Rectal Cancer Surgery
Defunctioning stoma, anastomotic leakage and postoperative monitoring

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Straight is the line of duty, curved is the line of beauty, follow the straight line thou shalt see the curved line ever follows thee.

Karen Blixen, from “Seven Gothic Tales”

To my family
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ABSTRACT

The understanding of the mesorectal spread in rectal cancer has lead to wide acceptance of total mesorectal excision (TME) as the surgical technique of choice for carcinoma in the lower and mid rectum. While oncological results and survival have improved with TME-surgery, morbidity and mortality remain important issues. The most feared complication is symptomatic anastomotic leakage. The aim of this thesis was to focus on the role of the defunctioning stoma, risk factors, and postoperative monitoring in regard to anastomotic leakage in sphincter saving resection of the rectum.

Intraoperative adverse events were analysed in a retrospective population based case-control study in which all patients who underwent elective anterior resection in Sweden between 1987 and 1995, and who died within 30 days or during the initial hospital stay (n=140), were compared with patients chosen at random (n=423) who underwent the same operation during the same period, but survived the operation. Intraoperative adverse events were more frequent in those who died, and reconstruction of an anastomosis judged unsatisfactory by the surgeon improved the outcome.

In a population based retrospective case-control study, risk factors for symptomatic anastomotic leakage were investigated in a randomly chosen sample of patients who underwent anterior resection in Sweden between 1987 and 1995 (n=432). Twelve per cent of the patients developed symptomatic leakage, and 25% of the patients with leakage ended up with a permanent stoma. In multivariate regression analysis, low anastomosis, preoperative radiotherapy, male gender and intraoperative adverse events were independent riskfactors for anastomotic leakage.

In a randomised multicentre trial patients operated with sphincter saving TME-surgery for rectal cancer were randomised to a defunctioning stoma (n=116) or not (n=118). The overall rate of symptomatic leakage was 19%. Patients without a defunctioning stoma leaked in 28% and patients with a defunctioning stoma in 10%, a statistically significant difference (p<0.001) not previously demonstrated in any randomised trial of adequate size.

Postoperative monitoring with computed tomography scan (CT-scan) on postoperative day 2 and 7, and C-reactive protein (CRP) daily in 33 patients operated on with anterior resection of the rectum, demonstrated larger pelvic fluid collections in patients with leakage before the leakage was clinically diagnosed. CRP was increased from postoperative day 2 and onwards in patients in whom clinical leakage was diagnosed on median postoperative day 8.

In 23 patients who underwent anterior resection of the rectum, intraperitoneal metabolism was investigated using microdialysis technique measuring the carbohydrate metabolites lactate, pyruvate and glucose. Intraperitoneal cytokines IL-6, IL-10 and TNF-α were collected through a pelvic drain and analysed. In patients who developed leakage, the lactate/pyruvate ratio was increased near the anastomosis on postoperative day 5 and 6, as well as IL-6 and IL-10 which were increased postoperatively day 1 and 2, while TNF-α was higher on day 1.

Key words: Anterior resection of the rectum, total mesorectal excision, TME, anastomotic leakage, defunctioning stoma, risk factors, intraoperative adverse events, population based study, postoperative monitoring, CT-scan, microdialysis, cytokines.
LIST OF PAPERS

This thesis is based on the following papers which are referred to in the text by their Roman numerals (I-V).


IV  Assessment of pelvic fluid collection and C-reactive protein after anterior resection of the rectum for cancer. P Matthiessen, M Henriksson, O Hallböök, E Grunditz, B Norén, G Arbman. Submitted for publication.

V  Early detection of anastomotic leakage by intraperitoneal microdialysis and intraperitoneal cytokines after anterior resection of the rectum for cancer? P Matthiessen, I Strand, K Jansson, C Törnquist, M Andersson, J Rutegård, L Norgren. Submitted for publication.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>TME</td>
<td>Total Mesorectal Excision</td>
</tr>
<tr>
<td>PME</td>
<td>Partial Mesorectal Excision</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>ERUS</td>
<td>Endorectal Ultrasound</td>
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<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>TNM</td>
<td>Tumour, Node, Metastasis</td>
</tr>
<tr>
<td>CRM</td>
<td>Circumferential Resection Margin</td>
</tr>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>UICC</td>
<td>Union International Contre le Cancer</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray (radiation unit)</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>SRCR</td>
<td>Swedish Rectal Cancer Registry</td>
</tr>
<tr>
<td>IOAE</td>
<td>Intra-Operative Adverse Events</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>WBC</td>
<td>White Bloodcell count</td>
</tr>
<tr>
<td>IPM</td>
<td>Intraperitoneal Microdialysis</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleucine 6</td>
</tr>
<tr>
<td>IL-10</td>
<td>Interleucine 10</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumour Necrosis Factor alpha</td>
</tr>
<tr>
<td>L/P</td>
<td>Lactate/Pyruvate</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
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INTRODUCTION

Background
Rectal cancer is among the most frequent cancers in the world. While there is considerable geographical variation, it is most frequent in the Western world, where the incidence is increasing\textsuperscript{13}. Lifestyle factors such as high intake of fat and calories, as well as alcohol and tobacco, have been suggested as risk factors, while increased intake of fibre is associated with a decreased risk\textsuperscript{3, 69}. However, dietary risk factors are not fully understood\textsuperscript{11}. A small proportion of all rectal cancers can be linked to hereditary disorders such as hereditary non polyposis colorectal cancer (HNPCC)\textsuperscript{102}, which constitute 2-5% of all rectal cancers, or familial adenomatous polyposis (FAP), which represents less than one percent. Rectal cancer is more common in males and the median age at diagnosis is around 70 years. In Sweden around 1600 new rectal cancers are diagnosed each year, which represents around 30% of all colorectal cancers\textsuperscript{117}.

The prognosis for rectal cancer has improved since the 1960s, and in Sweden the 5-year relative survival rate has increased from 36% during the period 1960 to 1965 to nearly 58% during the period 1995 to 1999\textsuperscript{13}. This positive development can probably be attributed to a combination of factors such as earlier diagnosis, better preoperative tumour staging, improved perioperative care, introduction of improved surgical technique, structural changes, and adjuvant treatments such as irradiation\textsuperscript{7, 60, 120, 144, 147, 153}. In recent years, local recurrence has been reduced to less than 10% in Sweden\textsuperscript{117}, however, for those it affects, this condition is still difficult to treat, painful, and leads to death in two thirds of cases\textsuperscript{123}. Around one third of patients with rectal cancer will be diagnosed with metastatic disease, most often hepatic or pulmonary, and further improvement of diagnosing and treating metastatic disease is a major challenge for the future.

Diagnosis and staging
The rectum is defined as the bowel that is reached within 15cm from the anus (anal verge) by a rigid rectoscope. Diagnosis is made by multiple biopsies through a rectoscope or a flexible endoscope. The tumour is then inspected, and if it can be reached from the anus, it is assessed by digital palpation, which gives important information regarding possible fixation of the tumour. Modern tumour staging aims at evaluating the local and distant spread of the disease. Magnetic resonance imaging (MRI)\textsuperscript{7, 17} and endo-rectal ultrasound (ERUS)\textsuperscript{46} are used to examine the degree of invasion through the rectal wall, and the number of infiltrated lymph nodes, the two most important prognostic factors for local recurrence and survival in patients with rectal cancer. Computed tomography scan (CT-scan) of the abdomen and the thorax, or ultrasound of the liver and plain x-rays of the lungs, are performed to assess possible spread of the disease outside of the rectum\textsuperscript{49}. 
The aim of these preoperative 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\textsuperscript{145} (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>
</tbody>
</table>
| T1 = invasion into the submucosa  
T2 = invasion into the muscularis propria  
N0 = no involvement of lymph nodes  
M0 = no distant metastases |

| T3-4 N0 M0         | stage II                 | Dukes’ B              |
| T3 = invasion into the serosa or perirectal fat.  
T4 = invasion of adjacent organs and/or breaching of the visceral peritoneum  
N0 = no involvement of lymph nodes  
M0 = no distant metastases |

| T1-4 N1-2 M0       | stage III                | Dukes’ C              |
| N1 = 1-3 perirectal lymph nodes involved  
N2 ≥ 4 perirectal lymph nodes involved  
M0 = no distant metastases |

| T1-4 N0-2 M1       | stage IV                 | Dukes’ D              |
| M1 = distant metastases |

The preoperative TNM classification is necessary in order to decide whether preoperative adjuvant treatment such as radiotherapy is needed. Factors of importance for prognosis and for treatment planning include the extent of tumour invasion of the rectal wall, invasion of lymph nodes, involvement of the circumferential resection margin (CRM)\textsuperscript{113, 132, 154}, and the presence of distant metastases. Positron Emission Tomography scan (PET scan) is a method of evaluating patients with metastatic disease, most often hepatic metastases, in order to assess whether curative surgery can be attempted and recently a combination of PET and CT-scan (PET/CT) has been introduced\textsuperscript{143}. These factors will guide the multidisciplinary team consisting of colorectal surgeons, medical oncologists, radiologists, and pathologists, in deciding the proper treatment for the individual patient with
rectal cancer. The definitive histo-pathological staging is available only after surgery, and the postoperative TNM-classification will therefore influence the decision to give adjuvant or palliative postoperative treatment such as irradiation or chemotherapy.

The surgical margin in the resected specimen is an important predictor of prognosis and is described by the Residual Tumour Classification (R-classification) as proposed by the UICC (Union International contre le Cancer) as shown below (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Residual tumour classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0</td>
</tr>
<tr>
<td>R1</td>
</tr>
<tr>
<td>R2</td>
</tr>
</tbody>
</table>

DEVELOPMENT OF RECTAL CANCER SURGERY

The French surgeon Lisfranc described the first perineal operation to remove a rectal cancer in 1826. The first procedure with resection of a part of the rectum including anastomosis and restored bowel continuity was described by Kraske in 1885. This operation was based on a posterior incision including removal of the coccyx. Healing was often disturbed and frequently resulted in rectal fistulas and high morbidity. In 1892 Maunsell introduced an abdominal procedure in which the colon was pulled through the anus and a coloanal anastomosis constructed. Because of poor anorectal function this operation never became popular. At this time little was known about the spread of rectal cancer, and it was not until the pathological studies of Miles in 1908 that the operation described by Kraske was generally abandoned in favour of the abdomino-perineal resection (APR) proposed by Miles. This procedure was further refined, and in 1923 Miles reported a postoperative mortality of 10% and a local recurrence rate of 30%. Miles’ operation became the gold standard for rectal cancer surgery for several decades.

In 1921, Hartmann introduced an operation where in the first step, the sigmoid colon was divided and a colostomy fashioned. In a second operation the rectum was closed distal to the tumour and removed, leaving the anal canal and a rectal stump. This procedure gained some popularity, and is still in use today as a one step procedure. Based on the pathological studies by Dukes and others in the 1930s, Dixon and Best popularised the sphincter saving operation in the 1940s, generally called anterior resection of the rectum, in contrast to the posterior resection introduced by Kraske, and the sphincter saving operation slowly started to gain
popularity. With the introduction of mechanical staplers in the 1970s this change in surgical strategy accelerated and permanent colostomies became less common. With the circular staplers it has become possible to perform an anastomosis all the way down to the pelvic floor, and the single stapling technique has evolved into the double stapling and the triple stapling techniques. The transanally sutured anastomosis described by Parks in the 1970s is an important option for preservation of the sphincters in very low tumours.

To obtain an oncologically safe resection, it was first believed that a 5cm distal tumour margin was necessary, but in the 1980s a distal margin of 2cm was proposed and widely accepted as oncologically sufficient. Recently, the “2cm rule” has been challenged by some, suggesting that 1cm is an oncologically safe distal margin. In 1932 Dukes proposed a morphological classification system for rectal cancer which has since been widely used and correlates well with prognosis. It was noted by several authors already in the 1930s that tumour spread distal to the rectal cancer was rare, and in 1949 Best and Blair turned the focus of cancer spread in the lateral direction as they concluded that: “lateral spread is a factor which is probably not so clearly understood because it is possible that our surgical specimens have not been excised widely enough in this direction and thereby are not permitting a true analysis.” Based on such ideas concerning the understanding of the lateral spread of cancer in the mesorectum, and, as demonstrated in pathological studies by Quirke, the concept of total mesorectal excision (TME) was introduced by Heald in 1982.

The principles of TME surgery are based on sharp dissection under direct vision in embryological avascular planes, excising the rectum together with an intact mesorectum covered posteriorly and laterally by the mesorectal fascia. This technique has also been referred to as “specimen oriented surgery.” TME surgery is applied in sphincter saving excision, as well as in abdomino-perineal resection and in Hartmann’s procedure. With TME surgery, local recurrence rates at the 5-year follow-up, in patients without adjuvant therapy, were reported by Heald as early as 1986 at less than 5%. This is in contrast to recurrence rates of nearly 40% that were previously reported with conventional, pre-TME technique. The results of Heald initiated some debate, but recurrence rates below 10% have repeatedly been reported from single centre series, and the TME technique has now been widely adopted by colorectal surgeons worldwide.

An even wider lateral excision, aimed at resecting the so-called lateral lymphnodes, has been proposed but not widely accepted due to increased urogenital morbidity and absence of proven oncological advantages. In tumours situated in the upper rectum, at 12-15cm above the anal verge, many surgeons prefer to divide the mesorectum at a distance of 5cm distal to the lower edge of the tumour, although the operation is performed with TME-technique in all other respects. This procedure is often called partial mesorectal excision (PME) and has been reported to account for 20% to 36% of anterior resections of the rectum. During the mid 1990s a project was initiated that provided formal instruction in TME surgery to a group of surgeons in the Stockholm area.
Follow-up of patients operated on by these surgeons with TME training demonstrated for the first time a significantly improved outcome and survival in a population based setting. Recently, a local recurrence rate of 9% at the 5-year follow-up was demonstrated on a national basis in Sweden.

**Local excision for rectal cancer**

In curative surgery for rectal cancer, local procedures are generally not recommended. In T1 tumours a local procedure such as transanal endoscopic microsurgery (TEM) or a conventional transanal resection may be considered, but these procedures are generally reserved for medically frail patients or when the procedure is palliative. If a locally resected rectal adenoma contains invasive adenocarcinoma, an abdominal resection should be considered, with or without adjuvant treatment.

**ADJUVANT TREATMENT**

Historically, local recurrence has been a major problem in rectal cancer surgery with local recurrence rates up to nearly 40% as late as in the 1980s. Numerous studies have been conducted using various forms of pre- and postoperative irradiation therapies. Preoperative radiotherapy, often administered as 5 Gray (Gy) for five consecutive days (5 x 5 Gy) followed by immediate surgery, has repeatedly demonstrated reduction in the local recurrence as well as increased cancer specific survival. A reduction in local recurrence rate has also been shown with postoperative radiotherapy, although accompanied by a higher morbidity compared with preoperative irradiation. The proponents of postoperative radiotherapy argue that it should be given to patients in whom involvement of lymph nodes (N1-2) or circumferential margins (CRM+) is demonstrated, and that preoperative radiotherapy leads to overtreatment. In the only randomised trial comparing preoperative with postoperative irradiation, the local recurrence rate was lower and short- and long-term adverse events decreased in those who had received preoperative radiotherapy.

In fixed tumours, longer preoperative radiotherapy of around 44-50 Gy for up to five weeks is often used, with delayed surgery after 4-6 weeks. Long course radiotherapy is sometimes used in combination with preoperative chemotherapy. This treatment modality is also proposed by some for T3 tumours. With the development of chemotherapy in recent years, this treatment modality has in fact resulted in complete pathological response in a minority of the treated patients, resulting in a resected specimen without any residual cancer. However, the drawback is that numerous adverse events are associated with both irradiation and chemotherapy. Acute and short-term side effects and complications of radiotherapy are well described, as well as various long-term complications, and an increased risk of secondary cancers after radiotherapy has recently been
demonstrated. It is therefore of importance to balance reduced local recurrence and increased survival with late complications. A future challenge will be to further refine the selection of those patients who will most likely benefit from irradiation and chemotherapy.

MORBIDITY IN SPHINCTER SAVING RESECTION

Morbidity is generally categorised as medical or surgical complications. Infectious complications may be regarded as medical or surgical complications. Total morbidity associated with anterior resection of the rectum is generally described as affecting 30-35% of the patients operated on, both in single centre series as well as in population-based registries (Table 3). Early mortality is generally defined as death within 30 postoperative days, sometimes including the total length of the initial hospital stay if exceeding 30 days, and ranges from 0.6% to 7% in sphincter saving TME surgery.

When assessing morbidity it is also relevant to consider urgent reoperation and 30-day mortality, which may be considered as “hard” variables, in contrast to anastomotic leakage, defined in numerous ways and sometimes categorised as major or minor, which may be considered as a “softer” variable. Morbidity in patients who underwent anterior resection of the rectum from a single centre series by Law and a population based national cohort from the Swedish Rectal Cancer Registry (SRCR) are compared below (Table 3).

Table 3. Morbidity in anterior resection of the rectum. Comparison between a single centre series and a national registry (SRCR).

<table>
<thead>
<tr>
<th>Author</th>
<th>ref.</th>
<th>years operated</th>
<th>n</th>
<th>complications</th>
<th>leak rate</th>
<th>reop. rate</th>
<th>30-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Law</td>
<td>[86]</td>
<td>1993–2002</td>
<td>622</td>
<td>32.6%</td>
<td>19.9%</td>
<td>5.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>SRCR</td>
<td>[117]</td>
<td>2003</td>
<td>825</td>
<td>33.9%</td>
<td>22.5%</td>
<td>9.7%</td>
<td>8.9%</td>
</tr>
</tbody>
</table>

Legend: *Including urinary tract infection and urinary retention.
†not stated
ANASTOMOTIC LEAKAGE

Background and Prevalence

Despite the progress in recent decades regarding surgical technique and perioperative care, sphincter saving TME surgery for rectal cancer is associated with a morbidity rate of around 30-35% and a 30-day mortality of than 0.6% to 7% and a 30-day mortality of than 0.6% to 7% [117]. The most feared complication is symptomatic anastomotic leakage, which is associated with an increased risk of early mortality in up to 19% [116] in multicentre studies, and in up to 42% in single centre series [78]. If leakage occurs, the risk for the patient of ending up with a permanent stoma has been reported to vary between 10% and 100% [136]. The incidence of symptomatic anastomotic leakage in stapled anastomosis has been described in numerous studies as being between 1% and 24% [15, 28, 35, 47, 86, 115, 122, 131, 136, 155].

Definition

There is no uniform definition of symptomatic anastomotic leakage, also referred to as clinical or clinically evident leakage, which makes comparisons between different studies difficult. In one overview including 31 different studies analysing leakage in colorectal anastomoses published between 1993 and 1999, a definition of anastomotic leakage was provided in 19 of the 31 studies [18]. Some authors included leakages only from the circular anastomosis, while others also included leakage from straight staple lines. Rectovaginal fistulas are considered as an anastomotic leakage by some [40, 82], as well as pelvic abscess without radiologically proven leakage [136]. Leakage without clinical symptoms, sometimes referred to as asymptomatic, subclinical, or radiological leakage, has been demonstrated in 5% to 10% [77, 115, 138].

In one study minor leakage was defined as a leakage which did not require abdominal reoperation [16]. One disadvantage of such a definition is that patients without defunctioning stoma in whom a leakage occurs, and in whom urgent abdominal reoperation is likely [97], will frequently be classified as having a major leakage, in contrast to defunctioned patients with leakage, where only a minority will need urgent abdominal reoperation. The concept of pelvic sepsis has been proposed as symptomatic leakage comprising all staple lines, rectovaginal fistula, and pelvic abscess without proven radiologic leakage mechanism [82]. The concept of pelvic sepsis puts the focus on the clinical consequences, not the mechanism itself that leads to the condition, and as such is relevant to the patient and the colorectal team.

Mechanisms of anastomotic leakage

The mechanisms which may lead to clinical anastomotic leakage are not clearly understood. Insufficient vascularisation of the distal colon and/or the rectal stump are considered as possible mechanisms of leakage [54, 156]. Tension in the anastomosis
is also considered to enhance leakage, although this is difficult to study in humans. A presacral haematoma might become infected and thereby affect the healing process of the anastomosis\textsuperscript{63,140}. However, some authors have proposed that the infected haematoma is secondary to an already present anastomotic leakage, which could also be the case regarding the pelvic fluid collection\textsuperscript{138}.

**Risk factors**

In recent years several investigations have assessed possible risk factors for symptomatic anastomotic leakage after anterior resection of the rectum. The strongest risk factor is low anastomosis. Pakkastie and Vignali found that the high risk level for leakage was less than 7cm, Karanjia <6cm, Rullier <5cm, and Eriksen <3cm above the anal verge. Low anastomosis\textsuperscript{36, 78, 121, 136, 155} and male gender\textsuperscript{20, 36, 85, 136} have turned out to be independent risk factors in multivariate regression analysis in several retrospective single centre and population based studies. Other variables which have been shown to be independent risk factors in multivariate analysis studies are absence of a defunctioning stoma\textsuperscript{28, 126, 131}, absence of pelvic drain\textsuperscript{126}, excessive intraoperative bleeding\textsuperscript{86, 115}, multiple blood transfusions\textsuperscript{52}, excessive operation time\textsuperscript{142}, obesity in males\textsuperscript{136}, preoperative radiotherapy\textsuperscript{36}, smoking\textsuperscript{146}, abuse of alcohol\textsuperscript{146}, and increased age\textsuperscript{116}. Preoperative radiotherapy, regarded by some authors as a risk factor\textsuperscript{131}, has not turned out to be a risk factor in any randomised trial\textsuperscript{76, 147}. Epidural analgesia has been proposed as a risk factor for anastomotic leakage due to increased intraluminal pressure in the gastrointestinal tract in response to this treatment modality\textsuperscript{23}. However, in a review of 12 randomised trials, no evidence for an association between epidural analgesia and anastomotic leakage was found\textsuperscript{68}. A retrospective study found a difference in leakage rates between two brands of mechanical staplers, and there is now an ongoing multicentre trial addressing this issue\textsuperscript{41}. In conclusion, further investigations are needed to develop our understanding of what are true risk factors for symptomatic anastomotic leakage.

**Diagnosis**

In a review study from 2001 comprising 31 studies analysing anastomotic leakage in colorectal anastomosis\textsuperscript{18}, the most frequent ways of diagnosing the leakage were by water soluble contrast and plain x-ray. However, CT-scan, with or without rectal contrast, is an increasingly employed method\textsuperscript{115}. Other methods used by clinicians are flexible sigmoideoscopy, rigid rectoscopy, and digital palpation. Leakage is sometimes discovered at laparotomy, or even at autopsy\textsuperscript{98}. There are few reports on the postoperative day on which symptomatic leakage is diagnosed. In four studies, together comprising 94 symptomatic leakages, the leakage was diagnosed on median postoperative day 7, 10, 10 and 11, respectively\textsuperscript{52, 77, 115, 136}. In one study, 3/17 leakages were diagnosed after hospital discharge\textsuperscript{115}, which underlines the important fact that symptomatic leakages may appear at a late stage, and as concluded in
one systematic overview, this may lead to an underestimation of leakage rates. If leakage could be diagnosed earlier, and proper measures subsequently taken earlier, morbidity and mortality could possibly be decreased.

**Types of anastomosis**

The sphincter saving rectal resection was generally performed with an end to end anastomosis, also referred to as straight anastomosis, although the side to end anastomosis was described by Baker as early as 1950. Initially, all anastomoses were handsewn, but from the 1970s and onwards the use of mechanical staplers increased rapidly. The J-pouch anastomosis was introduced independently by Lazorthes and Parc in 1986 in an attempt to improve functional outcome. Recently the coloplasty was introduced by Z’graggen as an alternative to the J-pouch. One randomised trial demonstrated lower leakage rates with the J-pouch compared to the end to end anastomosis (15% vs 2%; p=0.03). A randomised trial comparing the J-pouch with the side to end anastomosis (10% vs 8%), as well as

**Figure 1a-d. Leakage in different types of anastomoses.**

**Figure 1a.** Leakage from the circular stapler line.

**Figure 1b.** Leakage from the efferent limb of a J-pouch anastomosis.

**Figure 1c.** Leakage from the efferent limb of a side to end anastomosis.

**Figure 1d.** Rectovaginal fistula.
one comparing the J-pouch with the coloplasty (0% vs 7%), did not demonstrate any significant differences in symptomatic leakage rates\textsuperscript{64, 93}. In a recent meta-analysis, the J-pouch was compared with the end to end anastomosis, as well as with the coloplasty, but no significant differences regarding leakage rates could be demonstrated\textsuperscript{61}.

Defunctioning stoma

The role of the defunctioning stoma in anterior resection of the rectum for rectal cancer has been controversial for several decades. In some studies, the defunctioning stoma has been associated with a decreased anastomotic leakage rate\textsuperscript{28, 126, 131}, in other investigations the leakage rate has not differed\textsuperscript{39, 47, 101}, or has even increased with a defunctioning stoma\textsuperscript{141}. Despite these conflicting data, the prevailing opinion among colorectal surgeons seems to be that a defunctioning stoma does not decrease the risk of symptomatic anastomotic leakage, but rather decreases the clinical consequences when a leakage occurs\textsuperscript{2, 97}. When the patient is defunctioned and leakage occurs, the need for urgent reoperation is less frequent, as has been repeatedly demonstrated\textsuperscript{47, 97}. In one large population based study, the need for urgent laparotomy in defunctioned patients was 25%, while in patients without a stoma, laparotomy was required in 71%\textsuperscript{47}.

The issue of randomised studies comparing defunctioning stoma with no defunctioning stoma has been discussed by several authors. It has been suggested that undertaking such trials might not be possible because they would be wrong from an ethical point of view\textsuperscript{47, 85, 131}. Nevertheless, three such studies have been undertaken, by Graffner in 1983, by Pakkastie in 1997, and by Pimentel in 2003\textsuperscript{53, 122, 129}. Since these trials randomised a total of 50, 38 and 36 patients, respectively, the numbers are too limited to draw firm conclusions. Only one of these studies had a statistical power calculation, which stipulated randomisation of 222 patients, but because of insufficient patient recruitment the trial was discontinued\textsuperscript{122}. Whether to choose a loop colostomy or a loop ileostomy has been much debated, and several studies regarding this issue have been undertaken\textsuperscript{33, 87, 159}. No major advantages for either type of defunctioning stoma have been demonstrated in these studies. Presently, however, the loop ileostomy seems to be preferred by a majority of colorectal surgeons.

Perianastomotic blood flow

Adequate blood supply is essential in anastomotic healing. Perianastomotic microcirculation was assessed in one study using laser Doppler flowmetry to measure transmural colonic bloodflow at the site of the colon intended for the anastomosis\textsuperscript{54}. Measurements were made before and after dissection and construction of the J-pouch in 30 patients. Bloodflow was decreased in end to end compared to J-pouch anastomosis, and there was no difference regarding whether the descending or the
sigmoid colon was used. In another study comprising 55 patients out of whom 22 had rectal cancer, it was also demonstrated using laser Doppler technique that a decrease in blood flow in the rectal stump was associated with an increased risk of anastomotic leakage\textsuperscript{156}.  

**Pelvic fluid collection**

After rectal excision, a pelvic fluid collection can be radiologically demonstrated\textsuperscript{63, 137}. Since the pelvic dissection leaves some raw surfaces, it is generally assumed that the pelvic fluid collection consists to some degree of blood, which may enhance bacterial growth, with the subsequent risk of bacterial infection. The role of the infected pelvic fluid collection remains unclear, and one unanswered question is in fact whether it is the infected pelvic fluid collection or the haematoma that breaks through the anastomosis and causes a leak\textsuperscript{63}, or whether it is through the leak that bacteria invade the pelvic fluid collection and cause infection\textsuperscript{138}.  

**Pelvic drainage**

In randomised studies including patients operated on with anterior resection of the rectum, no differences in leakage rates have been seen in patients with or without pelvic drainage\textsuperscript{105}. In a retrospective multicenter trial comprising 924 patients, those drained leaked in 10%, while those not drained leaked in 23%\textsuperscript{126}. However, findings are not conclusive and two meta-analyses concluded that drainage could not be recommended for routine use in rectal resection\textsuperscript{128, 151}.  

**Ano-rectal function**

In a few studies, anorectal function has been evaluated in patients with clinical leakage after reversal of the defunctioning stoma\textsuperscript{14, 57, 114}. In one study, 19 patients with leakage were compared to 19 non leakers\textsuperscript{57}. After median 30 months there was no difference in sphincter function measured by manometry. The so-called neorectal volume, compliance at sensation of filling, urge to defecate, and maximum tolerated volume, were significantly lower in patients with leakage. Similar results were reported in a study comprising 11 patients with leakage matched by 11 non-leakers\textsuperscript{114}. In that study, reduced “neorectal volume”, and a higher frequency of evacuation problems were reported, but only a trend for more faecal urgency and incontinence. However, these results were in contrast to a study in which 22 patients with leakage were compared with 111 without leakage\textsuperscript{14}. In these patients, there was no difference in Cleveland Clinic Continence scores, with mean 7.2 (±5.3) in leakers versus 7.4 (±5.8) in non leakers. In addition, the sphincter function was similar, while maximum tolerable volume and rectal compliance were slightly but not significantly worse. These studies suggest that continence remains undisturbed after clinical leakage.
Local recurrence and survival

In recent studies an increased risk for local recurrence following anastomotic leakage has been demonstrated, as have both increased recurrence and decreased survival. In one investigation 406 patients underwent potentially curative anterior resection out of whom 6% developed clinical leakage\textsuperscript{25}. Local recurrence at five years follow-up was 41% in those with leakage, compared with 12% in non leakers (relative risk 3.7; CI 95%:1.3-10.8), results similar to another study which also included only rectal cancer patients (relative risk 3.8; CI 95%:1.8-7.9)\textsuperscript{8}. In another single centre study 814 patients with stage I-III rectal rectal cancer, not including patients receiving neoadjuvant or adjuvant treatment therapy, were analysed\textsuperscript{106}. Overall anastomotic leakage was 11 % and local recurrence within 5 years 14%. However, in patients with leakage, recurrence was 22%, compared with 13% in non leakers (relative risk 1.7; CI 95%:1.02-2.8), and cancer related death at 5 years was increased in multivariate analysis (relative risk 1.6; CI 95%; 1.1-2.2). In conclusion, these findings suggest that symptomatic anastomotic leakage increases the rate of local recurrence and decreases survival.
AIMS OF THE STUDY

- To investigate intraoperative adverse events in relation to outcome measured as early mortality after anterior resection of the rectum in a nationwide case-control study.

- To analyse variables considered as potential risk factors for symptomatic anastomotic leakage after anterior resection of the rectum in a population-based nationwide case-control study.

- To compare the rate of clinical anastomotic leakage and short term morbidity in sphincter saving TME-surgery for rectal cancer in a multicentre trial in which patients were randomised to a defunctioning stoma or not.

- To assess the postoperative conditions locally and systemically by postoperative CT-scan, blood samples and bedside physiological parameters in patients undergoing anterior resection of the rectum.

- To analyse intraperitoneal carbohydrate metabolites and intraperitoneal cytokines as potential markers of intestinal ischemia and inflammatory response in patients after anterior resection of the rectum for cancer.
PATIENTS AND METHODS

This thesis is based on five investigations, two population based retrospective studies (Paper I-II), one randomised multicentre trial (Paper III), and two prospective non randomised trials (Paper IV-V). A summary of the study populations and characteristics of the patients including operative details from Papers I-V are described below (Tables 4 and 5).

Table 4. Study populations in paper I-V

<table>
<thead>
<tr>
<th>Study population</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper I</td>
<td>563</td>
</tr>
<tr>
<td>Patients who underwent anterior resection of the rectum in Sweden between 1987 and 1995 and who died within 30 days (n=140) were compared with patients chosen at random who survived the same operation during the same period of time (n=423).</td>
<td></td>
</tr>
<tr>
<td>Paper II</td>
<td>432</td>
</tr>
<tr>
<td>Patients surviving anterior resection of the rectum (n=423) and a random sample of non survivors (n=9) from Paper I were compared to assess risk factors for symptomatic anastomotic leakage.</td>
<td></td>
</tr>
<tr>
<td>Paper III</td>
<td>234</td>
</tr>
<tr>
<td>Patients who underwent low anterior resection for rectal cancer in 21 hospitals in Sweden between 1999 and 2005 were randomised to a defunctioning stoma (n=116) or not (n=118) and assessed for symptomatic leakage.</td>
<td></td>
</tr>
<tr>
<td>Paper IV</td>
<td>33</td>
</tr>
<tr>
<td>Patients operated on with anterior resection of the rectum in three hospitals between 2002 and 2003 were assessed by CT-scan and serological investigations in a prospective non-randomised study.</td>
<td></td>
</tr>
<tr>
<td>Paper V</td>
<td>23</td>
</tr>
<tr>
<td>Patients who underwent anterior resection of the rectum between 2002 and 2004 were assessed by intraperitoneal microdialysis and intraperitoneal cytokines in a prospective non-randomised study.</td>
<td></td>
</tr>
</tbody>
</table>

Intraoperative adverse events and outcome after anterior resection of the rectum (Paper I)

The patients analysed in paper I consisted of two subgroups of a national cohort of 6833 patients who underwent elective anterior resection of the rectum in Sweden between 1987 and 1995. Of these patients, 140 (2.1%) died within 30 days or during the initial hospital stay. The non-survivors (n=140) were compared with a random sample of who underwent the same operation during the same period of time, but who were alive after 30 days and discharged from hospital before or after day 30 (nested control group; n=423). Patient identification was obtained from the in-hospital registry of the Swedish National Board of Health and Welfare. The non-survivors originated from the 69 hospitals with reported 30-day mortality,
and the randomly chosen survivors from 84 hospitals. During this period, a total of 93 hospitals (median per year 86; range 80-87) performed anterior resection of the rectum in Sweden. The initial selection consisted of 146 non-survivors and 465 survivors, but not all of the patients could be analysed, and some were excluded. The response rate was 100% for the cases and 97% for the control group (Table 6). The aim of this study was to compare the two groups, survivors and non-survivors, regarding the presence of intraoperative adverse events and intraoperative measures taken, and regarding the outcome of surgery measured as 30-day mortality or survival, and to assess the frequency of intraoperative adverse events on a population basis.

**Table 5.** Characteristics of the patients and operative details in Paper I-V

<table>
<thead>
<tr>
<th>Paper</th>
<th>I (cases)</th>
<th>I (control group)</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>140</td>
<td>423</td>
<td>432</td>
<td>234</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>Age (years)</td>
<td>76</td>
<td>70</td>
<td>70</td>
<td>69</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Female (%)</td>
<td>27</td>
<td>52</td>
<td>52</td>
<td>46</td>
<td>43</td>
<td>47</td>
</tr>
<tr>
<td>BMI</td>
<td>23.3</td>
<td>24.7</td>
<td>24.6</td>
<td>24.9</td>
<td>25.4</td>
<td>25.2</td>
</tr>
<tr>
<td>Level of tumour (cm)*</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Cancer stage IV (Dukes’ D)</td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
<td>4%</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Preoperative radiotherapy</td>
<td>18%</td>
<td>16%</td>
<td>16%</td>
<td>79%</td>
<td>76%</td>
<td>91%</td>
</tr>
<tr>
<td>Level of anastomosis (cm)</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>TME</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>100%</td>
<td>85%</td>
<td>91%</td>
</tr>
<tr>
<td>Operation time (minutes)</td>
<td>213</td>
<td>170</td>
<td>173</td>
<td>210</td>
<td>238</td>
<td>245</td>
</tr>
<tr>
<td>Bleeding (ml)</td>
<td>1000</td>
<td>600</td>
<td>650</td>
<td>550</td>
<td>1000</td>
<td>1150</td>
</tr>
<tr>
<td>Defunc. stoma</td>
<td>15%</td>
<td>17%</td>
<td>17%</td>
<td>50%</td>
<td>52%</td>
<td>49%</td>
</tr>
<tr>
<td>Pelvic drainage</td>
<td>52%</td>
<td>56%</td>
<td>56%</td>
<td>97%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*level above anal verge in cm measured by a rigid rectoscope
† not stated

<table>
<thead>
<tr>
<th>Patients initially selected</th>
<th>Non-survivors (cases) (n)</th>
<th>Survivors (control group) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgent operation</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Sigmoid resection</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Hartmann’s operation</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Patient file not found</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>No hospital response</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Operated on in 1986</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Excluded</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>Analysed</td>
<td>140/140 (100%)</td>
<td>423/437 (96.8%)</td>
</tr>
</tbody>
</table>

Risk factors for anastomotic leakage after anterior resection of the rectum (Paper II)

The study population in paper II consisted of the randomly chosen survivors (n=423) and a subgroup of non-survivors (n=9) who underwent anterior resection of the rectum in Sweden between 1987 and 1995, thus a subgroup of the patients in Paper I. These 432 patients represent a sample size of 6.3% of the total number of anterior resections of the rectum reported in Sweden between 1987 and 1995. The aim of this investigation was to assess variables considered as possible risk factors for symptomatic leakage. The variables included in this analysis were patient related variables: age, gender, cancer stage (Dukes’ stage), preoperative radiotherapy, body mass index (BMI) and surgery related variables: operation time, level of anastomosis (cm above anal verge measured by a rigid rectoscope), type of anastomosis (stapled or handsewn), presence of a defunctioning stoma, pelvic drain, and presence of intraoperative adverse events. Due to the retrospective nature of the present study, the proportion of valid data was less than 100% for a majority of the variables (Table 7).
### Table 7. Proportion of valid data for each variable considered for analysis in paper II

<table>
<thead>
<tr>
<th>Variable</th>
<th>Proportion of valid data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient related</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>100</td>
</tr>
<tr>
<td>Gender</td>
<td>100</td>
</tr>
<tr>
<td>Preoperative radiotherapy</td>
<td>98</td>
</tr>
<tr>
<td>Cancer stage (Dukes’ stage)</td>
<td>96</td>
</tr>
<tr>
<td>Comorbidity*</td>
<td>95</td>
</tr>
<tr>
<td>Level of the tumour (cm)</td>
<td>92</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>78</td>
</tr>
<tr>
<td>ASA score**</td>
<td>46</td>
</tr>
<tr>
<td>Smoking**</td>
<td>38</td>
</tr>
<tr>
<td><strong>Surgery related</strong></td>
<td></td>
</tr>
<tr>
<td>Defunctioning stoma</td>
<td>99</td>
</tr>
<tr>
<td>Intraoperative adverse events***</td>
<td>98</td>
</tr>
<tr>
<td>Pelvic drain</td>
<td>97</td>
</tr>
<tr>
<td>Type of anastomosis</td>
<td>95</td>
</tr>
<tr>
<td>Level of anastomosis</td>
<td>84</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>82</td>
</tr>
<tr>
<td>Bleeding (ml)****</td>
<td>80</td>
</tr>
</tbody>
</table>

Legend:  * not entered into analysis because data were not deemed to be of acceptable quality or were difficult to categorise.  
** not analysed because of a high proportion of missing data  
*** as described by the surgeon in the operative report  
**** analysed as part of intraoperative adverse events

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**Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum - a randomised multicentre trial (Paper III)**

In this multicenter trial patients who underwent low anterior resection of the rectum for cancer were randomised to a defunctioning stoma (n=116) or no defunctioning stoma (n=118). The primary endpoint was symptomatic anastomotic leakage, which was verified by radiological, endoscopic or clinical investigations. There was no specific time limit for diagnosing the leakage. Radiological leakage without clinical symptoms was not included. The secondary endpoint was postoperative morbidity within 90 days of the initial rectal resection, but morbidity beyond 90 days was also reported. The patients were assessed on postoperative day 5 (day of surgery = day 0) in regard to body temperature, evacuating stools or > 100 ml of faeces in the stoma appliance, >1000ml oral intake of fluids per 24 hours,
and whether there was ongoing antibiotic treatment or not. Patient related inclusion criteria were patient consent, preoperative biopsy proven adenocarcinoma of the rectum (≤15 cm above the anal verge measured with a rigid rectoscope), absence of major comorbidity, expected survival > 6 months, with the latter two criteria as judged by the surgeon. Intraoperative inclusion criteria were anastomosis ≤7 cm above the anal verge, two intact anastomotic rings, negative air leakage test, and absence of intraoperative adverse events necessitating a defunctioning stoma, as judged intraoperatively by the surgeon. Randomisation was performed intraoperatively after construction and testing of the anastomosis, by means of a sealed envelope opened in the operating theatre. The randomisation envelopes were sent to each hospital in blocks of 12 without hospital stratification. Patients were analysed on an intention to treat basis. All 65 hospitals in Sweden performing rectal cancer surgery in 1999 were invited to participate. Twenty-one hospitals participated in the trial between December 1999 and June 2005 and randomised a total of 234 patients.

Assessment of pelvic fluid collection and C-reactive protein after anterior resection of the rectum for cancer (Paper IV)

In the present study patients were assessed postoperatively after anterior resection of the rectum (TME 85%, PME 15%) by means of a CT-scan of the pelvis on postoperative day 2 and 7, and by blood samples and clinical investigation daily during the hospital stay. The aim was to describe postoperative conditions in the pelvis and systemically. Thirty-three patients were included from three hospitals. A CT-scan of the pelvis was performed according to a study protocol, including 3 mm slices, on postoperative day 2 and 7 in order to assess postoperative pelvic fluid collections, pelvic drainage output, and to investigate whether there was postoperative shrinkage of the mesocolon in the left colon proximal to the anastomosis, which, if present, could induce tension in the colorectal anastomosis.

The latter question was assessed by means of suturing two 9 mm metal clips to the colon mesentery before construction of the anastomosis, which, after completion of the anastomosis, were positioned dorsally (i.e. in a presacral position) at a distance of 2 cm and 12 cm proximal of the colorectal anastomosis. The distances between the clips were measured on postoperative day 2 and 7, each patient thus being his or her own control. C-reactive protein (CRP) and white blood cell count (WBC) were analysed daily throughout the hospital stay. Pelvic drain output was recorded for each 24-hour period. Patients were monitored clinically with daily registrations of systolic and diastolic blood pressure, heart frequency and body temperature.
Early detection of anastomotic leakage by intraperitoneal microdialysis and intraperitoneal cytokines after anterior resection of the rectum for cancer? (Paper V)

In paper V, 23 patients who underwent anterior resection of the rectum (TME 91%, PME 9%) were monitored postoperatively using intraperitoneal microdialysis technique (IPM) and analysis of cytokines in intraperitoneal fluid. The aim of this study was to assess the feasibility of intraperitoneal monitoring of the biochemical markers glucose, pyruvate, lactate, IL-6, IL-10 and TNF-α as a method of detecting changes in intraperitoneal carbohydrate metabolism and inflammatory response in patients operated on with anterior resection of the rectum, and to assess differences in patients with or without postoperative complications.

Intraperitoneal microdialysis (IPM)

Microdialysis catheters were applied at three different locations: one intraperitoneally near the anastomosis, one intraperitoneally in the central part of the abdominal cavity, and one placed subcutaneously in the right pectoral region. The catheter near the anastomosis was placed partially in a retroperitoneal position in the right side of the pelvis and only the distal 5cm were intraperitoneally positioned. The distance of the tip was thus deemed to be at a distance of not more than 5cm from the anastomosis.

The catheter placed in the central part of the abdominal cavity, typically between the greater omentum and the small intestines, was not fixated and thus, in principle, was freely floating in the abdominal cavity. The catheter placed subcutaneously was regarded as a reference catheter. With the IPM technique of passive diffusion, molecules with a molecular weight of less than 20 kiloDalton, can pass through the semi-permeable membrane at the tip of a microdialysis catheter, 30 mm in length and with a diameter of 0.9 mm. Molecules such as glucose and the metabolites of carbohydrate metabolism, lactate and pyruvate, can pass freely. The fluid entering the microdialysis catheter is continuously being pumped away at a volume of 0.3 uL/minute (Figure 2).

It is of importance that the lactate dehydrogenase (LDH) has a molecular weight of more than 20 kiloDalton and subsequently cannot influence the relation between lactate and pyruvate in the microdialysis catheter, the lactate/pyruvate ratio (L/P ratio). Lactate levels are increased when ischemia is present, but also in states of hypermetabolism, and for this reason the lactate/pyruvate ratio, which is considered as a marker of ischemia, was deemed more appropriate to monitor than lactate alone. The patients were monitored with microdialysis for 6 postoperative days following surgery.

Intraperitoneal cytokines

The cytokines IL-6, IL-10 and TNF-α were analysed from intraperitoneal fluid which was collected from an 18 French pelvic drain, starting at 6:00 pm on the day of surgery, median 3 hours (range 0-5) after the end of the operation, and then
collected every six hours during the next 42 postoperative hours. IL-6, IL-10 and TNF-α were determined using an enzyme-labelled, chemiluminescent sequential immunometric utilising an Immulite® instrument (DPC, Los Angeles, California, USA) according to the manufacturer’s instructions.

**Figure 2.** Principles of the microdialysis catheter. (With permission of CMA Microdialysis AB, Stockholm, Sweden).

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**Legend.**

A. Passive exchange of intraperitoneal fluid in the abdominal cavity.

B. Microdialysis fluid pumped actively in distal direction at 3μL/min through the outer lumen of the microdialysis catheter

C. Fluid after exchange by passive diffusion actively pumped in retrograde direction at 3μL/min through the inner lumen of the microdialysis catheter.

D. Opening where the fluid enters the inner lumen.

E. Semi-permeable membrane, 30 mm in length, allowing passive diffusion of molecules up to 20 kiloDalton
METHODOLOGICAL CONSIDERATIONS

Paper I

This was a case control study with no matching of any patient related factors in the control group. The reason this study design was selected was because the aim was to obtain a true population based incidence of adverse events and measures taken in the survivors (nested control group), which would not have been possible in controls matched for variables such as age and gender. The analysis of adverse events was based on the way in which these adverse events were described by the surgeons in the operative reports documented immediately after the operation. It is reasonable to assume that all surgeons did not describe adverse events in the same way or with the same frequency. Due to the retrospective nature of this study, it was not possible to validate these operative reports in retrospect. However, when making the operative report, the surgeon was unaware of the postoperative course of the individual patient, and in this sense the operative report could be regarded as a prospective documentation of relevant events of the operation, including possible adverse events and subsequent measures taken.

Paper II

In order to obtain a representative sample of patients, a number of non survivors corresponding to the proportion of early mortality in the national cohort of patients who underwent anterior resection of the rectum in Sweden between 1987 and 95 (140/6833; 2.1%), were chosen at random from the total number of non survivors. This selection was performed by the Department of Medical Statistics, Örebro University Hospital, and yielded a random selection of nine non survivors (9/(9+423); 2.1%) who were added to the group of 423 randomly chosen survivors, resulting in a total study population of 432 patients, and representing a total sample size of 6.3% (432/6833).

Some of the variables in paper II were categorised in a way which was deemed relevant from a clinical point of view, such as the level of anastomosis (<6cm, 6.1-10cm and 10.1-15cm). Other variables were categorised to obtain groups of comparable size, such as BMI (three categories; ≤22, 23–26, >26) and age (four categories; ≤62, 63-70, 71-76, ≥76). These categorisations were arbitrary and could have been done differently. Comorbidity was frequently incompletely described and deemed difficult to categorise, and was therefore not analysed. The ASA (American Society of Anesthesiologists) score, an indicator of comorbidity, and smoking, were considered for analysis, but excluded due to a large proportion of missing data (Table 7).
**Paper III**

Intraoperative randomisation using sealed envelopes in the operation theatre was deemed to be a simple procedure with high compliance.

**Papers IV-V**

Both of these investigations were considered explorative and comprised no randomisation or power calculation. In paper IV, the volume of the pelvic fluid collection was assessed by measuring the maximal length in the three planes and calculated by the formula:

\[
\frac{\text{maximal length} \times \text{maximal width} \times \text{maximal height}}{2}
\]

This formula gives an approximation of the fluid collection and was deemed adequate by the radiologist (MH) who reviewed the CT-scans. In paper V the microdialysis data were analysed by computer “on line” and in principle thus available for the surgeon during the patient’s in-hospital period. However, the “on-line” results were not taken into account, and subsequently did not influence the postoperative treatment of the patients. Cytokines were analysed after hospital discharge.
STATISTICS

In papers I-V categorical variables were analysed with the \( X^2 \) test or \( X^2 \) test for trend. Continuous variables were analysed by the Mann-Whitney U test, ANOVA, or by non parametric log rank test.

In paper I, a proportion of three survivors in the control group for each non survivor was deemed statistically acceptable\(^74\).

In paper II, variables considered as possible risk factors for anastomotic leakage were analysed in univariate and multivariate stepwise logistic regression analysis. P-values \( \leq 0.10 \) in the univariate analysis were entered into the multivariate logistic regression analysis.

In paper III the hypothesis was a leakage rate of 7.5% with, and 15% without a defunctioning stoma. A statistical power of 80% was deemed adequate and required 220 randomised patients.

In paper V collected data demonstrated non parametric distribution with relatively large variation between, but also within, individuals. For this reason, median values were calculated for each individual and 24-hour postoperative period, and when groups of individuals were compared, the median value of each individual was used to calculate the median value of the group.

In all statistical calculations a p-value of less than 5% was considered significant. All statistical analyses were carried out using the SPSS\(^\text{®} \) version 11 (SPSS, Chicago, Illinois, USA), and the Statistix\(^\text{®} \) version 8 (Analytical Software, Tallahassee, Florida, USA).

ETHICS

The investigations in papers I-II were approved by the ethics committee of Linköping. The trial in paper III was initially approved by the ethics committee in Linköping, and hereafter by the ethics committees in the five remaining health care regions of Sweden. The study in paper IV was approved by the ethics committee in Linköping and Örebro, and by the Radiation Protection Committee in Örebro. The study in paper V was approved by the ethics committee in Örebro.
RESULTS AND DISCUSSION

Intraoperative adverse events and outcome after anterior resection of the rectum (Paper I)

In contrast to postoperative complications, frequently reported in the literature, intraoperative adverse events, or intraoperative complications, are not often described\(^{86, 116, 130}\). In this presentation, the study population was randomly chosen from a national cohort, a design which avoids selection bias. This investigation demonstrated that intraoperative adverse events were more common in the non-survivors than in the survivors, 46% vs. 30% (OR 1.9; 95% CI: 1.3, 2.9; p<0.001). It is noteworthy that in those who survived, nearly one third of all anterior resections comprised at least one intraoperative adverse event. Bleeding considered as an adverse event by the surgeon was more common in the non-survivors, both when it had a specified source, and when it did not. The most frequently specified source of bleeding was the presacral veins (Table 8).

Table 8. Intraoperative measures taken as a consequence of intraoperative adverse events related to the anastomosis and different sources of bleeding in patients operated on with anterior resection of the rectum in Sweden between 1987 and 1995.

<table>
<thead>
<tr>
<th>Measure of intraoperative adverse events</th>
<th>non-survivors n=140 (%)</th>
<th>survivors n=423 (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extra sutures at the anastomosis with or without defunctioning stoma</td>
<td>25 (17.8%)</td>
<td>43 (10.2%)</td>
<td>ns</td>
</tr>
<tr>
<td>Defunctioning stoma only</td>
<td>14 (10%)</td>
<td>30 (7.1%)</td>
<td>ns</td>
</tr>
<tr>
<td>Restapling or redo of an anastomosis considered unsatisfactory, with or without defunctioning stoma</td>
<td>2/18 (1.4%)</td>
<td>19/50 (4.5%)</td>
<td>p=0.034*</td>
</tr>
<tr>
<td>Bleeding, diffuse</td>
<td>8 (5.7%)</td>
<td>3 (0.7%)</td>
<td>p&lt;0.001*</td>
</tr>
<tr>
<td>Bleeding, specified source of which was from presacral veins</td>
<td>9 (6.4%)</td>
<td>11 (2.6%)</td>
<td>p=0.034*</td>
</tr>
</tbody>
</table>

\(^*\)X\(^2\) test

Gross contamination of faeces was more frequent in non-survivors (7.9% vs. 3.1%; p=0.015). The proportions of anastomoses constructed with mechanical staplers were comparable between the groups, 74% vs. 76%, respectively, but stapled anastomoses were less often tested for leakage in the non-survivors than in the survivors (71% vs. 82%; p=0.011). It is possible that a higher degree of testing among those who died might have revealed more defective anastomoses and allowed adequate reconstruction, possibly leading to better outcome. This highlights the importance of intraoperative testing of anastomotic integrity\(^{141}\).
This study also addressed the issue of measures taken by the operating surgeon as a consequence of occurring intraoperative adverse events. There was no difference regarding outcome when the measure taken was adding extra sutures at the anastomosis, with or without defunctioning stoma, or defunctioning stoma only. When the anastomosis was judged unsatisfactory by the surgeon, not including defective anastomotic rings or positive air leakage test, the anastomoses were restapled or completely resutured in 38% of the survivors, compared to 11% of the non-survivors (Table 8).

When anastomotic leakage was present, there was a tendency for increased risk for 30 day mortality in women compared with men, although significance could not be demonstrated in analysis of interaction (p=0.100). Moreover, in women the risk of 30 day mortality was increased the lower the anastomosis was situated (level of anastomosis categorised as ≤6cm, 6.5-10cm, 10.5-15cm) (p=0.038; $X^2$ test for trend), while the risk among men was not correlated to the anastomotic level.

In conclusion, the presence of intraoperative adverse events increased the risk of early mortality after anterior resection of the rectum. An anastomosis deemed unsatisfactory should be completely reconstructed.

**Risk factors for anastomotic leakage after anterior resection of the rectum (Paper II)**

Paper II deals with possible risk factors for symptomatic leakage and comprised 432 randomly chosen patients from a nationwide cohort (sample size 6.3%) who underwent anterior resection in Sweden between 1987 and 1995. Of these patients, 91% had rectal cancer and the majority of the remaining 9% rectal adenoma. Risk factors for anastomotic leakage after anterior resection of the rectum have been dealt with in numerous studies, mostly single centre series, but recently also in multicentre investigations. Because of various definitions of anastomotic leakage, results are sometimes difficult to compare. In the present study, the definition included leakage from circular as well as from straight staple lines, rectovaginal fistula and pelvic abscess without proven radiological leakage. With this definition, which has also been labelled as pelvic sepsis, the rate of symptomatic leakage was 12%.

**Level of anastomosis**

Towards the end of the study period, TME surgery was in the process of being introduced in Sweden. Because of the retrospective nature of this study, it was not deemed possible, with acceptable validity, to assess operative reports in regard to whether TME-surgery had been performed or not. It is clear, however, that only a minority of the patients were operated on with the TME technique. Since it has been claimed by some that TME surgery per se will lead to a higher rate of anastomotic leakage, the leakage rate may appear higher than would have been expected in this predominately “pre-TME” period. However, this may reflect anas-
tomotic height rather than the TME technique itself. In this study, the median anastomotic height was 8cm. In anastomoses situated at ≤7cm, compared with >7cm, leakage rates were 30% and 7%, respectively (OR 4.5; 95% CI: 2.3, 8.8; p<0.001). Moreover, the leakage rate was 4% when the anastomosis was situated between 10.5 and 15cm above the anal verge, 13% between 6.5 to 10cm, and 25% at ≤6cm above the anal verge (Figure 3).

**Figure 3.** Distribution of level of anastomosis in anterior resection of the rectum in a random sample of 432 patients operated on in Sweden between 1987 and 1995 with and without anastomotic leakage. Missing data (n=70)

Leakage in one out of four patients with low colorectal anastomosis is indeed high however, it must be taken into account that these operations were performed by a large number of surgeons in 84 different hospitals, and that the yearly mean number of anterior resections per hospital was 9 per year during the study period (median 6.6, range 0.3-28.0). A certain proportion of these surgeons were general surgeons without specialisation in colorectal surgery, and these findings highlight the issue of case load and degree of specialisation in rectal cancer surgery. Nevertheless, higher leakage rates have not been demonstrated in hospitals with low case loads, in contrast to local recurrence and early mortality.98, 133, 153

**Total mesorectal excision (TME)**

In Sweden TME surgery gained wide acceptance during the latter half of the 1990s, which also lead to introduction of formal educational programmes for colorectal surgeons95, creation of colorectal units, and introduction of the multi-disciplinary team144. Nevertheless, when comparing an anastomotic leakage rate of 12% in anterior resection during the period 1987-1995 with the present (2003)
leakage rate of 10% according to the Swedish Rectal Cancer Registry (SRCR), questions may be raised regarding the degree of improvement. However, a leakage rate of 10% in patients where TME surgery is used for the majority should be compared with rates for patients in whom a minority had TME surgery and the median anastomotic height was 8cm. It must also be taken into account that although nearly all patients in Sweden are operated on today with the TME technique, not all patients undergo a TME operation all the way down to the pelvic floor. Since anastomotic height, in contrast to tumour height, is not reported in the SRCR, an unknown proportion of patients undergo partial mesorectal excision (PME), a proportion reported to be between 20% and 36%.

Since higher anastomoses leak less frequently, an increased proportion of PME will result in a decreased leakage rate.

**Gender**

In the present study men leaked in 17% compared to 8% in women, a finding not previously demonstrated in any population based study. However, similar results are found in the SRCR with more than 6000 anterior resections performed between 1995 and 2003, and have recently been reported in other population based studies (Table 9).

**Table 9. Anastomotic leakage rate in relation to gender.**

<table>
<thead>
<tr>
<th>time period operated on</th>
<th>n</th>
<th>ref.</th>
<th>leakage rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>total</td>
<td>females</td>
</tr>
<tr>
<td>Paper II</td>
<td>1987-1995</td>
<td>432</td>
<td>-</td>
<td>12.3%</td>
</tr>
<tr>
<td>Bulow et al</td>
<td>1996-1998</td>
<td>212</td>
<td>[19]</td>
<td>15.1%</td>
</tr>
<tr>
<td>Eriksen et al</td>
<td>1993-1999</td>
<td>1958</td>
<td>[36]</td>
<td>11.6%</td>
</tr>
<tr>
<td>SRCR*</td>
<td>1995-2003</td>
<td>6041</td>
<td>[117]</td>
<td>9.3%</td>
</tr>
</tbody>
</table>

Legend: *Swedish Rectal Cancer Registry

**Defunctioning stoma**

In the present study 17% of the patients (72/432) were initially defunctioned. This was hospital policy, or “routine” treatment, in 17% of the patients with defunctioning stoma (12/72), while in 83% (60/72) the defunctioning stomas were fashioned for a specific reason stated in the operative report. Forty out of 72 defunctioning stomas were constructed because of the presence of intraoperative adverse events (IOAE), 12 were “routine” defunctioning stomas, and 20 were fashioned because of comorbidity or increased age (Table 10).
Table 10. Anastomotic leakage rate in relation to intraoperative adverse events (IOAE) and defunctioning stoma.

<table>
<thead>
<tr>
<th></th>
<th>IOAE stoma</th>
<th>IOAE no stoma</th>
<th>no IOAE stoma</th>
<th>no IOAE no stoma</th>
<th>entire study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leakage rate</td>
<td>10/44</td>
<td>16/90</td>
<td>1/28</td>
<td>26/270</td>
<td>53/432</td>
</tr>
<tr>
<td>(%)</td>
<td>(23%)</td>
<td>(18%)</td>
<td>(4%)</td>
<td>(10%)</td>
<td>(12%)</td>
</tr>
</tbody>
</table>

This study demonstrated that defunctioning stoma in patients with IOAE did not decrease the leakage rate. When symptomatic leakage occurred, patients with a defunctioning stoma required urgent reoperation in 18% (2/11), compared to 76% (34/42) in those not defunctioned (76% vs 18%; p<0.001), a proportion similar to figures in previous reports. The final outcome for those without a defunctioning stoma and leakage was that 86% (36/42) had one or more urgent reoperations and a defunctioning stoma, and 25% (13/53) out of these became permanent stomas. In patients without leakage less than 1% (3/379) ended up with a permanent stoma due to various complications.

Comparison with data from the Swedish Rectal Cancer Registry

Of the patients operated on with anterior resection in Sweden between 1987 and 1995, 17% were initially defunctioned, a proportion which increased to 37% in patients operated on between 1999 and 2003 as reported to the Swedish Rectal Cancer Registry (SRCR). This can probably be explained by the introduction of TME surgery in the mid 1990s, and a subsequent lower level of anastomosis, as well as an increased use of preoperative radiotherapy, from 16% to 49% (Table 11). However, defunctioning stoma had no impact on leakage rates. It has been claimed by some that preoperative radiotherapy is a risk factor for leakage and a reason to defunction, although irradiation has not been proved to be a risk factor for leakage in any randomised study.

In the SRCR, which comprises more than 6000 anterior resections for rectal cancer reported from 1995 to 2003, and a rate of completeness of 99%, half of the patients (49%) had preoperative radiotherapy and those irradiated leaked more often (Table 11). One possible explanation for this difference could be that during 1987-1995 opposite radiation portals were used in a large proportion of the patients, in contrast to the later period, when more sophisticated three- or four portal techniques were used. During both periods, however, gender and preoperative radiotherapy influenced leakage rates.

In this nationwide setting, low anastomosis, the presence of intraoperative adverse events, male gender and preoperative radiotherapy were found to be independent risk factors for symptomatic anastomotic leakage. These risk factors should be taken into account when the decision to create or not to create a defunctioning stoma is made. Following leakage the risk for permanent stoma was 25% and the associated early mortality was 7.5%.
Table 11. Patients in Paper II compared with patients reported to the Swedish Rectal Cancer Registry (SRCR) regarding gender, preoperative radiotherapy and defunctioning stoma in relation to symptomatic anastomotic leakage.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>432</td>
<td></td>
<td>6041</td>
<td></td>
</tr>
<tr>
<td>Total leakage</td>
<td>12.3%</td>
<td></td>
<td>9.2%</td>
<td></td>
</tr>
<tr>
<td>Leakage, men</td>
<td>17.1%</td>
<td></td>
<td>10.3%</td>
<td></td>
</tr>
<tr>
<td>Leakage, women</td>
<td>7.7%</td>
<td>p=0.003*</td>
<td>7.6%</td>
<td>p&lt;0.001*</td>
</tr>
<tr>
<td>Preop radiotherapy (RT)**</td>
<td>16.4%</td>
<td></td>
<td>49.0%</td>
<td></td>
</tr>
<tr>
<td>Leakage, preop RT</td>
<td>31.3%</td>
<td></td>
<td>11.5%</td>
<td></td>
</tr>
<tr>
<td>Leakage, no preop RT</td>
<td>8.6%</td>
<td>p&lt;0.001*</td>
<td>9.3%</td>
<td>p&lt;0.001*</td>
</tr>
<tr>
<td>Defunctioning stoma***</td>
<td>16.7%</td>
<td></td>
<td>36.8%</td>
<td></td>
</tr>
<tr>
<td>Leakage, stoma</td>
<td>15.3%</td>
<td></td>
<td>10.4%</td>
<td></td>
</tr>
<tr>
<td>Leakage, no stoma</td>
<td>11.7%</td>
<td>n.s.*</td>
<td>9.3%</td>
<td>n.s.*</td>
</tr>
</tbody>
</table>

Legend:  
* Patients compared within Paper II and within the SRCR; X² test  
** Preoperative radiotherapy reported 1995-2003; n=6006  
*** Defunctioning stoma reported 1999-2003; n=2941

Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum - a randomised multicentre trial (Paper III)

The role of the temporary stoma in low anterior resection of the rectum for carcinoma has been controversial for at least the last four decades\(^{42}\) and numerous retrospective studies have been presented\(^{28, 51, 78, 97, 101, 126, 131, 136}\). In the three randomised trials previously conducted, there were trends towards decreased leakage rates in defunctioned patients, but due to limited numbers, no firm conclusions could be drawn\(^{53, 122, 129}\). However, in the present randomised multicentre trial, patients without a defunctioning stoma leaked in 28%, compared with 10% in defunctioned patients (p<0.001; OR 3.4; 95% CI: 1.6, 6.9), results not previously demonstrated in any randomised trial of adequate size (Table 12).

Table 12. Randomised trials on defunctioning stoma in anterior resection of the rectum for rectal cancer.

<table>
<thead>
<tr>
<th>Author.</th>
<th>reference</th>
<th>year</th>
<th>n</th>
<th>leakage, total</th>
<th>leakage, no stoma</th>
<th>leakage, stoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graffner,</td>
<td>[53]</td>
<td>1983</td>
<td>50</td>
<td>8% (4/50)</td>
<td>12% (3/25)</td>
<td>4% (1/25)</td>
</tr>
<tr>
<td>Pakkastie</td>
<td>[122]</td>
<td>1997</td>
<td>38</td>
<td>24% (9/38)</td>
<td>32% (6/19)</td>
<td>16% (3/19)</td>
</tr>
<tr>
<td>Pimentel</td>
<td>[129]</td>
<td>2003</td>
<td>36</td>
<td>8% (3/36)</td>
<td>11% (2/18)</td>
<td>6% (1/18)</td>
</tr>
<tr>
<td>Paper III</td>
<td></td>
<td></td>
<td>234</td>
<td>19% (45/234)</td>
<td>28% (33/118)</td>
<td>10% (12/116)</td>
</tr>
</tbody>
</table>
**Rectovaginal fistula**

The leakage rate of 19% in paper III is higher than in many other studies\(^{35,78,86}\), but comparable to rates reported in some investigations\(^ {47,122,150}\). One factor contributing to the high rate of leakage was the fact that as many as 20% (9/45) of the leakages were rectovaginal fistulas. Comparable results are rare but have recently been described\(^ {82}\). In the present trial, only 2/9 rectovaginal fistulas were actually reported as symptomatic leakages, although 6/7 patients with rectovaginal fistulas who were not initially defunctioned were reoperated and had a defunctioning stoma. Subsequently, only 1/7 patients who developed a rectovaginal fistula without having a defunctioning stoma at the initial operation was treated conservatively, a proportion similar to that for the patients initially not defunctioned who developed symptomatic leakage other than rectovaginal fistula, in whom 4/26 were managed without abdominal reoperation and stoma.

**Leakage after hospital discharge**

Another factor contributing to the high leakage rate was the fact that 40% (18/45) of the leakages occurred after hospital discharge upon a second admission. When reported in the literature, this proportion is often lower\(^ {114}\) although comparable figures have been reported\(^ {10}\). It is possible, that these late leakages may be underreported\(^ {18}\). Moreover, it may also be the case that earlier hospital discharge, popularised by Kehlet in the late 1990s\(^ {6}\), has contributed to an increased proportion of patients in whom leakage is diagnosed after hospital discharge.

**Comparison between randomised and non randomised patients**

Another aim of the present study was to assess also patients who were operated on at the participating hospitals but who were not randomised. Twenty-one hospitals participated for a mean period of 21 months, and randomised 234 patients. Data on the non-randomised patients who were operated on at the participating hospitals between 1999 and 2003 were obtained from the SRCR (Table 13). Data from the period 2004-2005 were not available when this thesis was completed (February 2006).

**Table 13.** All patients reported to the Swedish Rectal Cancer Registry (SRCR) who were operated on with an abdominal resection procedure for rectal cancer at the hospitals participating in the present study during a part of the study period, 1999-2003.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal rectal resections reported to the registry</td>
<td>939</td>
</tr>
<tr>
<td>Abdomino-perineal resection</td>
<td>269 (29%)</td>
</tr>
<tr>
<td>Hartmann’s resection</td>
<td>143 (15%)</td>
</tr>
<tr>
<td>Anterior resection</td>
<td>527 (56%)</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>56/527 (11%)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>3/527 (0.6%)</td>
</tr>
</tbody>
</table>
The randomised patients and those who were not randomised were compared in regard to demographic data and operative details. Among the randomised patients cancer stage IV was less common, and preoperative radiotherapy more frequent (Table 14).

Table 14. All patients operated on with anterior resection at the participating hospitals, 1999–2003. Data on the non randomised patients were obtained from the Swedish Rectal Cancer Registry (SRCR).

<table>
<thead>
<tr>
<th></th>
<th>Not randomised 1999-2003 (n=376)</th>
<th>Randomised 1999-2003 (n=151)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>70 (28-90)</td>
<td>69 (42-84)</td>
<td>ns</td>
</tr>
<tr>
<td>Female gender</td>
<td>45%</td>
<td>49%</td>
<td>ns</td>
</tr>
<tr>
<td>ASA score, median (range)</td>
<td>not stated</td>
<td>2 (1-4)</td>
<td>-</td>
</tr>
<tr>
<td>BMI, median (range)</td>
<td>not stated</td>
<td>24.9 (19.3-36.4)</td>
<td>-</td>
</tr>
<tr>
<td>Cancer stage IV (Dukes’ D)</td>
<td>12%</td>
<td>4%</td>
<td>p=0.013</td>
</tr>
<tr>
<td>Tumour height above anal verge, cm, median (range)</td>
<td>10cm (3-15)</td>
<td>10cm (2-15)</td>
<td>ns</td>
</tr>
<tr>
<td>Preoperative radiotherapy</td>
<td>45% (170/376)</td>
<td>79% (118/151)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Defunctioning stoma</td>
<td>47% (176/376)</td>
<td>46% (70/151)</td>
<td>ns</td>
</tr>
<tr>
<td>Level of anastomosis, cm</td>
<td>not stated</td>
<td>5cm (2-7)</td>
<td>-</td>
</tr>
</tbody>
</table>

*X² test

Anastomotic leakage

The rate of anastomotic leakage for all patients operated on at by the participating hospitals during the period 1999-2003 was 11% (56/527). In those randomised it was 19% (45/234). An increased leakage rate among the randomised patients was expected because they comprised only anastomoses at 7cm or less, in contrast to those not randomised, who also included high anterior resection (Partial Mesorectal Excision; PME). However, since the level of anastomosis is not stated in the SRCR, the proportion of PME in those not randomised remains unknown. In a Danish multicentre trial by Bulow comprising 212 anterior resections using the TME technique, the overall proportion of PME was reported to be 20%, and in a large single centre series it was 36%86. It is therefore reasonable to expect approximately 15-20% PME in the non randomised group, with a subsequent lower risk of anastomotic leakage, despite the fact that there was no difference in level of the tumour between the groups. This assumption is supported by the fact that anastomoses >7cm accounted for 17% of the reported exclusion criteria (Table 15).
Table 15. Most frequently reported reasons for not randomising patients in the present study, 1999-2005 (n=305).

<table>
<thead>
<tr>
<th>Reason for not randomising</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative adverse event (any kind)</td>
<td>86 (28%)</td>
</tr>
<tr>
<td>No patient consent</td>
<td>77 (25%)</td>
</tr>
<tr>
<td>Anastomosis &gt;7 cm</td>
<td>53 (17%)</td>
</tr>
<tr>
<td>Advanced stage IV cancer and/or T4 tumour</td>
<td>30 (10%)</td>
</tr>
</tbody>
</table>

Other possible explanations for a lower leakage rate in the non randomised patients could be that rectovaginal fistulas were seldom reported as leakages, as was the case in the randomised patients, and possibly also a tendency to underreport leakages diagnosed after hospital discharge, although this could not be proved. One major difference between the groups was that the randomised patients received preoperative radiotherapy in 79% compared with 45% in those not randomised (p<0.001). Since tumour height and age were similar, there is no obvious explanation for the higher proportion of irradiated patients among those randomised. One possible reason could be that the randomised patients, of whom 86% had an ASA-score of ≤2, were deemed to be in better physical condition, and thereby more fit to receive preoperative radiotherapy. However, since the ASA-score is not stated in the SRCR, this remains a speculation.

**Level of the anastomosis**

The level of the tumour above the anal verge was preoperatively assessed by rigid rectoscopy in 88% of the patients, and the level of the anastomosis was assessed by rectoscopy intraoperatively or postoperatively, or both, in 95%. Data on the distal resection margin as stated by the pathologist were available in 84%. A majority of the resected specimens underwent patho-anatomical assessment after fixation in formalin. The relations between tumour height, level of the anastomosis, and the distal resection margin were compared (Table 16).

Table 16. Relations between the level of the tumour, the level of the anastomosis, and the distal resection margin.

<table>
<thead>
<tr>
<th></th>
<th>mean (SD)</th>
<th>median (range)</th>
<th>available data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of the tumour (cm)</td>
<td>9.7 (2.5)</td>
<td>10 (3-15)</td>
<td>88% (207/234)</td>
</tr>
<tr>
<td>Level of anastomosis (cm)</td>
<td>4.9 (1.0)</td>
<td>5 (2-7)</td>
<td>95% (222/234)</td>
</tr>
<tr>
<td>Distal resection margin (cm)</td>
<td>3.4 (2.0)</td>
<td>3 (0-9)</td>
<td>84% (196/234)</td>
</tr>
</tbody>
</table>

Legend: SD=standard deviation.
The difference between the mean level of the tumour and the mean level of the anastomosis was thus 4.8cm, and the difference between the mean distal resection margin and the level of anastomosis can be calculated at 1.4cm, a finding which can be explained by the distance represented by the distal stapler ring, and possible shrinkage due to formalin fixation in a majority of the specimens. It is noteworthy that the distal resection margin in the patients in Paper II was also 3.4cm (SD 1.9), median 3cm (range 0-10) with available data in 86%, thus nearly identical data in patients operated on ten years earlier but with an anastomosis at median 8cm (1.5-15) above the anal verge.

The level of the anastomosis was assessed in relation to the frequency of symptomatic leakage. The proportion of leakages was 31% at the 3cm level, 25% at 4cm, 20% at 5cm, 21% at 6cm, and 6% when the anastomosis was situated at 7cm above the anal verge (not significant; $X^2$ test for trend) (Figure 4).

**Figure 4.** Distribution of the anastomotic level in 234 patients operated on with low anterior resection of the rectum in relation to symptomatic anastomotic leakage. Missing data (n=12)

![Bar chart showing distribution of anastomotic levels](image)

**Type of anastomosis**

Three types of anastomoses were used by the participating surgeons, the J-pouch, the side to end, and the end to end (straight) anastomosis. The use of the J-pouch anastomosis decreased over time, in contrast to the side to end anastomosis which increased over time (Figure 5). The J-pouch anastomosis leaked in 21% (22/102), the side to end in 19% (18/91) and the end to end anastomosis in 13% (5/38) (not significant; $X^2$ test for trend). In three patients the type of anastomosis was not stated.
**Figure 5.** Type of anastomosis and trends over time in 234 patients operated on with low anterior resection of the rectum. One patient operated on in 1999 not included. Missing data (n=3).

**Registry validation**

For all registries, the issue of validation and possible underreporting of data should be considered. In a retrospective case-control study presented recently in a thesis by Jestin,

of 1381 patients who underwent anterior resection of the rectum in two specified health care regions in Sweden between 1995 and 2000, 132 (9.6%) had reported symptomatic leakage, and were compared with 255 randomly chosen controls without reported leakage. Nevertheless, it was found that 13 patients (4.9%) of the controls had symptomatic leakage within 30 days. If this sample size of 18% is assumed to be representative, 4.9% units should be added to the reported leakage rate of 9.6%, yielding an overall leakage rate of 14.5%. These findings may raise questions regarding how data were reported. However, research based on existing population based registries, including randomised multicentre trials in cooperation with a population based registry, are important as instruments for validating existing registries. Increased use of these registries for research purposes will presumably further refine registration procedures and thereby increase the overall quality and validity.

**Mortality**

In contrast to the elevated leakage rate in this trial, there was no early mortality, which is typically reported at between 0.6% and 3%, but may be as high as 7% in TME surgery. In the present trial, if three deaths are included that occurred after 30 days, and that were related to the rectal resection, one in a non leaker and two in leakers, the mortality was still low (1.3%). In two multicentre trials with patients who underwent TME anterior resection, the 30-day mortality associated with leakage was 14% and 19%, respectively.
Defunctioning stoma

In the present trial the defunctioning stoma decreased the rate of symptomatic leakage significantly. However, when assessing the overall role of the defunctioning stoma, a number of aspects must be considered. Several adverse events related to the defunctioning stoma may occur when the stoma is present, such as stoma care problems, skin irritation, high output with possible dehydration, intestinal obstruction, stoma prolapse and stomal hernia. After reversal of the stoma, intestinal obstruction, hernia at the site of the reversed stoma, wound infection, abdominal abscess, peritonitis, and possibly even death, may occur\textsuperscript{55,131,47}.

Table 17. Reasons for persisting loop stoma or end colostomy in patients initially defunctioned (16/116) and initially not defunctioned (20/118).

<table>
<thead>
<tr>
<th>Patients initially defunctioned (n=16).</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor anorectal function</td>
<td>4</td>
</tr>
<tr>
<td>Poor medical condition</td>
<td>2</td>
</tr>
<tr>
<td>Patient refusal for another operation</td>
<td>1</td>
</tr>
<tr>
<td>Death unrelated to surgery</td>
<td>1</td>
</tr>
<tr>
<td>Waiting for scheduled reversal</td>
<td>2</td>
</tr>
<tr>
<td>Progressive liver metastases</td>
<td>5</td>
</tr>
<tr>
<td>Second, non colorectal cancer*</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients urgently reoperated with a defunctioning stoma because of symptomatic leakage (n=20)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor anorectal function</td>
<td>4</td>
</tr>
<tr>
<td>Anastomotic stricture</td>
<td>3</td>
</tr>
<tr>
<td>Conversion to end colostomy at urgent reoperation</td>
<td>3</td>
</tr>
<tr>
<td>Poor medical condition</td>
<td>1</td>
</tr>
<tr>
<td>Anastomotic leakage after reversal, patient refusal for another operation</td>
<td>1</td>
</tr>
<tr>
<td>Loop ileostomy at 2 years, deemed permanent</td>
<td>1</td>
</tr>
<tr>
<td>Reversal not decided at median 13 months</td>
<td>4</td>
</tr>
<tr>
<td>Waiting for scheduled reversal</td>
<td>1</td>
</tr>
<tr>
<td>Progressive liver metastases</td>
<td>1</td>
</tr>
<tr>
<td>Second, non colorectal cancer*</td>
<td>1</td>
</tr>
</tbody>
</table>

Legend: *diagnosed after the rectal resection

For various reasons not all loop stomas will be reversed as initially planned. The rate of permanent stoma in patients initially defunctioned after rectal excision for cancer (loop stoma or loop stoma converted to end colostomy) is between 3\% and 19\%\textsuperscript{4,28,126,131}. In paper III, after a follow-up of median 42 months (range 6-72), 86\% (100/116) of the patients initially defunctioned had been reversed and were free of stoma of any kind at median 5 months (2-22) after the initial rectal resection. Thus, of the patients initially defunctioned, 14\% had a stoma of any kind, compared
to 17% in those initially not defunctioned (14% vs. 17%; not significant). The most frequent reasons for a persisting stoma were poor anorectal function, liver metastases and anastomotic stricture (Table 17).

Early mortality after elective reversal of a defunctioning stoma is not often reported in larger series. However it was reported to be 1.6% by Dixon back in 1948, and in recent studies has been reported to be between 0.5% and 1.9% 29, 47, 55, 89 (Table 18). In the present study there was one death within 30 days. This risk of early mortality should be taken into account when the decision to create or not to create a defunctioning stoma is made. Moreover, it should be added to the total risk of early mortality (30-day mortality), which is 0.6% to 7% in large series of TME surgery19, 35, 86, and presently (2003) 2.5% in Sweden according to the SRCR.

**Table 18.** Early mortality after elective reversal of a defunctioning loop stoma after anterior resection of the rectum for cancer.

<table>
<thead>
<tr>
<th>Author</th>
<th>year</th>
<th>reference</th>
<th>Mortality</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dixon</td>
<td>1948</td>
<td>[18]</td>
<td>1.6%</td>
<td>(7/426)</td>
</tr>
<tr>
<td>Hallböök*</td>
<td>2002</td>
<td>[116]</td>
<td>1.1%</td>
<td>(1/94)</td>
</tr>
<tr>
<td>Leester</td>
<td>2002</td>
<td>[117]</td>
<td>1.6%</td>
<td>(1/64)</td>
</tr>
<tr>
<td>Gastinger</td>
<td>2005</td>
<td>[78]</td>
<td>0.5%</td>
<td>(3/636)</td>
</tr>
<tr>
<td>Paper II</td>
<td>-</td>
<td>-</td>
<td>1.9%</td>
<td>(1/54)</td>
</tr>
<tr>
<td>Paper III</td>
<td>-</td>
<td>-</td>
<td>1.0%</td>
<td>(1/101)</td>
</tr>
</tbody>
</table>

*including only patients with rectal cancer (n=94)

**Leakage and local recurrence**

Other findings in recent studies are increased local recurrence and decreased survival associated with symptomatic anastomotic leakage8, 127. However, these series often comprise patients operated on over a long period of time, with a substantial proportion of the operations before the TME era. If these results also withstand the test of time in regard to TME surgery, the defunctioning stoma must also be considered from the perspective of local recurrence and survival.

In summary, the present randomised multicenter trial has demonstrated a decreased leakage rate in defunctioned patients in low anterior resection, a result never before demonstrated in any randomised trial of adequate size. Based on these results, and taking into account various aspects of the defunctioning stoma including reversal, the use of a defunctioning stoma in low anterior resection of the rectum can be recommend.
Assessment of pelvic fluid collection and C-reactive protein after anterior resection of the rectum for cancer. (Paper IV)

In paper IV different methods of postoperative monitoring after anterior resection of the rectum were assessed. The aim was to investigate postoperative conditions in the pelvis by means of CT-scans, blood samples, and clinical bedside parameters. Thirty-three patients who underwent anterior resection of the rectum for rectal cancer (n=32) and rectal adenoma (n=1) at three hospitals were included. Since the rate of symptomatic anastomotic leakage was high, 9/33, it was possible to compare leakers with non leakers. The initial hypothesis postulating shrinkage of the distal colon mesentery and thereby possibly increased anastomotic tension, was not confirmed since no differences could be demonstrated in metal clip distances between postoperative day 2 and day 7.

The CT-scans revealed larger presacral fluid collections on the seventh postoperative day in leakers as compared to non leakers, as well as an increase in presacral fluid between postoperative day 2 and 7 in leakers. In a previous study by Sagar, pelvic collection volumes after drainage treatment were measured and found to be comparable with our findings\textsuperscript{137}.

**Drainage**

All patients had an active pelvic drain in use for median 3 (2-6) postoperative days, and 28/33 had their drains 3 days or less. There was no difference between leakers and non leakers when comparing the total amount of evacuated drainage fluid, although a trend for evacuating larger volumes during the first 24 hours was seen in the leakers, with median 374ml (range 115-950) compared to 202ml (25-1350) in non leakers (p=0.075). The total volume drained in all patients was median 450ml (25-2667): median 365ml (25-2667) in non leakers and median 684ml (115-1735) in leakers (not significant). These drained volumes were higher than those reported by Hilsabeck\textsuperscript{63}, 450ml compared to 257 ml. In one retrospective multicentre trial comprising 924 patients\textsuperscript{126}, the leakage rate was 10% in those with a drain, and 23% in those without. However, no randomised investigation has demonstrated any reduction in leakage rate in drained patients\textsuperscript{105, 138}, and in two metaanalyses the routine use of drain was not recommended\textsuperscript{128, 151}.

**C-reactive protein**

C-reactive protein (CRP) and white blood cell count (WBC) were analysed daily as possible markers of postoperative adverse events. CRP levels were comparable on the first postoperative day, but thereafter significantly increased in patients who later developed leakage, which was diagnosed on median day 8 (4-14). There were no leakages after hospital discharge. The increased CRP levels already demonstrated on the second postoperative day seem to represent an inflammatory process present before the symptomatic leakage was diagnosed (Figure 6).
Figure 6. C-reactive protein serum levels in patients operated on with anterior resection of the rectum without (n=24) and with (n=9) symptomatic leakage. Median values, interquartile range and outliers *.

However, if this ongoing elevation in CRP levels mirrors an already existing leakage, or if it reflects a different pattern of inflammatory response after major pelvic surgery, possibly associated with an increased risk of developing leakage, cannot be concluded from these data. Further investigations on postoperative inflammatory response are needed.

White blood cell count

A decrease in WBC has been reported after preoperative irradiation, and is also associated with an increased risk of postoperative complications58. In the present study, with daily analysis of WBC in all patients (91% complete sample rate), there was a significant WBC decrease on postoperative day 1-5 in irradiated patients. However, in this small series there was no difference in postoperative complication rates, and larger prospective investigations are needed to assess the possible influence on postoperative morbidity.
In summary, an important finding in the present explorative study was an increase in CRP-levels from postoperative day 2 and onwards in patients who later had a symptomatic leakage diagnosed. Regular monitoring of CRP in the postoperative period is recommended and if a prolonged elevation occurs, the suspicion of clinical leakage should be high.

**Early detection of anastomotic leakage by intraperitoneal microdialysis and intraperitoneal cytokines after anterior resection of the rectum for cancer? (Paper V)**

The aim of this prospective study was to assess postoperative intraperitoneal carbohydrate metabolism monitored by intraperitoneal microdialysis (IPM) and intraperitoneal cytokines, a technique recently described in gastro-intestinal surgery\(^\text{71}\), and to explore metabolic differences in regard to symptomatic leakage. The rate of symptomatic leakage was 7 out of 23 and leakage was diagnosed on median postoperative day 14 (range 2-22). There were four patients with leakage during the initial hospital stay on median day 6 (2-14) and three with leakage diagnosed after hospital discharge upon readmission on median day 20 (18-22).

**Microdialysis**

Glucose, pyruvate and lactate were monitored by three microdialysis catheters for six postoperative days. One catheter was located near the colorectal anastomosis, one was freely floating in the central abdomen, and one was placed in subcutaneous tissue. An increased lactate/pyruvate ratio (L/P ratio) was detected near the anastomosis in leakers on postoperative day 5 (p=0.029) and 6 (p=0.009), compared with non leakers (Figure 7). In the present study with a limited number of patients, there were no statistically significant differences for other postoperative days regarding the L/P ratio, or regarding glucose.

The L/P ratio near the anastomosis in non leakers was 16-17 on the first postoperative day, it decreased for the next two days, and then stabilised around 13-14. Similar results were seen in recent studies in patients who underwent right sided hemicolecctomy\(^\text{71,72}\). Moreover, there were no differences when comparing men with women (Figure 8) as well as patients with and without defunctioning stoma (Figure 9). In leakers, there was no such initial decrease, and from day four and onwards, the L/P ratio rose to 19, accompanied by a simultaneous trend for a decrease in glucose, from around 7 to 4 mmol.
**Figure 7.** Lactate/pyruvate ratio (L/P ratio) during six postoperative days following anterior resection of the rectum in patients without (n=14) and with symptomatic anastomotic leakage (n=7). Median values, interquartile range and outliers "*".

![Box plot figure](image)

† Mann-Whitney U test

**Figure 8 and 9.** Lactate/pyruvate ratio (L/P ratio) near the anastomosis during six postoperative days following anterior resection of the rectum in patients without leakage (n=16) in relation to gender defunctioning stoma.

No statistically significant differences between groups (Mann-Whitney U test).

**Figure 8.**

Lactate/pyruvate (L/P) ratio in patients without leakage (n=16) in relation to gender

![Graph figure](image)

**Figure 9**

Lactate/pyruvate (L/P) ratio in patients without leakage (n=16) in relation to defunctioning stoma

![Graph figure](image)
**Interpretation**

The findings of an elevated L/P ratio on day 5 and 6 in patients who were diagnosed with symptomatic leakage on median postoperative day 14 were interpreted as a shift from an aerobic to a more anaerobic metabolism, with a subsequent increase in lactate, decrease in pyruvate, and decrease in glucose due to increased consumption. These changes in metabolism were seen before the leakage was clinically diagnosed. A larger investigation is needed to confirm these results.

**Cytokines**

A pelvic drain was used for two postoperative days to collect peritoneal fluid used for analysis of cytokines IL-6, IL-10 and TNF-α. In leakers, IL-6 and IL-10 were significantly increased on day 1 and 2, and TNF-α was increased on day 1. This finding should be assessed keeping in mind that the clinical diagnosis of the leakage was made on median postoperative day 14. This raises the question of whether these differences in cytokines represent an already ongoing inflammatory process associated with a leakage, not yet diagnosed by the clinician, or whether they are a reflection of a different pattern of inflammatory response after major pelvic surgery, similar to that of CRP in Paper IV.

In addition, not only were the levels of IL-6 and IL-10 increased, but there was also a tendency for a difference in pattern of response in cytokines measured every six hours postoperatively in leakers as compared with non leakers. Due to a limited number of observations, no statistical significance was obtained when cytokines were measured and compared in non leakers and leakers every 6 hours postoperatively (Figure 10a). However, when the same observations were analysed comparing the first and second postoperative day in non leakers and leakers, IL-6 was increased in leakers (Figure 10b). However, these findings need to be confirmed by a larger investigation.

In conclusion, the findings in this explorative investigation indicate that early detection of an anastomotic leakage might be possible by means of postoperative intraperitoneal monitoring. Further investigations are needed in order to achieve a better understanding of the inflammatory response in the peritoneal cavity.
Figure 10a-b. Intraperitoneal IL-6 levels in patients operated on with anterior resection of the rectum, monitored postoperatively for median 45 hours (range 42-48) and measured every 6 hours on 8 occasions (time 1-8) starting at 6:00 pm the day of surgery (Figure 10a). The same set of observations analysed as postoperative day 1 and 2 (Figure 10b). Patients without (n=14) and with symptomatic anastomotic leakage (n=7). Median values, interquartile range and outliers "*".

Figure 10a

![Box plot of IL-6 levels in patients operated on with anterior resection of the rectum](image)

Time 1-8; * Mann-Whitney U test

Figure 10b

![Box plot of IL-6 levels in patients operated on with anterior resection of the rectum](image)

day 1

p=0.002*

day 2

p=0.012*

* Mann-Whitney U test
SUMMARY

The presence of intraoperative adverse events in patients undergoing anterior resection of the rectum was more frequent in patients with early mortality compared with survivors. Bleeding and major spillage of faeces were intraoperative adverse events that were more common in those who died. An anastomosis that was considered unsatisfactory by the surgeon during the operation was more often completely reconstructed in the survivors.

Low anastomosis, the presence of intraoperative adverse events, male gender, and preoperative radiotherapy were independent risk factors in multivariate regression analysis for symptomatic anastomotic leakage in patients undergoing anterior resection of the rectum. After symptomatic anastomotic leakage, one out of four patients ended up with a permanent stoma of any kind, and the early mortality associated with symptomatic leakage was 7.5%, compared with the mortality rate of 2.1% for the complete cohort.

Defunctioning stoma in low anterior resection of the rectum decreased the rate of symptomatic leakage, 10% vs 28% (p<0.001), a result never before demonstrated in any randomised trial of adequate size. The rate of permanent stoma was not different in patients initially defunctioned and in those not defunctioned. Rectovaginal fistulas and leakage diagnosed after hospital discharge contributed substantially to the overall symptomatic leakage rate.

C-reactive protein was increased from the second postoperative day and pelvic fluid collections were increased in patients who developed symptomatic anastomotic leakage.

An increase in the intraperitoneal lactate/pyruvate ratio on postoperative day 5 and 6, and an increase in intraperitoneal cytokines IL-6, IL-10 on postoperative day 1 and 2, and in TNF-α on day 1, were demonstrated in patients who developed symptomatic anastomotic leakage before the leakage was diagnosed clinically.
GENERAL CONCLUSIONS

• Defunctioning stoma decreased the risk for symptomatic anastomotic leakage. Taking into account the overall morbidity in those with and without initial defunctioning, a defunctioning stoma can be recommended in low anterior resection of the rectum.

• Low anastomosis, the presence of intraoperative adverse events and male gender were independent risk factors for symptomatic anastomotic leakage in the present population based setting, and as such, they constitute additional reasons for considering a defunctioning stoma.

• In sphincter saving TME surgery, it is the low anastomosis that restores bowel continuity and thereby spares the patient a permanent stoma. The anastomosis is the most vulnerable component in this procedure, and therefore an anastomosis can be accepted only if it is considered optimal. If this is not the case, complete reconstruction, or omission, of the anastomosis should be considered.

• Increased serum levels of C-reactive protein proved to be a strong indicator of symptomatic anastomotic leakage, and postoperative monitoring is recommended. If increased levels persist, the suspicion of anastomotic leakage should be strong.

• Intraperitoneal monitoring of the lactate/pyruvate ratio and cytokines IL-6, IL-10 and TNF-α, demonstrated increased levels in patients before the leakage was clinically diagnosed. The present results indicate that intraperitoneal markers may have a role in early detection of symptomatic anastomotic leakage.
SUMMARY IN SWEDISH -
SAMMANFATTNING PÅ SVENSKA

Bakgrund

Den ökade kunskapen om hur cancer i ändtarmen sprider sig lokalt i den närmast omgivande vävnaden, det s.k. mesorektum, har lett till att den operationsmetod, total mesorektal excision (TME), som introducerades på 1980-talet av den engelske kirurgen Heald, och som i Sverige har fått allmän spridning under senare halvan av 1990-talet, nu är allmänt accepterad som den korrekta operationsmetoden för tumörer i nedre och mellersta delen av ändtarmen.

Införandet av TME-tekniken har medfört väsentligt förbättrade onkologiska resultat i form av lägre frekvens återfall av cancer i lilla bäckenet (lokalrecidiv) samt förbättrat 5-årsöverlevnad. Detta kunde först visas i serier från enskilda sjukhus i England och USA, men på senare tid även i data från Svenska Rektalcancer Registret. TME-tekniken innebär ett omfattande kirurgiskt ingrepp i lilla bäckenet oavsett om tarmen skarvas ihop eller om en permanent stomi anlägges. Komplikationer i någon form förekommer hos cirka en tredjedel och dödligheten inom 30 dagar är omkring 2-3%. I de fall då tarmen kan skarvas (resektion av rektum med anastomos) är läckage i tarmskarven (symptomatiskt anastomosläckage) den enskilt mest fruktade komplikationen.

Syfte

Denna avhandling har tre huvudsakliga syften. Det första var att undersöka betydelsen av den avlastande stomin i förhållande till risken att utveckla symptomgivande anastomosläckage, och dess roll i det fortsatta postoperativa förloppet hos patienter med och utan sådant läckage. Det andra syftet var att undersöka tänkbare riskfaktorer för anastomosläckage i ett populationsbaserat patientmaterial med målsättningen att bättre kunna identifiera patienter med förhöjd risk. Det tredje syftet var att utveckla och värdera metoder att undersöka och följa nyopererade patienter med en tarmskarv i lilla bäkenet, med målsättningen att upptäcka anastomosläckage tidigare. Nedan presenteras en kort sammanfattning av de fem delarbetena.

Delarbete I

I det första delarbetet analyserades intraoperativa komplikationer i en retrospektiv populationsbaserad fall-kontroll studie. Samtliga patienter som opererades i Sverige med resektion av rektum och skarvning av tarmen under åren 1987-95 och som avled inom 30 dagar eller under operationsvårdsfallet (n=140), jämfördes med slumpmässigt utvalda patienter (n=423), som genomgick samma typ av operation under samma tidsperiod, men som överlevde ingreppet. Untersökningen
visade att intraoperativa komplikationer förekom oftare hos de som avled (46% jämfört med 30%). Dessutom förbättrades överlevnaden om en anastomos som av kirurgen under operationen bedömts som icke tillfredsställande rekonstruerades. Förekomst och typ av intraoperativa komplikationer liksom åtgärder vidtagna av kirurgen på grund av dessa intraoperativa komplikationer analyserades, vilket ej tidigare beskrivits i ett populationsbaserat patientmaterial.

Delarbete II
Det andra delarbetet analyserade tänkbara riskfaktorer för anastomosläckage. I en populationsbaserad retrospektiv studie undersöktes 432 patienter som utgjorde en delmängd av patienterna i delarbete I. Det totala antalet patienter som opererades med främre resektion av rektum i Sverige under åren 1987-95 var 6833 patienter enligt Socialstyrelsens slutenvårdsregister, och de 432 undersökta patienterna motsvarade således ett stickprov på 6,3%. Symptomatiskt anastomosläckage förekom hos 12% av patienterna, och 25% av dem med läckage fick slutligen en permanent stomi. Risken för att avlida inom 30 dagar efter anastomosläckage var 7,5%. I multivariat regressionsanalys visade sig låg anastomos (<6cm ovan anus), manligt kön, intraoperativa komplikationer och preoperativ strålbehandling vara oberoende riskfaktorer för att utveckla symptomgivande anastomosläckage. Jämförbara resultat har tidigare påvisats i serier från enskilda sjukhus men ej i ett populationsbaserat patientmaterial.

Delarbete III
Delarbetet baserades på en randomiserad multicenterstudie med patienter som opererades med låg resektion av rektum (≤7cm ovan anus) och anastomos för rektalcancer med TME-teknik. Patienterna lottades (randomiserades) till avlastande stomi (n=116) eller inte (n=118). Totalt utvecklade 19% av patienterna symptomatiskt anastomosläckage. Patienter med avlastande stomi hade läckage i 10%, och de utan avlastande stomi hade läckage i 28%. Denna skillnad var statistiskt säkerställd (p<0,001) och har tidigare inte påvisats i någon randomiserad studie av tillräcklig storlek. Av de patienter som randomiserades till att få stomi hade 86% fått stomin nerlagd vid en uppföljningstid på median 42 månader (spridning 6-72), jämfört med 83% av patienterna randomiserade till att få stomi, en skillnad som inte är statistiskt säkerställd. Denna studie är den första som har kunnat vetenskapligt påvisa att en avlastande stomi minskar risken för anastomosläckage, den mest fruktade komplikationen efter denna typ av operation.

Delarbete IV
I det fjärde delarbetet följdes prospektivt 33 patienter med skiktröntgen av lilla bäckenet postoperativt dag 2 och 7, blodprover och kliniska undersökningar, efter att ha opererades för rektalcancer med resektion av rektum och anastomos. Tre sjukhus (Örebro, Linköping och Norrköping) deltog i denna undersökning. Skiktröntgen påvisade större vätskeansamlingar i lilla bäckenet hos de som senare fick ett symptomgivande anastomosläckage diagnosticerat.
C-reaktivt protein i serum ("snabbsänka") var förhöjd postoperativt från dag 2 och framåt hos de som fick ett anastomosläckage kliniskt diagnosticerat på median dag 8 (spridning 4-14). Vita blodkroppar i serum (LPK) var förhöjda hos de som fått strålbehandling före operationen, men detta ökade inte risken för anastomosläckage eller andra komplikationer.

**Delarbete V**

I det sista delarbetet analyserades 23 patienter som opererades för rektalcancer med resektion av rektum och anastomos. Patienterna följdes under de första 6 postoperativa dygnen med avseende på kolhydrat-metabolism och interleukiner i bukhålan. Med mikrodialys-teknik monitorerades förtöpande glukos, pyruvat och laktat med intraperitoneala katetrar. Via ett bäckendränage mättes de intraperitoneala interleukinerna IL-6, IL-10 och TNF-α under de två första dygnen. Hos de patienter som utvecklade symptomatiskt anastomosläckage på median postopeativ dag 14 (spridning 2-22) var laktat/pyruvatkvoten nära anastomosen förhöjd dag 5 och 6, interleukinerna IL-6 och IL-10 var förhöjda dag 1 och 2 och TNF-α förhöjd dag 1.

**Sammanfattning.**

I de två första delarbetena redovisas data från nationella kohorter i syfte att öka förståelsen för vilka patienter som har ökad risk för anastomosläckage och övriga komplikationer, vilket ej tidigare har redovisats från populationsbaserade material. I det tredje delarbetet har för första gången i en randomiserad studie med att tillräckligt stort antal patienter visats att avlastande stomi minskar risken för symptomatiskt anastomosläckage. Denna fråga har debatterats i den kirurgiska litteraturen i åtminstone tre decennier utan att konsensus uppnåtts. Avlastande stomi kan nu tack vare denna undersökning, med hög grad av evidens, rekommenderas vid låga anastomoser. I de fjärde och femte delarbetena redovisas undersökningsfynd och ny metodik som kan ha en potential att bidra till att den mest fruktade komplikationen efter rektalcancer kirurgi med bevarande av tarmkontinuiteten, anastomosläckage, kan upptäckas tidigare och att morbiditet och mortalitet därigenom ska kunna reduceras.
Dúbium sapiéntiae inítiu
René Descartes
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REFERENCES


29. 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.


107. Miles W. Cancer of the rectum. *Lettsomian lectures* 1923; **63**.


113. Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 2002; **26**: 350-357.


