathologist, and clinical nurse specialist. The team decides on an appropriate treatment plan based on disease stage, clinical presentation and patient condition, in accordance with national treatment guidelines. (27)

Following the team-conference, the patient is taken back into office and given information about diagnosis and treatment options. Contact with a cancer nurse specialist is established. In the majority of cases, a hospital admission for surgical resection of the tumor is planned, sometimes following a neoadjuvant radiotherapy or chemotherapy regime.

Low anterior resection involves a hospital admission of approximately 6-12 days, depending on whether the operation is performed with an open or laparoscopic approach, and whether a defunctioning stoma is created at resection or not. If the postoperative course is uneventful and, in case of a newly constructed stoma, the patient has learned how to handle the stoma appliance, he or she is discharged from the hospital.
Following patient discharge, a second multi-disciplinary team-conference is scheduled for discussion of intraoperative findings and pathological evaluation of the surgical specimen. If necessary, the disease stage is adjusted, and the team decides on an appropriate postoperative treatment regime. This might include adjuvant chemotherapy treatment.

Outpatient visits at the surgical department are scheduled to surgeon, nurse, and, if necessary, stoma therapist, as part of a predesigned follow-up scheme. If appropriate, the patient is referred to an oncological unit handling adjuvant treatment. Following the clinical post-operative check-up one month after discharge, the patient is scheduled for routine clinical follow-up visits including CEA-analysis and radiological imaging at 12 and 36 months after surgery, according to the National Guidelines for Colorectal Cancer. (27) Local traditions may differ from the national guidelines, and at Örebro University Hospital, rectal cancer patients are scheduled for an additional follow-up visit 5 years after surgery including CEA-analysis, radiological imaging and a colonoscopy. If there is no sign of recurrence, patients are considered cured. If a defunctioning stoma was constructed, stoma reversal is scheduled if postoperative diagnostic imaging is normal and the patient deemed fit for surgery.

Exceptions to this typical course of action are common, and might in fact be more of a rule than the exception. Cancer care for a specific patient often requires adjustments to individualize the standardized treatment plan, taking each patient’s personal prerequisites into account.

Common discourses of the original plan include postoperative complications, such as surgical site infections, stoma-related complications, or anastomotic leakage. These might involve prolonged hospital admission, further diagnostic imaging, unplanned reoperations or other interventions, intensive level care, as well as unplanned readmissions after discharge. (28) Ultimately, there is a considerable rate of mortality associated with rectal cancer surgery. (29) (30)

Every step along the treatment path involves the use of healthcare resources with the associated costs. As there are approximately 2000 new rectal cancer cases yearly in Sweden, of which the majority undergoes surgical resection, the basic treatment regime alone involves a considerable amount of resources for the healthcare provider. Unexpected complications can increase the total costs unproportionally and need to be carefully analysed in order to identify preventable costs. (31)
Paper IV aimed at describing the necessary healthcare resources for in-patient care and analysing the associated costs within 5 years, with regard to if patients had a defunctioning stoma created at index operation or not. Table 1.

Table 1: Examples of costs for hospital admission (per diem), low anterior resection, reoperation for complications, stoma reversal, and stoma care. All costs are converted to € and inflation-adjusted to match the year 2014.

<table>
<thead>
<tr>
<th>Local costs (€)</th>
<th>Length of stay#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission, per diem costs</td>
<td>528</td>
</tr>
<tr>
<td>Low anterior resection, open approach with DS</td>
<td>16.544*</td>
</tr>
<tr>
<td>Laparoscopic low anterior resection with DS</td>
<td>17.812*</td>
</tr>
<tr>
<td>Low anterior resection, open approach, no DS</td>
<td>16.797*</td>
</tr>
<tr>
<td>Laparoscopic low anterior resection, no DS</td>
<td>15.380*</td>
</tr>
<tr>
<td>Reversal of loopileostomy without intestinal resection</td>
<td>9.712</td>
</tr>
<tr>
<td>Reversal of loopileostomy with intestinal resection</td>
<td>9.912</td>
</tr>
<tr>
<td>Reoperation for anastomotic leakage</td>
<td>23.878</td>
</tr>
<tr>
<td>Reoperation for ileus</td>
<td>12.704</td>
</tr>
<tr>
<td>Exploratory laparotomy</td>
<td>21.597</td>
</tr>
<tr>
<td>Stoma care – loopileostomy (per year)</td>
<td>3.850</td>
</tr>
<tr>
<td>Stoma care – colostomy (per year)</td>
<td>3.300</td>
</tr>
</tbody>
</table>

* based on national data from 2014 regarding university/regional hospital care
# mean length of stay in days

Defunctioning stoma

The term “stoma” is derived from the greek word στόµα meaning “mouth”, describing an opening of the body to the outside environment. A stoma can be either a natural opening or a surgically created artificial opening. Surgical stomas are most commonly positioned along the gastrointestinal tract as part of the treatment plan of gastrointestinal diseases. Colorectal cancer is a common underlying reason for a surgically created stoma, especially in situations of bowel obstruction due to tumor growth.
It can be created both in an acute setting and in elective surgery with the intention of permanent or temporary usage. The temporarily used, so-called “defunctioning” stoma in rectal cancer surgery has a special indication. It is intended for situations where an anastomosis is created following intestinal resection. To protect the anastomosis and allow for optimal healing conditions, the defunctioning stoma (DS) deviates the faecal stream for a limited amount of time. (32) When healing is achieved, often after testing of the anastomotic integrity by for example rectal contrast enema, the DS is reversed, and normal bowel continuity is regained.

The role of the DS in low anterior resection of the rectum for cancer is the focus of interest in this thesis. There is no consensus in the current literature as to the optimal timing of stoma reversal, but reversal is generally considered safe around 8-12 weeks postoperatively. (33) (34) (35) Aspects of the timing of stoma reversal are addressed in Paper I. Randomization to DS or no DS forms the principle difference between the study groups assessed in Papers II-IV.

**Anorectal function**

Anorectal function (AF) is a complex interplay between the anus, rectum, and musculature of the pelvic floor that facilitates defecation and preserves continence. Normal AF requires the ability to hold and distinguish between flatus and stool, and to withstand the urge to defecate for a certain amount of time. Impairment of these functions can have a large impact on individual patients’ Quality of Life (QoL), with subsequent social consequences. (36) Many patients experience impaired AF following rectal surgery, with varying symptoms including incontinence for flatus or stool, pain on defecation, constipation, fragmentation of bowel movements, and urgency to defecation. (37) (38) (39) (40) (41) Following low anterior resection (LAR), these symptoms are common and known as a syndrome called Low Anterior Resection Syndrome (LARS). Major LARS-symptoms are found in at least one third of patients following LAR, (42) (43) (44) making it a clinically relevant postoperative complication. Preoperative radiotherapy, total mesorectal excision (TME), anastomotic leakage following LAR, female gender, and younger age at LAR constitute risk factors for major LARS. (45) (46) Long-term AF after LAR is assessed by means of a bowel function questionnaire in Paper III.
**Anastomotic leakage**

In the studies included in this thesis, anastomotic leakage (AL) was defined as postoperative signs of peritonitis caused by leakage from any surgical stapler line, recto-vaginal fistula or pelvic abscess upon clinical assessment. (47) (48) (12) Leakage was verified by digital examination, inspection of the wound, inspection of drain contents, rectoscopy and/or radiological investigations without time limit. Radiologically demonstrated leakage without clinical symptoms was not included. This definition is relatively broad and may have contributed to the high rate of AL in the original RECTODES trial, which forms the base of the studies in Papers II-IV.

The grading of postoperative complications within 30 days for the purpose of registration in the Swedish Rectal Cancer Registry (SRCR) is based on the classification proposed by Dindo in 2004. (49) The SRCR does not provide a definition of AL, and the diagnosis of AL is at the discretion of the treating surgeon.

When the original trial was designed, no generally accepted definition for AL was available. In 2010, the International Study Group of Rectal Cancer (ISGRC) proposed a definition and grading of AL following AR of the rectum. It defines AL as a defect of the intestinal wall integrity at the anastomotic site leading to a communication between the intra- and extraluminal compartments. Leakage Grade A is defined as requiring no active therapeutic intervention, Grade B requiring active therapeutic intervention but manageable without re-laparotomy, and Grade C requiring re-laparotomy. Application of this definition in future studies is expected to standardize reporting of outcomes and facilitate comparison of the results from different studies. (50)

AL is the most feared complication following rectal cancer surgery with preserved bowel continuity, which often involves a low anastomosis positioned within a few cm above the anal verge. The clinical manifestation of AL can be very dramatic, with pelvic sepsis leading to prolonged hospital stay, further diagnostic imaging, necessity of intensive level care, unplanned reoperations, and even untimely death. (51) (32) (52) Increased short- and long-term mortality rates ranging from 6-22% have been reported following AL. (53) (54) (55) (56) (57) AL can present early in the postoperative course diagnosed before hospital discharge following LAR (early leakage, EL). But it can also present as late leakage (LL) after hospital discharge, upon unplanned readmission.
Aspects of the manifestation of LL in comparison with EL are addressed in Paper II. Aspects of necessary healthcare resources and costs related to the occurrence of AL are addressed in Paper IV.
AIMS OF THE THESIS

The comprehensive aim of this thesis was to improve understanding of the role of the defunctioning stoma in low anterior resection of the rectum for cancer, with regard to timing of stoma reversal and development of anastomotic leakage, impact on long-term anorectal function, as well as aspects of cost-effectiveness.

Paper I: To assess the timing of reversal of the defunctioning stoma following low anterior resection of the rectum for cancer, as well as risk factors for a defunctioning stoma to become permanent in non-reversed patients.

Paper II: To compare patients with anastomotic leakage following low anterior resection of the rectum for cancer diagnosed during the initial hospital stay (early leakage) with patients in whom leakage was diagnosed after hospital discharge (late leakage).

Paper III: To evaluate anorectal function 5 years after low anterior resection of the rectum for cancer with regard to whether patients had a defunctioning stoma at initial resection or not. Changes over time were assessed in comparison to the anorectal function evaluated 1 year after rectal resection.

Paper IV: To analyse costs and necessary healthcare resources in patients undergoing low anterior resection with or without defunctioning stoma within the first 5 postoperative years.
PATIENTS AND METHODS

Patients

All patients included in this thesis underwent low anterior resection (LAR) of the rectum for cancer. Paper I retrospectively analysed patients who underwent LAR at the Department of Surgery, Örebro University Hospital, between June 1995 and December 2007. All patients had a defunctioning stoma (DS) constructed at LAR, which was later reversed. Patients undergoing LAR without a DS at index operation, or who later had an unplanned DS constructed, were not included. Patients who never had their DS reversed were excluded from the primary analysis, but formed part of the secondary analysis.

Papers II-IV were based on a patient cohort of 234 patients included in the RECTODES trial (REctal Cancer Trial On DEfunctioning Stoma, NCT 00636948). Preoperative inclusion criteria were adenocarcinoma of the rectum, planned LAR, and informed consent. Intraoperative inclusion criteria were anastomosis ≤ 7 cm above the anal verge, negative intraoperative air leakage test, intact anastomotic stapler rings, and the absence of major adverse events during index surgery as judged by the surgeon. If no exclusion criteria were present, the patients were randomized intraoperatively to receive a DS (n=116) or no DS (n=118) by means of a sealed envelope. There were 3 cases of violation of the protocol (2 patients randomized to the no-stoma group received a stoma, and 1 patient randomized to the stoma group did not receive a stoma).

Methods

In Paper I, the primary analysis included patients who underwent LAR for rectal cancer with DS and subsequent stoma reversal (n=106). Patient and surgery related variables were analysed, including the time interval between LAR and stoma reversal. Stoma reversal was planned within 4 months of LAR. Stoma reversal later than 4 months following LAR was defined as delayed reversal. The secondary analysis included patients who underwent LAR with DS and who never had their stoma reversed (n=28). Risk factors for a stoma becoming permanent were analysed as part of the secondary analysis.
Studies II-IV formed secondary end points of the RECTODES trial. **Paper II** analysed 45 patients with symptomatic AL from the original patient cohort of 234 patients. Of these 45 patients, 27 had their leakage diagnosed during the initial hospital stay (early leakage, EL), and in 18 the leakage was diagnosed after hospital discharge upon readmission (late leakage, LL). Copies of the original patient files were assessed regarding patient and surgery related variables. Patient characteristics, operative details, postoperative course, and anatomical localization of the leakage were analysed. An index scale ranging from 0 points (best outcome) to 4 points (worst outcome) was employed for postoperative monitoring on postoperative day five (POD 5), including morning temperature, per oral intake, passed stool, and ongoing antibiotic treatment. Morning temperature <37.5° Celsius (C), per oral intake >1000 ml per 24 hours, passing stools or excretion of >100 ml in the stoma appliance, and no ongoing antibiotic treatment, all rendered zero points each. Morning temperature >37.5° C, per oral intake <1000 ml per 24 hours, no passed stools or excretion of <100 ml in the stoma appliance, and ongoing antibiotic treatment, all rendered one point each.

**Paper III** evaluated long-term AF following LAR in the patient cohort of 234 patients, with regard to whether patients initially had a DS or not. AF was evaluated in stoma-free survivors using a standardized bowel function questionnaire 5 years after the initial resection in the group randomized to no DS (n=65), and 5 years after reversal of the DS in the stoma group (n=58). In a secondary analysis, the AF of the study cohort at 5 years was compared to the AF after 1 year, as evaluated by the same bowel function questionnaire. All patients also answered the health measure questionnaire EQ-5D-3L, a standardized measure of the subjective health status.

**Paper IV** evaluated costs and necessary healthcare resources within 5 years of LAR, with regard to whether patients initially had a DS or not. Unplanned stoma formation, total number of days with any type of stoma, total length of hospital stay, reoperations, and total associated inpatient costs within 5 years of LAR were analysed. A secondary analysis evaluated the subgroup of patients with symptomatic AL (n=45).

Because actual costs for the study population could not be obtained retrospectively, representative costs for hospital admissions based on surgical procedure codes were calculated. Calculation was based on local cost data and available national data. Local costs were inflation-adjusted to match the year 2014, assuming an average annual increase in healthcare costs of 2.57% between 2006 and 2014. All costs were converted from
Swedish crowns (SEK) to Euros (€), based on the annual average exchange rate for 2014 (9.0968 SEK/€) published by the Swedish Central Bank (Sveriges Riksbank, www.riksbank.se). National data was retrieved from the national database for the year 2014 of the Swedish Association of Local Authorities and Regions (SALAR, Sveriges Kommuner och Landsting, www.skl.se).

Every surgical procedure in the patient population was then assigned a total mean cost representing one hospital admission. Less frequent abdominal reoperations, where representative mean costs could not be obtained, were assigned the local mean cost for exploratory laparotomy. Table 7.

**Anorectal function questionnaire**

All patients in Paper III received the standardized bowel function questionnaire published by Hallböök et al in the mail to evaluate postoperative anorectal function. (58) They were asked to assess various aspects of AF such as stool frequency, urgency, evacuation difficulties, use of medication, fragmentation of bowel movements, incontinence, effect on well-being, and whether the patients would prefer a permanent stoma rather than accepting their present AF. Paper III evaluated ten questions of this standardized bowel function questionnaire, which has been used in earlier studies to assess bowel function after surgery for rectal cancer. (58) (48)

The ordinal scale used in questions 2 through 7 and 9 was translated into a numerical scale from 1 to 4, with 1 point representing the optimal AF and 4 points representing the worst AF, as assessed by the patients. A fecal incontinence score was calculated by adding the scores in questions 5 through 7, resulting in a scale ranging from 3 points (best continence) to 12 points (worst continence). Table 2. All patients also answered the health measure questionnaire EQ-5D-3L, a standardized measure of the subjective health status. (59)
Table 2: Patient questionnaire for evaluation of bowel function  
(adapted from Hallböök et al) (58)  
(Scoring: never = 1, less than once per week = 2, 1-6 times weekly = 3, every day = 4)

1. How many times do you usually pass a motion?

<table>
<thead>
<tr>
<th></th>
<th>During the day?</th>
<th>At night?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

2. How often do you need medication to be able to open the bowel?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Less than once a week</th>
<th>1-6 times weekly</th>
<th>Every day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</table>

3. How often do you experience difficulty in emptying the bowel?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Less than once a week</th>
<th>1-6 times weekly</th>
<th>Every day</th>
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<tbody>
<tr>
<td></td>
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</tbody>
</table>

4. How often do you need to return to the toilet within one hour to empty the bowel?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Less than once a week</th>
<th>1-6 times weekly</th>
<th>Every day</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

5. How often do you break wind involuntarily?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Less than once a week</th>
<th>1-6 times weekly</th>
<th>Every day</th>
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</table>

6. How often do you have leakage if the motion is loose?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Less than once a week</th>
<th>1-6 times weekly</th>
<th>Every day</th>
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</thead>
<tbody>
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<td></td>
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</table>

7. How often do you have leakage if the motion is not loose?

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Less than once a week</th>
<th>1-6 times weekly</th>
<th>Every day</th>
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</tr>
</tbody>
</table>
8. How long can you withstand the urge to pass a motion if there is no toilet available?

15 minutes or longer  less than 15 minutes

9. Does bowel function adversely affect your general well-being?

Not at all  A little  Quite a bit  A lot

10. Would you prefer a stoma if this helped you with your bowel problems?

Yes  No

Statistics

Mann-Whitney U test, Kruskal-Wallis test, and paired t-test were employed for comparisons between groups with regard to ordinal variables, when appropriate. Chi-square test and Fisher’s exact test were employed for categorical variables. For comparison of cost-effectiveness between groups, distribution-independent Bootstrap analysis was employed. P-values less than 0.05 were considered significant.

Statistix version 9 (Analytical Software, Tallahassee, FL) and SPSS version 17 (SPSS, Chicago, IL) software packages were used for statistical calculations.

Ethical considerations

The study in Paper I was approved by the local ethics committee of the Uppsala-Örebro health care region. Permission for the study that formed the basis of Papers II-IV was granted by the ethics committee of the Linköping healthcare region, as well as by the regional ethics committees of each of the participating hospitals. All included patients gave informed consent.
RESULTS AND DISCUSSION

Paper I: When are defunctioning stomas in rectal cancer surgery really reversed? Results from a population-based single center experience.

This study included 140 consecutive patients who underwent LAR with formation of a DS between June 1995 and December 2007. Of 140 patients, 111 (79%) underwent subsequent stoma reversal and 29 (21%) did not. Six patients refused written consent and were excluded from further analysis. Thus, 106 reversed patients could be analysed in the primary analysis, and 28 non-reversed patients could be analysed in the secondary analysis.

Figure 1: Distribution over time of stoma reversals following LAR for rectal cancer (n = 106). Stoma reversals at >24 months included reversal at 26 (n=1), 31 (n=1) and 33 (n=1) months after LAR.
In 42% (36/86) of the patients with delayed stoma reversal, a medical reason for the delay was identified. The most important patient-related reasons for delayed reversal were non-surgical complications during the postoperative period in 20% (17/86), symptomatic anastomotic leakage (AL) following LAR in 12% (10/86), and postoperative adjuvant chemotherapy in 10% (9/86). The most common non-surgical complications contributing to delayed stoma reversal were cardiovascular complications and thrombo-embolism. In the remaining 58% of the patients (50/86) no health-related reason for delayed stoma reversal was identified. A total of 21% of the patients (28/134) who underwent LAR with DS were never reversed.

There is no consensus in the current literature as to the optimal timing of stoma reversal, but reversal is generally considered safe around 8-12 weeks postoperatively. (60) (34) With this approach, adequate healing can be obtained while avoiding the prolonged presence of a DS with subsequent higher morbidity and mortality, as well as higher treatment costs. (61) In the present study, a practical approach was used by defining timely reversal as within 4 months of LAR. Patients were scheduled for an outpatient follow-up visit one month after hospital discharge following LAR. Stoma reversal was then planned with the intention to be performed within 4 months after LAR, if the patient was deemed fit for surgery. It was a disappointing finding that only 19% of all reversed patients were reversed within this 4-months limit. Several valid reasons for delayed reversal were identified in the patient group not reversed within 4 months of LAR. Among those, the most common reasons were non-surgical complications, symptomatic AL, and adjuvant chemotherapy. These are recognized as factors delaying timely reversal of a DS following LAR in the current literature. (34) (62) (63) (64) In a surprisingly large percentage of patients (58%), no medical reason for delayed reversal could be identified. The authors conclude that this was due to the fact that stoma reversal was given lower priority on surgical waiting lists when competing with other benign conditions requiring surgery. This problem has been addressed by previous reports stating low priority as a factor contributing to delayed stoma reversal. (65) (66) (63) (64)

As a secondary analysis, a comparison was performed between the patients who had their stoma reversed (n=106) and those who did not (n=28). Two principal differences between these groups were identified. First, a significantly larger proportion of patients in the non-reversed group had stage IV cancer compared with those who had their stoma
reversed; 54% (15/28) compared with 5% (5/106) (OR 23.3; 95% CI: 7.3–74.7; P<0.001). And second, symptomatic AL following LAR was more frequent in those not reversed compared with those reversed, 43% (12/28) compared with 12% (13/106) (OR 5.4; 95% CI: 2.1–13.8; P<0.001).

One in five patients in this study were never reversed and kept the DS as a permanent stoma. Cancer stage IV and symptomatic AL following LAR were identified as risk factors for a DS to become permanent in this study. Results from recently published large studies have demonstrated that there is a risk between 18% and 25% for a DS to become permanent, and symptomatic AL and increased age were identified as independent risk factors. (34) (63) (67) (68)

As a consequence of the above findings, our institution has adopted a new policy offering patients a date for scheduled stoma reversal before hospital discharge. In a follow-up study including patients undergoing LAR with DS at our institution between 2008 and 2014 (n=94), we found that a higher percentage of patients were reversed within 4 months (33%). Among delayed reversals, only 29% were due to low priority on surgical waiting lists. Adjuvant chemotherapy was the most common reason for delayed reversal (39%), followed by symptomatic AL (12%), and non-surgical complications (6%). (69) These results are gratifying despite further room for improvement.

**Paper II: Early and late symptomatic anastomotic leakage following low anterior resection of the rectum for cancer: are they different entities?**

In this study we assessed 45 patients of the original patient cohort with symptomatic anastomotic leakage (AL). Of these, 27 patients were diagnosed during the initial hospital stay on median POD 8 (early leakage, EL), and 18 patients were diagnosed after hospital discharge upon readmission on median POD 22 (late leakage, LL). EL was numerically more common in males, while LL was more common in females (37% females in EL vs. 61% in LL; P=0.11). Patients with EL had a longer operation time at LAR, 240 compared with 190 minutes (P=0.006), and numerically greater intraoperative blood loss, 750 compared with 500 ml (P=0.071), as compared with LL. These findings may be indicative of more complex surgical circumstances during LAR in patients who later developed EL.
Male patients are considered to be technically more demanding when performing TME surgery due to the narrow male pelvis. Postoperative monitoring showed an increased POD 5 index in EL compared with LL, median 2 compared with 1 (P=0.004). The most frequent anatomical localization of the leakage in EL patients was the circular stapler line of the end to end anastomosis, J-pouch or side to end anastomosis, and the majority was located posteriorly or laterally in the anastomosis. In LL, most leakages originated from the transverse stapler line of the efferent limb of the J-pouch or side to end anastomosis, and the majority was located anteriorly in the anastomosis. Table 3.

The differences in anatomical origin of the leakages in the two groups are an interesting finding. One interpretation of this observation is that, in patients without a DS, the pressure from the passing faecal stream may be lower along the transverse stapler lines and in the anterior parts of the anastomosis, where the anastomosed tissues are partly covered by the prostate gland or the posterior section of the vaginal wall. Symptoms from a leakage

Table 3: Type of anastomosis and localisation of leakage.
Type of anastomosis in 45 patients operated with LAR for cancer with leakage diagnosed before (early leakage) or after (late leakage) hospital discharge. Fisher’s exact test.

<table>
<thead>
<tr>
<th>Type of stapler line</th>
<th>Early leakage (n=27)</th>
<th>Late Leakage (n=18)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circular stapler line</td>
<td>74% (20/27)</td>
<td>44% (8/18)</td>
<td>P=0.057*</td>
</tr>
<tr>
<td>J-pouch</td>
<td>10</td>
<td>4</td>
<td>ns</td>
</tr>
<tr>
<td>Side to end</td>
<td>6</td>
<td>3</td>
<td>ns</td>
</tr>
<tr>
<td>End to end</td>
<td>4</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td>Posterior quadrant</td>
<td>13</td>
<td>2</td>
<td>P=0.096</td>
</tr>
<tr>
<td>Anterior quadrant</td>
<td>2</td>
<td>6</td>
<td>P=0.003</td>
</tr>
<tr>
<td>Lateral quadrant</td>
<td>5</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Transverse stapler line</td>
<td>11% (3/27)</td>
<td>33% (6/18)</td>
<td>P=0.057*</td>
</tr>
<tr>
<td>Efferent limb, j-pouch</td>
<td>2</td>
<td>3</td>
<td>ns</td>
</tr>
<tr>
<td>Efferent limb, side to end</td>
<td>1</td>
<td>3</td>
<td>ns</td>
</tr>
<tr>
<td>Unidentified stapler line</td>
<td>15% (4/27)</td>
<td>22% (4/18)</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Not including leakages from unidentified stapler lines (n=8)
in these areas may therefore be concealed and diagnosis of LL may be delayed, even though the leakage arises at a similar postoperative time point as EL. The proportion of patients with recto-vaginal fistulas was numerically increased in LL compared with EL in this study. This type of anastomotic leakage is generally diagnosed at a later stage, a finding that is probably due to the natural and permanent drainage of the vagina. (75) (76) The proportion of patients with a DS in the LL group was numerically increased compared with EL, which was a non-significant finding due to the small sample size. The DS might additionally have contributed to conceal possible symptoms of AL by deviating the faecal stream and therefore mitigating the effects of AL.

An alternative interpretation is that EL is caused by technical imperfections during LAR that give rise to anastomotic tension and strain, typically located posteriorly in a low anastomosis. Clinical symptoms therefore become apparent early in the postoperative course. LL on the other hand may be due to impaired microcirculation in the anastomosis or the transverse stapler lines and therefore progresses biologically more slowly. (77) (78) The partial ischemia in the compromised tissues gives rise to milder and delayed symptoms of anastomotic leakage, which in turn delays diagnosis. In this scenario it is likely that impaired microcirculation arises in the most aborally located tissues of the surgical reconstruction, such as the transverse stapler line of the J-pouch or side to end anastomosis.

In an earlier publication by our group, patients with LL (n=18) were compared with patients who had no leakage (NL, n=189). (79) This comparison showed that patients with LL had a postoperative course resembling patients with NL with regard to postoperative recovery on POD 5 and length of initial hospital stay. Table 4. The only difference was the proportion of patients on antibiotic treatment, which was considerably higher in the LL group compared with NL. Reasons for antibiotic treatment were suspected urinary tract infections, chest infections or elevated CRP without proven focus of infection. These findings may in fact have represented an adverse component of the postoperative course related to AL, noted by the clinician and subsequently treated with antibiotics. The antibiotics may have contributed to conceal clinical signs of AL, and may have led to earlier hospital discharge in the LL group. However, the length of the initial hospital stay was median 10 days for both the NL group and those patients later diagnosed with LL, respectively, which was in contrast to an initial hospital stay of 28 days in patients diagnosed with EL.
In conclusion, Paper II demonstrates that leakage diagnosed after hospital discharge is common and often arises from a different anatomical origin compared with EL. These findings indicate that early and late leakage after low anterior resection of the rectum may represent different entities.

Table 4: Postoperative recovery on day 5 (POD 5) and length of hospital stay in all 234 patients, comparing the group with no leakage (n=189) with patients diagnosed with early leakage (n=27) and late leakage (n=18).

<table>
<thead>
<tr>
<th></th>
<th>No Leakage n=189</th>
<th>Early Leakage n=27</th>
<th>Late Leakage n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature &gt;37.5 ºC</td>
<td>16% (30/186)</td>
<td>33% (7/21)</td>
<td>18% (3/17)</td>
</tr>
<tr>
<td>Passed stool or excretion &gt;100 ml in stomal/24 h</td>
<td>78% (144/185)</td>
<td>40% (8/20)</td>
<td>83% (15/18)</td>
</tr>
<tr>
<td>Per oral fluid intake &gt;1000 ml/24 h</td>
<td>76% (143/187)</td>
<td>52% (10/21)</td>
<td>78% (14/18)</td>
</tr>
<tr>
<td>Ongoing antibiotic treatment</td>
<td>4% (7/186)</td>
<td>33% (7/21)</td>
<td>28% (5/18)</td>
</tr>
<tr>
<td>Initial hospital stay, days, median (range)</td>
<td>10 (5-60)</td>
<td>28 (8-81)</td>
<td>10 (7-31)</td>
</tr>
</tbody>
</table>

Paper III: Evaluation of long-term anorectal function after low anterior resection: A 5-year follow-up of a randomized multicenter trial

Paper III assessed AF 5 years after LAR in 123 patients of the original study cohort (n=234). A total of 111 patients could not be evaluated, because 66 patients had died, 20 were alive with a permanent stoma, 2 were unable to participate due to dementia, and 23 were non-responders. Of all non-responders, 7 were from the no-stoma group and 16 from the stoma group (10% vs. 22%, P=0.049). Thus, the participation rate of all eligible patients was 84% (123/146), which was high considering the long follow-up time in a population of rectal cancer patients.

In non-responders (n=23), some differences were observed when comparing with the participating patients (n=123). At initial surgery, non-responders were older (median 69 vs. 65.5 years, P=0.08), had a higher
ASA class (ASA ≥ 3: 34% vs. 7%; P<0.001), and showed a trend towards increased BMI (27.2 vs. 24.8; P=0.09). Fewer patients among non-responders received preoperative radiotherapy (65% vs. 83%; P=0.0507). AL was more frequent among non-responders compared to participating patients (26.1% (6/23) vs. 8.9% (11/123); P=0.019). There were no differences between the two groups regarding gender distribution, cancer stage, and median level of anastomosis. The observed differences imply that the group of non-responders were overall older with a higher degree of comorbidity, which might have led to a higher rate of postoperative complications. The same factors may have contributed to these patients being non-responders in the follow-up study. Despite the differences observed in patients lost to follow-up, which may be a bias in the present study, the author considers the participating study population a representative sample of the original study population to evaluate long-term AF.

Comparison between AF in patients with initial DS (n=58) and in patients without initial DS (n=65) showed no differences regarding stool frequency at night, need for medication to open the bowel, difficulty in emptying the bowel, fragmentation of bowel movements, or urgency. When asked if patients preferred a permanent stoma rather than accepting their present AF, one patient in each group would have favoured a permanent stoma. Analysis of the incontinence scores (questions 5-7) revealed a numerical difference between the two groups showing a trend for better continence in the no-stoma group, albeit not statistically significant (mean (SD) score 5.8 (1.9) in the no-stoma group vs. 6.4 (1.8) in the stoma group; P=0.056; Student’s t-test). Similarly, analysis of the daytime stool frequency revealed a trend towards a lower stool frequency in the no-stoma group without reaching statistical significance. A statistically significant difference was found regarding the adverse effect of bowel function on general well-being in favour of the no-stoma group (median score 1 in the no-stoma group vs. 2 in the stoma group; P=0.033). Table 5.

As a secondary analysis, a direct comparison was performed including all patients who answered the bowel function questionnaire both at 1-year follow-up and at 5-year follow-up (n=120). The evaluation was carried out in a paired fashion, with all patients serving as their own controls. This comparison revealed no statistically significant differences between the groups in all studied aspects with the exception of the general effect on well-being, which was significantly improved in the no-stoma group at 5-year follow-up (median score 1 in the no-stoma group at 5-year follow-up compared with median score 2 in the no-stoma group at 1-year follow-up,
P=0.042). These findings indicate that there might in fact be a difference in long-term anorectal function between groups in favour of the no-stoma group. This study represented a secondary end point of the RECTODES trial, originally designed to assess the incidence of AL as a primary end point. Thus, no separate power calculation for the end point in this study was performed, which is an acknowledged weakness. It is possible that a trial with an adequate sample size for the assessment of AF as a primary end

Table 5: Results from bowel function questionnaire at 5-year follow-up

<table>
<thead>
<tr>
<th></th>
<th>no stoma n=65</th>
<th>stoma n=58</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Stool frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>daytime, median (range)</td>
<td>2.5 (1-9)</td>
<td>3 (1-10)</td>
<td>0.10*</td>
</tr>
<tr>
<td>nighttime, median (range)</td>
<td>0 (0-4)</td>
<td>0 (0-3)</td>
<td>0.70*</td>
</tr>
<tr>
<td>2) Need for medication to open bowel, ranked 1-4, median (range)</td>
<td>1 (1-4)</td>
<td>1 (1-4)</td>
<td>0.19*</td>
</tr>
<tr>
<td>3) Evacuation difficulties, ranked 1-4, median (range)</td>
<td>1 (1-4)</td>
<td>1 (1-4)</td>
<td>0.82*</td>
</tr>
<tr>
<td>4) Need to return to toilet within one hour, ranked 1-4, median (range)</td>
<td>3 (1-4)</td>
<td>3 (1-4)</td>
<td>0.98*</td>
</tr>
<tr>
<td>5-7) Incontinence, ranked 3-12, median (range)</td>
<td>6 (3-10)</td>
<td>6 (3-10)</td>
<td>0.062*</td>
</tr>
<tr>
<td>8) Withstand the urge to pass a motion less than 15 minutes, % (n)</td>
<td>32.9% (21/64)</td>
<td>33.3% (19/57)</td>
<td>0.95*</td>
</tr>
<tr>
<td>9) AF effect on general well-being, ranked 1-4, median (range)</td>
<td>1 (1-4)</td>
<td>2 (1-4)</td>
<td>0.033*</td>
</tr>
<tr>
<td>10) Prefer permanent stoma, % (n)</td>
<td>1.7% (1/59)</td>
<td>1.9% (1/52)</td>
<td>1.0*</td>
</tr>
</tbody>
</table>

* Mann Whitney U test,
* Chi2 test
point may find further differences between the groups, which could not be detected with certainty in this study.

A further weakness of this study is the fact that the bowel function questionnaire used in this study was never formally validated. The questionnaire was designed by a group of experts during the late 1990’s. At this time, no standard questionnaire was available for evaluating bowel function that included aspects of urgency and fragmentation of bowel movements, which were considered important aspects of postoperative bowel function in rectal cancer patients based on clinical experience. The questionnaire was published by Hallböök et al in 2000 and was used in the present study according to the original trial protocol. (58)

Since the publication of Paper III, a new bowel function questionnaire called LARS-score (Low Anterior Resection Syndrome-Score) has been introduced in clinical practice. (43) (80) The LARS score is a 5-item measurement scale developed to evaluate postoperative bowel dysfunction in rectal cancer patients. The final score was weighted according to patients’ perception of bowel dysfunction and personal bother of certain bowel dysfunction symptoms on general QoL. The questionnaire was condensed into 5 aspects of bowel dysfunction reflecting the largest impact on patient-reported QoL, which were found to be incontinence for gas and liquid stool, high number of daily bowel movements, fragmentation of bowel movements, and urgency.

The LARS-score ranges from 0-42 points, with higher numbers representing a larger impact of bowel function on QoL (0-20 points: no LARS; 21-29 points: minor LARS; 30-42 points: major LARS). Urgency was overall considered to have the largest single impact of QoL, which was a finding in discordance with physician-reported factors of bowel dysfunction influencing QoL in rectal cancer patients. (46) Table 6.

The findings reported by Emmertsen et al that form the base of the LARS-score confirm the importance of urgency and fragmentation of bowel movements, which led to the development of the bowel function questionnaire used in Paper III. It is an interesting coincidence that 4 out of the 5 measures evaluated in the LARS-score can be directly extracted from our bowel function questionnaire.
Table 6: LARS-score (81)

The aim of this questionnaire is to assess your bowel function. Please tick only one box for each question. It may be difficult to select only one answer, as we know that for some patients symptoms vary from day to day. We would kindly ask you to choose one answer which best describes your daily life. If you have recently had an infection affecting your bowel function, please do not take this into account and focus on answering questions to reflect your usual daily bowel function.

Q1: Do you ever have occasions when you cannot control your flatus (wind) ?

- No, never 0
- Yes, less than once per week 4
- Yes, at least once per week 7

Q2: Do you ever have any accidental leakage of liquid stool?

- No, never 0
- Yes, less than once per week 3
- Yes, at least once per week 3

Q3: How often do you open your bowels?

- More than 7 times per day (24 hours) 4
- 4-7 times per day (24 hours) 2
- 1-3 times per day (24 hours) 0
- Less than once per day (24 hours) 5

Q4: Do you ever have to open your bowels again within one hour of the last bowel opening?

- No, never 0
- Yes, less than once per week 9
- Yes, at least once per week 11
Q5: Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?

- No, never: 0
- Yes, less than once per week: 11
- Yes, at least once per week: 16

Add the scores from each of the five answers to one final score.
Interpretation: 0-20 = No LARS, 21-29 = Minor LARS, 30-42 = Major LARS

In 2015, our research group presented follow-up data regarding AF in the patient cohort included in Paper III using the LARS score. Eighty-seven surviving stoma-free patients were evaluated 12 years after LAR, revealing a higher overall LARS score in the group randomized to DS+ (P=0.041), as well as a numerically increased proportion of patients with major LARS (59% compared with 50%, not significant). DS- performed better with regard to incontinence for flatus (P=0.023) and liquid stool (P=0.005), and showed a trend toward improved urgency (P=0.099), as compared with DS+. (82) These findings reflect the trends detected in Paper III, and seem to confirm that a DS may in fact have an impact on long-term AF.

It is difficult to define a biological explanation for this impact, and the literature is scarce regarding possible contributing factors. Diversion proctitis and colitis are one possible explanation for changes in long-term AF. (83) (84) This form of inflammation in the excluded bowel segments after temporary or permanent diversion was first described by Glotzer et al in 10 patients without a history of inflammatory bowel disease in 1981. (85) Changes in the metabolism of short chain fatty acids (SCFA) and the alteration of colonic microflora have been suggested as factors influencing the development of diversion colitis, and SCFA enemas have been used as a treatment option with varying results. (86) (87) (88) (89) Another possible explanation are morphological changes in the anal sphincter during faecal diversion. (90) (91) But overall, there is little evidence advocating that temporary faecal diversion should have a lasting effect on long-term AF, as most of the observed changes are reversible.

Overall, it is an interesting finding that the LARS score detected differences in AF between the two randomized groups, which could not be
detected with the bowel function questionnaire used in Paper III. Despite the limited sample size, a significantly improved AF was found in favour of the group randomized to no DS. These findings imply that there is in fact a detectable impact of faecal diversion on long-term AF, and that the questionnaire used in Paper III was not powerful enough to detect this with statistical certainty.

**Paper IV: Costs and resource use following defunctioning stoma in low anterior resection: A long-term analysis of a randomized multicenter trial.**

The overall cost analysis revealed mean inpatient costs of € 21,663 per patient randomized to DS+ and € 15,922 per patient randomized to DS- within 5 years of LAR, resulting in an average cost-saving of € 5,741 per patient in DS- (p=0.003; CI 95%: € 1,942 - 9,541). Due to the fact that the cost analysis was based on calculated representative costs, there was assumed to be a large uncertainty in these results. Thus, robustness of this data was tested with two sensitivity analyses. In a first analysis, costs were based on available national data with a higher total cost for patients with AL, which showed an average cost-saving of € 3,696 per patient in DS- (p=0.098; CI 95%: € -693 - 8,084). Table 7. Bootstrapping confirmed the expected cost-savings in DS- with a probability of 96%. A second sensitivity analysis excluding all patients with a complex clinical course (n=22), where a retrospective cost assessment was difficult and implied large uncertainty, revealed an average cost-saving of € 5,287 per patient in DS- (p=0.002; CI 95%: € 1,930 - 8,644). Bootstrapping confirmed the expected cost-savings in DS- with a probability of 100%.

The Bootstrap method is used to assign measures of accuracy to statistical estimates by random sampling with replacement. (92) The analysis is distribution-independent and can be helpful in the assessment of cost-effectiveness in the setting of clinical trials and medical decision-making. (93) (94) The Bootstrap method was applied on the above data set to balance the skewed distribution of the data between the two randomized groups. It confirmed with high statistical certainty that there was a cost-saving associated with randomization to no DS in this data set.

AL proved to be an important factor influencing overall costs for the healthcare provider. Patients with AL in this study accounted for one third of the total hospital stay, and half of all unplanned reoperations. Cost
analysis in patients with AL and DS- revealed an average total cost of € 34.724 per patient, compared with € 30.120 per patient with AL and DS+ within 5 years of LAR. This difference of € 4.604 per patient was non-significant with the given sample size (p=0.37; CI 95%: € -5849 - 15.057).

Sensitivity analysis using available national data was nearly significant and revealed a cost-saving of € 11.570 in patients with AL and DS+, as compared with AL and DS- (p=0.057; CI 95%: € -395 - 23.534). Considering the results of the sensitivity analysis, it is reasonable to assume that DS+ entails significant cost-savings in patients with AL when evaluating an adequate sample size. Overall, AL is considered to be the most expensive complication of LAR with regard to necessary healthcare resources. (95) (96) (56) DS has been shown to decrease the rate of symptomatic AL, and to mitigate the effects of symptomatic AL when it occurs. (97) (53) (12)

**Table 7:** Mean hospital admission costs and length of stay associated with surgical procedure codes, total costs in €, mean length of stay in days

<table>
<thead>
<tr>
<th>Procedure Description</th>
<th>local patient 2006-2014 Costs (€)</th>
<th>Length of stay</th>
<th>registry 2014 Costs (€)</th>
<th>Length of stay</th>
<th>national for data 2014 Costs (€)</th>
<th>Length of stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>reoperation for anastomotic leakage</td>
<td>23.878</td>
<td>19</td>
<td>32.762</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>reversal of loopileostomy without intestinal resection</td>
<td>9.712</td>
<td>8</td>
<td>8.262</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>reversal of loopileostomy with intestinal resection</td>
<td>9.912</td>
<td>7</td>
<td>9.963</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ileus</td>
<td>12.704</td>
<td>12</td>
<td>21.717</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>abdominoperineal resection with permanent colostomy</td>
<td>15.462</td>
<td>11</td>
<td>19.595</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>incisional/parastomal hernia</td>
<td>5.358</td>
<td>3</td>
<td><em>na</em></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>permanent colostomy only</td>
<td>10.625</td>
<td>11</td>
<td><em>na</em></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>exploratory laparotomy</td>
<td>21.597</td>
<td>21</td>
<td>18.387</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean per diem cost of hospital admission (2014)</td>
<td>528</td>
<td>1</td>
<td><em>na</em></td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*all costs are inflation-adjusted for the year 2014

*na* = not available
The rationale behind the use of the DS is lowering costs and improving the associated morbidity and mortality for patients with AL. However, the DS entails its own morbidity and mortality, and thus the necessity of further healthcare resources. (98) (99) Stoma creation has been shown to be an independent risk factor for unplanned readmission following colorectal surgery. (100) (101) (28)

Estimation of costs for treatment of AL turned out to be complicated in the present study. There is a lack of consistency in the usage of surgical procedure codes for diagnosis of or reoperation for AL at our institution. Furthermore, few patients presently undergoing LAR for rectal cancer do not receive a DS. Thus, abdominal reoperation for AL in patients without DS following LAR is uncommon, and the associated current costs could not be evaluated representatively. As a surrogate, mean hospital admission costs for similar representative scenarios were evaluated. These included local costs for rectal cancer patients undergoing high anterior resection without DS, who later required reoperation for AL (n=7), and patients undergoing LAR with DS, who later required reoperation due to leakage from the rectal anastomosis following reversal of the temporary stoma (n=3). All patients were recruited from the local patient registry, regardless of surgical procedure code. Local costs were then compared to mean national costs for hospital admissions due to AL using the available, but unfortunately rarely used, surgical procedure code for reoperation because of AL in rectal cancer patients during 2014.

Of all patients randomized to DS-, 30.5% (36/118) required a stoma at some point during the 5 years following LAR. These 36 patients accounted for a total of 34068 days with any type of stoma, which resulted in a median time with a stoma of 839 days (range 98-1820). DS- required median 1 hospital admission, and median 12 days in hospital when combining all admissions within 5 years of LAR. Eighty-two patients (69.5%) remained stoma-free during the entire follow-up period.

All patients randomized to DS+ had a stoma at some point during the study period. The 116 patients accounted for a total of 33398 days with any type of stoma, which resulted in a median time with a stoma of 196 days (range 13-1825). DS+ required median 2 hospital admissions, and median 22 days in hospital when combining all admissions within 5 years of LAR.

It was an unexpected finding that the two randomized groups of patients required such a similar total number of days with a stoma within 5 years of LAR. Associated costs for stoma care from the point of view of
the healthcare provider can thus be assumed to be similar, despite the uneven distribution of patients with a stoma across the two randomized groups.

An interesting observation was the difference in the number of days spent with a loopileostomy and a colostomy, respectively, in the two randomized groups. In the group randomized to DS-, days with a colostomy accounted for 43% of all days spent with a stoma within 5 years of LAR. In DS+, this number was 16%. As the clinical manifestation of AL is generally more dramatic in patients without a DS, the observed difference may be explained by the necessity of definitive measures in the face of this feared complication. Surgeons treating a patient with AL, and without the protective DS, possibly chose to create a permanent colostomy more readily during the clinical course.

A total of 103 patients in DS+ underwent planned reversal of the loopileostomy after a median time of 6 months. There were a further 32 unplanned reoperations in DS+, most commonly due to ileus (n=9), AL (n=5) and unsatisfactory anorectal function (n=5). Planned hospital readmission and operative costs for stoma reversal proved to be the most cost-driving factor in patients randomized to DS+. There is no consensus in the current literature as to the optimal timing of ileostomy reversal, but reversal is generally considered safe around 8-12 weeks postoperatively. (33) (34) (35) Additionally to possibly enhancing the individual patient’s QoL, there are large potential cost-savings in reducing the amount of time spent with a DS by planning and performing stoma reversal as early as feasible after LAR. (102) (103)

DS- required a total of 70 unplanned reoperations, most commonly due to AL (n=37), reversal of an urgently created loopileostomy (n=13), and ileus (n=6). Extended hospital stay or readmission and unplanned reoperation for AL were the most cost-driving factors for patients randomized to DS-.

Current practice in Sweden involves the routine formation of a DS in LAR in more than 90% of cases. (15) The present cost analysis implies that such a high percentage of DS in LAR cannot be assumed to be cost-effective. The challenge lies in identifying those patients at greatest risk to develop AL, and further research is necessary to determine which patients will benefit most from a DS. An issue of interest in this context is the Health-related QoL in patients with a stoma. The current literature is ambivalent concerning the impact of temporary and permanent stomas on QoL, (104) (105) (106) and there is a lack of reliable data regarding long-term QoL in patients with AL. According to current policy in Sweden, a
threshold of SEK 500,000 (~ € 55,000) per gained Quality-Adjusted Life Year (QALY) is employed for decisions about subsidized medicine. (107) This is in line with current accepted threshold ranges in the UK (£ 20,000 – 30,000 per gained QALY) and the US (US$ 50,000 – 100,000 per gained QALY). (108) (109) Thus, an average gained 0.1 QALYs per patient would be necessary to compensate for the higher treatment costs associated with the routine formation of a DS in LAR in this study.

In conclusion, the overall cost analysis in this study revealed significantly higher treatment costs for patients randomized to DS+, regardless of the cost-savings associated with the reduced frequency of symptomatic AL in these patients.
CONCLUSION

The general aim of this thesis was to improve understanding of the role of the defunctioning stoma in low anterior resection of the rectum for cancer, with regard to timing of stoma reversal and development of anastomotic leakage, impact on long-term anorectal function, as well as aspects of cost-effectiveness.

Paper I concluded that four in five patients experienced a delayed stoma reversal. The majority of the delays were due to the low priority given this surgical procedure within the present local health care system. One in five patients undergoing LAR for rectal cancer with defunctioning stoma ended up with a permanent stoma.

Paper II concluded that symptomatic anastomotic leakage appears both before and after hospital discharge, and indicates that early and late leakage after low anterior resection of the rectum may represent different entities.

Paper III found that anorectal function was impaired for many patients following low anterior resection, but the temporary presence of a defunctioning stoma after rectal resection did not affect long-term outcome of anorectal function. Anorectal function did not change between 1 and 5 years follow-up.

Paper IV concluded that randomization to defunctioning stoma following low anterior resection was overall more expensive than no defunctioning stoma, despite the cost-savings associated with a reduced frequency of anastomotic leakage.

Den första studien utvärderade patienter opererade med låg främre resektion och avlastande stomi vid Universitetssjukhuset i Örebro. Tidpunkt för nedläggning av stomin utvärderades, och i fall av försenad nedläggning, anledningen till förseningen. Vi fann att 19% av stomierna lades ned i tid (inom 4 månader), medan 81% blev försenade. Vanligaste anledning till försening (58%) var den låga prioriteringen av ingreppet inom den lokala sjukvårdsorganisationen. En femtedel av patienterna behöll stomin som en permanent stomi.

De övriga 3 studierna baserades på 234 patienter opererade med låg främre resektion av rektum och som randomiserades till avlastande stomi eller ingen stomi. Studie II analyserade förekomst av anastomosläckage i patientgruppen beroende av tidpunkten för diagnos före utskrivning (tidiga läckage) eller efter utskrivning från sjukhuset (sena läckage). Vi fann att sena läckage var vanliga och förekom oftare på en annan anatomisk position än tidiga läckage. Fyndet kan tyda på att tidiga och sena läckage har olika uppkomstmechanismer.

Studie III avsåg utvärdering av långsiktig anorektal funktion, beroende av randomiseringen till stomi eller ingen stomi. Studien genomfördes med två enkäter som berörde avföringsvanor och välmående. Vi fann inga skillnader mellan grupperna bortsett från ett ökat självpålev att välmående i icke-stomi gruppen 5 år efter låg främre resektion. I jämförelse med den anorektala funktionen utvärderat efter 1 år fann vi ingen förändring av funktionen över tid.
Studie IV utvärderade nödvändig hälsoekonomiska resurser och slutenvårdskostnader i samband med en avlastande stomi inom 5 år efter låg främre resektion. Det medförde en högre kostnad att randomiseras till en avlastande stomi, trots besparingarna som en avlastande stomi medförde hos de patienter som drabbades av anastomosläckage.
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