Aspects of anastomotic leakage, anorectal function and defunctioning stoma in Low Anterior Resection of the rectum for cancer
"And Ehud put forth his left hand, and took the dagger from his right thigh and thrust it into his belly. And the haft also went in after the blade: and the fat closed upon the blade, so that he could not draw the dagger out of his belly: and the dirt came out"

Judges 3:21-22 (King James Version)

Ehud's mortal attack on King Eglon of Moab might be the first recorded observation of a traumatic opening into the bowel, foreshadowing the surgically constructed stoma.
Aspects of anastomotic leakage, anorectal function and defunctioning stoma in Low Anterior Resection of the rectum for cancer
Abstract


Rectal cancer is a common malignant disease affecting nearly 2000 individuals each year in Sweden. The main treatment is surgical en bloc resection of the tumor together with its lymphatic and vascular supply, aiming at removal of all tumor tissue and, if possible, restoration of bowel continuity. Anastomotic leakage (AL) is a feared complication after rectal resection and a defunctioning stoma is often used to decrease the risk for, and consequences of, an anastomotic leakage. The general aim of this thesis was to improve the understanding of anastomotic leakage, defunctioning stoma and anorectal function, in patients with rectal cancer who underwent low anterior resection (LAR) of the rectum due to cancer. The first three studies evaluated different aspects of a set of 234 patients, randomized to a defunctioning stoma or not, and prospectively assessed, after LAR.

In the first study we assessed patients with AL diagnosed after hospital discharge (late leakage, LL). We found that 7.7% (18/234) developed LL although their initial postoperative course was seemingly uneventful. In the second study we investigated whether a defunctioning stoma affected long term postoperative anorectal function (AF). Patients were randomized to a defunctioning stoma or nor after LAR, and AF was evaluated after one year by a questionnaire comprising several AF variables. We found no difference in AF between patients defunctioned or not. Many patients had an impaired AF, but few would have preferred a permanent stoma. In a third study, the risk and the reasons for a permanent stoma after LAR were assessed in the same set of patients. In conclusion, one patient out of five ended up with a permanent stoma after LAR, and half of the patients with a permanent stoma had previous symptomatic anastomotic leakage. In the fourth study, 18 patients undergoing LAR with a defunctioning stoma were assessed with regard to early stoma reversal. From this feasibility study we conclude that early stoma reversal after LAR may be feasible but patient selection is complex and the risk for complications must be considered.

Keywords: Rectal cancer, defunctioning stoma, anorectal function, low anterior resection, postoperative monitoring, early stoma reversal.

Rickard Lindgren, School of Health and Medical Sciences
Örebro University, SE-701 82 Örebro, Sweden.
# Table of contents

LIST OF PAPERS ............................................................................................................. 9

ABBREVIATIONS ........................................................................................................... 10

INTRODUCTION ............................................................................................................ 11
  Background .................................................................................................................. 11
  Diagnosis .................................................................................................................... 12
  Treatment ................................................................................................................... 13
    Adjuvant treatment ................................................................................................... 13
    Surgery ..................................................................................................................... 14
    Anastomotic leakage ................................................................................................. 16
    Defunctioning stoma ................................................................................................. 17
    Anorectal function ................................................................................................... 19

AIMS OF THE THESIS ................................................................................................. 20

PATIENTS AND METHODS ......................................................................................... 21
  Patients .......................................................................................................................... 21
  Methods ....................................................................................................................... 23
    Definition of Anastomotic Leakage .......................................................................... 23
    Anorectal function questionnaire ............................................................................. 24
    Postoperative monitoring protocol .......................................................................... 26
    Statistical methods .................................................................................................. 27
  Ethics ........................................................................................................................... 27

RESULTS AND DISCUSSION ..................................................................................... 28
  (Paper I) ..................................................................................................................... 28
  (Paper II) .................................................................................................................... 31
  (Paper III) ................................................................................................................... 35
  (Paper IV) .................................................................................................................. 39

CONCLUSION ............................................................................................................. 47

SUMMARY IN SWEDISH ............................................................................................. 48

ACKNOWLEDGEMENTS ............................................................................................. 50

REFERENCES ............................................................................................................. 51

PAPERS I–IV ................................................................................................................. 62
List of papers

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

I  Symptomatic anastomotic leakage diagnosed after hospital discharge following low anterior resection for rectal cancer.

II  Does a defunctioning stoma affect anorectal function after low rectal resection? Results of a randomized multicenter trial.

III What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial.

IV  Feasibility of early closure of defunctioning stoma and postoperative monitoring in low anterior resection of the rectum for cancer.
Manuscript
Lindgren R MD, Andersson M MD, PhD, Jansson K MD, PhD Ljungqvist O MD, PhD and Peter Matthiessen MD, PhD

Reprints were made with the permission of the publishers.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>APR</td>
<td>Abdomino-Perineal Resection</td>
</tr>
<tr>
<td>AR</td>
<td>Anterior Resection</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CRC</td>
<td>Colo Rectal Cancer</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive Protein</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>ERUS</td>
<td>Endorectal Ultrasound</td>
</tr>
<tr>
<td>LAR</td>
<td>Low Anterior Resection</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>PCT</td>
<td>Procalcitonin</td>
</tr>
<tr>
<td>RT</td>
<td>Radio therapy</td>
</tr>
<tr>
<td>SRCCR</td>
<td>The Swedish Rectal Cancer Registry</td>
</tr>
<tr>
<td>TEM</td>
<td>Transanal Endoscopic Microsurgery</td>
</tr>
<tr>
<td>TME</td>
<td>Total Mesorectal Excision</td>
</tr>
<tr>
<td>TNM</td>
<td>Tumour, Node, Metastasis</td>
</tr>
<tr>
<td>UICC</td>
<td>Union International Contre le Cancer</td>
</tr>
</tbody>
</table>
Introduction

Background
More than one million individuals will develop colorectal cancer (CRC) worldwide every year (1). There is a great geographical variation in incidence, with the lowest rates in Africa and Asia, and the highest in western countries in which it is the second leading cause of cancer deaths. In Sweden, CRC is the third most common cancer, accounting for nearly 6000 new cases every year. CRC is uncommon before 40 years of age and the median age at diagnosis is approximately 70 years of age in rectal cancer and 75 in colon cancer.

The majority, about 80%, of CRC occur sporadically. Risk factors include increasing age, male sex, previous colonic polyps or colorectal cancer and environmental factors. The environmental factors are associated with a western lifestyle such as high-fat and red meat diet, inadequate intake of fibre, obesity, diabetes mellitus, smoking, and high consumption of alcohol. (2) Inflammatory bowel disease, Ulcerative colitis and Crohn’s disease, accounts for a part of the incidence (3,4) and the risk increases with duration of the illness (4), as well as with the extent of inflammation. (5)

About one fifth of CRC cases are hereditary. Approximately 5% of these belong to a defined hereditary syndrome and the remaining 15% represent hereditary CRC without any identified genetic cause. The most common defined hereditary syndromes are the Lynch syndrome, also known as hereditary non-polyposis colorectal cancer syndrome (HNPCC), accounting for 2–5% of all CRC, and familial adenomatous polyposis syndrome (FAP), accounting for <1%. (6, 7)

About one third of CRC are situated in the rectum, defined as an adenocarcinoma located completely or to some part within 15 cm from the anal verge, measured with a rigid rectoscope. (8) The incidence of rectal cancer in Sweden is higher in men than in women (27.5 versus 15.2 per 100 000) and slightly increasing, but the age standardised incidence rate has been rather stable during the last decades. (9)

Rectal cancer develops from adenoma through a sequence of well defined histological steps called the adenoma-carcinoma sequence (10), a process that takes several years. In the early stage of disease, rectal cancer may lack symptoms, whereas later on patients often present with blood in their stools. Other symptoms are changes in bowel habits, anaemia or anal pain.
Diagnosis

A patient who present with symptoms that might originate from a rectal tumor should be examined by rectoscopy. The diagnosis of rectal cancer is made by a histopathological examination of biopsies from the tumor. If the tumor can be reached from the anus, it is also assessed by digital palpation regarding possible fixation. Once the diagnosis of rectal cancer is made, a staging of the disease regarding depth of tumour invasion, lymph node involvement and distant metastases, is mandatory before treatment. Magnetic resonance imaging (MRI) and endorectal ultrasound (ERUS) are used in assessing the depth of tumour invasion and involved lymphnodes. (11,12) Computed tomography scan (CT-scan) of the abdomen and the thorax, or ultrasound of the liver and plain x-ray investigation of the lungs, are used to assess potential distant spread of the disease. (13) Sometimes a combination of CT-scan and Positron emission tomography scan (PET scan) is used to further evaluate patients with metastatic disease. (14) Beside the radiological evaluation of possible local and distant spread of the cancer, a colonoscopy, a barium enema or CT scan of the colon should be carried out to rule out synchronous tumors in the colon. The aim of these pre-treatment investigations is to characterise the extent of the disease according to the TNM-classification (Tumour, Node, Metastasis), which can be translated into other staging systems (15) and will give guidance in deciding the proper treatment for the individual patient. Table 1.

Table 1. The TNM system in relation to the AJCC/UICC staging system and the Dukes’ classification.

<table>
<thead>
<tr>
<th>TNM classification</th>
<th>AJCC/UICC staging system</th>
<th>Dukes’ classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-2 N0 M0</td>
<td>stage I</td>
<td>Dukes’ A</td>
</tr>
<tr>
<td>T1 = invasion into the submucosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 = invasion into the muscularis propia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 = no involvement of lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0 = no distant metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3-4 N0 M0</td>
<td>stage II</td>
<td>Dukes’ B</td>
</tr>
<tr>
<td>T3 = invasion into the serosa or perirectal fat.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 = invasion of adjacent organs and/or breaching of the visceral peritoneum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 = no involvement of lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0 = no distant metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-4 N1-2 M0</td>
<td>stage III</td>
<td>Dukes’ C</td>
</tr>
<tr>
<td>N1 = 1-3 perirectal lymph nodes involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2 = 4 perirectal lymph nodes involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0 = no distant metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-4 N0-2 M1</td>
<td>stage IV</td>
<td>Dukes’ D</td>
</tr>
<tr>
<td>M1 = distant metastases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The postoperative staging of the disease is an important factor providing an indication of the prognosis.

**Treatment**

The prognosis for rectal cancer has gradually improved during the last decades. The cancer specific 5-year survival is at present about 70% in Sweden. (9) The main treatment is surgical en bloc resection of the tumor together with its lymphatic and vascular supply. Advances in surgical technique together with the use of adjuvant oncologic treatment accounts for the improvement in survival. Modern treatment of rectal cancer is complex and involves not only colorectal surgeons but also physicians specialised in the field of oncology, radiology and pathology. Together these specialists form a multidisciplinary team (MDT) dealing with all aspects involved in rectal cancer treatment. (16) To improve treatment results, follow-up of patients is one important factor. In Sweden, a national quality control registry, The Swedish Rectal Cancer Registry (SRCR), has been in use since 1995. In the S CRC, population based data are prospectively recorded. (17) These data include preoperative assessments and treatments, operative data, complications and data comprising follow-up for five years after the operation for all patients with rectal cancer. The S CRC has been validated (18, 19) and has coverage of over 96% of all patients diagnosed with adenocarcinoma in the rectum, a figure reached by cross matching with the national cancer registry. Thus, the S CRC is a powerful instrument for evaluating rectal cancer treatment on a national level.

**Adjuvant treatment**

Numerous studies have been conducted using various forms of irradiation therapies, before or after surgery. (20, 21) Preoperative radiotherapy (RT), often administered as 5 Gray (Gy) for five consecutive days (5 x 5 Gy) followed by immediate surgery, has repeatedly demonstrated reduction in local recurrence as well as increased cancer specific survival. (22, 23, 24) A reduction in local recurrence rate has also been shown with postoperative RT (25), although accompanied by a higher morbidity compared with preoperative RT. (20) Short course preoperative RT (5 x 5 Gy) has become the standard radiotherapy regimen in Sweden for patients with potentially resectable tumors.

For locally advanced tumors, longer preoperative RT combined with preoperative chemotherapy is standard of care. (26, 27) Chemotherapy can
also be used in the postoperative setting, in case of lymphnode involvement. A combination of postoperative RT and chemotherapy can be used when the tumor is not radically resected.

Surgery
The history of surgery as treatment for rectal cancer is more than 200 years old. Descriptions of perineal operations for removal of rectal tumors date as far back as to the 18th century. (28) In 1885, Kraske described the first procedure with resection of a part of the rectum and anastomosis, made through a posterior incision. (29) Morbidity and mortality were high and the lack of insight with regard to the mechanism of tumor spread lead to poor oncological results. The pathological studies by Miles in the early 20th century changed the results substantially, and the sphincter saving resections were abandoned in favour of the abdomino-perineal resection (APR) proposed by Miles. (30) Around the same time, Hartmann introduced a two-step procedure for removing rectal tumors, comprising a permanent colostomy and leaving the anal canal and a rectal stump. (31) This procedure, somewhat modified, is still in use today. Based on further pathological studies in the 1930s, Dixon introduced the concept of anterior resection (AR), with a sutured anastomosis, in the 1940s. (32) The term “anterior resection” referred to surgery performed through an abdominal incision, in contrast to Kraske’s “posterior resection” undertaken through a posterior perineal incision. The number of sphincter saving resections slowly started to increase and later accelerated with the introduction of circular stapling devices in the 1970s. (33) Refinement of the stapler technique including double and triple stapling made it possible to fashion an anastomosis at all levels in the pelvis. (34) Another important contribution was the transanal sutured coloanal anastomosis described by Parks. (35)

The rationale for preserving the anus must rely on the knowledge of the pattern of tumor spread so that no residual tumor cells are left behind. An oncological safe resection was earlier believed to have a five cm distal margin to the tumor, but in the 1980s a distal margin of two cm was proposed and widely accepted. (36) Even this has been challenged and current data suggests that a distal margin of one cm (37) or less (38) is oncologically safe. As it was early noted that tumor spread distal to the tumor was rare, focus was set on cancer spread in the lateral direction. The pathologist Quirke investigated transverse sections of rectal specimens and found a high predictive value for subsequent local cancer recurrence when the circumferential margin was involved. (39) The paramount importance
of this finding was the oncological basis for the total mesorectal excision (TME) described by Heald in 1982. (40) The TME concept is based on a meticulous sharp dissection under direct vision with removal of an intact mesorectum and by remaining in the avascular plane between the visceral and parietal pelvic fascia, often called “the holy plane”. With this technique of en bloc resection of the rectum and its surrounding perirectal lymphatic tissue, contained within a thin fascial layer, Heald reported a 5-year local recurrence rate of less than 5% without any adjuvant treatment. (41) This was in great contrast to previously reported recurrence rates of about 40% with conventional surgery. (42, 43) The results by Heald were initially questioned but recurrence rates below 10% have later been reported from several centers having adopted the TME technique. (44, 45) Today, TME is the gold standard in rectal cancer surgery worldwide. In Sweden it was introduced nationally in the mid 1990s through several workshops and training programmes. (46) TME surgery can be applied in sphincter saving operations as well as in APR or Hartmann’s procedure. In tumors situated in the upper part of the rectum, 12cm or more from the anal verge, many surgeons prefer to divide the mesorectum at a distance of five cm distal to the lower edge of the tumor, although the operation is performed with TME technique in all other aspects. This is often called partial mesorectal excision (PME) and the operation is sometimes referred to as high AR, in contrast to the low anterior resection (LAR) in which the dissection continues down to the pelvic floor.

Rectal cancer surgery continues to evolve and the greatest changes during the last two decades have been the introduction of laparoscopic resections (47) and the transanal endoscopic microsurgery (TEM), the latter currently often used for adenomas but in some instances in T1 or T2 tumors, especially in medically frail patients. (48)

The most important reason for failure to cure and subsequent death in patients with rectal cancer, is the development of metastases. One third of the patients operated on for rectal cancer will develop metastatic disease, and the most common sites are the liver and the lungs. A minority of the patients are potentially curable, as metastatic disease is usually widespread and not amenable to surgical treatment. Palliative chemotherapy provides a limited prolongation of survival. (49, 50)
Anastomotic leakage
There are different types of anastomoses used in sphincter saving resections of the rectum. Initially, end to end anastomosis was generally performed. Later on, the end to side, J-pouch and the transverse coloplasty pouch were introduced. (51, 52, 53) Regardless of which type of anastomosis used, anastomotic leakage is still one of the most important and serious complication after rectal resections, leading to significant postoperative morbidity and mortality. (42, 54)
The incidence of reported symptomatic anastomotic leakages has a wide range, from 2.6% to 26.2%. (44, 55, 56, 57, 58) One reason for these differences in rates of leakage is probably the fact that no uniform definition of anastomotic leakage exists. Some authors include only leakage from the circular staple line, while others also include leakage from the straight stapler line, as well as rectovaginal fistulas. The definition of symptomatic anastomotic leakage used in this thesis is found in the methods section.

Possible risk factors for developing anastomotic leakage have been assessed in several studies, in which low anastomosis has turned out to be the strongest risk factor. (59, 60) A multitude of other variables have shown to be independent risk factors in studies comprising multivariate analysis, like male gender, increased age, intraoperative adverse events, preoperative radiotherapy, smoking, non-specialized surgeons and diabetes mellitus. (61, 62, 63, 64, 65, 66, 67)

The mechanisms behind anastomotic leakage are not fully understood but factors which may be of importance are insufficient vascularisation, tension in the anastomosis and infection in a presacral haematoma.

Symptomatic anastomotic leakage may present with dramatic features of pelvic sepsis, early in the postoperative course, however symptoms may occur at a later stage, be mild and resemble other conditions. These late anastomotic leakages are previously described in only a few studies. Paper I deals with late anastomotic leakage.

**Defunctioning stoma**

The history of stomas spans many centuries, however the earliest stomas were not created by surgeons but by the force of nature as a result of strangulated hernia or penetrating abdominal trauma. There are descriptions of the French surgeon Pillore performing a cecostomy for the treatment of an obstructing rectal cancer already in 1776. The technique of colostomies evolved but it took long time before the use of ileostomies became widespread. The early ileostomies were technically crude and this fact in combination with the lack of optimal stoma devices led to significant skin complications. A breakthrough came in 1952 when Brook described the “Brook ileostomy” in which the ileal end was evaginated and the mucosa sutured to the skin. (68) This dramatically decreased the chronic inflammation and ulceration associated with ileostomies. Development of training in enterostomal therapy together with better stoma equipment
made the use of ileostomies widespread. In 1971 Turnbull and Weakly were the first to describe the loop ileostomy, using it in combination with two colostomies to decompress patients with toxic megacolon. (69) Currently, loop ileostomies are often used to deviate a colorectal anastomosis.

Defunctioning of the anastomosis in LAR has been subject to debate during the last several decades. There have been conflicting data with regard to whether a defunctioning stoma reduces the rate of anastomotic leakage or decreases the clinical consequence when a leakage occurs. The randomized controlled multicentre trial RECTODES (Rectal Cancer Trial On Defunctioning Stoma) contributed in providing answer to this much debated question. This trial demonstrated that patients randomized to a defunctioning stoma in LAR had a significantly lower rate of symptomatic anastomotic leakage compared to those who were randomized to no defunctioning stoma, 10.3% versus 28.0% (P<0.001). (70) A meta-analysis of four randomised clinical trials (RCT) and 21 non-randomized trials with regard to the efficacy of a defunctioning stoma in low anterior resection for rectal carcinoma was published in 2009. The authors concluded that a covering stoma seems to be useful to prevent anastomotic leakage and also to decrease the rate of urgent re-operations. (71) The same conclusions were also drawn in a Cochrane review from 2010 in which six RCT were included. (72) Today it seems safe to say that a defunctioning stoma is recommended in LAR. Defunctioning with a loop ileostomy is often the choice because it is easy and safe to construct as well as to close. These defunctioning stomas are usually reversed after two to three months. (73) However, some patients remain with a stoma longer, for example due to adjuvant chemotherapy. A loop ileostomy may in some sense represent a continuous morbidity for the patient, with stoma related complications and subsequently, a negative effect on quality of life. (74)

Figure 3. Loop ileostomy with skin erosion due to leakage of ostomy effluent.  
Figure 4. Loop ileostomy with peristomal hernia.
The possibility of early reversal of defunctioning stomas, previously addressed in only a few studies, has recently been assessed with encouraging results. (75) Paper IV deals with early reversal of defunctioning stomas in LAR for cancer.

Even though the aim in LAR is to restore bowel continuity, some patients will ultimately end up with a permanent stoma. The risk of a permanent stoma after LAR is assessed in Paper III.

**Anorectal function**

The aim in modern rectal cancer surgery is not only removal of all tumor tissue, but also, whenever possible, restoring bowel continuity. The primary reason for aiming at an AR with an anastomosis, and thus avoiding the permanent stoma which is the result in APR and Hartmann’s procedure, is to improve the quality of life of the patient. A permanent stoma is associated with significant morbidity and sometimes decreased quality of life. (76) However, many patients end up with an impaired anorectal function after LAR, with various degrees of incontinence, evacuation difficulties and increased stool frequency. (77, 78, 79) Factors that may influence anorectal function after LAR are RT, low anastomosis and symptomatic anastomotic leakage (80, 81, 82), however all factors are not known. In paper II, the possibility of a defunctioning stoma affecting postoperative anorectal function, is assessed.
Aims of the thesis

The general aim of this thesis was to improve the understanding of anastomotic leakage, defunctioning stoma and anorectal function in patients with rectal cancer who have undergone a low anterior resection.

To assess patient characteristics and the postoperative course of patients who had a late symptomatic anastomotic leakage.
(Paper I)

To investigate if a temporary defunctioning stoma had an effect on the long term postoperative anorectal function.
(Paper II)

To assess the risk and the reasons for a permanent stoma after low anterior resection of the rectum.
(Paper III)

To investigate the possibility of early reversal of a defunctioning stoma.
(Paper IV)
Patients and methods

Patients

All patients included in the four studies of this thesis underwent low anterior resection of the rectum due to rectal cancer. The set of patients in Paper I, II and III are identical, representing a prospectively collected study population, randomised to a defunctioning stoma or no stoma. Data from this set of patients have been previously published with regard to defunctioning stoma and symptomatic anastomotic leakage (the RECTODES trial, 70). Paper I, II and III analyses secondary endpoints of this study. These patients were included from December 1999 through June 2005, from 21 of the 65 hospitals in Sweden performing rectal cancer surgery (65 in 1999; 55 in 2005). To assess possible selection bias, the randomized patients were compared with those not randomized (all patients not randomized but operated on with anterior resection of the rectum for cancer during the period of participation of each participating hospital). Data on patients not randomized were obtained from the Swedish Rectal Cancer Registry.

The preoperative inclusion criteria were biopsy proven adenocarcinoma of the rectum located at $\leq 15$ cm above the anal verge measured with a rigid rectoscope, age $\geq 18$ years, informed consent, ability to understand the study information, and estimated survival of $>6$ months as judged by the surgeon. Intraoperative inclusion criteria were anastomosis at $\leq 7$ cm above the anal verge, negative air leakage test, intact anastomotic staple rings, and the absence of major intraoperative adverse events as judged by the operating surgeon. If no exclusion criteria were present, the patients were randomized intraoperatively after the construction and testing of the anastomosis, by opening a sealed envelope in the operating room. All patients had preoperative bowel preparation and prophylactic antibiotics according to the standard treatment of each hospital. Furthermore, preoperative irradiation, chemotherapy, and the use of pelvic drainage were at the choice of the surgeon.

All together 234 patients were randomized which represented 28.5% (234/821) of all the anterior resections performed by the participating hospitals. The most frequent reasons for not randomizing patients were the presence of intraoperative adverse events prompting a defunctioning stoma (28%), absence of patient consent (25%), anastomosis $>7$ cm above the anal verge (18%), and advanced TNM stage IV cancer and/or T4 cancer (10%). Table 2, 3.
Table 2. *Demography of the study population and the patients not randomised.*

<table>
<thead>
<tr>
<th></th>
<th>Not randomised § (n=587)</th>
<th>Randomised to stoma (n=116)</th>
<th>Randomised to no stoma (n=118)</th>
<th>p-value ¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>69 (28-90)</td>
<td>68 (32-86)</td>
<td>67.5 (43-84)</td>
<td>ns*</td>
</tr>
<tr>
<td>Female gender</td>
<td>44.3%</td>
<td>39.7% (46/116)</td>
<td>50.8% (60/118)</td>
<td>ns*</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>not stated</td>
<td>25.0 (19.3-35.9)</td>
<td>24.8 (21.1-36.6)</td>
<td>-</td>
</tr>
<tr>
<td>ASA score 1 or 2</td>
<td>not stated</td>
<td>83.2%</td>
<td>89.2%</td>
<td>-</td>
</tr>
<tr>
<td>Tumour level above the anal verge, cm median (range)</td>
<td>10 (3-15)</td>
<td>10 (4-15)</td>
<td>10 (3-15)</td>
<td>ns*</td>
</tr>
<tr>
<td>TNM-stage IV cancer</td>
<td>17.0%</td>
<td>4.3%</td>
<td>3.4%</td>
<td>p&lt;0.001**</td>
</tr>
<tr>
<td>Preoperative radiotherapy</td>
<td>54.9%</td>
<td>81.0%</td>
<td>77.1%</td>
<td>p&lt;0.001*</td>
</tr>
</tbody>
</table>

§  data from the SCCR available until December 31, 2004.
¶  Comparison between the non-randomised patients and the group of all randomised patients.  * Mann Whitney U test  ** χ² test
Table 3. Operative details in the randomised patients.

<table>
<thead>
<tr>
<th></th>
<th>Stoma* (n=116)</th>
<th>No stoma** (n=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time</td>
<td>220 (110-605)</td>
<td>200 (100-541)</td>
</tr>
<tr>
<td>Intraoperative bleeding</td>
<td>550 (50-4500)</td>
<td>550 (50-2500)</td>
</tr>
<tr>
<td>Anastomotic level, cm</td>
<td>5 (2-7)</td>
<td>5 (2-7)</td>
</tr>
<tr>
<td>median (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defunctioning stoma</td>
<td>99.1%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

* Including one case of violation of the study protocol analysed on intention to treat basis
** Including one case of violation of the study protocol analysed on intention to treat basis

Due to the number of patients and the comparison with the non randomised patients, we deem that this set of patients is a representative sample of patients with rectal cancer treated with a LAR, in regard to the scientific questions assessed in Paper I-III.

Patients in study IV were patients with rectal cancer planned to have a low anterior resection of the rectum with a defunctioning stoma at the University hospital of Örebro. They were included during a time period of two years, starting in January 2008. Twenty-one patients were entered into the study, but three were excluded due to unexpected intraoperative findings which led to conversion to a Hartmanns procedure. Thus eighteen patients met the inclusion criteria and could be analysed.

Methods

Definition of Anastomotic Leakage
The definition of anastomotic leakage used in these studies was clinical; peritonitis caused by leakage from any staple line, rectovaginal fistula, and
pelvic abscess without radiologically proven leakage mechanism. Leakage was verified by clinical (digital palpation, inspection of drain contents), endoscopic (rigid rectoscopy, flexible sigmoidoscopy), or radiologic (rectal contrast study, CT scan) investigations. Radiologically demonstrated leakage without clinical symptoms was not included.

Anorectal function questionnaire
In paper II, the postoperative anorectal function was assessed in patients who had undergone LAR, and a comparison was made between those who had been randomised to a defunctioning stoma or not. The evaluation of postoperative anorectal function was done 12 months after the initial rectal resection in the no stoma group, and 12 months after reversal of the defunctioning stoma in the stoma group. The comparison was made by a bowel function questionnaire sent to the patients by mail. The present questionnaire has previously been described (83), and comprises questions which assess various aspects of anorectal function such as stool frequency, urgency, evacuation difficulties, fragmentation of bowel movements, incontinence, lifestyle alterations, medication and whether the patients would prefer a permanent stoma rather than accepting their present anorectal function. Table 4.  
The ordinal scale used in questions 2 through 7 and 9 was translated into a numerical scale in which 1 point corresponded to the optimal AF, and 4 points to the worst AF, as judged by the patient. A faecal incontinence score was calculated by adding the points obtained in questions 4, 5 and 6 together, and thus forming a scale ranging from 3 points (best continence) to 12 points (worst continence). Non parametric statistical test were used for comparing the two groups.

Table 4. Questions evaluated in the patient questionnaire and answering alternatives.

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

   During the day? _ Number  At night? _ Number

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

   Never less than, 1-6 times every day
   once a week weekly

24
3. How often do you experience difficulty in emptying the bowels?

   Never  less than,  1-6 times  every day
         once a week    weekly

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

   Never  less than,  1-6 times  every day
         once a week    weekly

5. How often do you brake wind involuntarily?

   Never  less than,  1-6 times  every day
         once a week    weekly

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

   Never  less than,  1-6 times  every day
         once a week    weekly

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

   Never  less than,  1-6 times  every day
         once a week    weekly

8. How long can you withstand the urge to pass a motion
   if there is no toilette available?

   15 minutes  less then
   or longer    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

Postoperative monitoring protocol
In paper IV we assessed the possibility of early reversal of a defunctioning stoma. Patients were monitored after the initial LAR using a specially designated study protocol. Figure 7.

The intention was stoma reversal on postoperative day (POD) 14 if criteria according to the protocol were met. Body temperature, heart frequency, blood pressure, per oral intake, CRP and PCT were monitored daily during the initial 6 days of the postoperative period. A CT-scan with rectal contrast, as well as a clinical evaluation by two independent colorectal surgeons, were performed on POD 6. If the inclusion criteria were met, a decision was taken on POD 6 to perform stoma reversal on POD 14. The inclusion criteria on POD 6 were: body temperature <37.5 degrees Celsius, CRP <100 mg/L, a CT-scan of the pelvis and abdomen with no signs of anastomotic leakage or any other adverse findings, blood pressure, heart frequency, per oral intake deemed acceptable, as well as a normal clinical examination. The patients who met these criteria on POD 6 were dis-
charged from hospital and had another clinical examination by one colorectal surgeon on POD 13 upon their planned readmission. If the clinical assessment on POD 13 was deemed normal, early stoma reversal was scheduled for the following day, thus on POD 14.

**Statistical methods**
In the studies of this thesis, categorical variables were analyzed using the Chi-square test, and when samples were small, the Fischer’s exact test was employed. Continuous variables were analysed with the Mann–Whitney U-test or the two-sample t-test. In all statistical calculations a P-value of less than 5% was considered significant. In paper III a univariate analysis with categorized patient related variables was performed in which P-values less than 0.10 were considered for a multivariate stepwise logistic regression analysis. A Kaplan-Meier curve was used to present crude survival. All statistical calculations were carried out by the Statistix® version 9 (Analytical Software, Tallahassee, Florida, USA) and the SPSS® version 12 and 17 (SPSS, Chicago, Illinois, USA).

**Ethics**
The RECTDODES trial formed the basis for paper I-III and was approved by the ethics committee of the Linköping health care region as well as by the ethic committees of each of the participating health care regions. All participating patients gave informed consent. Paper IV was approved by the local ethics committee of the Uppsala/Orebro healthcare region, and all patients who accepted participation had to sign an informed consent.
Results and Discussion

Symptomatic anastomotic leakage diagnosed after hospital discharge following low anterior resection for rectal cancer.

(Paper I)
In this study we analysed patients who developed a late symptomatic anastomotic leakage, defined as a leakage diagnosed after hospital discharge, on urgent or unplanned hospital readmission. Out of the 234 patients, 45 (19,2\%) had a symptomatic anastomotic leakage of which eighteen were defined as late leakages (LL). This constituted 7,7\% (18/234) of the whole cohort and 40\% (18/45) of the leaks. The LL were diagnosed on median postoperative day 22 (11-172), mostly by CT-scan. Figure 8.

![Graph showing postoperative day of diagnosis of symptomatic anastomotic leakage](image)

Figure 8. Postoperative day of diagnosis of symptomatic anastomotic leakage

The overall anastomotic leak rate of 19,2\% might seem high compared to most other studies, however several factors could explain this result. One is the multitude of different definitions of anastomotic leakage. In a systematic review, Bruce et al found 29 different definitions of anastomotic leakage with regard to the lower gastrointestinal tract. (84) The lack of a universally accepted definition may explain to some extent the differences in
leakage found in various studies. We have used a rather broad definition including leakage from all stapler lines, recto-vaginal fistula and pelvic abscess without proven leakage mechanism. Moreover, we also did not include a time limit for diagnosing the leaks, in contrast to some studies which include only leakages occurring during the initial hospital stay or within the first 30 postoperative days. Other factors that could explain the increased leak rate are the level of the anastomosis at median 5 cm (2-7cm) from the anal verge, as well as a high percentage of patients having had preoperative radiotherapy (80%). Both low anastomosis and neoadjuvant radiotherapy are regarded as risk factors for anastomotic leakage.

Anastomotic leakage is usually associated with rather dramatic features of pelvic sepsis, especially in undeductioned patients, and the subsequent need for immediate treatment during the postoperative course. The fact that 40% of the symptomatic anastomotic leakages in our study were diagnosed after hospital discharge was therefore an unexpected finding. Not many other studies have addressed this issue, even though comparable high rates of late leakages have previously been described. Hyman and colleagues reported 42% (14/33) leakages diagnosed after hospital discharge from a prospective database over 10 years with 1223 patients undergoing intestinal resection and anastomosis. (85) We believe that the issue of late leakages merits more attention.

To investigate whether there may have been indications in the postoperative course predicting the leakages diagnosed after hospital discharge, a comparison was made between the LL group and the patients who did not have symptomatic leakage (no leakage NL). For this purpose some clinically relevant parameters were assessed on postoperative day five. We found no differences between these two groups regarding body temperature, stools passed/excretion in stoma or oral fluid intake. However, in the LL group, 28% (5/18) had ongoing antibiotic treatment on postoperative day five, compared to 4% (7/186) in the NL group, which was a statistically significant difference (P<0.001). Table 5. Reasons stated for antibiotic treatment were suspected urinary or respiratory tract infections as well as an increase in CRP only. Considering the relatively low numbers of patients in the LL group, conclusions must be drawn with caution, but the difference in antibiotic treatment may be indicative of the process leading to anastomotic leakages in the LL group, misinterpreted as infections. However, the most important finding is the similarity of straightforward postoperative course in both groups, also leading to the same initial length of hospital stay, ten days in median. The fact that patients with a seemingly
uncomplicated postoperative course still can develop a symptomatic anastomotic leakage is important for all colorectal surgeons to keep in mind, together with a high index of suspicion when patients are deemed to have “diffuse” postoperative infections. The consequence of this is also the need for detailed information to patients about the continuing risk for complications, following surgery and hospital discharge.

**Table 5. Postoperative recovery**

*Recovery on postoperative day 5 in 234 patients operated on with low anterior resection of the rectum for cancer with symptomatic anastomotic leakage diagnosed during the initial hospital stay (early leakage), leakage diagnosed after hospital discharge (late leakage), or without symptomatic leakage (no leakage).*

<table>
<thead>
<tr>
<th></th>
<th>Early Leakage (n=27)</th>
<th>Late leakage (n=18)</th>
<th>No leakage (n=189)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature, °C ≥37.5</td>
<td>33% (7/21)</td>
<td>12% (2/17)</td>
<td>9% (16/186)</td>
<td>P=0.003&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stools passed or excretion of &gt;100 ml in stoma/24 h</td>
<td>40% (8/20)</td>
<td>83% (15/18)</td>
<td>80% (149/186)</td>
<td>P&lt;0.001&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Per oral fluid intake &gt; 1000 ml/24 h</td>
<td>52% (10/21)</td>
<td>78% (14/18)</td>
<td>78% (146/187)</td>
<td>P=0.009&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ongoing antibiotic treatment</td>
<td>33% (7/21)</td>
<td>28% (5/18)</td>
<td>4% (7/186)</td>
<td>P&lt;0.001&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hospital stay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial hospital stay, days, median (range)</td>
<td>28 (8-81)</td>
<td>10 (7-31)</td>
<td>10 (5-60)</td>
<td>P&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hospital stay including readmission for any reason days, median (range)</td>
<td>30 (8-85)</td>
<td>21.5 (8-90)</td>
<td>13 (5-66)</td>
<td>P&lt;0.001&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>§</sup> excluding patients with leakage diagnosed on postoperative day 3 (n=1) and day 4 (n=5).
<sup>§</sup> Chi square test  <sup>*</sup> Kruskal-Wallis test
Recovery on postoperative day five in the early leakage (EL) group compared with the LL group, as well as with those without leakage, demonstrates a clear difference with worse outcome on day five for the EL. Table 5. However, the different clinical features of the symptomatic anastomotic leakages diagnosed in the LL group and EL group raises the question of whether they are two different entities, caused by different mechanisms. One factor that might explain some of the difference between the two groups is the exact site of leakage. The type of anastomoses used were either a J-Pouch, side-to-end or end-to-end, all performed with the double or triple stapling techniques. There were no differences in the distribution of the type of anastomosis between the three groups. The EL-group had an increased proportion of leakages in the circular stapler line as compared with the LL-group, in which leakages in the transverse stapler line were more common. Although speculative, it may make sense that a leakage from a circular stapler line, possibly more exposed to fecal pressure, produces a more “dramatic” leakage, earlier in the postoperative course, as compared with a leakage from a transverse stapler line. Nevertheless, the entity late leakage continues to puzzle the author.

Does a defunctioning stoma affect anorectal function after low rectal resection? Results of a randomized multicenter trial.

(Paper II)
Anorectal dysfunction following LAR is well documented. Many factors may influence the postoperative anorectal function and all are probably not known. In this randomized controlled multicentre trial, we assessed whether a temporary defunctioning stoma affected anorectal function in the long run. The 234 patients undergoing LAR for cancer were randomized to a defunctioning stoma or not. At follow up, 33 patients were excluded due to having a permanent stoma, leaving 201 patients eligible for evaluation with the bowel function questionnaire earlier described. 181 patients (90%) answered the questionnaire, 90 from the the no-stoma group and 91 from the stoma group. Besides temporary stool deviation, there were no differences between the two groups with regard to parameters which could possibly affect anorectal function such as age, gender, level of anastomosis, radiotherapy or type of anastomosis. Time to evaluation was median 12 months in both groups thus 12 months after LAR in the no-stoma group and 12 months after stoma reversal in the stoma group. Median time with a defunctioning stoma was 6 months.
The results from the bowel function questionnaire demonstrated no overall
difference between the two groups. Table 6. A statistically significant dif-
ference was however found in question 4, regarding fragmentation of bow-
el movements, even though median rank was equal. We deem that this
single variable does not alter the overall impression of the results.

Table 6. Results from the bowel function questionnaire, primary analysis.

<table>
<thead>
<tr>
<th></th>
<th>Stoma group</th>
<th>No stoma group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=90</td>
<td>n=91</td>
<td></td>
</tr>
<tr>
<td>Stool frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>daytime, median (range)</td>
<td>3 (1-15)</td>
<td>3 (1-11)</td>
<td>P=0.33</td>
</tr>
<tr>
<td>night time median (range)</td>
<td>0 (0-5)</td>
<td>0 (0-6)</td>
<td>P=0.24</td>
</tr>
<tr>
<td>Need for medication to open the bowel, ranked 1-4, median (range)</td>
<td>1 (1-4)</td>
<td>1 (1-4)</td>
<td>P=0.24</td>
</tr>
<tr>
<td>Difficulty in emptying the bowels, ranked 1-4, median (range)</td>
<td>1 (1-4)</td>
<td>1 (1-4)</td>
<td>P=0.68</td>
</tr>
<tr>
<td>Need to return to the toilet within one hour, ranked 1-4, median (range)</td>
<td>3 (1-4)</td>
<td>3 (1-4)</td>
<td>P=0.035</td>
</tr>
<tr>
<td>Incontinence, ranked 3-12 median (range)</td>
<td>6 (3-12)</td>
<td>6 (3-12)</td>
<td>P=0.42</td>
</tr>
<tr>
<td>Withstand the urge to pass a motion less then 15 minutes</td>
<td>35 %</td>
<td>25 %</td>
<td>P=0.15</td>
</tr>
<tr>
<td>AF affect on general well being, ranked 1-4 (range)</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
<td>P=0.073</td>
</tr>
<tr>
<td>Prefer permanent stoma</td>
<td>3.5 %</td>
<td>2.4 %</td>
<td>P=0.67</td>
</tr>
</tbody>
</table>

This primary analysis was made according to intention-to-treat, resulting
in the finding that some patients in the no stoma group actually had a stoma
during a period, due to an urgent reoperation because of anastomotic leakage. To avoid any bias in regard to this finding, a secondary analysis
was undertaken, excluding all patients having had anastomotic leakage and subsequent reoperation with formation of a defunctioning stoma. The results from this secondary analysis were similar to the primary analysis. Based on these data we conclude that a temporary defunctioning stoma has no lasting effect on anorectal function following LAR.

The scientific question in this study, whether temporary fecal diversion has a lasting effect on anorectal function after LAR or not, may not be intuitively obvious. One major reason for impaired anorectal function after LAR is the pelvic dissection with possible injury to sphincter muscle or its innervation. Another possible reason for impaired anorectal function may be neoadjuvant radiotherapy. But is there any obvious reason why a temporary stoma could induce a lasting negative effect? It is known that changes can occur in the bowel when it is excluded. Most surgeons are aware of the fact that proctitis can develop after faecal exclusion of the rectum. (86, 87) The diversion proctitis, and colitis, which histologically resemble ulcerative colitis, is postulated to be due to lack of luminal short chain fatty acid (SCFA). The rational for this hypothesis is that luminal instillation of SCFAs reverses these abnormalities (88). Sailer et al even found morphologic changes in the anal sphincter after temporary stool deviation, although reversible (89). Thus, changes may occur due to fecal diversion and our question was whether the defunctioning of the bowel has the potential to induce alterations with regard to neorectal capacity, compliance, bowel motility or neuromuscular healing, and hence the outcome of postoperative anorectal function. We could however not find any lasting negative effect in regard to anorectal function due to temporary fecal diversion in the present study. To our knowledge, no other study has addressed the exact same question, and therefore comparison with previous publications is not possible.

A striking finding, when analysing the results, was the wide range in the answers. Assessing the stool frequency, with median three stools during the day and none during the night, this appears ordinary. However, some of these patients had more than ten bowel movements per day and some even more than ten per night, a disastrous result for the individual patient. The same type of distribution was found regarding “need for medication to open the bowel” as well as “evacuation problems”, illustrated in questions number two and three, in which median rank was moderate, however with a wide range. The median incontinence rank score was six, which roughly could be translated in to one episode of incontinence less than once a week. This might not seem much but any fecal incontinence may be devastating
to the individual patient, although depending on the social situation. In regard to these variables there was also a wide range of events, including patients reporting to have incontinence problems every day.

Incontinence is often the anorectal dysfunction after LAR that is most frequently discussed, but others may be equally important. One important finding in this study was the high degree of urgency, described in question eight. The results show that about one third of the patients in the whole cohort could not withstand the urge to pass a motion for 15 minutes. It is easy to understand how socially disabling this may be. Ho et al found similar results assessing 87 patients undergoing LAR. They concluded that urgency and clustering of bowel movements were the most common postoperative bowel symptoms. (90)

Despite the fact that many patients in the present study had obvious anorectal dysfunction, only very few would have preferred a permanent stoma. This indicates a very negative attitude towards stoma and one may speculate in whether these patients would in fact benefit from a permanent stoma in regard to their quality of life.

The bowel function questionnaire used in this study has strengths as well as weaknesses. Many papers dealing with postoperative anorectal dysfunction focus on the issue of incontinence, for which the Wexner Continence Grading Scale is the most frequently used. (91) Table 7. The sum is determined by the total score of 5 parameters on a scale from 0 (=absent) to 4 (daily). The parameters employed are: frequency of incontinence to gas, liquid stool, solid stool, need to wear pad, an lifestyle changes due to anorectal function. A score of 0 means perfect control, while a score of 20 represents complete incontinence. However, the coping mechanisms of the patient are not taken into consideration. Thus, in fact this will mean that a hypothetically completely incontinent patient who spends a considerable amount of time on the toilet, would not report incontinence to gas, liquid or formed stool, moreover would not need a pad, and therefore would only have a “daily impact on his quality of life”, which means a score of 4 as compared with the more appropriate score of 20. As earlier pointed out, our questionnaire takes several additional parameters into account, thus giving a better total view of anorectal function. The weakness however, is that the present bowel function questionnaire has not been validated, nor is it widely used, a fact which makes it more difficult to compare the present results with other studies with regard to postoperative anorectal function.
Table 7. The Wexner score.

<table>
<thead>
<tr>
<th>Type of incontinence</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never</td>
</tr>
<tr>
<td>Solid</td>
<td>0</td>
</tr>
<tr>
<td>Liquid</td>
<td>0</td>
</tr>
<tr>
<td>Gas</td>
<td>0</td>
</tr>
<tr>
<td>Wears pad</td>
<td>0</td>
</tr>
<tr>
<td>Lifestyle alteration</td>
<td>0</td>
</tr>
</tbody>
</table>

Never, 0; rarely, <1/month; sometimes, <1/week, ≥1/month; usually, <1/day, ≥1/week; always, ≥1/day.
0 perfect; 20, complete incontinence.

The follow up time of 12 months in the present study may by some be considered as relatively short. In order to assess whether there may be a time dependent factor, both in regard to the willingness to accept a permanent stoma, and in regard to possible differences in the AF between the two groups, it would be of interest to undertake an analysis with a longer follow up time.

What is the risk for a permanent stoma after low anterior resection of the rectum for cancer? A six-year follow-up of a multicenter trial.

(Paper III)
The aim in rectal cancer surgery is removal of all tumor tissue, with as little damage as possible to adjacent structures, in combination with restoration of bowel continuity. Low anterior resection with a coloanal anastomosis is the treatment of choice to avoid a permanent stoma. However, some patients undergoing LAR will, for various reasons, ultimately end up with a permanents stoma. In this study we analysed the long term risk and risk factors for a permanent stoma after LAR. Of the 234 patients who underwent LAR, 19% (45/234) ended up with a permanent stoma after a median follow up of 72 months (42-108). Figure 9. 25 patients had a permanent end sigmoid stoma (ESS), constructed at a median of 22 months (range 1-71) following the LAR. The main reason for constructing the ESS was anorectal function considered unacceptable (n=18). In 20 patients who had a defunctioning loop ileostomy (LIS), this stoma was considered per-
manent at a median of 12.5 months (range, 1–47) after the LAR. The main reasons for the LIS to be considered permanent were metastatic disease (n=6) and bad anorectal function (n=6).

FIGURE 9. Outcome in patients undergoing LAR of the rectum for cancer and randomly assigned to defunctioning stoma or no defunctioning stoma to obtain a permanent stoma or not at a median follow-up time of 72 months after the LAR.*Including 4 patients who had a loop transverse colostomy. LIS=loop ileostomy; ESS= end sigmoid stoma.
A multivariate analysis demonstrated that symptomatic anastomotic leakage (P<0.001) and age>75 years (P=0.005) were independent risk factors for a permanent stoma. In those patients with symptomatic anastomotic leakage 56% (25/45) ended up with a permanent stoma after a median follow-up of 6 years. This was in contrast to patients without symptomatic anastomotic leakage, in whom the risk for a permanent stoma was 11% (20/188) (56% vs 11%; P 0.001; OR 10.5; 95% CI 5.0–22.2). In those patients primarily diverted, 16% ended up with a permanent stoma, in contrast to 22% in those primarily nondiverted (not significant; 22% vs 16%; P= 0.26).

Gender and pRT did not influence the rate of permanent stomas. Slightly less than half of the patients, 45%, were women. The risk for having a permanent stoma was 18% in women and 20% in men (not significant). In the whole cohort 79.8% had pRT. In those with a permanent stoma 84% had pRT, and in those without 79% (not significant).

One important finding in this trial was that one out of five patients who underwent a LAR with anastomosis for rectal cancer ultimately ended up with a permanent stoma at a follow-up of 6 years. Comparison with previous studies are limited because nearly all deal primarily with the frequency of defunctioning stomas which were never reversed, rather than the overall rate of permanent stomas, as reported in the present study. There are however three recent studies comprising comparable data. (92, 93, 94)

Table 8. Junginger et al analysed consecutive patients undergoing LAR between 1985 and 2007 in one University hospital in Germany. They ended up with quite similar findings as compared with our study, with an 18% rate of permanent stomas after a median follow up of about six years. They also found that the rate of permanent stomas did not change over time. Hassan et al focused on the impact of radiotherapy in regard to permanent stoma rate, analysing 192 patients undergoing rectal resection and coloanal anastomosis between 1982 and 2001 at two surgical departments in the USA. Their conclusion was that radiotherapy, whether administered pre or post operatively, significantly increased the need for a permanent stoma. This finding could not be confirmed in our study nor in the study by Junginger et al nor by Nelson et al. Recurrent disease and anastomosis related complications are however factors that repeatedly have been shown to increase the risk for permanent stoma.
Table 8. Publications regarding the overall rate of permanent stomas after low anterior resection of the rectum due to cancer.

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication year</th>
<th>Nr of patients</th>
<th>Median follow-up (months)</th>
<th>Rate of permanent stomas</th>
<th>Factors associated with permanent stomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindgren et al</td>
<td>2011</td>
<td>234</td>
<td>72</td>
<td>19%</td>
<td>*Anastomotic leakage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*Age&gt;75 years</td>
</tr>
<tr>
<td>Junginger et al</td>
<td>2010</td>
<td>397</td>
<td>73,5</td>
<td>18%</td>
<td>*Anastomosis related complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*Local recurrence.</td>
</tr>
<tr>
<td>Nelson et al</td>
<td>2009</td>
<td>201</td>
<td>51</td>
<td>14%</td>
<td>*Local recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*Postoperative complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*Poor anorectal function</td>
</tr>
<tr>
<td>Hassan et al</td>
<td>2008</td>
<td>192</td>
<td>62</td>
<td>24%</td>
<td>*Anorectal dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*Recurrent disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*Radiotherapy</td>
</tr>
</tbody>
</table>

There are two other important studies on this issue, focusing on the rate of defunctioning stomas not reversed. den Dulk et al (95) analysed a subgroup of 924 patients in the Dutch TME trial and found that 19% of defunctioning stomas had become permanent, after a median follow-up time of 7 years. David et al (96) analyzed data from a British national registry and found that one out of four patients operated on from 2001 to 2003 with LAR and a defunctioning stoma, had a persisting defunctioning stoma at a follow-up of 3 years. These patients ended up with a loop ileostomy as a permanent stoma, a type of stoma never intended to be permanent, and moreover, which is inferior with regard to stoma handling compared with a permanent end sigmoid stoma. It would probably benefit a majority of these patients if they were converted from a loop ileostomy to an end colostomy.
Comparing the results of these studies, our conclusion that nearly one patient out of five will ultimately end up with a permanent stoma after LAR seems to accurately reflect results in modern treatment of rectal cancer. The risk for a permanent stoma is important to bear in mind when planning sphincter saving surgery for rectal cancer, and underlines the fact that we must be thorough and sincere when we inform our patients, an opinion shared by Gemellus. (97)

Feasibility of early closure of defunctioning stoma and postoperative monitoring in low anterior resection of the rectum for cancer.

(Paper IV)
Anastomotic leakage is one of the most feared complications after low anterior resection of the rectum. A defunctioning stoma has been shown to decrease the risk of anastomotic leakage and consequently defunctioning of low anastomosis has increased in Sweden. (9) Reversal of defunctioning stomas are usually planned to be performed 2 to 3 months after the initial cancer surgery but many patients will be left with their stoma longer. This may for example be due to adjuvant chemotherapy. However, in our institution we have seen medical as well as non-medical factors which influence the length of the time interval to stoma reversal. Due to insufficient operative capacity, stoma reversals have often been given low priority, subsequently leading to a longer period with a temporary stoma for the patient. The presence of the defunctioning stoma is associated with stoma related complications which may affect the quality of life in these patients. The goal has therefore been reversal relatively soon, however taking into account that the anastomosis should be healed and the patient fit for additional surgery.

Encouraging results have been shown in a few studies with stoma reversal as soon as 1-2 weeks after the initial cancer surgery. (75, 98, 99) We have studied the possibility of early stoma reversal in a feasibility study, aiming at stoma reversal on postoperative day 14. Twenty-three patients with rectal cancer were planned for LAR with a defunctioning stoma during a two year period at our institution. Two patients were not asked, while the remaining 21 were asked to participate and all of them accepted. These underwent rectal resection but in three cases the planned LAR was intraoperatively converted to a Hartmanns procedure, resulting in 18 assessable patients. Median age was 65 years, 7/18 were women, and 14/18 had preoperative radiotherapy. Nine patients were excluded because they did
not meet the inclusion criteria of the study protocol earlier described. Two patients met the inclusion criteria but did not have their stoma reversed early. This was due to an intraoperatively diagnosed subcutaneous abscess in the midline incision in one case, and due to a strike among nurses in one case. In all, seven patients had an early stoma reversal on POD 14.

Four out of seven patients had an uneventful postoperative course, while three needed a reoperation due to the following complications; leakage in the colorectal anastomosis (n=1), recto-vaginal fistula (n=1) and leakage in the ileo-ileal anastomosis (n=1). The included patients in the early stoma reversal group were compared to those who were operated with LAR and a defunctioning stoma during the two years which preceded the present study, thus from January 2006 to December 2007, and who had their defunctioning stoma closed after the conventional period of minimum three months. The need to reoperate and operation time were increased in the early stoma reversal group, compared with those who had reversal at conventional time. Table 9. The degree of surgical complexity of the early reversal group was judged as to be increased by the operating surgeon, as compared with the expected average complexity. CRP and PCT were monitored on POD 1 to 6. On POD 6, the nine patients who met the inclusion criteria had a median CRP of 24 mg/L and PCT of 0.17 ng/L. Median CRP peaked on POD 2 and median PCT on POD 1 in this group. The patients who did not meet the inclusion criteria had a median CRP of 70 mg/L and PCT of 0.30 ng/L on POD 6. CRP and PCT showed comparable distribution over time.
Table 9. Comparison between early and late stoma reversal groups concerning the reversal operation.

<table>
<thead>
<tr>
<th></th>
<th>Early reversal (n=7)</th>
<th>Late reversal (n=33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to stoma reversal days (range)</td>
<td>14 (14-15)</td>
<td>223 (69-532)</td>
<td></td>
</tr>
<tr>
<td>Operation time minutes (range)</td>
<td>95 (75-115)</td>
<td>76 (39-152)</td>
<td>0.015</td>
</tr>
<tr>
<td>Intraop. bleeding ml (range)</td>
<td>125 (0-250)</td>
<td>50 (50-150)</td>
<td>0.086</td>
</tr>
<tr>
<td>Colorectal surgeon as first operator or first assistant</td>
<td>100 % (7/7)</td>
<td>64% (21/33)</td>
<td>0.06</td>
</tr>
<tr>
<td>Reoperation within 90 days</td>
<td>43% (3/7)</td>
<td>6% (2/33)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

In this feasibility study, half of the patients met the inclusion criteria according to our protocol and 7/18 actually had an early stoma reversal, on POD 14. Three out of seven of these patients had postoperative complications requiring reoperation. The results of the present pilot study compare unfavourable with previously published results. (75) The major limitation of this study was the limited number of patients, and conclusions must therefore be drawn with caution. Considering the size of our catchment area of 280 000 inhabitants, we had expected about 40% more patients included during the study period of two years. We also had postulated a higher proportion of early reversals among those included.

One question which arises is whether these results demonstrate that early reversal of a defunctioning stoma may be generally disadvantageous and therefore should not be recommended, or, that our study contained flaws, for example in inclusion criteria. The protocol stated that a patient had to
have a CT-scan deemed normal, normal body temperature, and a CRP<100mg/L. Furthermore, two colorectal surgeons had to evaluate the data collected in the study protocol on POD 6, and hereafter decide whether the patient could be accepted for early reversal. A physical examination deemed satisfactory on POD 13 was also required. Compared to the only large randomized trial by Alves et al, (75) which excluded patients with “infection or organ failure in the postoperative period” and those with radiological signs of anastomotic leakage on POD 7, we find that our inclusion criteria were more strict. This is also supported by the fact that in the trial of Alves et al, the proportion of patients deemed eligible for early stoma reversal was about 70%.

In analysing our excluded patients, we found that 3/9 did not develop symptomatic postoperative morbidity at all, with the exception of a transient increase in temperature on POD 13 (n=1). The remaining two patients were excluded due to CRP>100 (n=1), and findings on CT scan on POD 6 (n=1), in which the CT scan gave rise to some suspicion of a twisted anastomosis. Table 10. These patients may nevertheless have been suited for early reversal and would probably not have been excluded in the French trial.

**Table 10. Outcome in the excluded patients. Patients grouped by main reason for exclusion.**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>CRP&gt;100 POD 6</th>
<th>Symptomatic AL</th>
<th>Radiologic AL</th>
<th>Fever POD 13</th>
<th>Abnormal CT-scan, not AL</th>
<th>In total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluded</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>90 day mortality</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Re. op permanent stoma</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Reversal of defunctioning stoma</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Median time to reversal (days)</td>
<td>245</td>
<td>200</td>
<td>137</td>
<td>90</td>
<td>180</td>
<td></td>
</tr>
</tbody>
</table>

AL=Anastomotic leakage
In summary, there was nothing indicating that the design of the study protocol was the reason for the unfavourable outcome in some of the patients undergoing early stoma reversal. Based on the empirical experience from our pilot study, alterations of the principles of the present study protocol may be discussed, such as performing the CT-scan on POD 13 instead of on POD 6, and daily CRP monitoring until POD 13. Other potential improvements which may be considered could be monitoring of other biochemical markers, of which one is the group of intraperitoneal cytokines, which have previously showed encouraging results in predicting symptomatic anastomotic leakage. (100, 101, 102) We did however use Procalcitonin (PCT) as a complimentary biochemical marker in addition to CRP. While CRP was analyzed and assessed continuously, PCT was analysed at a later stage and thus blinded to the investigators during the study. As it turned out, these two markers showed similar distribution over time and PCT did not seem to provide any additional information compared with CRP. Figure 10-13.

**Figure 10. Boxplot comparing postoperative CRP among excluded and included patients.**
Figure 11. Boxplot comparing postoperative PCT among excluded and included patients.

Figure 12. Diagram presenting postoperative CRP and PCT in one patient from the excluded group.
We chose a two week delay between the LAR and the stoma reversal. This may be considered a disadvantageous time point for a second operation due to the opinion held by many surgeons that dense adhesions may be frequent at this stage in the postoperative course. The question whether this may have affected the present results is however justified. Some of the findings may indicate that this may be the case considering that the reversal operations in the pilot study had longer operation time than the comparison group, and had a tendency for increased intra operative bleeding, and that surgical complexity was rated as increased, as compared with the stoma reversals performed after a minimum of three months. One of the patients who required a reoperation in the early stoma reversal group had a leakage in the ileo-ileal anastomosis. This complication is uncommon after reversal of a defunctioning stoma, (73) and may have been the result of a technically more complex operation. Our rationale for choosing a two week interval was a compromise between on one hand stoma reversal as soon as possible, and on the other hand a period of time long enough to

Figure 13. Diagram presenting postoperative CRP and PCT in one patient from the included group.
reasonably be able to rule out the possibility of anastomotic leakage. Moreover, this time period should provide enough time for the patients to be fit for a second operation. The two week delay was also an advantage with regard to the logistics at our institution in which elective colorectal surgery was performed only on tuesdays and thursdays. Evaluating pros and cons for reversal after two weeks instead of after seven to ten days, it is however not obvious that a shorter time interval would have changed the results of the present study.

In conclusion, we find that early stoma reversal is feasible but patient selection is complex and the possibility of an increased risk for postoperative complications should be considered. The outcome including those needing reoperation in the early stoma reversal group, cannot be contributed to any obvious flaws in the study design, but may however, because of the limited number of patients in this pilot study, be due to coincidence. However, the discussion in paper I in regard to the relatively high proportion of late anastomotic leakages must not be forgotten, and moreover, may be another explanation for the outcome in our study. Would that be the case, there may in fact be a reason to question the idea of early stoma reversal.
Conclusion

The general aim of this thesis was to improve the understanding of anastomotic leakage, defunctioning stoma and anorectal function in patients who have undergone low anterior resection for rectal cancer.

Symptomatic anastomotic leakage diagnosed after hospital discharge following LAR for cancer is not uncommon and has an immediate clinical postoperative course which may appear uneventful.
(Paper I)

A temporary defunctioning stoma after LAR did not affect anorectal function compared with patients operated on without a stoma and evaluated after one year. Many patients experienced impaired anorectal function as well as lifestyle alterations, but only a few would have preferred a permanent stoma.
(Paper II)

One patient out of five ended up with a permanent stoma after LAR of the rectum for cancer, and half of the patients with a permanent stoma had previous symptomatic anastomotic leakage.
(Paper III)

Early stoma reversal after LAR may be feasible but patient selection appears complex and the risk for complications must be considered.
(Paper IV)
**Summary in Swedish**

Sammanfattning på svenska


De första tre studier utvärderade en kohort av 234 patienter opererade med låg främre resektion av rektum som är prospektivt utvärderade och randomiserades till en avlastande stomi eller inte.

I den första studien utvärderade vi patienter med anastomosläckage som diagnostiseras efter utskrivning från sjukhus (sena läckage). Vi fann att 7,7 % (18/234) utvecklat ett sent läckage vilket var 40 % (18/45) av alla anastomosläckage i denna patient kohort. Deras initiala postoperativa period föreföll komplikationsfri, men de behandlades i högre grad med antibiotika den femte postoperativa dagen jämfört med de patienter som inte fick något anastomosläckage.


I en tredje studie analyserades samma uppsättning av patienter gällande risken för och orsakerna till en permanent stomi efter låg främre resektion. Sammanfattningsvis fick en patient av fem en permanent stomi efter och hälften av patienterna med en permanent stomi hade haft ett symtomatisk anastomosläckage.
I en pilotstudie analyserades möjligheten till tidig nedläggning av avlastande stomier hos 18 patienter som genomgått låg främre resektion med avlastande stomi. Slutsatsen från denna studie var att tidig stomi nedläggning kan vara möjligt men patienturvalet är komplext och risken för ökade komplikationer måste beaktas.
Acknowledgements

I would like to express my gratitude to all persons who have been involved in the work making this thesis possible. My very special thanks to:

Peter Matthiessen, my excellent main tutor, good friend and colleague, for everything.

Lars Norgren, former head of the Department of Surgery and co-tutor, for solid support of my research.

Jörgen Rutegård, former head of the Colorectal unit and co-tutor, for support and teaching me surgery.

Olle Ljungqvist, professor of Surgery, for solid support.

Elisabeth Aveborn, stomal therapy nurse, for help and advice in stoma handling.

Magnus Anderssson, head of the Colorectal unit, for teaching me good surgery.

Anders Magnusson, for excellent help in medical statistics.

Gustav Gustafsson and Mansour Poushin, Department of Surgery, Karlskoga Hospital, for an excellent introduction to the art of surgery.

Colleagues and friends at the Department of Surgery, Örebro University hospital.

Anna and my parents, for love, understanding and patience during my work with this thesis.
References


30 Miles WE. A method of performing abdominoperineal excision for carcinoma of the rectum and the terminal part of the pelvic colon. The Lancet 1908; 2: 1812-1813.

32 Dixon CF. Anterior resection for malignant lesions of the upper part of the rectum and lower part of the sigmoid. Ann Surg 1948; 128:425-442.


78  Rasmussen OO, Petersen IK, Christiansen J. Anorectal function following low anterior resection. Colorectal Dis 2003; 5: 258-61


83 Hallböök O, Sjödahl R. Surgical approaches to obtaining optimal bowel function. Seminars in Surgical Oncology 2000; 18: 249-58


Papers I–IV


35. Söderqvist, Fredrik (2009). Health symptoms and potential effects on the blood-brain and blood-cerebrospinal fluid barriers associated with use of wireless telephones.


41. Gustafsson, Sanna Aila (2010). The importance of being thin – Perceived expectations from self and others and the effect on self-evaluation in girls with disordered eating.

42. Johansson, Bengt (2010). Long-term outcome research on PDR brachytherapy with focus on breast, base of tongue and lip cancer.

43. Tina, Elisabet (2010). Biological markers in breast cancer and acute leukaemia with focus on drug resistance.


46. de Leon, Alex (2010). Effects of Anesthesia on Esophageal Sphincters in Obese Patients.


52. Loiske, Karin (2011). Echocardiographic measurements of the heart. With focus on the right ventricle.


