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In treatment of rectal cancer, anterior resection has the benefit of sphincter preservation but suffer from a common complication in anastomotic leakage. Although much is known about preventive measures and risk factors, anastomotic leakage remains a significant concern. There is a paucity in previous research of long-term implications of anastomotic leakage. Based on five papers, this thesis describes aspects regarding time of diagnosis, effects on bowel continuity and long-term functional outcome in patients with anastomotic leakage after anterior resection..

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Abstract

Background: Anterior resection has the benefit of enabling bowel continuity, but suffer from a common complication in anastomotic leakage.There is a paucity in previous research of long-term implications of anastomotic leakage after anterior resection.

Aims: To gain general knowledge of the morbidity related to anastomotic leakage after anterior resection for rectal cancer, specific aims were:

I. To investigate late detected anastomotic leakage after anterior resection regarding incidence, and evaluate its clinical features and clinical variables associated to late detected anastomotic leakage.
II. To evaluate how often bowel continuity is restored in long-term follow-up after anastomotic leakage in anterior resection and clinical factors related to a permanent stoma.
III. To explore rectal contrast studies of patients with anastomotic leakage for predicitve features related to an outcome of permanent stoma.
IV. To evaluate the effect of anastomotic leakage after anterior resection on long-term bowel dysfunction
V. To evaluate the effect of anastomotic leakage after anterior resection on Quality of Life, as well as to evaluate the effect of maintained bowel continuity in anastomotic leakage patients on Quality of Life.

Methods: Paper I-III, a retrospective cohort of patients subjected to anterior resection in the Southern healthcare region of Sweden was used to identify patients with anastomotic leakage according to a study protocol definition. This group of anastomotic leakage patients was investigated with respect to late leakage, permanent stoma in long-term follow-up and radiological features associated with an outcome of permanent stoma. In paper IV and V a retorspective cohort of patients subjected to anterior resection in the Southern, Western and Northen healthcare regions of Sweden 2007-2013 was used, the effect of anastomotic leakage on bowel dysfunction and Quality of life was investigated using propensity score mathcing models.

Results and conclusions: Anastomotic leakage after anterior resection is associated with signifcant long-term morbidity. Late detected anastomotic leakage after anterior resection is common and related to use of a defunctioning stoma at anterior resection. Two-thirds of all patients with anastomotic leakage after anterior resection end up with a permanent stoma in long-term follow-up, wheras in patients with bowel continuity there is a doubled risk of severe bowel dysfunction. However, no superiority in Quality of Life related to outcome in bowel continuiuty could be demonstrated.

Key words Anastomotic leakage, anterior resection, rectal cancer, bowel dysfunction, low anterior resection syndrome

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Table of Contents

Original papers

This thesis is based on the following papers, referred to by their Roman numerals

I. Jutesten H, Draus J, Frey J, Neovius G, Lindmark G, Buchwald P, Lydrup ML. Late leakage after anterior resection: a defunctioning stoma alters the clinical course of anastomotic leakage. Colorectal Disease. 2018 Feb; 20(2):150-159. doi: 10.1111/codi.13914.

II. Jutesten H, Draus J, Frey J, Neovius G, Lindmark G, Buchwald P, Lydrup ML. High risk of permanent stoma after anastomotic leakage in anterior resection for rectal cancer. Colorectal Disease. 2019 Feb;21(2):174-182. doi: 10.1111/codi.14469.

III. Jutesten H, Lydrup ML, Landberg A, Risberg D, Ekberg O, Zackrisson S, Buchwald P. Radiological findings in anastomotic leakage after anterior resection may predict a permanent stoma. Acta Radiol Open. 2020 Jan 6;9(1):2058460119897358. doi: 10.1177/2058460119897358.

IV. Jutesten H, Buchwald P, Angenete E, Rutegård M, Lydrup ML. High risk of low anterior resection syndrome in long-term follow-up after anastomotic leakage in anterior resection for rectal cancer. Manuscript, submitted for publication.

V. Jutesten H, Buchwald P, Angenete E, Rutegård M, Lydrup ML. Quality of life in long-term follow up after anastomotic leakage in anterior resection for rectal cancer. Manuscript.

Abbreviations

AJCC	American Joint Committee on Cancer
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
CI	Confidence Interval
CRC	Colorectal Cancer
CRP	C-Reactive Protein
CT	Computed Tomography
HR	Hazard Ratio
LARS	Low Anterior Resection Syndrome
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratio
PACS	Picture Archiving and Communications System
PASiS	Regional web-based patient administrative system (Patient Administrativt System i Sjukvården)
PME	Partial Mesorectal Excision
pTNM	pathological Tumor Node Metastasis stage
RR	Relative Risk
SCRCR	Swedish ColoRectal Cancer Registry
TME	Total Mesorectal Excision
TNM	Tumor Node Metastasis stage
UICC	Union for International Cancer Control

Background

Colorectal cancer

Epidemiology

Colorectal cancer (CRC) is the third most common cancer, with almost 2 million new cases and nearly 900 000 deaths it is accounting for approximately 10 % of all diagnosed cancers and cancer related deaths each year worldwide[1]. Two thirds of all CRC are located in the colon, whereas the one third are found within 15 cm from anal verge and is referred to as rectal cancer[1, 2]. The median age at diagnosis of CRC is approximately 70 years, with alarming reports of an increasing incidence mainly for rectal and left-sided colon cancer in young adults[1, 3, 4]. There is a geographical variation In CRC where the highest rates are seen in Europe, North America and Oceania, although with predictions of a future increases in incidence and mortality mainly in social and economic developing countries[1, 5]. About 20-25% of CRC patients will present with metastatic disease at the time of diagnosis, and 20-25% will develop metastasis later[6]. However, decreasing trends in CRC mortality are seen in developed countries where the overall 5-year cancer specific survival has reached approximately 65%, whereas it remains under 50% in developing countries[1, 5, 7, 8].

Risk factors

Male sex and increasing age are both associated to CRC incidence, and some 10-20% of all patients with CRC have positive family history[9, 10]. Cancer susceptibility genes associated with CRC risk have been identified, but all factors contributing to heritability are not fully understood[9, 11]. Among CRC patients, 5-7% are affected by a well-defined hereditary colorectal cancer syndrome classified as non-polyposis (Lynch syndrome and familial colorectal cancer) and polyposis syndromes[12]. Identifying patients affected by hereditary colorectal cancer syndrome is of great importance since it provides conditions for a surveillance strategy, optimal handling when finding CRC as well as appropriate counseling for relatives at risk. Due to increased risk for CRC, colonoscopy surveillance programs are also recommended for patients with previous history of CRC or adenomas, and for patients with long-standing inflammatory bowel disease[13, 14].

Environmental risk factors for CRC have been identified including smoking[15], excessive alcohol intake[16], obesity[17], diabetes[18] and processed meat intake[19], and patients with a family history of colorectal cancer have been suggested to have a particular susceptibility to these environmental factors[20]. It has also been suggested that certain bacterial species affecting colonic microbiota could play part in CRC development[21].

It has been reported that colon and rectal cancers differ in association with environmental risk factors. Some factors (physical activity, diet, smoking) are stronger mediators of risk for colon cancer than rectal cancer, suggesting that a healthy lifestyle is better at preventing colon cancer than rectal cancer[22].

Diagnosing rectal cancer

Onset of symptoms such as change in bowel or bleeding should generally prompt colonoscopy. By means of optimal bowel preparation and careful mucosal inspection, a colonoscopy can detect neoplastic lesions, rule out synchronous lesions elsewhere in the colon or rectum and in cases of adenomas and selected cases of early stages of CRC provide therapeutic excision. CT colonography is a complementary imaging method for diagnosis but lacking therapeutic capability, most often used in cases where colonoscopy for some reason fails[23].

Staging makes the groundwork for further therapy

Upon discovery of rectal cancer, staging of the tumor follows usually according to the TNM (Tumor, Node, Metastasis) system provided by American Joint Committee on Cancer (AJCC) [24]. The TNM system evaluates local tumor growth (T) from the depth of invasion through layers of the bowel wall, locoregional lymphnode involvement (N) and presence of distant metastasis (M). Whereas final pathological assessment of TNM stage with prognostic implication is done after surgery, clinical TNM stage based on imaging and clinical findings preoperatively and constitutes the basis for therapeutic recommendations preferably made at a multidisciplinary team conference[25]. Locoregional staging for rectal cancer is done with MRI at times with the support of endorectal ultrasonography to better assess extent of tumor invasion in cases with superficial growth[26-28]. Presence of distant metastasis can be evaluated with CT scan, with the addition of MRI of the liver in case of diagnostic uncertainty, and CT-PET in selected cases where curative treatment for metastatic disease is considered[28, 29].

Clinical TNM, relation of tumor to mesorectal fascia, extramural venous invasion, presence of lateral node disease and level from anal verge directs further management, where surgery, with or without additional oncological therapy, is the cornerstone of curative treatment[30, 31].

Neoadjuvant treatment

In order to reduce the risk of local recurrence, neoadjuvant (preoperative) oncological treatment is used in intermediate to high-risk patients[32]. Short-course radiotherapy (5 x 5 Gray) is mainly a treatment for rectal cancer evaluated as resectable. It was reported to improve overall and cancer specific survival and reduce local recurrence rates in the Swedish Rectal Cancer Trial[33], local control was further confirmed in the Dutch TME trial but without effect on overall survival[34, 35]. A traditional approach of immediate surgery after radiotherapy has been challenged by the Stockholm III trial, where delaying surgery 4-8 weeks was shown to have the same effect on tumor outcome, but with less postoperative complicatons[36, 37]. In rectal cancers with clinically threatened resection margins, neoadjuvant chemoradiotherapy using 45-50 Gray in 25-28 fractions in with flouropyrimidine as a radiation sensitizer followed by an interval of 8-10 weeks before surgery, is used to improve the chance of curative resection[30]. However, in an ongoing trial the combination of short-course neoadjuvant radiotherapy, followed by chemotherapy and subsequent surgery is evaluated as an alternative with possibly better downstaging and systemic effect[38].

After neoadjuvant treatment, up to one fifth of all patients have a complete response without any detectable residual tumor making organ preserving watch-and-wait strategies the subject of ongoing clinical trials, but still not an established treatment[39].

Table 1. TNM classification in relation to staging according to AJCC/UICC classification

The 8th edition of the American Joint Committee on Cancer and Union for International Cancer Control TNM staging

TNM Classification	AJCC / UICC stage
T1-2 N0 M0	Stage I
T1 = Invasion of submucosa	
T2 = Invasion of muscularis propria	
N0 = No involvement of lymph nodes	
M0 = No distant metastasis	
T 3-4 N0 M0	Stage II
T3 = Invasion into serosa or perirectal fat	
T4 = Invasion into adjacent organ and/or breeching visceral peritoneum	
N0 = No involvement of lymph nodes	
M0 = No distant metastasis	
T 1-4 N1-2 M0	Stage III
N1 = 1-3 perirectal lymph nodes involved	
N2 = >4 perirectal lymph nodes involved	
M0 = No involvement of lymph nodes	
T1-4 N0-2 M1	Stage IV

Surgery for rectal cancer

A brief history

Rectal cancer surgery has undergone extensive changes since its introduction in the early 19th century. Early development was mainly about finding different approaches in order to achieve access to the rectum in a manner that allowed resection. It was followed by later phases of development involving oncological and functional improvements in parallel.

The perineal approach was introduced by Lisfranc in 1826 when he performed an en bloc resection of the perineum and rectum for a distal rectal cancer, leaving a distal bowel end for uncontrollable excretion through the perineal opening. The procedure was later improved by Lockhart-Mummery by adding stoma formation to the procedure[40]. In 1908 Miles reported optimized access to the rectum in a procedure where a combined entry from the abdominal cavity and the perineum was used, an early model to the procedure in current practice known as *abdominoperineal resection*. Miles furthermore introduced the groundbreaking concept of removal of mesentery in order to prevent local recurrence of cancer[41]. The posterior approach was developed by Kraske who proposed mobilization of the upper rectum by incising the gluteus maximus and levator ani from the left side of the sacrum[42]. The anterior approach, in which the rectum is resected from the abdominal cavity, was established by Hartmann reporting a procedure that evolved into what in current practice is known as *Hartmann's procedure*[42]. The original concept was a two-stage procedure (where the first operation was for stoma formation only). Today Hartmann's procedure is one-step operation where the rectum is resected from the abdominal cavity, the distal end of rectum is closed and left in situ and a single-barrel colostomy is created. Furthermore, in the pursuit of better functional outcomes, entering the era of sphincter preservation, Dixon reported in the 1940s rectal resection using the anterior approach followed by constructing a two-layered anastomosis aligning the colon to the rectal remnant[43]. This procedure of rectal resection using an anterior approach followed by anastomosis is in current practice known as *anterior resection*, it has been further improved by introduction of stapling devices and the double stapling technique enabling the creation of an anastomosis deep in the pelvis[44, 45].

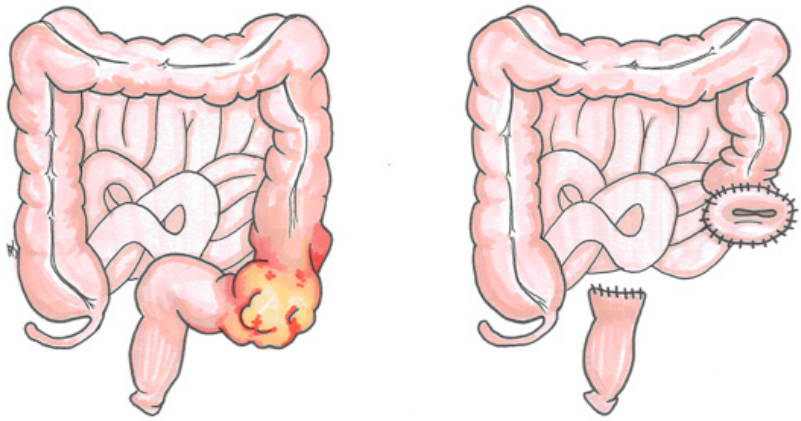

Figure 1. Ilustration of Hartmann's procedure.
In this illustration a sigmoid cancer is removed, the same principles apply for rectal cancer. The distal bowel end is left in situ and an end-colostomy is constructed. Copyright Aimee Rowe and TeachMeSurgery, reproduced with permission.

Current practice of surgery for rectal cancer

Local excision

Endoscopic *en bloc* local excision is a viable treatment option in selected T1N0 rectal cancer patients, and although with a requirement of substantial technical skill, it can be performed safely and with cost-effectiveness[46, 47]. However, after local excision of a T1 cancer some patients have risk of synchronous metastatic invasion of local lymph nodes, where pathology reports of lymphovascular infiltration, perineural infiltration and mucinous subtype are risk factors suggesting a need for additional mesorectal excision surgery[48].

Resection surgery

Regardless of the choice of surgical approach, the same oncological principles apply. For rectal cancers engaging the mid- and lower rectum, total mesorectal excision (TME) - implying dissection in embryological planes removing the entire mesorectum without breeching the mesorectal fascia - is now the gold standard of surgical practice that once revolutionized rectal cancer treatment by a greatly reducing the risk of recurrence[49]. However, evidence of rectal cancers not spreading distally in the mesorectum beyond 5 cm of the tumor border has made partial mesorectal excision (PME) a safe option in treatment of rectal cancer in the upper rectum[50, 51].

Apart from local excision used in selected cases, three major surgical procedures for radical resection of rectal cancer dominate current practice, differentiated by their ability to restore bowel continuity and applicability for different patient categories.

I. **Anterior resection** which the operation highlighted in this thesis and also is the most commonly performed procedure for rectal cancer in Sweden. It is suitable for cancers in the mid- and upper rectum and in selected cases of cancer in the lower rectum. The procedure is different from the other operations, as it provides the benefit of sphincter preservation and bowel continuity through the making of an anastomosis joining the colon to the rectal remnant.

II. **Abdominoperineal resection** which involves complete removal of the rectum including the sphincter complex and to varying extent also pelvic floor, resulting in a permanent colostomy. It is commonly used in cases of very low rectal cancer and always necessary in cases where the tumor infiltrates the sphincter complex.

III. **Hartmann's procedure** which is a rectal resection where the sphincter complex is left in place and the distal end of the rectum is left in situ, also involving the formation of a permanent colostomy. As this procedure is somewhat less invasive it is commonly used in comorbid patients at high risk for major surgery or in patients with impaired sphincter function.

There are different techniques available for constructing the anastomosis in anterior resection where straight end-to-end or side-to-end are the two most commonly used in Sweden. Other options are colonic J-pouch or transverse coloplasty. Colonic J-pouch, transverse coloplasty and straight side-to-end have all been reported to be better in functional outcome compared to straight end-to-end, but only for the first year after surgery[52].

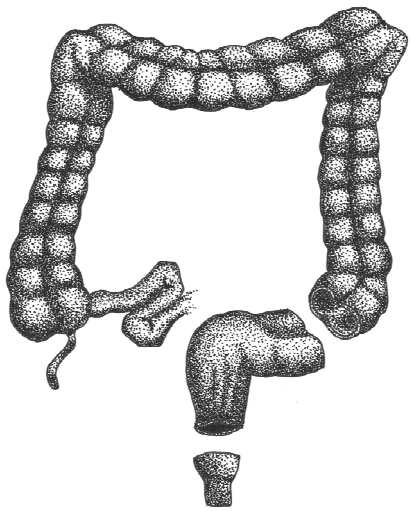

Figure 2. Illustration of anterior resection where the affected rectal segment is resected.
Illustration by Daniel Risberg, reproduced with permission.

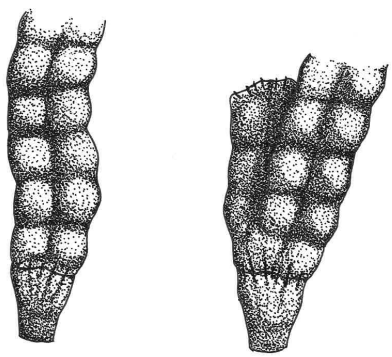

Figure 3. Illustration of anterior resection where resection is followed by anastomosis.
Two techniques are illustrated: end-to-end anastomosis (left) and side-to-end anastomosis (right). Illustration by Daniel Risberg, reproduced with permission.

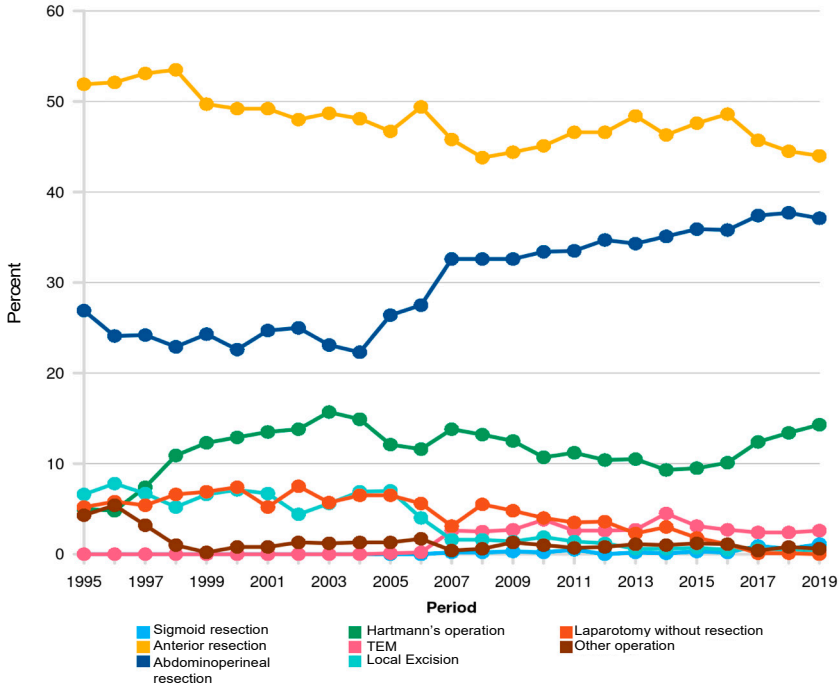

Figure 4. Rectal cancer treatment trends in Sweden from 1996-2019
Data from the Swedish Colorectal Cancer Registry (15th December 2020). Publication with permission from the registry holder.

TEM = Transanal Endoscopic Microsurgery.

Morbidity related to anterior resection

Anastomotic leakage

After joining two bowel ends in an anastomosis, a failure to heal with subsequent leakage of luminal contents – anastomotic leakage – is a major concern. In the context of anterior resection anastomotic leakage is associated with increased risk of local cancer recurrence, reduced overall as well as cancer specific survival, and increased healthcare costs[53-56].

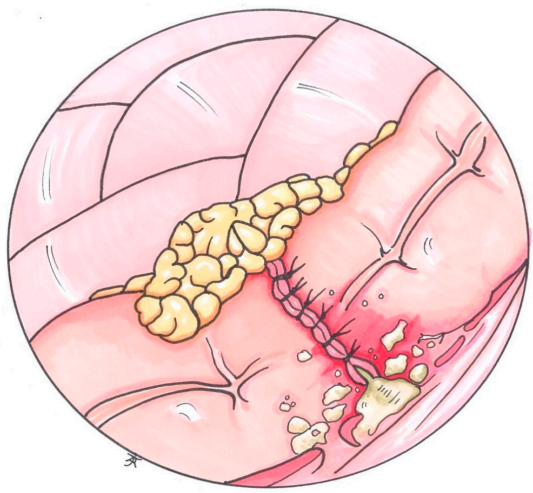

Figure 5. Illustration of anastomotic leakage.
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Prevalence and definition of anastomotic leakage

The prevalence of anastomotic leakage in colorectal surgery varies according to anatomical site, an anastomosis involving the small bowel or colon usually is reported with a leakage rate under 3%[57], whereas the colorectal/coloanal anastomoses made in anterior resection have leakage rates ranging from 4 to over 20%[58-62]. The considerable variation in reported leakage rate following anterior resection has several potential explanations: differences in operation technique, perioperative care, patient selection and the fact that long follow-up seems to be necessary in order to detect all leakages[58]. Furthermore, the lack of a consensus definition for anastomotic leakage after anterior resection has most likely played a part, prompting the International Study Group of Rectal Cancer (ISREC) to develop a definition that enables comparison of studies. The ISREC definition[63] dictates that anastomotic leakage should be defined as a defect of the intestinal wall at the

anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extra luminal compartments. A pelvic abscess in the proximity of the anastomosis should be considered an anastomotic leakage. Furthermore, a grading of anastomotic leakage should be done according to the impact on clinical management. Grade A anastomotic leakage results in no change in the patient's management, whereas grade B leakage requires active therapeutic intervention but is manageable without relaparotomy. Grade C anastomotic leakage requires relaparotomy.

Risk factors for anastomotic leakage

Risk factor analysis for anastomotic leakage after anterior resection has been a prolific research area with numerous published studies identifying several risk factors among which some are more established in the literature, whereas others remain debatable. Among risk factors with strong support in the literature are male sex[62, 64, 65], a distal anastomosis[60, 64-68], smoking[69-71], excessive alcohol consumption[70], and high American Society of Anesthesiologist (ASA) score[72]. Poor nutritional status, electrolyte disturbances and hypoalbuminemia have been identified as risk factors for anastomotic leakage in colorectal surgery in general[57]. In the laparoscopic setting of anterior resection, anastomotic leakage is commonly reported as related to the use of multiple staplers ($\geq$ 3 cartridges) for rectal transection[59, 73]. Tumor size as well as advanced neoplastic stage has also been reported as risk factors for anastomotic leakage after anterior resection[59, 60, 73, 74]. Considering medication, corticosteroid seems related to anastomotic leakage[75], whereas a clear relationship has not been established for nonsteroidal anti-inflammatory drugs[76-78]. Blood loss greater than 100 ml and blood transfusion are related to anastomotic leakage but also possibly surrogate markers for poor technique or demanding surgery[60, 74], a reasoning that also can be argued considering the relation of anastomotic leakage to prolonged operation time[60, 68, 73, 79]. Whether neoadjuvant oncological treatment is a risk factor for anastomotic leakage is controversial, an association of anastomotic leakage with neoadjuvant radiotherapy/radiochemotherapy has been reported[59 60, 65, 80], but also been challenged in meta-analysis[81]. Some other authors have emphasized the importance of adequate time interval from radiotherapy to surgery, and although they detect a vulnerability in somewhat different time-spans (<4 days or 11-17 days after radiotherapy), they both advocate extension of time to surgery in order to prevent anastomotic leakage[80, 82].

Anastomotic leakage prevention

Identifying modifiable risk factors (such as smoking, alcohol intake, nutritional status), could be part of a prehabilitation program. Preoperative inspiratory muscle training, physical exercise training, nutritional support and relaxation exercises have been suggested as way to improve functional recovery, although an impact on anastomotic leakage has not yet been established[83, 84].

Mechanical bowel preparation alone prior to colorectal surgery has not been able to decrease the rate of anastomotic leakage[85], but a combination of antibiotics and mechanical bowel preparation has been reported as related to reduced anastomotic leakage rate[86-88], although another study using the same database reported that the effect was related antibiotics alone[89]. The possible impact of an upstream stoma in the specific case of rectal cancer surgery has yet to be evaluated in this context, and it has been suggested that a rectal enema alone may be sufficient[90], why the role of mechanical bowel preparation in addition to prophylactic antibiotics in rectal cancer surgery is yet to be settled.

Randomized controlled trials have established a reduced rate of symptomatic anastomotic leakage related to defunctioning stoma use [91, 92]. However, evidence for a mere mitigating effect against the consequences but no effect on anastomotic leakage rate has been produced in a propensity-matched analysis[93] and leakage rates remain constant in population-based studies despite widespread use[94]. This in addition to stoma related morbidity[95] and common failures to reestablish bowel continuity after anterior resection[96, 97], has called into question whether defunctioning stomas are performed to an extent that is reasonable and a more selective use has been argued[94]. Early evaluation of anastomotic integrity followed by early closure of the defunctioning stoma has been reported as a safe way to reduce the stoma related morbidity. By minimizing the time at risk for chronic dehydration and renal failure, while still benefitting from its protective properties in patients at risk for septic complications due to development of anastomotic leakage, it is reported as a safe option[98].

The effect of central ligation of the inferior mesenteric artery close to aorta, commonly referred to as high tie, has been the subject of debate both in terms of its benefits regarding capability to increase lymph node harvest[99, 100], but also its relation to anastomotic leakage. Although high-tie rarely is reported as a major risk-factor for anastomotic leakage, there are some meta-analyses that demonstrate such a relationship[101, 102], whereas others do not[100, 103]. However, uncompromised vascular perfusion is a prerequisite for healing and hope has been attached to the possibly preventive capability of fluorescence perfusion angiography, i.e. intravenous injection of a fluorophore that enables the surgeon to visualize blood flow using a near-infrared camera. One meta-analysis based on heterogeneous studies reported reduced rate of anastomotic leakage related to its intraoperative use[104]. However, this could not be confirmed in a multicenter randomized study which only reported extension of resection margins before making the anastomosis, without corresponding reduction in the rate of anastomotic leakage[105].

The air-leak test, meaning intraoperative installation of air in the rectum while having the anastomosis under water enabling visualization of air bubbles, has been the subject of a meta-analysis concluding no reduction in anastomotic leakage related to its use, but a way of identifying patients at risk of leakage[106]. Other studies

have indicated that suture repair alone may be insufficient upon detecting a positive air-leak test, instead advocating revision of the anastomosis and/or defunctioning in such circumstances[107-109]. The benefit of peroperative placement of a pelvic drain in order to reduce anastomotic leakage rate after making a extraperitoneal anastomosis was reported from two meta-analysis[59, 110], but contradicted by two previous meta-analysis[111, 112] and a later randomized trial showing no difference in terms of pelvic sepsis, nor was there any difference related to early (< 5 days) or late (> 5 days) drain removal[113].

Another preventive option is the use of a transanal tube put in the rectal lumen during the operation and left in place for decompression of the rectum postoperatively. Three meta-analyses have reported its use as related to lower rates of anastomotic leakage, this effect can be detected even if the tube is used in addition to a defunctioning stoma, but it is not established that it can replace a defunctioning stoma[114-116].

The effect of diameter of circular stapler device on anastomotic leakage has been evaluated with varying results[68, 73], but precompression before stapler firing is believed to reduce anastomotic leakage based on animal models and some clinical findings[73, 117]. Dog-ears from the transverse stapler-line in the double stapling technique is believed to be a weak spot prone to anastomotic leakage and techniques to avoid this have been suggested[118]. Circular stapler devices from the two largest manufacturers have been compared in a randomized trial, where no difference in leakage rate could be detected[119].

The pathogenesis of anastomotic leakage

Although several risk factors have been identified, the way they contribute to anastomotic leakage is poorly understood. Despite numerous studies on risk factor evaluation and surgical technique the anastomotic leakage rate prevails, and it has been argued that improved understanding of the underlying pathophysiology is the way forward[120]. The healing of an anastomosis is characterized by three phases: inflammation, proliferation and remodeling. The greatest risk of leakage is believed to occur in the inflammatory phase due to high proteolytic activity, followed by increasing strength when new collagen is produced by fibroblasts and smooth muscle cells[121]. Disorders in this process have been suggested to be the origin of anastomotic leakage, and altered microbiota has been proposed as a main triggering factor[120]. Collagenase producing pathogens (Pseudomonas aeruginosa and Enterococcus faecalis) have demonstrated disruptive capacity in tissue healing in animal models[122, 123]. A better understanding of the pathophysiological processes that impact the anastomotic healing is most certainly a major area to be explored in order to prevent anastomotic leakage and design interventions.

Anastomotic leakage detection

The clinical presentation of anastomotic leakage after anterior resection may vary markedly. It ranges from fulminant sepsis to a more insidious onset or even asymptomatic surprise finding on routine investigations before defunctioning stoma reversal[58], making establishment of the diagnosis at times difficult. However, delayed intervention in order to manage symptomatic anastomotic leakage is related to generally poorer outcomes including increased postoperative mortality[124, 125], prompting need for methods facilitating early detection. C-reactive protein (CRP) and procalcitonin (PCT) can both detect anastomotic leakage when used as screening markers in the early postoperative period[126, 127], although unable to discriminate from other complications[128]. The Dutch leakage (DULK) score is one of several early warning score systems developed in order to reduce time to diagnosis in the early postoperative setting. It consists of 13 clinical parameters, and was shown to reduce the delay in diagnosis from 4 to 1.5 days[129]. It was later refined into a modified DULK score where the included scoring parameters was reduced to four, but although having a high negative predictive value over 97 percent, it has a positive predictive value of 17 percent which limits its practical use[57].

In order to support at tentative diagnosis of anastomotic leakage there are various diagnostic options, the main radiological modalities are: CT (+/- intravenous contrast, +/- oral contrast), water-soluble contrast enema combined with plain x-ray or finally a combination of water-soluble contrast enema and CT. Comparison of the modalities is difficult since conducted studies have varying or omitted anastomotic leakage definition, varying location of the anastomosis and often limited sample size. Yet another variation is regarding whether the examination was done to evaluate a clinical suspicion of anastomotic leakage or as a routine examination in order to evaluate anastomotic integrity prior to defunctioning stoma reversal[130]. Poor sensitivity is the main concern as a false-negative CT finding can provide false security and is reported to be associated with delayed reintervention, which in turn is related to high mortality and increased length of stay[131]. One meta-analysis reported an overall sensitivity of 68 percent when using CT (with and without intravenous and /or oral and/or rectal contrast) in order to evaluate anastomotic leakage in a mix of colorectal procedures[130]. However, looking at studies specifically evaluating clinically suspected anastomotic leakage after rectal surgery, a combination of rectal contrast and CT has been reported to detect anastomotic leakage with 77-97 percent sensitivity[132, 133], and use of rectal contrast is reported to add a significantly higher predictive value to CT[133]. When used as a routine investigation prior to defunctioning stoma reversal, 100 percent sensitivity has been reported for leakage detection using the combination of CT and rectal contast[57].

Water-soluble contrast enema in addition to plain x-rays is most often reported in the context of routine investigation before defunctioning stoma reversal, although it

has been argued that it in this situation does not provide an added value in case of a normal endoscopic evaluation and digital exam[134, 135].

The estimated sensitivity for anastomotic leakage detection using endoscopy is rarely investigated, but one study report 72 percent sensitivity for anastomotic leakage after anterior resection when using endoscopy of the rectum upon clinical suspicion of leakage[132].

Classification of anastomotic leakage

The large variation in presentation of anastomotic leakages has led to different ways to classify the leakages in order to find patterns with an implication on outcome. Grading of severity based on intervention is one approach, exemplified by the previously described ISREC classification, division into asymptomatic or symptomatic anastomotic leakage at the time of detection is another way. Classification into symptomatic leakage usually relies on different obvious clinical presentations such as signs of peritonitis and pus or fecal discharge from abdominal drains or vagina when referring to symptomatic leakages, whereas surprise findings on evaluation of anastomotic integrity before defunctioning stoma reversal most commonly represent asymptomatic leakages[136, 137]. However, these lines of symptomatic/asymptomatic classification are somewhat blurred in clinical practice, especially in cases of mild symptoms that could be part of a normal postoperative course. This makes correct classification reliant on sensitivity to symptoms and upon late detected leakages a reconsideration of previous symptoms. Still, merit for use of this terminology is found in some reports where asymptomatic leakages have a better prognosis in terms of risk for cancer recurrence[136] and functional outcome[138].

Another approach is considering time from operation to leakage detection with subsequent classification into early as opposed to late leakages. Some studies have examined the proposed entities of early and late anastomotic leakage, using varying definitions but leakage detected before or after 30 postoperative days is the most common dividing line[139-141]. Although late leakages to some degree overlap asymptomatic leakages found on evaluation before stoma reversal, the late leakage group also contains very late serious septic complications[142, 143] and time of leakage detection has been characterized in relation to predisposing factors[140, 144].

Management of anastomotic leakage

Anastomotic leakage can lead to various treatments and several factors need to be considered in order to tailor the appropriate treatment for a patient. Firstly, the patient's condition indicates which measure that is most appropriate, illustrated in a leakage severity score proposed by McDermott et al. where a rise in leakage severity score prompts a corresponding escalation in care. It ranges from only detecting biochemical abnormalities rendering close observation (grade 1) to a patient in

septic shock causing intensive care and emergency laparotomy (grade 5)[57]. Moreover, age, comorbidity, anastomotic level, time from surgery to diagnosis and degree of anastomotic dehiscence are factors that need to be considered. Analysis of anterior resection patients from the Dutch Colorectal Audit showed that anastomotic leakage caused at least one reintervention in 72% of the cases: take down of the anastomosis and end-colostomy, surgical drainage and/or construction of a previously omitted defunctioning stoma were most commonly performed[58].

If the anastomotic leakage patient is severely ill in a septic condition, or have a anastomotic dehiscence engaging more than a third of the anastomotic circumference, removal of the anastomosis and constructing an end-colostomy is recommended[145]. After such an operation, reoperation at a later stage for re-establishment of bowel continuity is unusual[96]. However, for a leaking extraperitoneal anastomosis is anastomotic preservation often possible, which enables later bowel continuity. A "divert and drain" approach consisting of construction of a defunctioning stoma in addition to pelvic drain placement and abdominal washout, has been reported with 54-100 percent success rate in terms of no further need for interventions[146, 147] and increased likelihood of preservation of bowel continuity[148]. Some authors advocate this approach as particularly suitable after initial laparoscopic surgery, as laparoscopic approach to the reoperation has been reported to feasible in two thirds of all anastomotic leakages in need of a reoperation[149].

Patients who already have a defunctioning stoma present at the time of the leakage generally have a reduced need of operation for septic control[115, 146]. Among these, as well as among not defunctioned leakage patients who do not require reoperation, there are other treatment options. Percutaneous drainage, commonly CT guided using a transabdominal or transgluteal approach, is a feasible option for contained abscesses[150]. Transanal drainage, meaning transanal placement of a drainage catheter through the anastomotic defect into underlying abscess cavity for regular irrigation, is a long-established treatment method reported as suitable for defunctioned patients[151]. Endoscopic clipping has been described as applicable for anastomotic defects <15mm without luminal stenosis or underlying abscess, it is in case series of selected patients reported with a healing rate of 83-93%[152]. Endoscopic vacuum-assisted drainage is an improvement on the previously described transanal drainage. Using this method, an open pored polyurethane sponge is placed in the anastomotic defect, the sponge is connected to an evacuation tube which in turn is connected to a vacuum drainage system[153]. The sponge is exchanged every 48-72 hours with reduction of the size of the sponge as the anastomotic defect heals. This method has gained popularity mainly based on reports from retrospective studies, a meta-analysis reported a weighted mean endoscopic healing rate of 85.3 percent and a weighted mean stoma reversal rate of 75.9 percent[154]. However, although feasible and with satisfactory results in selected

patients, the advantage of endoscopic vacuum-assisted drainage over other treatment methods has never been established. One retrospective study found that the method had a rate of bowel continuity equal to other treatments in long-term follow-up[155].

Redo surgery after anastomotic leakage, which involves making of a new colorectal or coloanal anastomosis, is a last resort in order to restore bowel continuity after a failing treatment for anastomotic preservation. This surgery is complex due to distorted anatomy and adhesions after previous surgery and fibrosis resulting from pelvic sepsis. Some studies propose redo surgery as feasible in selected cases, where the success-rate in restoration of bowel continuity is reported from 66-92%[156-159]. The rate of bowel continuity after redo surgery is impacted by an overall 16% rate of major postoperative morbidity (including new anastomotic leakage and septic complications with need for reintervention) reported from tertiary specialist centers, as well as risk for poor functional outcome[160]. However, studies differ in patient composition and success-rate may be limited in cases where radiotherapy has been administered and low anterior resection was the original procedure[159], making patient selection central when considering redo surgery.

To summarize treatments for anastomotic leakage after anterior resection: control of a septic condition always has the highest priority even if it involves removal of the anastomosis and making a colostomy. In the case of a limited anastomotic defect and a controllable infection there are different treatment options available in order to establish anastomotic healing and in selected cases redo surgery can be considered after treatment failure. However, a question which has not been fully answered is whether bowel continuity after anastomotic leakage benefits the patient in terms of functional outcome and Quality of Life.

Long-term morbidity after anterior resection

Permanent stomas

Overall, despite being a sphincter-sparing procedure, the rate of long-term bowel continuity after anterior resection is reported to be 75-81%[96, 97]. In a meta-analysis of risk factors for non-closure of the intended temporary stoma in anterior resection, anastomotic leakage was reported as the most important risk factor, followed by cancer recurrence and comorbidity[161]. Furthermore, in a recent report from long-term follow-up of a randomized multi-center trial - originally evaluating effect of a defunctioning stoma on symptomatic anastomotic leakage in low anterior resection - the permanent stoma rate of 19% up until five years was further increased to 25% when investigating until in median 10 years. Anastomotic leakage was reported as the overall major risk factor for a permanent stoma, whereas impaired anorectal function was the most commonly stated reason followed by pelvic sepsis related to

anastomotic complications[162]. Furthermore, this study highlights how late the effects of an anastomotic leakage may occur. Among patients having a stoma made later than five years after surgery, pelvic sepsis related to the anastomosis was the major reason[162].

Considering the type of stoma that becomes permanent, a remaining loop-ileostomy should be regarded as an inferior outcome compared to conversion to an end-colostomy, given high risks of frequent hospital readmissions due to high output with consequent electrolyte imbalances and renal failure[163, 164]. However, despite this, a population based report indicate that almost half of the permanent stomas after anterior resection are remaining loop-ileostomies[165].

Functional outcome

The main objective of rectal cancer surgery is to cure or prolong the life of the cancer patient, while still ensuring an outcome with the best possible quality of life (QoL). Rectal cancer surgery has a negative impact on overall QoL[166], where different procedures have specific effects that may impact functional deteriorations in different ways. Bowel dysfunction is common after anterior resection, whereas sexual dysfunction and urinary dysfunction been identified as present to varying extent after rectal cancer surgery in general[167-169]. Comparing patients having anterior resection to patients having other rectal cancer procedures where a permanent stoma is intentionally constructed, there are morbidity and symptoms related to the permanent stoma (such as bulging, hernias, impaired body image and sexual problems). This counterbalance the impact of bowel dysfunction, but reports differ in terms of which procedure has the greatest impact on overall QoL[170, 171].

Low anterior resection syndrome (LARS)

In the context of low anterior resection, the common outcome of bowel dysfunction been has given a name: low anterior resection syndrome (LARS). The concept of LARS was investigated by Emmertsen et al while developing a questionnaire – LARS-score - aimed at estimating severity of bowel dysfunction by identifying bowel symptoms with most detrimental effect on QoL such as constipation, stool incontinence, urgency, abdominal pain and flatulence [167]. The validated questionnaire measures the severity of bowel dysfunction using a scoring system where each individual degree of symptom renders a score, the individual scores are summarized in a total score which forms the basis for an estimation of the extent of bowel dysfunction categorized as: no/minor/major LARS. Between 40% and 80% of patients subjected to low anterior resection are reported to have LARS to some degree within the first 12 months after surgery[172-176]. Although room for improvement is seen within the two years, major symptoms seem to have a high tendency to persist, possibly more so among younger patients and women[177, 178]. The degree of deterioration in bowel function compared to a preoperative state for an

individual patient can be difficult to establish since measurements just before the operation are affected by symptoms due to the rectal tumor. However, the prevalence of LARS has been investigated in a normal Danish population where a 10-15% prevalence of major LARS was reported, the highest rates were found in elderly (50-79 years) and in women[179]. This means that a high prevalence of LARS after anterior resection in part also must be seen in the light of preexisting problems.

Some risk factors for development of LARS after anterior resection have been identified, where low anastomotic height, radiotherapy, and a defunctioning stoma is most commonly reported[175, 180]. It has been suggested that a decreased rectal reservoir and denervation of the left colon during surgery leading to hypermotility of the neorectum could contribute to the development of LARS[181]. A disordered pattern of contractions of the neorectum in response to prolonged distention has been observed after anterior resection in combination with neoadjuvant treatment[182].

There are a few treatment possibilities for LARS. Bulking agents and anti-diarrhoeal medication is usually recommended as a first measure[183]. Pelvic floor rehabilitation (including pelvic floor muscle training, biofeedback training and rectal balloon training), sacral nerve stimulation, serotonin ($5\text{-}HT_{3)}$ receptor antagonists and transanal irrigation have all been reported as useful to varying extent in treatment of LARS[184]. A permanent stoma is a last resort if no improvement is noticed.

Whether anastomotic leakage is a risk factor for bowel dysfunction, specified as LARS or not, among patients with bowel continuity after anterior resection has been the subjects of a number of studies with varying results. Some studies point towards an effect[137, 138, 185, 186] whereas other do not[186-188]. Manovolumetric studies evaluating anastomotic leakage patients have shown reduced neorectal capacity[189, 190], findings coherent with a theory of an underlying biological mechanism where an anastomotic leakage after healing can leave a remaining trace, which leads to subsequent bowel dysfunction.

Sexual and urinary dysfunction

Sexual dysfunction and urinary dysfunction are also recognized complications after rectal cancer surgery in general, including symptoms such as voiding difficulties, urinary incontinence, erectile dysfunction, retrograde ejaculation, loss of lubrication and dyspareruniа[191]. Radiotherapy is reported risk factor for genitourinary dysfunction after anterior resection[169]. Surgical damage to autonomic nerves is also well known for having specific symptoms according to where the damage has occurred. Damage to sympathetic nerve fibers adjacent to the inferior mesenteric artery or superior hypogastric plexus related to symptoms of urinary and fecal incontinence, increased defecatory frequency, anejaculation or retrograde ejaculation. Damage to the inferior hypogastric nerve plexus, where parasympathetic and sympathetic fuse, causes voiding difficulties, urinary retention,

erectile dysfunction and loss of lubrication. The specific effect of anastomotic leakage after anterior resection on genitourinary symptoms is rarely investigated apart from a few studies with conflicting results: urinary dysfunction related to anastomotic leakage has been reported[188] as well as dismissed[187].

Aims

The overall objective of this thesis was to gain further general knowledge of anastomotic leakage after anterior resection for rectal cancer by characterizing features related to long-term morbidity.

Specific aims

Paper I To investigate late detected anastomotic leakage after anterior resection for rectal cancer regarding incidence and evaluate its clinical features such as associated factors and need for reintervention.

Paper II To assess how often bowel continuity is restored after anastomotic leakage in anterior resection for rectal cancer, and to evaluate clinical factors in anastomotic leakage patients related to an outcome of a permanent stoma.

Paper III To explore rectal contrast studies of patients with anastomotic leakage after anterior resection in the purpose of finding radiological features associated with an outcome of permanent stoma.

Paper IV To evaluate the impact of anastomotic leakage after anterior resection for rectal cancer on long-term bowel dysfunction.

Paper V To evaluate the impact of anastomotic leakage after anterior resection for rectal cancer on quality of life in cases where bowel continuity can be maintained and to explore patients with anastomotic leakage, irrespective of preserved bowel continuity, regarding effect of maintained bowel continuity on quality of life.

Material and methods

Ethics and approvals

All studies presented in this thesis were conducted in accordance with the regulatory norms and standards of the 1975 Helsinki Declaration. Ethical approval was granted prior to each study, for paper I-III from the regional ethical review board in Lund, for paper IV and V from the regional ethical review board in Umeå.

Data from the Swedish ColoRectal Cancer Registry was authorized by the registry holder before data extraction. All patients participating in paper I-III were informed with an opt-out possibility before review of medical recordings and registry data extraction. Written informed consent was obtained by all patients participating in in paper IV and V.

Data sources

The Swedish ColoRectal Cancer Registry (SCRCR*)* was used in all studies in order to identify patients exposed to anterior resection for rectal cancer as well as to provide patient characteristics. This is a national registry that was established in 1995 for rectal cancer, also including colon cancer since 2007. Data to the SCRCR is reported by clinicians from the individual hospital handling the patient and includes patient characteristics, preoperative staging, technical details regarding performed surgery, postoperative course including complications, pathology report and postoperative follow-ups regarding complications and cancer recurrence until five years after index surgery. An increase in the number of variables registered has taken place over time since the SCRCR was introduced.

The SCRCR is considered reliable for research as it has been evaluated with an average overall variable validity of 90 percent[192], although with an underreporting regarding anastomotic leakage[193].

Anastomotic leakage detected within 30 days of index surgery should be reported to SCRCR, regardless of whether it has been identified in-hospital or after discharge, but a shortcoming in the SCRCR is that the provision of a clear definition

of anastomotic leakage (or anastomotic insufficiency, which is the term used) is missing.

The regional web-based patient administrative system (PASiS) was employed in paper I-III as a complement in order to identify patients with omitted registration of anastomotic leakage in SCRCR. This is a registry kept for administrative purposes of booking and billing in the southern healthcare region, that records all hospital admissions and outpatient clinic visits and the reasons for these contacts in the form of diagnosis and operations in accordance with *The International Statistical Classification of Diseases, Injuries and Causes of Death* (ICD-10).

Review of medical records was performed in all studies of this thesis to varying extent in order to validate (paper I-III) *or* find and validate (paper IV-V) the exposure of anastomotic leakage according to study protocol (see further below). Clinical variables were also retrieved from medical records in all papers in order to complement SCRCR.

Review of radiological imaging was performed in paper III, getting access to rectal contrast studies from the Sectra Picture Archiving and Communications System (PACS), which is the digital platform that stores all imaging performed in the Skåne region.

Identification of study subjects

Identification of patients subjected to anterior resection for rectal cancer

The SCRCR was used in all papers of this thesis to identify the larger group of patients operated with anterior resection for rectal cancer as it has been reported to include 99 percent of all rectal cancers in Sweden[192].

Identification of patients with anastomotic leakage

The papers of this thesis are based on two separate retrospective cohorts, one is used in paper I-III, the other in paper IV and V. The process of identifying anastomotic leakage patients differed in these two cohorts, but was based on a consistent definition of anastomotic leakage (see further below).

A. **In paper I-III,** the SCRCR was used to identify possible cases of anastomotic leakage among patients subjected to anterior resection for rectal cancer between 2001 and 2011 in the Southern healthcare region of Sweden, using the following SCRCR variables: anastomotic insufficiency,

reoperation for anastomotic insufficiency, reoperation within 90 days of index surgery. Registrations of anastomotic leakage done within 30 days or discovered later and added to the registry in follow-up were both considered. Furthermore, the PASiS registry was employed as a complement in order to identify patients with omitted registration of anastomotic leakage in SCRCR. The PASiS registry was explored for rectal cancer patients with a hospital stay of more than 3 weeks and/or more than one readmission within 3 months after anterior resection. After identifying a case of possible anastomotic leakage, using SCRCR or PASiS, the case was subjected to further review of medical records in order to confirm or dismiss the anastomotic leakage diagnosis according to study protocol definition.

B. **In paper IV and V** the medical records of all patients subjected to anterior resection for rectal cancer between 2007 and 2013 in Northern, Western, and Southern healthcare regions of Sweden, as identified by SCRCR, were reviewed in order find cases of anastomotic leakage according to the study protocol definition.

Definition of anastomotic leakage

As previously mentioned, the International Study Group of Rectal Cancer (ISREC) have proposed a definition of anastomotic leakage after anterior resection[63], and all papers in this thesis used a definition of anastomotic leakage in accordance with the ISREC definition.

The definition of anastomotic leakage used in thesis is: leakage detected from any anastomotic staple or suture line, pelvic abscess (with or without radiologically verified leakage), or rectovaginal fistula. A postoperative anastomotic stricture without any other supporting evidence of anastomotic leakage was not regarded as anastomotic leakage.

There was a difference between the studies regarding the time frame within which anastomotic leakages were considered: in paper I-III all anastomotic leakages regardless of time to detection were included, whereas in paper IV and V included leakages detected within 3-90 days (the cohort had previously been used in order to evaluate effect of non-steroidal anti-inflammatory drugs (NSAID) on anastomotic healing, where leakages the first two days was regarded as technical failure of surgery[76]). Furthermore, although different approaches were used in order to identify cases of anastomotic leakage, the validation of the diagnosis was done by review of medical records using the study definition in all papers.

Study design

All papers in this thesis are observational studies.

Paper I

This was a retrospective multi-center cohort study evaluating rate and clinical features associated to late detected anastomotic leakage after anterior resection. The study included rectal cancer patients exposed to anastomotic leakage after anterior resection for rectal cancer performed from 1 January 2001 to 31 December 2011 at one of eleven different hospitals in the Southern Healthcare Region of Sweden. In patients with anastomotic leakage consistent with study protocol definition, review of medical records was performed at each individual hospital in order to record further clinical characteristics not provided by SCRCR such as surgical technical details from the anterior resection and clinical presentation of the anastomotic leakage. Whenever there was an overlap in reported data from SCRCR and medical records which was inconsistent, data retrieved from review of medical records was used for anastomotic leakage patients.

In the absence of a widely established time cut-off defining late anastomotic leakage, three different definitions of late anastomotic leakage were evaluated in this study: late leakage detected after hospital discharge (LLAHD), late leakage detected more than or equal to 30 postoperative days after anterior resection (LLPOD30) and late leakage detected more than or equal to 90 postoperative days after anterior resection (LLPOD90).

Postoperative time to detection of anastomotic leakage was established using time from anterior resection to date of first diagnostics verifying an anastomotic leakage and/or date of clear statement in medical records indicating that responsible clinician considered the patient to have anastomotic leakage. Each of the definitions of late leakage was analyzed independently of each other, and evaluated in their relation to clinical variables, clinical symptoms and need for reintervention.

Statistical methods: In patients who had anterior resection, clinical characteristics were evaluated and analyzed in univariate association anastomotic leakage. Within the group of patients with anastomotic leakage, clinical characteristics were evaluated and analyzed in univariate association to late anastomotic leakage, applying each of the three different definitions of late anastomotic leakage independently of each other.

Some clinical characteristics were subcategorized for analysis purposes. Age was dichotomized into $</\geq$ 70 years, tumor level was split into three levels in order to differentiate low-, mid- and high rectal cancer, subcategorization of ASA

(I+II/III+IV) was done to distinguish patients with significant comorbidity and subcategorization of T-stage (T 1+2; T3; T4) and UICC (I+II; III+IV) was based on expected cancer prognosis.

Continuous variables were analysed with the Kruskal-Wallis test and categorical variables were analysed using Fisher's Exact Test. A p-value < 0.05 was considered statistically significant.

Applying the each of the definitions of anastomotic leakage, clinical variables related to late leakage with a univariate p-value < 0.2 were included in stepwise binary logistic regression in order to identify confounder adjusted association to late anastomotic leakage, reporting Odds Ratio, and considering a p-value < 0.05 statistically significant.

Paper II

This retrospective cohort study evaluated long-term outcome in bowel continuity in patients with anastomotic leakage after anterior resection. The study included the patients with anastomotic leakage after anterior resection identified in paper I and used the same clinical data retrieved from medical records. In order to establish presence of long-term bowel continuity or not, an appointed surgeon at the local hospital used medical records to determine if a residual stoma at the time of follow up should be considered permanent. Furthermore, when reviewing medical records, the study protocol also requested information on type of remaining stoma and a justification for its existence. The long-term rate of bowel continuity after anastomotic leakage was investigated, as well as the association of permanent stoma to clinical characteristics and need for reintervention.

Statistical methods: The same approach as described for paper I was used when subcategorizing clinical characteristics. Within the identified group of patients with anastomotic leakage, clinical characteristics were evaluated and analyzed in univariate association to an outcome of permanent stoma, using the same principles for significance testing as described in paper I. Clinical variables related to an outcome of permanent stoma with a univariate p-value < 0.2 were included in stepwise binary logistic regression in order to identify a confounder adjusted association of clinical variables to permanent stoma, reporting Odds Ratio and considering a p-value < 0.05 statistically significant.

Paper III

This was a retrospective cohort evaluating radiological characteristics found in rectal contrast studies verifying anastomotic leakage in relation an outcome of permanent stoma. The study included a subgroup of the patients with anastomotic

leakage after anterior resection, identified as previously described in paper I and paper II. Inclusion criteria was anastomotic leakage after anterior resection for rectal cancer at one of six different hospitals in the Skåne region, and furthermore available imaging verifying anastomotic leakage. All imaging incorporating water soluble rectal enema was considered, regardless of whether CT or plain X-ray was used as imaging technique, whereas radiological investigations omitting rectal contrast was excluded.

The outcome of permanent stoma was established as described in paper II.

The selection of radiological characteristics evaluated was based on presumed reproducibility and consistency. These radiological characteristics were:

1 Leakage location in anastomosis – from circular staple line *or* from transverse staple line (in cases of side-to-end anastomosis)

2 Direction of initial contrast leaving the lumen – dorsal *or* ventral *or* lateral

3 Orientation of major fistula or leakage cavity - dorsal *or* ventral *or* lateral

4 Size of major fistula or cavity using maximum diameter measured in millimeter

5 Width of anastomotic defect, estimated by width of contrast fluid stream exiting the bowel lumen, measured according to maximum diameter perpendicular to the direction of the bowel lumen

6 Abscess formation, defined as a fistula or fluid collection in the pelvis containing air bubbles and/or surrounded by contrast uploading encapsulation.

Evaluation of rectal contrast studies was done by a senior radiologist (professor Olle Ekberg), thereby responsible for measurements and final interpretation of imaging reported in the paper.

Statistical methods: Baseline characteristics were assessed in included anastomotic leakage patients as well as excluded anastomotic leakage patients from the original cohort. In patients with rectal contrast studies verifying an anastomotic leakage, clinical characteristics were also evaluated in relation to an outcome of permanent stoma.

In order to establish a categorical relation of radiological characteristics to an outcome of permanent stoma," size of major fistula or leakage cavity" and" size of anastomotic defect" were dichotomized in" large" or" small" according to median diameter among included patients. Radiological characteristics were analyzed in univariate association to the outcome of permanent stoma.

Continuous variables were analysed with the Kruskal-Wallis test and categorical variables were analysed using Fisher's Exact Test. A p-value < 0.05 was considered statistically significant.

Paper IV

This retrospective multi-center study evaluated the effect of anastomotic leakage on bowel dysfunction. A cohort of patients operated with anterior resection for rectal cancer between 2007 and 2013 in 15 hospitals the Northern, Western, and Southern healthcare regions of Sweden was identified, this cohort had previously been used to study the relationship of non-steroidal anti-inflammatory drug intake and anastomotic leakage.

All living patients from the original cohort were contacted by mail between May and August 2018 to obtain written consent as well as answers to LARS-score and questions of current stoma status. The questionnaire also included other parts not evaluated in this study that concerned Quality of Life and life-style issues. Non-responding patients received a reminder letter once, six weeks from first dispatch.

Scoring of patient responses to the questionnaire was done according to guidelines where the sum of scores from the individual symptom domains gives overall evaluation of bowel dysfunction: no LARS (0–20), minor LARS (21–29), or major LARS (30–42).

Included were all responders not reporting a residual stoma or returning incomplete responses to any of the domains in LARS-score.

Statistical methods: The exposure was anastomotic leakage and major LARS was primary outcome, scores in individual symptom domains in LARS score was secondary outcome.

The effect of anastomotic leakage on the outcome was investigated using relative risk ratios (RRs), reporting 95% confidence intervals (CIs). Propensity score matching using logistic regression with anastomotic leakage as the dependent variable was made in order to establish comparable groups while adjusting for confounding effects.

Covariates in the propensity matching model were selected based on their collective potential confounding effect, using a causal diagram based on previous research and clinical reasoning when proposing tentative causal relationships. The propensity score model included the following covariates: sex (male *or* female); age at index operation (as a continuous variable); comorbidity (dichotomized to [any recorded comorbidity] *or* none); neoadjuvant treatment (none *or* [5 x 5 Gray] *or* [28 x 1.8 Gray + capecitabin / 25 x 2 Gray + capecitabin]); defunctioning stoma at index surgery (yes *or* no); mesorectal excision (partial *or* total); and Union for

International Cancer Control (UICC) tumour stage (I-II *or* III- IV). Propensity score matching was done in a 1:1 ratio without replacements and a match tolerance of 0.005 was used.

Comorbidity was dichotomized to distinguish healthy patients without significant comorbidity.

The model's balancing capability was assessed using standardized differences, evaluating effect size of remaining distribution imbalances after propensity score matching regarding included covariates as well as other clinical characteristics. A remaining standardized difference after matching of ≤ 0.2 was considered a small effect size.

Significance testing of univariate associations of clinical factors to exposure was made using chi-square test for categorical variables, Mann-Whitney U Test or Student's T-test when appropriate for continuous variables.

Evaluation of outcome was done using relative risk ratios (RRs) with 95% confidence intervals; a *P*-value ≤ 0.05 was considered statistically significant.

Paper V

In this study, we evaluated responses to questionnaires obtained from the same cohort as described in paper IV to evaluate the long-term effect of anastomotic leakage after anterior resection for rectal cancer on Quality of Life (QoL).

Two validated questionnaires were used: European organization for research and treatment of rectal cancer (EORTC) Quality of life Questionnaire (QLQ)-C30 and QLQ-CR29 (colorectal module). The EORTC QLQ-C30 is a self-assessment questionnaire developed for cancer patients, measuring QoL containing 30 items that generate weighted multi-item scales (one Global Health Scale, five functional scales and three symptom scales), and six single item questions addressing specific symptoms. The EORTC QLQ-CR-29 is a questionnaire developed as an adjunct to EORTC QLQ-C30 to measure QoL in colorectal cancer patients, in this questionnaire 29 items generate four scales (urinary frequency, blood/mucus in stools, stool frequency, body image) besides an evaluation of 19 individual items. Both questionnaires can be linearly transformed to provide a score from 0 to 100: a high score on Global Health Status or functioning scales represents a high QoL, while a high score on scales or single items evaluating symptoms corresponds to a high level of symptom. When using these evaluation tools, the size of difference or change over time that can be considered clinically relevant has been debated. For EORTC QLQ-C30, it has been proposed that a difference of 5-10 points should be considered "little" whereas a 10-20 point difference should be considered moderate[194].

Patients were sent the EORTC QLQ-C30 and QLQ-CR29 in the same questionnaire dispatch as previously described for paper IV. After including responding patients with bowel continuity without registration of cancer recurrence in SCRCR, anastomotic leakage was the exposure and primary outcome was overall QoL as evaluated by EORTC QLQ-C30 in Global Health Status. In a secondary analysis, the effect of anastomotic leakage on symptom and functional scales as well as individual symptoms were evaluated.

In another secondary analysis, including all anastomotic leakage patients regardless of stoma status without matching, the effect of bowel continuity on Global Health Status, symptom and functional scales as well as individual symptoms were evaluated.

Scoring and handling of missing data for EORTC QLQ-C30 and EORTC QLQ-CR29 in this paper was performed according to established guidelines.

Statistical methods: The effect of anastomotic leakage on the outcome of Global Health Status, symptom and functional scales as well as individual symptoms was investigated by a comparison of mean scores in exposed and unexposed group using Student's t-test, considering a p-value of < 0.05 as statistically significant. To establish comparable groups, propensity score matching was used. Propensity scoring was performed by use of logistic regression where anastomotic leakage was the dependent variable. Covariates were selected according to the same principles as described for paper IV, selected covariates were: sex; age (continuous variable); comorbidity (dichotomized to [any] or [none]); neoadjuvant treatment (dichotomized to [any] or [none]); mesorectal excision (partial or total); and UICC stage (dichotomized to [I-II] or [III-IV]). 1:1 matching without replacement and a match tolerance of 0.005 was used. The model's balancing capability was tested using standardized differences, considering < 0.2 as small effect size.

The effect of bowel continuity on QoL in patients with anastomotic leakage was evaluated by a comparison of mean scores without matching, using Student's t-test and considering a p value of < 0.05 statistically significant.

Results

Paper I

Out of 1442 anterior resections for rectal cancer 2001-2011 at eleven hospitals in south of Sweden, 161 cases of anastomotic leakage were identified in the SCRCR, of whom 139 met study protocol definition of anastomotic leakage. Yet five more cases of anastomotic leakage could be identified when reviewing registrations of reoperations in SCRCR and the PASiS registry, making the rate of identified anastomotic leakage 10% (144/1442) for the study period. Two patients objected to participation and in three cases medical records could not be retrieved, why the final study group consisted of 139 anastomotic leakages after anterior resection for rectal cancer.

Median time from anterior resection to data collection was 87 (range 21-167) months.

Time to detection of anastomotic leakage

Median time to detection of anastomotic leakage was 15 (range 2-2059) days. Using the three different definitions of late leakage, 48.9% (68/139) were detected after hospital discharge, 23.0 % (32/139) were detected $\geq$ 30 days after anterior resection and 7.9% (11/139) were detected $\geq$ 90 days after anterior resection.

The incidence of anastomotic leakage, from anterior resection to detection, is demonstrated in Diagram 1.

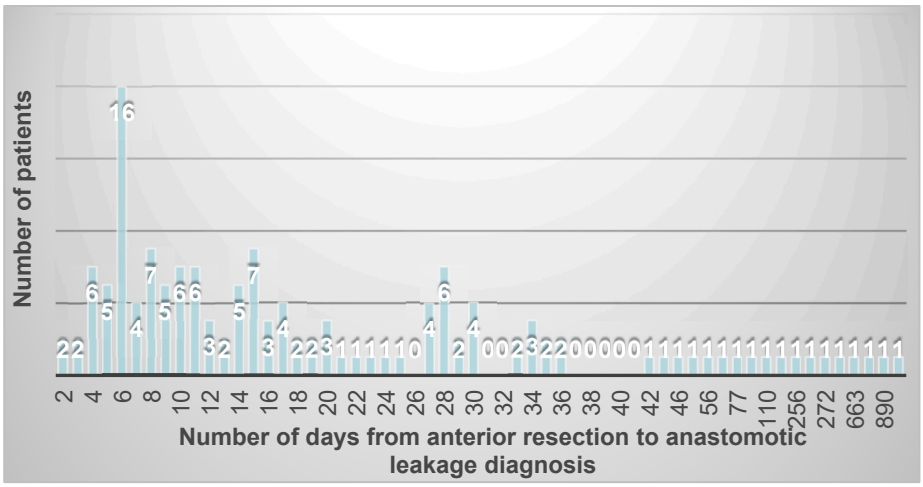

Diagram 1. Incidence of anastomotic leakage after anterior resection for rectal cancer
Specified as days from anterior resection to detection of anastomotic leakage.

Clinical characteristics related to late anastomotic leakage after anterior resection

An overview of a selection of clinical characteristics in patients subjected to anterior resection for rectal cancer, specified as with or without anastomotic leakage and furthermore specified in three different categories of late leakage is demonstrated in Table 2. Neoadjuvant therapy (p=0.01), intraoperative bleeding (p<0.001) and tumor level ≤ 5 cm from anal verge (p=0.005) were all in univariable analysis related to anastomotic leakage.

There was a tendency of neoadjuvant therapy being more often distributed in all categories of late leakage than in anastomotic leakages overall, although in univariate analysis only significantly more present in late compared to early leakage when using the definition based on hospital discharge. A defunctioning stoma from index procedure was significantly related to all categories of late compared to leakage in univariate analysis.

In binary logistic regression was female sex (OR 2.582; CI 1.096 -6.084; p=0.003), neoadjuvant radiotherapy (OR 3.307, CI 1.189-9.199, p=0.022) and a defunctioning stoma from index procedure (OR 2.591, CI 1.090 – 6.154; p=0.031) related to late leakage detected after hospital discharge. Furthermore, in binary logistic regression was a defunctioning stoma at index procedure related to late leakage detected ≥ 30 days after anterior resection (OR 4.477, CI 1.675-13.439; p=0.003) and late leakage detected ≥ 90 days after anterior resection (OR 9.440, CI 1.677-53.136; p=0.011).

Table 2. Clinical characteristics of patients subjected to anterior resection for rectal cancer with and without anastomotic leakage.

Late anastomotic leakage is specified according to three different study definitions.

[1] Data available from 1. January 2007: Anterior resection, no leakage n 694; All anastomotic leakages n 61; LL after hosptial discharge n 29; LL≥30 days after anterior resection n 13; LL≥90 days after anterior resection n 14

[2] Data available from 1. March 2003

	ANTERIOR RESECTION WITHOUT ANA-STOMOTIC LEAKAGE	ALL ANA-STOMOTIC LEAKAGES	LATE ANA-STOMOTIC LEAKAGE, DETECTED AFTER HOSPITAL DISCHARGE	LATE ANA-STOMOTIC LEAKAGE DETECTED ≥ 30 DAYS AFTER ANTERIOR RESECTON	LATE ANA-STOMOTIC LEAKAGE DETECTED ≥ 90 DAYS AFTER ANTERIOR RESECTION
No of patients	1298	139	68	32	11
Age ≥ 70 years	42 % (n 543)	39 % (n 54)	29 % (n 20)	34 %(n 11)	18 % (n 2)
Male sex	54 % (n 705)	62 % (n 86)	51 % (n 35)	53 % (n 17)	45 % (n 5)
ASA III / IV [1]	8 % (n 59)	16 % (n 10)	14 % (n 4)	8 % (n 1)	0 % (n 0)
Neoadjuvant radiotherapy	51 % (n 666)	63 % (n 87)	78 % (n 53)	69 % (n 22)	73 % (n 8)
Tumor level (cm from anal verge)					
0 - 5	2 % (n 30)	6 % (n 8)	3 % (n 2)	3 % (n 1)	0 % (n 0)
6-10	48 % (n 627)	57 % (n 79)	68 % (n 46)	56 % (n 18)	36 % (n 4
11-15	47 % (n 615)	37 % (n 51)	28 % (n 19)	37 % (n 12)	64 % (n 7)
Defunctioning stoma at anterior resection	60 % (n 776)	54 % (n 75)	69 % (n 47)	81 % (n 26)	90 % (n 10)
Median days from anterior resection to anastomotic leakage (range)		15 (2 - 2059)	29 (8 - 2059)	46 (30 - 2059)	363.5 (110 - 2059)
No of patients [2]	1086	112	56	23	11
UICC stage					
I – II	44 % (n 482)	56 % (n 63)	64 % (n 36)	56 % (n 13)	54 % (n 6)
III	30 % (n 327)	35 % (n 39)	30 % (n 17)	35 % (n 8)	45 % (n 5)
IV	9 % (n 102)	9 % (n 10)	5 % (n 3)	9 % (n 2)	0 % (n 0)
Missing	16% (n 175)	0	0	0	0
Local recurrence	4 % (n 46)	8 % (n 9)	4 % (n 2)	9 % (n 2)	0 % (n 0)

Symptoms, clinical findings and interventions related to late leakage after anterior resection

An overview of the distribution of symptoms found in late detected anastomotic leakage after anterior resection as well as need for reintervention is outlined in Table 3. A classification of asymptomatic leakage was more common in the in all the late leakage groups compared to early leakage and leakage overall, especially in the late leakage detected $\geq$ 90 days after anterior resection. However, the asymptomatic classification made by the reporting clinician was based on a symptom free clinical course up until bowel continuity was restored, although 9 out of 14 asymptomatic patients developed symptoms in the aftermath to defunctioning stoma reversal preceded by an evaluation of anastomotic integrity.

Fever was less common in all late leakage groups compared to early leakages, whereas peritonitis was less common in late leakages detected after hospital discharge and late leakage detected > 30 days after anterior resection compared to each respective early leakage group.

In a long-term follow-up, relaparotomy was called for in 62% (87/139) of all leakages. The need for relaparotomy was equal comparing all definitions of early to late leakage, except for in leakages detected $\geq$ 90 days where 82% (9/11) eventually had a relaparotomy. Although treatment without laparotomy (no treatment or intervention without laparotomy) overall was pursued as first action in response to anastomotic leakage in 55% (77/139) of all leakages, the success-rate in order to avoid a later laparotomy due to the anastomotic leakage was only 67% (52/77), thus making no treatment or treatment without laparotomy sustainable for 37% (52/139) of all anastomotic leakages in long-term follow-up. No clear pattern of better success-rate in avoiding later laparotomy when pursuing treatment without laparotomy related to early or late leakage could be detected.

Table 3. Clinical characteristics of patients subjected to anterior resection with anastomotic leakage.
Late ananstomotic leakage specified according to three different study definitions

	ALL ANASTOMOTIC LEAKAGES	LATE ANASTOMOTIC LEAKAGE, DETECTED AFTER HOSPITAL DISCHARGE	LATE ANASTOMOTIC LEAKAGE DETECTED ≥ 30 DAYS AFTER ANTERIOR RESECTON	LATE ANASTOMOTIC LEAKAGE DETECTED ≥ 90 DAYS AFTER ANTERIOR RESECTION
No of patients	139	68	32	11
Symptoms and clinical findings				
Asymptomatic	10 % (n 14)	21 % (n 14)	39 % (n 13)	73 % (n 8)
Fever	60 % (n 83)	48 % (n 33)	37 % (n 12)	18 % (n 2)
Clinical peritonitis	34 % (n 48)	18 % (n 12)	9 % (n 3)	18 % (n 2)
Abscess	32 % (n 45)	29 % (n 20)	44 % (n 14)	36 % (n 4)
Sinus	32 % (n 45)	32 % (n 22)	37 % (n 12)	45 % (n 5)
Rectovaginal fistula	41 % (n 22)	51 % (n 17)	47 % (n 7)	33 % (n 2)
Need fo intervention, full clinical course				
No intervention	4 % (n 5)	6 % (n 4)	9 % (n 3)	9 % (n 1)
Intervention without laparotomy	34 % (n 47)	41 % (n 28)	33 % (n 11)	9 % (n 1)
Laparotomy	62 % (n 87)	53 % (n 36)	56 % (n 18)	82 % (n 9)

Paper II

The cohort consisted of the 139 anastomotic leakage patients previously identified as described in paper I. After a median follow-up of 87 (range 21-165) months after anterior resection, 65% (90/139) of the anastomotic leakage patients had a permanent stoma.

Clinical characteristics related to outcome of permanent stoma after anastomotic leakage

Clinical characteristics in patients with anastomotic leakage, specified as with or without permanent stoma is outlined in Table 4. In univariate analysis, some clinical variables were related to an outcome of permanent stoma: female sex (p=0.04), lower tumor location (p=0.03) and neoadjuvant radiotherapy (p=0.01).

Presenting symptoms and need for intervention in relation to outcome of permanent stoma after anastomotic leakage

Table 5 outlines symptoms, need for intervention and time to detection of anastomotic leakage, where no specific symptom pattern associated with an outcome in bowel continuity could be established. The time to detection of anastomotic leakage was in median 12 (range 3-890) compared to 16 (range 2-2059) days in patients with bowel continuity and permanent stoma, respectively. However, no significant relation of time to detection of leakage could be established using either median time to detection of leakage or any of the definitions of late leakage described in paper I. Considering a full clinical course with long-term follow-up, relaparotomy was significantly more common in patients with a permanent stoma ($p<0.001$).

In binary logistic regression analyses were age $\geq$ 70 years (OR 3.89, CI 1.23-12.26; p=0.02) and relaparotomy (OR 15.66, CI 5.06-48.51; $p < 0.001$) significantly related to an outcome of permanent stoma, whereas neoadjuvant radiotherapy (OR 2.92, CI 0.92-9.30 p= 0.07) had a tendency of being related to an outcome of permanent stoma.

Type of permanent stoma after anastomotic leakage

In patients with permanent stomas, 67 % (60/90) were colostomies and 33% (30/90) were secondary or remaining ileostomies. Anastomotic leakage was stated as the primary reason for a remaining stoma in 76% (68/90), recurrent cancer disesase, comorbidity or patient's explicit choice were among the other reasons. In 42%

(29/68) of patients with anastomotic leakage as primary reason for remaining stoma was stoma formation first-line treatment for anastomotic leakage, in the remaining 58%, first-line conservative treatment ended-up with a a secondary stoma or residual defunctioning stoma.

Table 4. Clinical characteristics of patients with anastomotic leakage after anterior resection for rectal cancer. Specified as with and without permanent stoma as long-term outcome

	ALL ANASTOMOTIC LEAKAGES	BOWEL CONTINUITY	PERMANENT STOMA	P
No of patients	139	49	90	
Male sex	62 % (n 86)	73% (n 36)	55 % (n 50)	**0.04**
Female sex	38% (n 53)	27% (n 13)	45% (n 40)	
ASA Classification III/IV [1]	17 % (n 10)	25 % (n 5)	13 % (n 5)	**0.29**
Age ≥ 70 years	39 % (n 54)	29 %(n 14)	44 % (n 40)	**0.07**
Tumor level				
0-5	6 % (n 8)	0% (n 0)	9 %(n 8)	**0.03**
6-10	57% (n 79)	51% (n 25)	60% (n 54)	
11-15	37% (n 51)	47% (n 23)	31% (n 28)	
Missing	1% (n 1)	2 % (n 1)	0% (n 0)	
Neoadjuvant radiotherapy				
Yes	63% (n 87)	47% (n 23)	71% (n 64)	**0.01**
No	37% (n 52)	53 %(n 26)	29% (n 26)	
UICC stage[2]				
I-II	56% (n 63)	62% (n 22)	52% (n 41)	**0.56**
III	35% (n 39)	33%(n 12)	34% (n 27)	
IV	9% (n 10)	6% (n 2)	10% (n 8)	
Defunctioning stoma				
Yes	54 % (n 75)	51 % (n 25)	56 % (n 50)	**0.72**
No	46% (n 64)	49% (n 24)	44% (n 40)	
Level of resection				
PME	20% (n 28)	26% (n 13)	17% (n 15)	**0.18**
TME	75% (n 104)	67% (n 33)	79% (n 71)	
Missing	5% (n 7)	6% (n 3)	4% (n 4)	
High ligation of mesenteric artery				
Yes	26% (n 36)	37% (n 18)	20% (n 18)	**0.07**
No	65% (n 90)	59% (n 29)	68 % (n 61)	
Missing	9% (n 13)	4% (n 2)	12% (n 11)	
Circular Stapler				
Ch 29	45% (n 62)	53% (n 26)	40% (n 36)	**0.14**
Ch 31/33	45% (n 63)	37% (n 18)	50% (n 45)	
Missing	10% (n 14)	10% (n 5)	10% (n 9)	

[1] Data available from 1. March 2007: All anastomotic leakage n 58; Bowel Continuity n 20; Permanent Stoma n 38.

[2] Data available from 1. January 2003: All anastomotic leakage n112; Bowel Continuity n 36; Permanent Stoma n 76

Table 5. Presenting symptoms, need for intervention and time to diagnosis in patients with anastomotic leakage after anterior resection for rectal cancer.

Specified as with and without permanent stoma as long-term outcome.

	ALL ANASTOMOTIC LEAKAGES	BOWEL CONTINUITY	PERMANENT STOMA	P
No of patients	139	49	90	
Symptoms and clinical findings				
Fever	50 % (n 69)	43 % (n 21)	53 % (n 48)	0.29
Clinical peritonitis	9 % (n 12)	10 % (n 5)	8 % (n 7)	0.75
Abscess	53 % (n 74)	45 % (n 22)	58 % (n 52)	0.35
Sinus	21 % (n 29)	22 % (n 11)	20 % (n 18)	0.83
Rectovaginal fistula	41 % (n 22/53)	15 % (n 2/13)	50 % (n 20/40)	0.09
Need for intervention				
No intervention	4% (n 5)	10% (n 5)	0 % (n 0)	<0.001
Intervention without laparotomy	32% (n 44)	61% (n 30)	16% (n 14)	
Laparotomy	65% (n 90)	29% (n 14)	84% (n 76)	
Time to anastomotic leakage detection				
Early leakage < POD 29	77% (n 107)	80% (n 39)	76% (n 68)	0.68
Late Leakage > POD 30	23 % (n 32)	20% (n 10)	24% (n 22)	
Early Leakage < POD 89	92% (n 128)	98% (n 48)	89 % (n 80)	0,09
Late Leakage > POD 90	8% (n 11)	2% (n 1)	11% (n 10)	
Median days from anterior resection to detection of leakage	15 (2-2059)	12 (3-890)	16 (2–2059)	0.37

Paper III

From 1010 operated with anterior resection due to rectal cancer 2001-2011 in the in the Skåne region, 94 (9.3%) patients with anastomotic leakage were identified, and out of these 32 patients had rectal contrast imaging available that confirmed a diagnosis of anastomotic leakage. Clinical characteristics in included patients and excluded anastomotic leakage patients from the original cohort is illustrated in table 6, where no major differences could be established apart from less patients with low tumors ≤ 5cm from anal verge in included patients.

Table 6. Clinical characteristics in patients with anastomotic leakage after anterior resection, specified according to inclusion in study.

	ALL ANASTOMOTIC LEAKAGES IN ORIGINAL COHORT	INCLUDED PATIENTS WITH RADIOLOGICALLY VERIFIED ANASTOMOTIC LEAKAGE	OTHER METHOD TO ESTABLISH ANASTOMOTIC LEAKAGE	P
No of patients	94	32	62	
Bowel continuiuty	37% (n 35)	37% (n 12)	37% (n 23)	1.0
Male sex	62 % (n 67)	69% (n 22)	67% (n 40)	0.82
Age ≥ 70 years	37 % (n 35)	31 %(n 10)	40% (n 25)	
Tumor level				
≤ 5 cm	7 % (n 7)	0% (n 0)	11% (n 7)	0.09
Neoadjuvant radiotherapy				
Yes	60% (n 56)	53% (n 17)	63% (n 39)	0.38
No	40% (n 38)	47 %(n 15)	37% (n 23)	
Defunctioning stoma				
Yes	56 % (n 53)	59 % (n 19)	55% (n 34)	0.82
No	44% (n 41)	41% (n 13)	45 % (n 28)	
Level of resection				
PME	28% (n 26)	31% (n 10)	26% (n 16)	0.63
TME	72% (n 68)	69% (n 22)	74% (n 46)	
Anastomotc construction				
End-end	27% (n 25)	28% (n 9)	26% (n 16)	0.99
Side-end	71% (n 67)	72% (n 23)	66% (n 44)	
Missing	2% (n 2)	0% (n 0)	3 % (n 2)	
Asymptomatic	9% (n 8)	13% (n 4)	6 % (n 4)	0.44
Median days to detection of leakage (range)	14 (2-663)	16.5 (3-663)	11 (2-455)	0.24

Clinical characteristics in patients with a radiologically verified anastomotic leakage are outlined in table 7, specified with bowel continuity or permanent stoma. Age ≥ 70 years (p=0.004), side-to-end reservoir (p=0.05) were related to permanent stoma, a tendency of longer time to anastomotic leakage detection was seen in patients with permanent stoma (p=0.06).

Table 7. Clinical characteristics in patients with anastomotic leakage after anterior resection, specified according to outcome in bowel continuity.

	RADIOLOGICALLY VERIFIED ANASTOMOTIC LEAKAGE, OUTCOME OF BOWEL CONTINUITY	RADIOLOGICALLY VERIFIED ANASTOMOTIC LEAKAGE, OUTCOME OF PERMANENT STOMA	P
No of patients	12	20	
Male sex	83 % (n 10)	60% (n 12)	0.25
Age ≥ 70 years	0 % (n 0)	50 %(n 10)	0.004
Neoadjuvant radiotherapy			
Yes	33% (n 4)	65% (n 13)	0.15
No	77% (n 9)	35 %(n 7)	
Defunctioning stoma			
Yes	50 % (n 6)	65 % (n 13)	0.47
No	50% (n 6)	35%% (n 7)	
Level of resection			
PME	50% (n 6)	80% (n 16)	0.12
TME	50% (n 6)	20% (n 4)	
Anastomotc construction			
End-end	50% (n 6)	15 % (n 3)	0.05
Side-end	50% (n 6)	85% (n 17)	
Asymptomatic	0% (n 0)	20% (n 4)	0.27
Median days to detection of leakage	10.5 (4-29)	20.5 (3-663)	0.06
(range)			

Predefined radiological characteristics were evaluated in univariate association to outcome in bowel continuity as outlined in table 8. The most common feature was a dorsal (presacral) orientation of the leakage cavity seen in 27(84%) patients with a median size of 70 (range 50-88) millimeter. Exit of rectal contrast was most often also seen in the dorsal direction, present in 21(66%) of patients. Radiological signs consistent with abscess formation was seen in 11(34%) patients and the median size of radiologically visualized defect in anastomosis was 5 (range 4-10) millimeter in diameter.

Furthermore, radiological signs of an abscess and ≤ 5 mm diameter of sinus/fistula opening were related to an outcome of permanent stoma.

Table 8.Radiological characteristics in in patients with anastomotic leakage after anterior resection, specified according to outcome of bowel continuity or permanent stoma.

	RADIOLOGICALLY VERIFIED ANASTOMOTIC LEAKAGE, OUTCOME OF BOWEL CONTINUITY	RADIOLOGICALLY VERIFIED ANASTOMOTIC LEAKAGE, OUTCOME OF PERMANENT STOMA	P
No of patients	12	20	
Abscess formation			
Yes	8% (n 1)	50% (n 10)	0.02
No	92% (n 11)	50 %(n 10)	
Multiple cavities			0.63
Yes	8% (n 1)	20% (n 4)	
No	92% (n 11)	80% (n 16)	
Leak orientation			
Dorsal	67% (n 8)	65 % (n 13)	0.63
Ventral	25% (n 3)	10 % (n 2)	
Lateral	8% (n 1)	25% (n 5)	
Leak origin [1]			
Circular anastomosis	83% (n 5)	65% (n 11)	0.62
Stump	7% (n 1)	35 % (n 6)	
Width origin of leak $\leq$ 5 mm			
Yes	50% (n 6)	85% (n 17)	0.05
No	50% (n 6)	15& (n 3)	
Caviity or fistula size, diameter $\geq$ 70 mm			
Yes	50% (n 6)	65% (n 13)	0.47
No	50% (n 6)	35% (n 7)	

[1] Data only for patients with side-to end anastomosis bowel continuity (n 6) / permanent stoma (n 17)

Paper IV

As illustrated in figure 7, 1099 patients from the original cohort were offered participation out of whom 653 (59.4%) accepted and 544 were included in the study group. Median time from anterior resection to questionnaire response was 83.5 months (interquartile range 66-110 months).

In the final study group, consisting only of patients with bowel continuity, 42 patients had anastomotic leakage. The anastomotic leakages were mainly symptomatic (40/42) and were most often managed with interventions without laparotomy - ISREC B (34/42).

Clinical characteristics related to major LARS

Clinical characteristics were evaluated in relation to an outcome of major LARS where female sex ($p = 0.01$), neoadjuvant therapy ($p = 0.02$), defunctioning stoma at anterior resection ($p < 0.001$), total mesorectal excision ($p < 0.001$) and anastomotic leakage ($p = 0.01$) were in univariate analysis related to major LARS (table 9).

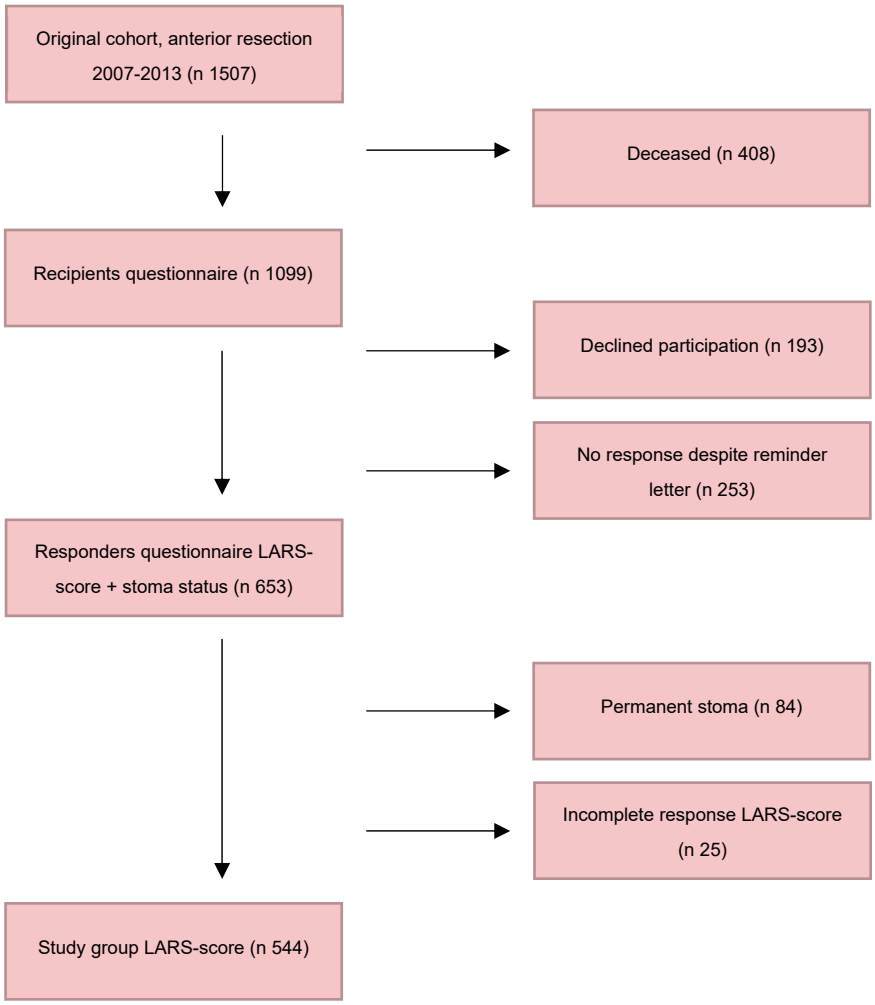

Fig 7. Recruitment process of inclusion in LARS-score from a cohort of 1507 patients subjected to anterior resection for rectal cancer 2007-2013

Table 9. Clinical characteristics of 544 patients with bowel continuity after anterior resection 2007–2013 due to rectal cancer, responding to LARS-score 5–11 years after index surgery, specified by outcome in LARS score

	NO MAJOR LARS (NO LARS + MINOR LARS)	MAJOR LARS	P
No of patients	286	258	
Male sex	180 (62.9%)	134 (51.9%)	0.01
Female sex	106 (37.1%)	124 (48.1%)	
Mean age at anterior resection (SD)	64.3 (9.6)	63.9 (9.0)	0.78
Comorbidity			
Yes	59 (20.6%)	46 (17.8%)	0.44
No	226 (79.0%)	212 (82.2%)	
Missing	1 (0.3%)	0 (0%)	
Neoadjuvant therapy			
Yes	141 (49.3%)	190 (73.6%)	0.02
5 x 5 Gy	*97 (33.9%)*	*150 (58.1%)*	
28/25 x 1.8/2 Gy + capecitabin	*44 (15,4 %)*	*40 (15.5%)*	
No	145 (50.7%)	68 (26.3%)	
Defunctioning stoma at anterior resection			
Yes	216 (75.5%)	234 (90.7%)	< 0.001
No	68 (23.8%)	24 (9.3%)	
Missing	2 (0.7%)	0 (0%)	
Mesorectal excision			
PME	116 (40.6%)	48 (18.6%)	< 0.001
TME	162 (56.6%)	205 (79.4%)	
Missing	8 (2.8%)	5 (1.9%)	
Anastomotic construcion			
End-end	82 (28.7%)	52 (20.2%)	0.07
Side-end/reservoir	199 (69.6%)	199 (77.1%)	
Missing	5 (1.7%)	7 (2.8%)	
Surgical approach			
Laparoscopy	22 (7.7%)	25 (9.7%)	0.45
Open surgery	260 (90.9%)	230 (89.1%)	
Missing	4 (1.4%)	3 (1.2%)	
UICC stage			
I + II	174 (60.8%)	152 (58.9%)	0.75
III + IV	105 (36.7%)	97 (37.6%)	
Missing	7 (2.4%)	9 (3.5%)	
Anastomotic leakage			
Yes	14 (4.9%)	28 (10.9%)	0.01
No	272 (95.1%)	230 (89.1%)	

Anastomotic leakage and major LARS

Overall, 47.4% (258/544) of patients in the study group had major LARS. In patients with and without anastomotic leakage, major LARS was reported in and 66.7% (28/42) and 45.8 % (230/502), respectively (table 10).

Table 10. Results from LARS scores in patients subjected to anterior resection due to rectal cancer (2007–2013) who had bowel continuity and answered LARS score, specified as patients with and without anastomotic leakage.

	TOTAL STUDY GROUP		
	No anastomotic leakage	Anastomotic leakage	RR (95% CI)
PRIMARY OUTCOME			
Major LARS	230 (45.8%)	28 (66.7%)	1.5 (1.1–1.8)
Minor LARS	125 (24.9%)	7 (16.7%)	0.7 (0.3–1.3)
No LARS	147 (29.3%)	7 (16.7%)	0.6 (0.3–1.1)
SECONDARY OUTCOME			
Do you ever have occasions where you cannot control your flatus (wind)?			
No never	123 (24.5%)	5 (11.9%)	0.5 (0.2–1.1)
Yes, less than once a week	161 (32.1%)	15 (35.7%)	1.1 (0.7–1.7)
Yes, at least once a week	218 (43.4%)	22 (52.4%)	1.2 (0.9–1.6)
Do you ever have accidental leakage of liquid or stool?			
No never	160 (31.9%)	9(21.4%)	0.7 (0.4–1.2)
Yes, less than once a week	342 (68.1%)	33(78.6%)	1.1 (0.9–1.4)
Yes, a least once a week			
How often do you open your bowels?			
More than 7 times a day	24 (4.8%)	4 (9.5%)	2.0 (0.7–5.5)
4-7 times a day	145 (28.9%)	19 (45.2%)	1.6 (1.1–2.2)
1-3 times a day	263 (52.4%)	17 (40.5%)	0.8 (0.5–1.1)
Less than once a day	70 (13.9%)	2 (4.7%)	0.3 (0.1–1.3)
Do you ever have to open your bowels within one hour of the last bowel opening?			
No never	89 (17.7%)	3 (7.1%)	0.4 (0.1–1.2)
Yes, less than once per week	171 (34.1%)	14 (33.3%)	1.0 (0.6–1.5)
Yes, at least once per week	242 (48.2%)	25 (59.5%)	1.2 (0.9–1.6)
Do you ever have such a stong urge to open your bowels that you have to rush to the toilet?			
No never	134 (26.7%)	7 (16.7%)	0.6 (0.3–1.2)
Yes, less than once per week	212 (42.2%)	16 (38.1%	0.9 (0.6–1.3)
Yes, at least once per week	156 (31.1%)	19 (45.2%)	1.4 (1.0–2.1)

As outlined in table 11, anastomotic leakage was after matching significantly related to major LARS with a relative risk ratio (RR) of 2.3 (95% confidence interval 1.4-3.9). Among individual symptoms estimated by LARS-score, urgency was significantly related to anastomotic leakage, RR 2.1 (95% confidence interval 1.1-4.1).

Clinical factors related to major LARS in anastomotic leakage patients

Table 12 shows results from a subgroup analysis of the 42 patients with anastomotic leakage, where clinical characteristics were related to an outcome of major LARS. The number of days from anterior resection to detection of anastomotic leakage was significantly longer in patients with compared to without major LARS, in median 18 (interquartile range (IQR) 11-19) and 9 (IQR 5-13.5) days respectively (p = 0.002). This relationship was further evaluated in in patients only subjected to intervention without relaparotomy (ISREC B), confirming longer time to detection (in median 18 (IQR 9.5-24) vs. 9 (IQR 6-16) days) related to major LARS (p=0.03). Furthermore, in patients with anastomotic leakage, UICC stage III-IV was related to major LARS (p=0.05), and female sex had a tendency to be associated with major LARS (p= 0.06). In female patients with anastomotic leakage, as many as 85.7% (12/14) had major LARS.

Table 11. Results from LARS scores in patients subjected to anterior resection due to rectal cancer (2007–2013) who had bowel continuity and answered LARS score, specified as two matched groups with and without anastomotic leakage

	PROPENSITY SCORE MATCHED GROUPS		
	No anastomotic leakage	Anastomotic leakage	RR (95% CI)
PRIMARY OUTCOME			
Major LARS	12 (28.6%)	28 (66.7%)	2.3(1.4–3.9)
Minor LARS	13(31.0%)	7(16.7%)	0.5 (0.2–1.2)
No LARS	17(40.5%)	7(16.7%)	0.4 (0.2–0.9)
SECONDARY OUTCOME			
Do you ever have occasions where you cannot control your flatus (wind)?			
No never	13(31.0%)	5 (11.9%)	0.5 (0.1–1.0)
Yes, less than once a week	15(35.7%)	15 (35.7%)	1.0 (0.6–1.8)
Yes, at least once a week	14(33.3%)	22 (52.4%)	1.6 (0.9–2.6)
Do you ever have accidental leakage of liquid or stool?			
No never	16(38.1%)	9(21.4%)	0.6 (0.3–1.1)
Yes, less than once a week	26(61.9%)	33(78.6%)	1.3 (0.9–1.7)
Yes, a least once a week			
How often do you open your bowels?			
More than 7 times a day	2 (4.8%)	4 (9.5%)	2.0 (0.4–10.3)
4-7 times a day	11 (26.2%)	19 (45.2%)	1.8 (0.3–1.1)
1-3 times a day	27 (64.3%)	17 (40.5%)	0.6 (0.4–1.0)
Less than once a day	2 (4.8%)	2 (4.8%)	1.0 (0.1–6.8)
Do you ever have to open your bowels within one hour of the last bowel opening?			
No never	7 (16.7%)	3 (7.1%)	0.4 (0.1–1.5)
Yes, less than once per week	14 (33.3%)	14 (33.3%)	1.0 (0.5–1.8)
Yes, at least once per week	21 (50.0%)	25 (59.5%)	1.2 (0.8–1.8)
Do you ever have such a stong urge to open your bowels that you have to rush to the toilet?			
No never	15 (35.7%)	7 (16.7%	0.5 (0.2–1.0)
Yes, less than once per week	18 (42.9%)	16 (38.1%)	0.9 (0.5–1.5)
Yes, at least once per week	9 (21.4%)	19 (45.2%)	2.1 (1.1–4.1)

Table 12. Clinical characteristics of 42 anastomotic leakage patients with bowel continuity after anterior resection 2007–2013 due to rectal cancer, responding to LARS-score 5–11 years after index surgery, specified by outcome in LARS score

	NO MAJOR LARS (NO LARS + MINOR LARS)	MAJOR LARS	P
No of patients	14	28	
Male sex	12 (85.7)	16 (57.1%)	0.06
Female sex	2 (14.3%)	12 (42.9%)	
Median age at anterior resection (IQR)	63.0 (59.0-67.0)	64.5 (57.0-69.0)	0.76
Comorbidity			
Yes	4 (28.6%)	7 (25.0%)	0.80
No	10 (71.4%)	21 (75.0%)	
Neoadjuvant radiotherapy			
Yes	8 (57.1%)	17 (60.7%)	0.29
5 x 5 Gy	*3 (21.4%)*	*12 (42.9%)*	
28/25 x 1.8/2 Gy + capecitabin	*5 (35.7%)*	*5 (17.9%)*	
No	6 (42.9%)	11 (39.3%)	
Defunctioning stoma at anterior resection			
Yes	11 (78.6%)	25 (89.3%)	0.35
No	3 (21.4%)	3 (10.7%)	
Mesorectal excision			
PME	3 (21.4%)	4 (14.3%)	0.56
TME	11 (78.6%)	24 (85.7%)	
Anastomotic construcion			
End-end	6 (42.9%)	6 (21.4%)	0.15
Side-end/reservoir	8 (57.1%)	22 (78.6%)	
Surgical approach			
Laparoscopy	3 (21.4%)	3 (10.7%)	0.37
Open surgery	11 (78.6%)	24 (85.7%)	
Missing	0 (0%)	1 (3.6%)	
UICC stage			
I + II	12 (85.7%)	15 (53.6%)	0.05
III + IV	2 (14.3%)	13 (46.4%)	
Median days to diagnosis of anastomotic leakage (IQR)	9.0 (5.0-13.5)	19 (11.0--33.0)	0.002

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Figure 8 demonstrates that out of 1029 patients eligible for inclusion, 615 (59.8%) responded in median 83.5 months (interquartile range 66-110) months after anterior resection. Overall, 80 patients (13%) had anastomotic leakage, out of whom 42 had bowel continuity. Out of all responders, 541 had bowel continuity.

Anastomotic leakage patients with bowel continuity and outcome in Quality of Life

In primary analysis, no effect of anastomotic leakage on Global Health Status evaluated by EORTC QLQ C-30 could be demonstrated either before or after matching. In secondary analysis using EORTC QLQ CR-29, faecal incontinence (p=0.036) and buttock pain (p=0.049) were related to anastomotic leakage (table 13+ table 14).

Quality of Life in anastomotic leakage patients, irrespective of bowel continuity

In evaluation of anastomotic leakage patients with and without bowel continuity, no significant differences could be detected in Global Health Status, nor in functional or symptom items or scales. However, in responses to EORTC QLQ-CR30, patients with bowel continuity had a tendency to be more bothered by diarrhea (p=0.086). On the other hand, residual stoma patients tended to report more problems of involuntary gas/feacal departure from the stoma bag than patients with bowel continuity had corresponding symptoms of feacal/gas incontinence, as evaluated by EORTC QLQ CR-29 (p=0.061) (table 15).

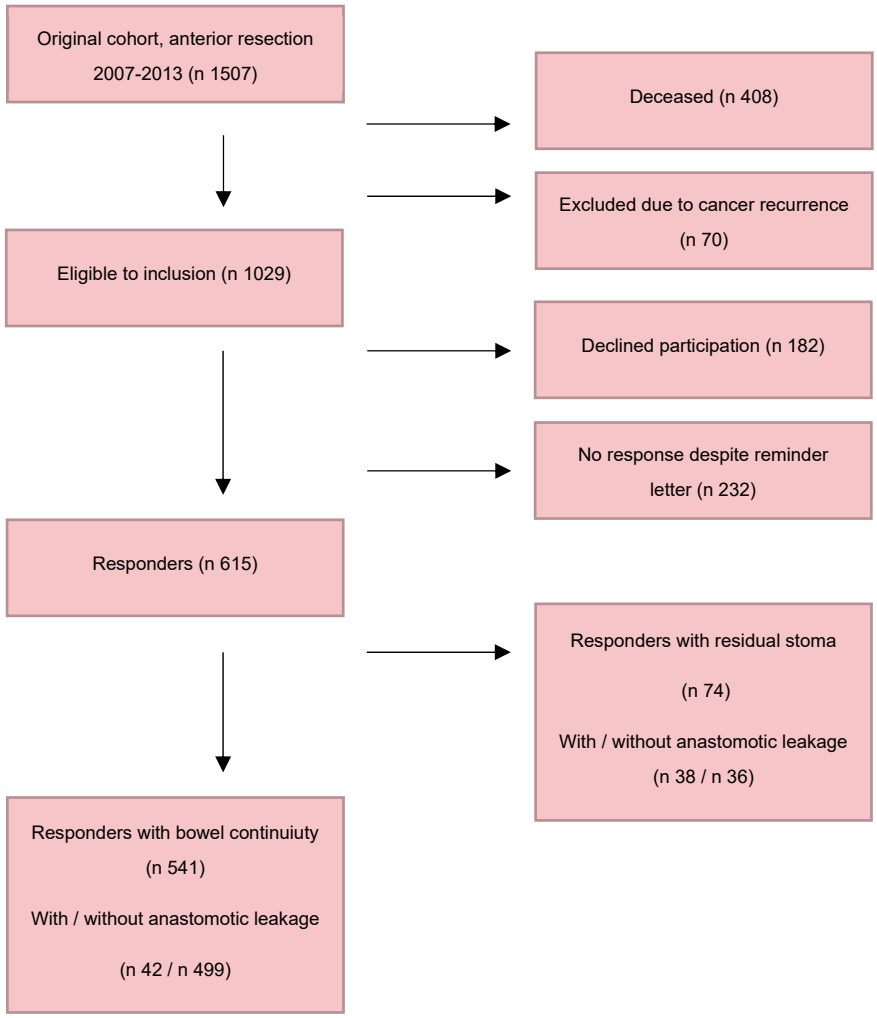

Figure 8. Recruitment process of inclusion in EORTC QLQ-C30 and QLQ-CR29 re from a cohort of 1507 patients subjected to anterior resection for rectal cancer 2007-2013

Table 13. Patients with bowel continuiuty after anterior resection 2007–2013, specified as with and without anastomotic leakage, responding to EORTC QLQ-C30 and EORTC QLQ CR-29 5–11 years after index surgery

	n	NO ANASTOMOTIC LEAKAGE Mean (SD)	n	ANASTOMOTIC LEAKAGE Mean (SD)	P
EORTC QLQ-C30					
Global Health Status	495	73.9 (19.8)	42	77.8 (18.5))	0.299
Functioning scale					
Physical functioning	493	86.9 (17.4)	41	88.7 (19.9)	0.536
Role functioning	492	86.2 (23.7)	41	85.4 (24.2)	0.833
Emotional functioning	494	84.0 (19.2)	42	85.3 (17.7)	0.655
Cognitive functioning	494	86.2 (17.5)	40	85.8 (18.3)	0.908
Social functioning	494	82.9 (23.3)	40	84.2 (20.7)	0.732
Symptom scale					
Fatigue	495	22.4 (22.1)	40	19.4 (22.9)	0.419
Nausea/vomiting	492	2.9 (9.9)	40	2.9 (7.4)	0.998
Pain	495	11.7 (20.8)	40	6.2 (12.9)	0.101
Dyspnoea	490	19.8 (26.3)	40	13.3 (23.6)	0.133
Insomnia	490	21.2 (27.8)	40	19.2 (22.5)	0.648
Apetite loss	490	5.4 (16.3)	40	4.2 (13.5)	0.630
Constipation	493	14.3 (24.6)	40	8.3 (18.1)	0.134
Diarrrhea	493	21.3 (28.0)	42	29.4 (32.3)	0.124
Financial difficulties	493	5.9 (17.5)	39	11.1 (26.9)	0.092
EORTC QLQ-CR29					
Functional items and scales					
Body image	470	80.0 (25.7)	40	81.7 (23.8)	0.699
Anxiety	467	71.3 (27.5)	41	73.2 (23.8)	0.675
Weight	471	81.6 (27.9)	41	76.4 (31.8)	0.260
Sex interest, male	245	62.7 (28.6)	25	68.0 (32.6)	0.386
Sex interest, female	202	82.3 (23.8)	12	75.0 (25.1)	0.301
Symptomatic items and scales					
Urinary frequency	474	40.4 (20.4)	40	42.1 (21.0)	0.624
Blood, mucus in stool	472	4.6 (18.1)	40	4.6 (12.5)	0.998
Stool frequency	430	11.1 (18.8)	38	13.6 (20.4)	0.476
Urinary incontinence	473	16.5 (24.4)	39	16.2 (25.2)	0.951
Dysuria	474	4.8 (14.4)	39	5.1 (16.3)	0.886
Abdominal pain	474	10.6 (21.6)	38	19.3 (60.8)	0.053
Buttock pain	476	10.8 (22.6)	40	15.0 (29.2)	0.278
Bloating	467	22.0 (28.7)	38	21.0 (26.2)	0.835
Dry mouth	472	21.9 (27.9)	41	25.2 (27.7)	0.466
Hairloss	465	10.1 (21.3)	41	12.2 (24.4)	0.553
Taste	468	7.7 (20.3)	39	10.2 (21.8)	0.465
Flatulence	471	35.7 (30.0)	38	40.3 (30.2)	0.355
Fecal incontinence	467	16.4 (22.5)	41	27.6 (27.8)	0.003
Sore skin	456	11.8 (22.4)	39	14.5 (25.1)	0.478
Impotence	247	54.9 (38.9)	25	49.3 (37.4)	0.492
Dyspareunia	122	12.0 (24.6)	6	11.1 (27.2)	0.930

Table 14. Patients with bowel continuity after anterior resection 2007–2013, specified as with anastomotic leakage compared to a propensity matched group without anastomotic leakage, responding to EORTC QLQ-C30 and EORTC QLQ CR-29 5–11 years after index surgery.

	n	NO ANASTOMOTIC LEAKAGE Mean (SD)	n	ANASTOMOTIC LEAKAGE Mean (SD)	P
EORTC QLQ-C30					
Global Health Status	42	73.2 (17.3)	42	77.8 (18.5)	0.297
Functioning scale					
Physical functioning	42	86.1 (16.5)	41	88.7 (19.8)	0.521
Role functioning	41	87.4 (19.6)	41	85.4 (24.4)	0.677
Emotional functioning	42	88.9 (14.8)	42	85.3 (17.7)	0.319
Cognitive functioning	42	88.1 (13.9)	40	85.8 (18.3)	0.529
Social functioning	42	85.3 (21.5)	40	84.2 (20.6)	0.806
Symptom scale					
Fatigue	42	18.8 (18.9)	40	19.4 (19.4)	0.887
Nausea/vomiting	42	1.2 (4.3)	40	2.9 (7.4)	0.201
Pain	42	12.3 (19.8)	40	6.2 (12.9)	0.107
Dyspnoea	41	19.5 (23.5)	40	13.3 (23.6)	0.242
Insomnia	41	13.8 (21.0)	40	19.2 (22.5)	0.273
Apetite loss	41	3.2 (10.0)	40	4.2 (13.5)	0.729
Constipation	42	9.5 (18.4)	40	8.3 (18.1))	0.769
Diarrrhea	42	20.6 (31.2)	42	29.4 (32.3)	0.211
Financial difficulties	42	5.5 (12.6)	39	11.1 (26.9)	0.231
EORTC QLQ-CR29					
Functional items and scales					
Body image	40	80.4 (17.6)	40	81.7 (23.8)	0.733
Anxiety	40	73.3 (21.6)	41	73.2 (23.8)	0.974
Weight	40	81.7 (29.2)	41	76.4 (31.8)	0.442
Sex interest, male	27	59.2 (31.1)	25	68.0 (32.6)	0.327
Sex interest, female	9	74.1 (32.4)	12	75.0 (25.1)	0.942
Symptomatic items and scales					
Urinary frequency	42	37.3 (20.1)	40	42.1 (21.0)	0.295
Blood, mucus in stool	40	4.1 (9.7)	40	4.6 (12.5)	0.835
Stool frequency	38	8.3 (13.8)	38	13.6 (20.4)	0.193
Urinary incontinence	41	14.6 (22.4)	39	16.2 (25.2)	0.764
Dysuria	41	4.1 (15.3)	39	5.1 (16.3)	0.764
Abdominal pain	41	4.1 (13.3)	38	19.3 (60.8)	0.122
Buttock pain	41	4.9 (14.1)	40	15.0 (29.2)	0.049
Bloating	37	18.0 (26.7)	38	21.0 (26.2)	0.621
Dry mouth	40	20.8 (28.9)	41	25.2 (27.7)	0.489
Hairloss	40	6.7 (17.2)	41	12.2 (24.4)	0.244
Taste	40	9.2 (23.8)	39	10.2 (21.8)	0.833
Flatulence	40	35.0 (27.2)	38	40.3 (30.2)	0.413
Fecal incontinence	41	15.4 (19.9)	41	27.6 (27.8)	0.036
Sore skin	38	6.1 (13.1)	39	14.5 (25.1)	0.071
Impotence	28	69.0 (39.9)	25	49.3 (37.4)	0.055
Dyspareunia	5	26.7 (27.9)	6	11.1 (27.2)	0.486

Table 15. Anastomotic leakage patients with and without bowel continuity after anterior resection 2007–2013, responding to EORTC QLQ-C30 and EORTC QLQ CR-29 5–11 years after index surgery.

	n	BOWEL CONTINUITY Mean (SD)	n	RESIDUAL STOMA Mean (SD)	P
EORTC QLQ-C30					
Global Health Status	42	77.3 (18.5)	38	72.1 (23.0)	0.282
Functioning scale					
Physical functioning	41	88.7 (19.9)	38	86.1 (15.2)	0.525
Role functioning	41	85.4 (24.2)	38	81.1 (28.8)	0.833
Emotional functioning	41	85.3 (17.7)	38	89.3 (13.6)	0.264
Cognitive functioning	40	85.8 (18.3)	38	87.7 (16.3)	0.633
Social functioning	40	84.2 (20.7)	38	82.0 (27.8)	0.698
Symptom scale					
Fatigue	40	19.4 (22.9)	38	24.0 (23.2)	0.388
Nausea/vomiting	40	2.9 (7.4)	38	7.0 (16.3)	0.153
Pain	40	6.2 (12.9)	37	14.0 (21.3)	0.057
Dyspnoea	40	13.3 (23.6)	37	18.9 (23.0)	0.297
Insomnia	40	19.2 (22.5)	38	17.5 (24.2)	0.760
Apetite loss	40	4.2 (13.5)	38	8.8 (22.8)	0.279
Constipation	40	8.3 (18.1)	38	5.3 (18.2)	0.458
Diarrrhea	41	28.4 (32.1)	38	16.7 (27.7)	0.086
Financial difficulties	39	11.1 (26.9)	38	4.4 (17.6)	0.199
EORTC QLQ-CR29					
Functional items and scales					
Body image	40	81.7 (23.8)	38	78.2 (30.0)	0.574
Anxiety	41	73.2 (23.8)	38	74.6 (26.2)	0.806
Weight	41	76.4 (31.8)	38	85.1 (26.5)	0.194
Sex interest, male	25	68.0 (32.6)	22	71.2 (23.7)	0.704
Sex interest, female	12	75.0 (25.1)	10	86.7 (17.2)	0.228
Symptomatic items and scales					
Urinary frequency	40	42.1 (21.0)	38	41.2 (21.0)	0.862
Blood, mucus in stool	40	4.6 (12.5)	38	7.0 (16.7)	0.467
Stool frequency	38	13.6 (20.4)	37	15.8 (21.1)	0.653
Urinary incontinence	39	16.2 (25.2)	37	18.0 (27.9)	0.771
Dysuria	39	5.1 (16.3)	37	2.7 (9.2)	0.438
Abdominal pain	38	19.3 (60.8)	36	11,1 (19.5)	0.444
Buttock pain	40	15.0 (29.2)	37	15.3 (25.6)	0.960
Bloating	38	21.0 (26.2)	35	21.9 (31.2)	0.900
Dry mouth	41	25.2 (27.7)	38	16.7 (25.4)	0.158
Hairloss	41	12.2 (24.4)	38	11.4 (26.0)	0.889
Taste	39	10.2 (21.8)	38	11.4 (19.4)	0.808
Flatulence	38	40.3 (30.2)	37	28.8 (28.5)	0.094
Fecal incontinence	41	27.6 (27.8)	38	15.8 (27.6)	0.061
Sore skin	39	14.5 (25.1)	38	30.7 (61.7)	0.134
Stoma care problems			37	5.4 (20.0)	
Embarrassment			37	26.1 (23.7)	
Impotence	25	49.3 (37.4)	27	48.1 (40.6)	0.914
Dyspareunia	6	11.1 (27.2)		25.0 (46.3)	0.527

Discussion

The aim of this thesis is to gain knowledge about the long-term morbidity related to anastomotic leakage after anterior resection. Whereas numerous previous studies have addressed questions of how to prevent and early detect a leakage, less is known about how to best deal with an anastomotic leakage after anterior resection once it has occurred. Although prevention is most desirable, the leakage rates prevail over time and remains the major stumbling block when doing anterior resection. Questions on how to make sense of the varying clinical presentations, how to predict chances to regain bowel continuity and if restoration of bowel continuity after anastomotic leakage really benefits the patient, are all part of everyday practise in colorectal surgery. This thesis addresses these questions and can hopefully by adding some knowledge of the long-term outcome, contribute to better decisions when dealing with the anastomotic leakage patient after anterior resection.

Late detected anastomotic leakage after anterior resection

In paper I, anastomotic leakage after anterior resection was evaluated with the finding that the rate of anastomotic leakage increases substantially with extended follow-up. In half of the patients the diagnosis is detected after hospital discharge, in one in four leakages later or equal to 30 days after anterior resection, and in almost one in ten 90 days has passed since index surgery. We also found that a defunctioning stoma is related to late detection of anastomotic leakage. However, we could not establish a reduced need for relaparotomy in patients with late detected anastomotic leakage in long-term follow-up.

The rate of anastomotic leakage and the proportion of late leakages

The fact that the rate of anastomotic leakage after anterior resection increases with extended follow-up has previously been evaluated where 40% of symptomatic leakages are reported to be detected after hospital discharge[139] and 32-51% of all leakages are detected more than 30 days after anterior resection[58, 140, 141, 144]. The rate of anastomotic leakages depend on how carefully the diagnosis is sought and what

definition of anastomotic leakage that is used. Using the SCRCR, where a clear definition of anastomotic leakage is lacking, involves a risk of identifying too few or incorrect cases of anastomotic leakage. The SCRCR have been validated three times regarding postoperative complications. Two studies concerning operations performed in the 90s showed somewhat contradictory results. The first, which did not specifically evaluate anastomotic leakage, reported a remarkably high proportion of 45% false-negative registrations of reoperations in general[195]. The second reported false-negative registrations of anastomotic leakage up to 30 days as a rarity (2.6%) compared to false-positive registrations (16.2%)[196]. A third more current study, evaluated SCRCR registrations of anastomotic leakage within 30 days after anterior resection between 2007 and 2013, in comparison to leakages detected in medical records using ISREC criteria. It revealed substantial false-negative rate of 29% regarding anastomotic leakage, as opposed to rare false-positive registrations present at 1.3% (and in these cases, most often rather misclassifications in time, as they were true anastomotic leakages detected after 30 days)[193]. When including leakages up until 90 days, the just mentioned study had a validated 14.7% leakage rate. This result could be expected to be fairly similar to the leakage rate in our study. Our 10% leakage rate suggest that we, despite using different search terms in SCRCR and the PASiS registry, have likely failed to include all anastomotic leakages from the time period. On the other hand, we performed chart review to validate all included anastomotic leakages, why false-positive cases can be ruled out in our study. Whether this has implications on our relative rate of late leakage is uncertain. In the mentioned study, missing SCRCR anastomotic leakage registrations were mainly before 30 days[193], suggesting a corresponding risk of relative underestimation of early leakages in our study. Speaking against a relative overestimation of late detected leakages in our results is similar rates of leakages detected after hospital discharge found in another study[139], and the fact that our 24% rate of leakages found later or equal to 30 days after anterior resection is in the lower range when compared to the 32-51% rate reported by other authors [58, 140, 141, 144]. However, study group composition must also be considered when evaluating external validity of our findings. In our study group, we had a relatively high proportion (47%) of tumours situated in the upper rectum, possibly explained by local therapeutic traditions of not performing anterior resections for tumours in the lower rectum. Studies that, compared to our findings, report higher rates of anastomotic leakage detected after 30 days exclusively evaluate low anterior resection[58, 140, 144]. In speculation, leakages from a low anastomosis have a greater chance of being confined to the pelvis, thereby reducing stormy symptoms and making them more prone to late detection.

Definition of late leakage after anterior resection

Some authors have suggested that late anastomotic leakage should be regarded as a separate entity in terms of clinical presentation and risk factors associated with its occurence[139, 140]. What dividing line that is most meaningful to use when exploring the concept of late leakage is debatable, and to some extent arbitrary. A common assumption is that this subset of leakages is not only late detected, but actually occurs late after a period of normal recovery. Arguing this, one possible dividing line is hospital discharge as once previously used[139], finding merits in a presumed evaluation of recovery as basis for discharging the patient. However, a disadvantage of using discharge as dividing line is inconsistencies when comparing studies, given different criteria for discharge in different settings. The most commonly used definition of late leakage is 30 days after anterior resection, which has also been argued to reflect a point in time that represent expected recovery[140], but also provides a cut-off that is independent of therapeutic traditions and facilitate comparison of studies. When exploring this concept, we used three definitions in our study in order to evaluate the clinical course in different time-frames as well as to make our results comparable to other studies. However, in hindsight realizing that we may have lost overview by using one definition too many. The late leakage after hospital discharge has been used only once and could probably have been omitted given its inconsistent character in lack of specific criteria for hospital discharge. On the other hand, the third category - leakage detected $\geq$ 90 days after anterior resection - finds merit in being reproducible and have value in identifying the very late detected leakages, which could be expected to be a rarity distinguished by specific characteristics.

Late leakage after anterior resection – a separate entity?

Support for late leakage being an entity of its own is found in studies evaluating risk factors for anastomotic leakage based on the time for diagnosis, and thereby suggesting a pathogenic mechanism that differs from early leakage. Neoadjuvant chemoradiotherapy[140, 144, 197], defunctioning stoma[144], female sex[197] and low level anastomosis[197] have been reported to be associated with late leakage after anterior resection. Although neoadjuvant treatment has been challenged as a predisposing factor for anastomotic leakage after anterior resection in general[81], some studies report neoadjuvant radiotherapy to have prolonged tissue effects affecting healing capacity differently over time[82]. It has therefore been argued that neoadjuvant treatment could cause a fragility in anastomotic healing, that predisposes for late leakages[144]. In our study, which evaluated characteristics associated to separate definitions of late leakage within the group of anastomotic leakages, we found in neoadjuvant treatment related to the category of late leakage detected after hospital discharge. Nevertheless, analysing the relation of several clinical variables to three

different definitions of late leakage constitutes a risk of false positive results due to multiple testing, why this finding related to only one category of late leakage can be argued to be randomly detected. However, defunctioning stomas were related to all categories of late leakage in multivariable analysis and could be regarded as a finding on more solid ground, as it is also coherent with findings from other studies. In the largest study to date evaluating late leakage after anterior resection, a defunctioning stoma had a protective role in early leakage, but was an independent risk factor for late leakage[144]. Furthermore, another study found that the protective properties of a defunctioning stoma regarding early leakage could not be demonstrated in late leakages[140].

The second motive for considering late leakage as separate entity has been based on identifying characteristic patterns of clinical presentation. Late leakage after anterior resection can be asymptomatic and is as such most often detected on evaluation of anastomotic integrity before stoma reversal[198]. However, the majority of late leakages detected more than 30 days after anterior resection are reported to be symptomatic, presenting with a wide range of symptoms occasionally including pelvic sepsis and necrotizing fasciitis[142-144]. So even if the most commonly reported manifestations of late leakage - abscesses, various types of fistulae, chronic sinus or stenosis[58, 140, 144, 197] , usually without development of generalized peritonitis[140] – suggest a limited infection as the most common presentation, this is contrasted by some reports of occasional more severe clinical presentations. For example, Yang et al. found that among late leakages with chronic sinuses (in this study most often found after stoma reversal) 4/33 progressed to necrotizing fasciitis[144]. In our study, we could not demonstrate a clear presentation pattern in terms of abscesses, fistulae or sinuses distinguishing early from late leakages, although symptoms of fever and generalized peritonitis was more common in early leakages. Asymptomatic leakages were also more common in patients with leakages detected $\geq$ 90 days after anterior resection. However, in the group considered as asymptomatic, the asymptomatic labelling was in fact only correct up until defunctioning stoma reversal (preceded by a normal evaluation of anastomotic integrity). After stoma reversal symptoms emerged in 9/14 asymptomatic patients, with development of rectovaginal fistulae, sinus and abscesses. Considerable time had usually passed from restoration of bowel continuity until the leakage was detected (in median almost a year later), suggesting that a small healing defect occasionally may remain undetected despite normal anastomotic evaluation before stoma reversal. It also demonstrates that very long follow-up is needed in order to detect all late leakages, and that significant morbidity due to anastomotic healing failure can arise years after anterior resection.

A third characteristic reported to distinguish late leakage is found by some authors in a reduced need for relaparotomy[140, 144]. In our study, we could not demonstrate such a relationship apart from when using the definition late leakage detected after

hospital discharge. This could possibly be explained by having longer follow-up than previous studies, and thereby including more cases of long but failing conservative treatments that eventually ended up in relaparotomy several years later, as well as by identifying late leakages detected long after stoma reversal.

All in all, when evaluating clinical characteristics related to late leakage in our study, we find some support for that most late leakages are less symptomatic in terms of fever and peritonitis. However, an assumption of that late leakages is about the same as asymptomatic/mildly symptomatic leakages is wrong, given occasional cases of significant morbidity and a similar need for relaparotomy in long-term follow-up.

Clinical implications of late leakage after anterior resection

It is reasonable to ask if the concept of late leakages has a place in gaining better understanding of anastomotic leakage after anterior resection, and furthermore, what benefit does implementation of the concept have in everyday clinical practise? Whether late anastomotic leakage is distinguished from early leakage by having a separate underlying pathogenic mechanism, where the leakage actually occurs later due to a vulnerability with late manifestations, remains unclear. An alternative hypothesis could be that late leakages merely are detected later, where a main common denominator could be the defunctioning stoma that ameliorates but to some extent also masks symptoms of anastomotic leakage. This reasoning makes "defunctioned leakage" (which often is late detected) an alternative to "late leakage" when interpreting the clinical anastomotic leakage panorama. In a time of wide-spread use of defunctioning stomas, knowledge of an altered clinical course of anastomotic leakage related to defunctioning stomas is valuable. From a practical point of view, it could arguably also be a more useful approach in dealing with follow-up after anterior resection in order to provide a vigilance that enables earlier detection.

Overall, the findings of our study confirm that late detected leakages after anterior resection are common with and an overall need for relaparotomy similar to early leakages in long-term follow-up. A common characteristic which unites all definitions of late leakage in our study, is the presence of a defunctioning stoma and its ameliorating effect on symptoms could be the main explanation for why some leakages are later detected. Future research investigating underlying mechanisms of late leakage but also evaluating implications on outcomes such as bowel continuity is warranted in order to further justify the consideration of late leakage as an entity of its own.

The risk of permanent stoma after anastomotic leakage in anterior resection

Paper II evaluated how often bowel continuity was restored after anastomotic leakage in anterior resection, finding that two thirds of all anastomotic leakage patients had a permanent stoma in long-term follow-up. Among anastomotic leakage patients, we found that relaparotomy and an age over or equal to 70 years was related to a permanent stoma, whereas an intended temporary defunctioning stoma from index procedure did not protect against a permanent stoma after anastomotic leakage.

A high rate of permanent stoma after anastomotic leakage

The very purpose of doing anterior resection instead of other operations in the treatment of rectal cancer is to maintain bowel continuity. However, several studies have described common failures to do so: a 19-24% permanent stoma rate after low anterior resection has been reported[96, 199, 200]. Among factors that are responsible for failure to re-establish bowel continuity after anterior resection are cancer recurrence, comorbidity and deteriorated bowel function, but anastomotic complications are reported to be the most significant risk factor[161, 162]. The estimations of long-term permanent stoma rate after anterior resection can be too low if follow-up is too short, conversions from initial bowel continuity to a permanent stoma are at times reported to happen years after initial defunctioning stoma reversal[162]. In our study, we evaluated permanent stoma rates after anastomotic leakage using review of medical records at least almost two and in median seven years after anterior resection, making our reported 65% rate of permanent stomas likely to reflect an end-result of anastomotic leakage. For example, recurrent leakage following stoma reversal after seemingly successful anastomotic leakage treatment did contribute in 7% to the total permanent stoma rate in our study. However, our permanent stoma rate is on the high end compared to the 22-69 % rate previously reported in anastomotic leakage patients after low anterior resection[58, 96, 201, 202], why study design can be considered as another possible reason. Observational research is subjected to selection bias where every therapeutic decision is made at the responsible surgeon's discretion, and a therapeutic choice rendering an end-result of a permanent stoma could partly be explained by variations in therapeutic tradition. The propensity to do anterior resection for rectal cancer has been demonstrated to have regional variations in Sweden[165]. The south of Sweden, which is evaluated in this study, leans towards a more restrictive approach when selecting patients for anterior resection[165] and in speculation could this have some impact on acceptance for a permanent stoma as a final outcome.

Factors related to a permanent stoma and clinical implications

From a clinical perspective, a main question of interest when treating a patient with anastomotic leakage after anterior resection is: what can be done in order to prevent a permanent stoma? We found that increasing age is related to permanent stoma, possibly reflecting both therapeutic attitudes and/or a reduced capacity to prevail through anastomosis salvage treatment. This could possibly be of guiding value when consulting elderly patients with anastomotic leakage, but cannot be a basis for improving the chances of bowel continuity. However, another finding in our study was that patients subjected to relaparotomy to a greater extent have a permanent stoma. This finding was coherent with previous reports of secondary or end-stoma formation due to anastomotic leakage being related to a permanent stoma[97, 202]. Nevertheless, this can hardly be seen as an argument for that relaparotomy should be avoided in order to save the anastomosis since nature of this study, as well as the studies just mentioned, are observational and not capable of making conclusions regarding causative treatment effects. A need for relaparotomy could just as well only reflect leakage severity. The hypothesis of that it is leakage severity, rather than the type of intervention called for, that determines outcome in bowel continuity is coherent with previous reports of asymptomatic leakages having better chances to restore bowel continuiuty[201, 202]. In further support of this reasoning, we found that in cases of relaparotomy where the anastomosis was left in place (only making a previously lacking defunctioning stoma and/or surgical drainage), the permanent stoma rate was in our study equal to cases where non-operative treatment had been pursued as the first intervention. In fact, considering impact of type of treatment, the only anastomotic leakage patients that stood out in our study were the very few (five anastomotic leakage patients) that had no treatment at all, among whom all regained bowel continuity.

Moving on, considering other factors that may improve stoma outcome, a defunctioning stoma made at anterior resection has – despite its mitigating effects on the clinical course of anastomotic leakage – no impact on chances for later bowel continuity after anastomotic leakage in the long run in our study. We found, coherent with several previous reports that a defunctioning stoma promotes non-operative treatment as a first measure [203], but in our study it did not address the long-term sequelae where primarily defunctioned and non-defunctioned leakage patients have the same outcome in terms of bowel continuity. Finally, considering factors that can be influenced in order to improve outcome in bowel continuity, early leakage detection has been reported to reduce short-term morbidity[131, 204], and it has also been suggested that early detection with subsequent early treatment also may reduce the permanent stoma rate[204, 205]. In our study was the time to leakage detection in median shorter (12 vs 16 days) in patients with bowel continuity, although no statistically significant difference could be demonstrated. Furthermore, among leakages detected $\geq$ 90 days after anterior resection in our study, almost all

(10/11) ended up with a permanent stoma. Although only substantiated by trends in our study, early detection with subsequent early onset of appropriate treatment is possibly one of the few things that can be influenced in order to improve outcome in bowel continuity once anastomotic leakage has occurred.

Radiological characteristics in rectal contrast studies in relation to outcome of permanent stoma

In paper III, we found an association of radiological findings in rectal contrast studies consistent with small diameter of sinus/fistula opening and abscess to an outcome of permanent stoma in anastomotic leakage after anterior resection for rectal cancer.

The need for predictors of outcome in treatment of anastomotic leakage

This study was of hypothesis generating nature and the findings can only be regarded as tentative given several limitations including a small sample size, risk of selection bias, multiple hypotheses testing and lack of adjustment for confounders. However, well aware of these shortcomings, the study could still find merit in exploring radiological findings in order to make groundwork for future research when trying to answer a significant question in everyday clinical practice – what chances does the patient with anastomotic leakage in front of me have to achieve bowel continuity? Aware of that half of the patients in long-term follow up after anterior resection have a chronic sinus[58], knowledge of predictive factors that justifies or dismisses continued efforts of anastomotic preservation would clearly benefit the patient as well as the surgeon.

There are three different clinical scenarios within which radiological signs of anastomotic leakage can be found: firstly, when the study is performed to confirm a symptomatic (clinical) leakage, secondly to evaluate healing of known leakage, and thirdly as an unexpected finding in an asymptomatic patient before stoma reversal. The prevalence of occult radiological leakages in asymptomatic patients after anterior resection is as high as approximately 15% if the study is done within the first four weeks after index surgery, but rapidly decreases to 1-6% if done later than 6 weeks after first operation[198]. This possibly reflects a high healing capacity in early stages of asymptomatic cases. The strategy performing serial contrast enemas while waiting for spontaneous healing can be adopted when finding persistent radiological signs of anastomotic leakage after treatment and recovery in initially symptomatic cases, as well as in throughout asymptomatic leakages.

However, when 12 months after anterior resection has passed a remaining sinus is reported unlikely to heal[206]. Using the waiting strategy, the reported success-rate in healing varies from 50-80%[198, 207, 208], where throughout asymptomatic patients appears to have the best conditions for healing and possibly even better outcome in terms of bowel continuity[201]. However, some patients never achieve full anastomotic integrity despite waiting. In cases of a remaining sinus (without underlying formation of a cavity) six months after index surgery, reversal of the defunctioning stoma in an at the time asymptomatic patient has been reported as feasible although 16% of these patients developed pelvic sepsis[207]. The risk of such septic complication after stoma reversal despite persistent radiological abnormalities has been argued to be higher in initially symptomatic leakages[198]. Furthermore, regardless of asymptomatic/symptomatic leakage, stoma reversal despite persistent radiological signs of leakage may involve a risk of negative impact on bowel function[209].

Comparison to previous literature

A few previous studies have explored the significance of different radiological characteristics in rectal contrast studies in relation to outcome of bowel continuity. The to the author's knowledge largest study was conducted by Hain et al.[210], who explored various outcomes in relation to site of leakage location. Hain et al. compared leakages from circular stapler line to leakages from transverse stapler line after side-to-end anastomosis in a cohort of 70 anastomotic leakages after anterior resection, but found no relation of leakage location to asymptomatic/symptomatic ratio, short-term morbidity, bowel continuity rate or outcome in bowel function. The distribution of leakage in relation to transverse staple line were similar to our findings – 39% (27/70) compared to 30% (7/23) in our study – as well as the finding of no relation to outcome in bowel continuity.

Lim et al.[201] investigated a cohort of 23 radiologically verified anastomotic leakages after anterior resection for outcome in bowel continuity in relation to asymptomatic/symptomatic presentation, and found that 10/10 asymptomatic leakages had healed in median 10.5 months after index surgery and all of these asymptomatic leakages achieved bowel continuity. This was in contrast to findings from our study where 0/4 asymptomatic leakages had bowel continuity restored, possibly to some extent explained by a long time to detection of asymptomatic leakages in our study (56-663 days after anterior resection) with consequently poorer conditions for healing. Furthermore, Lim et al evaluated radiological characteristics in relation to outcome anastomotic healing with the result that cavity and stricture was significantly related to non-healing, whereas type of track and its position did not impact outcome. The relation of a cavity to outcome of bowel continuity cannot be demonstrated in our study since the studies differs when evaluating this variable and

possibly also in composition of included patients. Lim et al. defined cavity as "a potential space where pooling of contrast was noted after drainage by gravity" and as a feature that could be seen associated or not with a sinus track. In our study, a cavity represented the compartment to which contrast leakage could be detected, making a cavity present in all patients to some extent. However, Lim et al. still speculates in agreement with findings from our study when suggesting that abscess formation in relation to a cavity may be a reason for non-healing. A similar reasoning is suggested by Zhou et al.[208] who evaluated 20 radiologically established anastomotic leakages after anterior resection or ileal pouch-anal anastomosis in relation to outcome of bowel continuity. Zhou et al. concluded that the simple short sinus or linear tracks had the best chances for healing, whereas sinuses with underlying pelvic cavities and/or stricture were more likely to lead to a permanent stoma. Finally, regarding other similar studies, Seo et al.[211] explored a cohort of 20 radiologically verified anastomotic leakages after anterior resection, by categorizing leakage morphology in rectal contrast studies in relation to outcome of bowel continuity. This study also found that throughout asymptomatic leakages to had a more favorable course – 5/6 asymptomatic leakages achieved bowel continuity - whereas a no clear pattern according to characterization of track or a suggested characterization according to shape of cavity could be established in relation to outcome.

The implications of this study

The results from this study could form basis for reasoning about how to best design future research. Choosing the right radiological variables with the greatest predictive capacity is crucial when addressing the question of predictive value of rectal contrast studies after anastomotic leakage. We choose radiological variables primarily based on presumed reproducibility and consistency, although it turns out that some findings may reflect an underlying biological process. In speculation, radiological findings consistent with appropriate drainage and reflecting a healing process from "inside-out", without leaving cavities or sinus tracks harboring undrained infections behind, seems to correspond to a more favorable outcome in terms of healing capacity. Our finding of radiological signs of abscess being related to failure of achieving bowel continuity is coherent with this reasoning, possibly reflecting an inability to spontaneous drainage. A narrow sinus opening could also correspond to failure of spontaneous drainage if combined with a long track or underlying cavity. However, a limitation in our study is that sinus track complexity in terms of length or branches is not accounted for in relation to outcome, which is something that should be considered in future research. Furthermore, another important aspect when evaluating rectal contrast studies after anastomotic leakage is when, why and in what patient the imaging is performed: a radiological finding may have a predictive value that is valid in one clinical context but not another. How

far the healing process has progressed in relation to time from the anterior resection, if the patient has been throughout asymptomatic or not, and if the patient has risk factors known to complicate tissue healing should be taken under consideration when interpreting the imaging, and also accounted for in future research.

To summarize, this study found that findings in rectal contrast studies after anastomotic leakage in anterior resection consistent with an abscess or small sinus opening seems to have unfavorable impact on outcome of bowel continuity, possibly corresponding to a failure of spontaneous drainage. The results suggest that including radiological findings reflecting an inability of spontaneous drainage is of importance when designing future research.

Anastomotic leakage in relation to major LARS and Quality of Life.

Paper IV demonstrated that severe bowel dysfunction - major LARS - is present in almost half of all patients in long-term follow-up after anterior resection. The relative risk of major LARS is doubled if bowel continuity can be restored after an anastomotic leakage with urgency as a predominant symptom. Paper V confirmed that the symptoms of bowel dysfunction related to anastomotic leakage persists over time and impacts QoL, although no effect on Global Health Status could be demonstrated. Outcome in bowel continuity after anastomotic leakage in anterior resection did not have demonstrable effect on QoL in our study.

Defining and estimating the prevalence of LARS

With improving oncological outcomes during the last decades, there is an increasing awareness of poor functional outcome suffered by many patients after sphincter–sparing surgery. Anterior resection has been established as related to a high rate of major LARS with some potential for improvement in the first one to two years[212] [213]. A 46-47.5% rate of major LARS, coherent with our findings, has previously been reported to be present more than a decade after anterior resection[214, 215]. This high rate of major LARS after anterior resection needs to be put in a context of high prevalence of LARS symptoms in the general population when evaluated by LARS-score. In a Danish population, some 19% of women and 10% of men aged between 50 and 79 years met criteria of major LARS[179], and it has been argued that LARS-score demonstrate a high sensitivity but low specificity[216]. Furthermore, LARS-score has been criticized for insensitivity to evacuatory dysfunction and overestimation in impact on QoL for some patients[217]. This calls into question whether LARS-score is the best way to evaluate LARS. A broad definition of LARS

has previously been suggested as: “Disordered bowel function after rectal resection, leading to a detriment in quality of life”[212], but not until recently has an international consensus definition of LARS been established[216]. This new consensus definition pin-points eight symptoms as well as eight consequences that are to be considered of the highest priority when defining LARS, where at least one symptom with a corresponding consequence should be present. Still, no new alternative instrument to LARS-score designed for this definition has yet been developed[216]. However, justifying the use of LARS-score as measuring instrument in our study: it is arguably the best instrument available today as it benefits from being a quick, validated screening tool for LARS with high correspondence to QoL[213]. Furthermore, by being widely adopted it overcomes inconsistencies when comparing our results to other studies. To the extent it can be argued that LARS-score does not correctly capture all aspects of LARS, this only affects our estimations of LARS prevalence. The main purpose of our study was to evaluate anastomotic leakage effect using major LARS as the outcome. When comparing outcome in LARS-score, there is no reason to believe that the reliability in LARS-score estimations should be related to anastomotic leakage exposure.

Anastomotic leakage and LARS

For the purpose of identifying patients at risk for major LARS prior to anterior resection, predictive models have been developed and incorporated in online tools (https://www.pelicancancer.org/our-research/bowel-cancer-research/polars/) using risk factors (age, gender, defunctioning stoma, TME, tumor height and neoadjuvant radiotherapy) to estimate an expected LARS-score[218]. In order to similarly guide patients with anastomotic leakage after anterior resection as whether to embark on anastomotic salvage treatment or not, the question of whether anastomotic leakage constitutes a risk for major LARS needed to be clarified.

In our study, we established a clear risk increase of major LARS after anastomotic leakage. The relationship of anastomotic leakage to bowel dysfunction has previously been investigated with different outcomes. Whereas some reports have suggested anastomotic leakage to be risk factor for bowel dysfunction[137, 138, 185, 186, 219], other studies report conflicting results[176, 187, 188, 220]. The choice of measuring instrument and cohort size seems to impact the outcome. In previous studies evaluating anastomotic leakage effect using LARS score, two previous studies have demonstrated an effect coherent with our finding[138, 219], whereas only one study using LARS score failed to demonstrate an effect despite the fact that 4/5 of the included anastomotic leakage patients had major LARS[176]. When using other measurement instruments than LARS-score in slightly larger cohorts (21-56 responders with anastomotic leakage), frequency, nighttime bowel movements, blood and mucus in stool and increased pad use were reported as more common in

the anastomotic leakage group[137, 185, 186]. In three studies using questionnaires other than LARS-score on smaller cohorts (16-27 responders with anastomotic leakage), no distinct effects of anastomotic leakage on bowel function were seen[188, 220, 221]. One main exception is a study with a substantial sample size (89 responders with anastomotic leakage) using a questionnaire from the Dutch TME trial, only to detect a modest anastomotic leakage effect[187].

In our study did the individual symptom of urgency stand out as more common in the anastomotic leakage group, a finding consistent with previous reports of impaired compliance and volume of the neorectum in anorectal manometry and volumetry in patients with anastomotic leakage[189]. It should be noted that the individual symptom of urgency is weighted the most in LARS-score by adding 16 points to the total score, a high rate of urgency in anastomotic leakage patients thereby also acts at the main contributing symptom to major LARS in our study.

Clinical factors related to major LARS in patients with anastomotic leakage

Beyond primary and secondary aims of paper IV, patients with anastomotic leakage were explored in a subgroup analysis for clinical factors related to major LARS. In this analysis, longer time to leakage detection was associated with major LARS (p=0.002). It could be argued that this is an effect related to leakage severity, where early leakage more often prompt laparotomy with anastomotic removal, leaving a subset of milder early leakages behind. However, earlier time to detection was significantly related to a better outcome in terms of major LARS also when analyzing patients handled with intervention without laparotomy (ISREC B), suggesting that time to detection matter even when laparotomy is not called for. This exploratory finding provides a glimpse of hope of that the clinical course can be influenced for the better. It is also coherent with reports of that treatment without laparotomy is more successful in terms of restoration of bowel continuity when initiated within six weeks of anterior resection[205]. Furthermore, female sex had a tendency to be associated with major LARS (p= 0.06) and 85.7% of female patients with anastomotic leakage had major LARS. This relationship was demonstrated in a limited subgroup of women with anastomotic leakage (n 14). However, it is consistent with reports of women having a higher rate of LARS in the general population[179] as well as after anterior resection[219], and possibly are some women already susceptible to LARS at larger risk for major LARS after anastomotic leakage. The finding of UICC stage III+IV being related to major LARS in univariate analysis is not supported by previous research. However, multivariable analysis was not carried out in this subgroup analysis, why confounding effects from neoadjuvant treatment must be considered as well as the fact that confounding could be introduced by the subcategorization of UICC stage.

Anastomotic leakage and Quality of Life

A close association of symptoms of bowel dysfunction and QoL has been demonstrated in previous reports using various instrument. Vironen et al. demonstrated that faecal incontinence and urgency both had a significant effect on social functioning, whereas urgency alone was related to mental health and general health perception[222]. Pucciarelli et al. showed that urgency was associated to physical functioning, role functioning and social functioning[223]. Using LARS-score, that has been developed with the very purpose of grading LARS based on impact on QoL[167], Emmertsen et al. reported major LARS twelve months after anterior resection to impact QoL in all EORTC QLQ-C30 functional scales, apart from cognitive functioning[213]. Furthermore, the impact of major LARS on QoL has been demonstrated to prevail in studies with long follow-up[178, 214].

When evaluating QoL in relation to anastomotic leakage after anterior resection, it has in previous studies been shown to have detrimental effect on various QoL-domains when using various instruments[137, 138, 185, 188, 201]. Marinatou et al. could by use EORTC QLQ-C30 show a significant decrease in Global Health Status related to anastomotic leakage[224]. However, unlike our study, Marinatou et al. included stoma patients in the anastomotic leakage group and in speculation could this contribute to the demonstrated effect. Moreover, when considering the lack of anastomotic effect on Global Health Status in our study in more detail, the mean score in Global Health Status for anastomotic leakage patients - 77.8 (SD 18.5) - is in line with what could be expected in a group of patients with high prevalence of major LARS. In comparison, when Emmertsen et al. used LARS-score and EORTC QLQ-C30 one year after rectal resection, mean scores in Global Health Status was 73.3 (SD 18.0) in patients with major LARS, while patients with no LARS had corresponding mean scores of 88.8 (SD 15.4)[213]. In other words, in our study the Global Health Status in patients with anastomotic leakage is as expected, whereas in patients without anastomotic leakage it is rather low. Considering that minor as well as major LARS has been shown to significantly impact overall QoL[213], it is could actually be the prevalence of no LARS in each group which essentially determines whether any effect on overall QoL could be detected. Possibly is the difference in prevalence of minor LARS is too limited in order to demonstrate any difference in Global Health Status comparing the groups in our study. Still, the findings of EORTC QLQ-CR 29 confirms symptoms of bowel dysfunction as more common in the anastomotic leakage group, coherent with finding from a previous report using the same instrument[138].

Bowel continuity after anastomotic leakage and Quality of Life

When evaluating anastomotic leakage patients, irrespective of bowel continuity, no effect of maintained bowel continuity on QoL could be demonstrated. The reason for this evaluation was the underlying question of what whether a stoma or bowel continuity provides the best long-term QoL after anastomotic leakage. A permanent stoma is also related to significant morbidity[170], and in our study no benefit of a stoma on QoL could be detected despite a high rate of major LARS in anastomotic leakage patients with bowel continuity. A limitation to our study is not knowing the reasons for a permanent stoma in either group. I could be that some of the stoma patients have a stoma due to intolerable major LARS, leading to underestimation of the impact of LARS on QoL. Furthermore, the groups not entirely comparable: the permanent stoma patients had total mesorectal excision and neoadjuvant treatment to a larger extent, and multivariable analysis was not carried out due to limited sample size. All in all, no major difference could be detected, and no firm conclusions could be drawn from this result.

Clinical implications

These studies demonstrate that anastomotic leakage is related to a doubled relative risk for major LARS after anastomotic leakage in anterior resection. Although a permanent stoma is not obviously better as it has its own morbidity, the patient should be informed of a high risk for major LARS when considering anastomotic salvage treatment. A tailored approach for each patient seems most reasonable where capacity to tolerate symptoms of major LARS in relation to sphincter function, life-style as well as personal wishes should be considered. Early detection of anastomotic leakage could be beneficial in relation to functional outcome, a finding of this study that hopefully can be confirmed in future research.

Methodological considerations

Observational research allows evaluation of exposures that cannot be randomized, such as anastomotic leakage. This means that despite inherent weaknesses in the observational study design, this was the necessary approach in order to investigate long-term morbidity related to anastomotic leakage. Furthermore, while randomized controlled trials are undoubtedly better to establish causal effects, there are still some benefits to observational research. Moreover, while a clinical trial is capable of addressing questions of causal effects within strictly defined borders of inclusion criteria, its generalisability to larger population can be overestimated. Observational

research has in that context an advantage in to a greater degree being able to evaluate various effects in a wider population.

However, research is driven by underlying questions and thinking that most often are of causal nature, for example: Does anastomotic leakage *cause* bowel dysfunction? As observational research is the major way to approach this question, careful attention is needed to establish as unbiased effect estimate as possible between exposure and outcome. During the work of this thesis, the author has developed knowledge of the concept of trying to derive causal inference in order to establish exposure effects and thereby achieving firmer conclusions. As a consequence, the first papers (I-III) are more descriptive and exploratory in study design, while the last papers (IV-V) have a more pronounced ambition to evaluate a hypothesis of exposure and effect.

Some major methodological challenges in observational research are outlined below, and are taken into consideration in relation to the individual studies of this thesis.

Hypothesis testing and sample size

Hypothesis testing contains a risk of type I error – false rejection of a true null hypothesis – as well as type II error – failure to reject null hypothesis when the alternative hypothesis is true. The type I error rate, or significance level, is the probability of rejecting the null hypothesis given that it is true. The rate of the type II error, usually named beta(β), is related to the power of a test, which equals $1-\beta$. The capability to reject the null hypothesis and establish an effect related to the exposure, is dependent of sample size, magnitude of difference in incidence (or means and variation) and accepted level of making a type I error. In order to determine the number of patients required to establish sufficient power, an estimation based on the mentioned factors can be done before starting the study.

All the studies in this thesis in this thesis could be prone to type II errors. Dealing with long-term evaluation of anastomotic leakage after anterior resection involves a risk of working with limited sample sizes. While having the benefit of working with SCRCR, a resource that enable great opportunities for observational research by provision of data that in international comparison stand out in coverage of a population, the registry has been found to underreport anastomotic leakage[193]. Furthermore, while investigating long-term outcome in bowel function after anastomotic leakage, at least half of the patients are unavailable to evaluation due to permanent stoma. As a consequence, evaluation of risk factors for anastomotic leakage based on the larger group of patients subjected to anterior resection is on more solid ground, whereas research evaluating characteristics within the group of anastomotic leakage patients (as in *paper I-III*) is generally struggling with limited

sample sizes. In *paper I-III*, it is possible that the identification of clinical factors related to late leakage or permanents stoma in many cases fail due to type II errors. The sample size of anastomotic leakage patients in *paper IV-V* is to a significant extent limited by the response rate, thereby not only restricting hypothesis testing but also challenging the external validity of the results (see further below). However, considering that the questionnaires concern a procedure performed 5-9 years ago, a limited response rate is to some extent expected. Arguably would a pre-study power calculation have been desirable in particular for *paper IV-V*, but a context of limited previous research, where the magnitude of anastomotic leakage effect to a large extent was unknown, hampered conditions for this.

Multiple hypothesis testing

Performing multiple hypothesis tests means an increasing risk of performing an erroneous test. The more tests are made, the more likely erroneous tests are to occur. There are several strategies that can be used in order to minimize the risk of multiple hypothesis testing, for example by increasing the p-value by the number of planned tests, such as Bonferroni correction. The objective of the planned investigation matters in this context. When doing work that could be regarded as exploratory or hypothesis generating, correction for multiple testing may not be needed if the nature of the analysis is clearly stated. However, in studies with a confirmatory approach a prospective hypothesis needs to be defined along with predefined outcome measure, and sequencing into primary and secondary objective should be stated in order to in advance show which analyses were considered to be of greatest importance.

Paper I-III are exploring unknown territories and of a more descriptive and exploratory nature. In these papers, exploratory hypothesis testing was carried out by analysing clinical factors related to late leakage or permanent stoma without a specified pre-study hypothesis of a particular exposure being related to a certain outcome which means a risk of type I errors. Consequentially when writing the discussion of this thesis, the author has consciously emphasized only the findings that are recurrent, exemplified in *paper I* where a defunctioning stoma was related to all categories of late leakage, for the rest focusing on descriptive findings of the studies. *Paper III* was clearly set out be exploratory which also makes it prone to type I errors by study design. It is also stated that the results should be regarded as tentative and serve as a basis for future research.

In *paper IV and V,* multiple tests are carried out especially considering the response means regarding all functional outcomes in QoL. However, in these papers are primary and secondary aim stated, making statistically significant findings beyond these aims of lower merit. The finding in *paper IV* of that major LARS was related to later detection could arguably be dismissed as it was beyond primary or secondary

analyses. However, as it is not highlighted as a major finding and could have implications of great interest, it is still discussed within the framework of this thesis to a greater extent than in the original manuscript.

Missing data

In the context of long-term follow-up is missing data a concern: either in the case of missing clinical variables in medical records and/or registry, or in the case of non-compliance by leaving incomplete or no response to a questionnaire. Missing data can be classified according to missing at random, that is that the missing data are completely unrelated to factors with potential impact on outcome (missing completely at random) or due to factors that can be accounted for (missing at random). Data missing at random leads to reduced statistical power while constituting a limitation on establishment of effect, but in in the case of an estimated effect it would be unbiased. The opposite is missing data not at random, where the missing data are related to factors influencing the outcome, which leads to biased estimates of effect.

Missing data has been taken under consideration in all papers of this thesis where complete case analysis has been the comprehensive strategy and missing clinical variables were reported. *In paper I-III,* considering analysis within the anastomotic leakage group where clinical variables are related to late leakage/permanent stoma, the proportion of missing data was limited with corresponding limited risk for introduction of bias. Furthermore, we had no reason to believe that there was any pattern of missing clinical variables from SCRCR or medical records related to late leakage or permanent stoma. *In paper IV-V* missing data regarding clinical variables were also limited and there was no missing data for any of the included covariates in matching among patients included in matching. However, considering outcome in *paper IV*, some patients (4%) were excluded from analysis due to failure to give complete responses to all items in LARS-score. In these patients, imputations were considered to minimize data loss, but the idea was rejected due to the complexity in design of LARS-score where different items are weighted differently, making imputations difficult and possibly unreliable. Furthermore, the data loss for uncomplete response was regarded limited.

Validity, confounding and different types of bias

The internal validity of a study, that is the extent to which a demonstrated effect can be considered credible, is determined by how well alternative explanations and sources of systemic errors have been ruled out. In contrast, external validity of a study refers to how well the results can be extrapolated to a larger population, that is the extent to which the results can be generalized. A confounding variable is a

variable that influences both the independent and dependent variable (exposure and outcome), that if not taken into account distorts the outcome of the analysis. Failure to adjust for all confounding relationships results in residual confounding. A mediator on the other hand is an intermediary in a causal chain between the independent and dependent variable, but without capability to influence the dependent variable by itself

In *paper I-III* all anastomotic leakages had been confirmed according to study protocol definition by review of medical records which strengthens internal validity with regard to this variable. On the other hand, a limitation is the fact that all cases of anastomotic leakage from the time period most likely is not included, why the generalizability – the external validity – of our findings could be questioned. Possibly could characteristics in not included anastomotic leakage patients have altered the rate of late leakage, the rate of permanent stoma and the established relationships to clinical characteristics. In order to increase external validity, review of medical records for all anterior resection patients could have been implemented. In *paper IV-V*, precisely this was done. Medical records for all patients subjected to anterior resection were reviewed according to a study protocol definition which secured the internal validity related to anastomotic leakage exposure. However, the external validity of findings in *paper IV-V* could also be questioned. There is a risk of selection bias concerning the included patients meaning a non-random inclusion, in *paper IV-V* exemplified in non-responder bias (there is a selection as to which patients choose to respond) and follow-up bias (there is a selection as to which patients are lost to follow-up). The implications are that if the included patients not are representative in terms of outcome in major LARS or QoL, for example if patients choosing to respond have more symptoms than non-responders, it could affect the outcome. The reduction in anastomotic leakage patients from original cohort to study group was a specific concern considering external validity. Most excluded leakage patients were excluded due to a permanent stoma and a limitation in the study was that the reason for permanent stoma was unknown. It is possible that some of the permanent stoma patients had their stoma due to major LARS, thereby possibly underestimating the anastomotic leakage effect on major LARS. However, no major pattern of clinical characteristics distinguishing eligible patients (recipients of the questionnaire) from included patients could be detected.

When dealing with data from registries and medical records information bias is also a concern, potentially distorting outcomes by misclassification of variables. Information bias can be differential - related to outcome thereby affecting results, or non-differential – occurring at random with the effect of reducing study power (in analogy with data not missing at random vs. missing at random). Considering information bias regarding clinical variables other than anastomotic leakage, the use of a combination of SCRCR, where the overall validity of data is reported to be

high[192], and variables retrieved from medical records, should have minimized the risk of information bias.

In order to adjust for confounding, multivariable regression was used in *paper I-II*. Identification of covariates included in these models was based on a univariate association of clinical characteristic to late leakage/ permanent stoma demonstrating $p < 0.2$. This way of identifying covariates can be problematic. When not considering any underlying causal mechanism, there is a consequential risk of including randomly detected findings that further on can be a source of error. This model was later abandoned in favour of thinking where causal inference was considered. Choosing the set of confounders to be adjusted for is a process that demands some thought: keeping in mind a risk of including mediators, losing precision by including to many or irrelevant confounders, but also to not take all relevant confounders into account resulting in residual confounding. Overmatching bias is a risk if matching is done with a non-confounding variable that is associated to the exposure but not the outcome, which can result in underestimation of exposure effect. In *paper IV and V* covariates were included in propensity scoring selected based on their collective confounding effect where reasoning of this was based on clinical knowledge and findings from previous research. In *paper IV* this was furthermore illustrated by the aid of a causal diagram. The propensity score was then used to match an exposed patient to an unexposed patient, thereby facilitating set-up that mimics a randomized trial, although still vulnerable to residual confounding not accounted for. However, this design was suitable especially for *paper IV*, where it facilitated not only an unbiased estimate of exposure effect, but also provided a way to quantify the result in a comprehensible way by reporting absolute and relative risk for major LARS.

Conclusions

This thesis outlines a significant long-term morbidity related to anastomotic leakage after anterior resection. The major conclusions are:

- Anastomotic leakage after anterior resection is often discovered late, in half of the cases after hospital discharge and in one in four after 30 days. A defunctioning stoma made at anterior resection is associated with later detection of anastomotic leakage. Late detected anastomotic leakages have a significant morbidity and the need for relaparotomy is similar to early detected leakages in long-term follow-up.

- Anastomotic leakage after anterior resection involves a high risk of permanent stoma, two thirds of the patients never have bowel continuity restored.

- Findings in rectal contrast studies upon diagnosis of anastomotic leakage after anterior resection could be a way to predict outcome in bowel continuity. Radiological signs of an abscess or small diameter of leakage opening may be related to permanent stoma.

- Among patients with bowel continuity, anastomotic leakage after anterior resection more than doubles the relative risk for major LARS in long-term follow-up.

- Anastomotic leakage after anterior resection impacts long-term QoL mainly by symptoms of bowel dysfunction. Whether a stoma or restoration of bowel continuity provides the best QoL after anastomotic leakage remains is unclear.

Future perspectives

This thesis evaluates the long-term morbidity of anastomotic leakage after anterior resection and to a large extent the result is a long description of how bad it is. The morbidity has long-lasting effects and if patient does not have a permanent stoma, there is high risk of a poor functional outcome anyway. Considering this, is research on prevention of anastomotic leakage the only thing that makes sense? Minimizing the effects of an anastomotic leakage after anterior resection will most likely be a concern in a colorectal surgeon's everyday practise in the foreseeable future. Future research should aim to improve the outcome in patients with anastomotic leakage.

A difficulty in evaluating anastomotic leakage patients is that conclusions are limited by sample size. In future research this need to be addressed, collaborations on national or multi-national level is desirable. Furthermore, although randomization is not possible for the actual occurrence of a leakage, various leakage treatments could be evaluated prospectively to a larger extent within the framework of collaborations. Some examples of research areas that would be beneficial to investigate in anastomotic leakage patients are:

- The impact of early detection on outcome in terms of bowel continuity and functional outcome. Routine screening of all anterior resection patients for leakage, for example by endoscopy and/or rectal contrast imaging before hospital discharge, could be an intervention that at least could be evaluated by comparison to a historic cohort.
- Prospective studies comparing different treatment methods for anastomotic leakage regarding long-term outcome in bowel continuity, preferably by randomization to one treatment or the other. For example, endoscopic vacuum-assisted drainage compared to transrectal drainage with catheter.
- Establishing effect of the various treatment methods for LARS in anastomotic leakage patients. Knowledge of to what extent leakage patients respond to treatment could be crucial when deciding on anastomotic salvage treatment or a permanent stoma.
- The impact of bowel continuity on overall QoL. This is a crucial question when deciding on anastomotic salvage treatment. Which has the most impact on QoL at group level for anastomotic leakage patients, a permanent stoma or a high rate of major LARS?

Populärvetenskaplig sammanfattning

Om man drabbas av cancer i ändtarmen står olika behandlingsmetoder till buds. För att uppnå bot krävs i regel ett kirurgiskt ingrepp, ofta kombinerat med strålbehandling och ibland med cytostatika. Det finns olika operationsmetoder för ändtarmscancer som bygger på att segmentet av ändtarmen där tumören finns opereras bort. Denna avhandling handlar om en den vanligaste operationen för ändtarmscancer som kallas för främre resektion. Fördelen med främre resektion i jämförelse med andra operationsmetoder är att tarmen kopplas ihop – man gör en så kallad anastomos - man kan då i det långa loppet undvika en stomi. En risk med operationen är dock att de tarmändar som skarvas inte läker ihop komplett, då uppstår det som kallas anastomosläckage. Tillståndet är relativt vanligt, det uppkommer i 10–15% vid främre resektion och leder till olika effekter på både kort och lång sikt. Tarminnehåll kan läcka ut till området vid sidan av tarmskarven och orsaka infektioner och ibland leder det till allvarlig blodförgiftning, men den störda läkningen har också andra effekter på lång sikt. Den här avhandlingen beskriver framförallt de effekter som uppkommer av ett anastomosläckage på lång sikt.

Till att börja med har vi undersökt tidpunkten för när diagnosen anastomosläckage ställs. Traditionellt har man beskrivit komplikationen som förekommande under det första veckorna efter operationen, men vi visar att det inte sällan är senare än så. I stor grupp av 139 patienter med anastomosläckage efter operationer utförda i Södra sjukvårdsregionen mellan 2001 och 2011, visade det sig att för varannan patient ställdes diagnosen först efter utskrivning från sjukhuset och i vart fjärde fall upptäcktes inte diagnosen förrän det gått minst 30 dagar sedan operationen. I vår undersökning var lång tid till upptäckt av läckaget förenat med användning av en tillfällig skyddande stomi. Våra beräkningar pekar på att skyddande stomi är den faktor som förändrar symtomen för anastomosläckage på ett sådant sätt att upptäckten blir sen.

Vi har även undersökt behandlingsutfallet för de 139 patienterna med anastomosläckage. Trots att främre resektion från början hade målet att undvika en permanent stomi, visar det sig att två tredjedelar av patienterna som drabbats av anastomosläckage får just en permanent stomi. Det är en högre andel än vad man kunde förvänta sig och delvis beror det nog på att haft en ovanligt lång uppföljningstid. Några patienter får sin permanenta stomi flera år efter den första operationen.

I en annan studie undersökte vi hur väl olika fynd i från röntgenbilder tagna av patienter med anastomosläckage förutsäger att utfallet av behandlingen ifråga om permanent stomi. Det visade sig att storleken på glipan i tarmskarven och tecken till en varhärd i anslutning till tarmskarven var förenat med en risk för att patienten skulle få permanent stomi. Denna studie var dock begränsad i sitt omfång, för att bekräfta resultaten skulle studien behöva göras om på en större grupp av patienter.

I de två avslutande studierna undersökte vi en annan grupp av patienter som drabbats av anastomosläckage efter främre resektion, de var opererade i norra, västra och södra sjukvårdsregionerna i Sverige mellan 2007 och 2013. Vi undersökte hur tarmfunktion och livskvalitet påverkats på lång sikt bland patienter där man kunnat undvika en permanent stomi efter ett anastomosläckage. Vi fann att bland patienter med anastomosläckage hade två tredjedelar en allvarlig tarmfunktionsstörning och att anastomosläckage innebär en dubblerad risk för att få allvarlig tarmfunktionsstörning. Av symtom som störde livskvaliteten var tarmsymtom det som dominerade bilden bland patienter med anastomosläckage.

Fynden av våra studier kan vara till nytta när man planerar operationen främre resektion, men även när man ska påbörja behandling av ett anastomosläckage och då välja mellan att försöka bevara skarven eller satsa på en stomi. Det är viktigt att känna till hur utfallet av olika behandlingar förhåller sig för att både patient och läkare ska kunna ta välinformerade beslut. Vi har även hopp om att våra resultat kan utgöra grund för framtida forskning riktat mot att förbättra behandlingen av patienter med anastomosläckage efter främre resektion.

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Errata

- In paper I, in results, under the paragraph “Clinical characteristics and operative details”, (page 153), in sentence starting “On multivariate logistic regression.”, should be *odds* ratio instead of hazard ratio throughout the paragraph.

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Appendix

Questionnaires

LARS-Score

EORTC QLQ-C30

EORTC QLQ-CR29

Syftet med denna enkät är att bedöma din tarmfunktion.

Kryssa bara i en ruta för varje fråga. Det kan vara svårt att välja endast ett svar, eftersom vi vet att symtomen varierar från dag till dag hos vissa patienter. Vi vill be dig att välja det svar som bäst beskriver ditt dagliga liv. Om du nyligen har haft någon infektion som påverkat tarmfunktionen, ska du inte räkna med den utan fokusera på att besvara frågorna för att återspegla din vanliga tarmfunktion varje dag.

LARS SCORE

Kryssa		
	Finns det tillfällen då du inte kan kontrollera gaser?	
☐	Nej, aldrig	0
☐	Ja, mer sällan än en gång i veckan	4
☐	Ja, minst en gång i veckan	7
	Har du någon gång oavsiktligt läckage av lös avföring	
☐	Nej, aldrig	0
☐	Ja, mer sällan än en gång i veckan	3
☐	Ja, minst en gång i veckan	3
	Hur ofta tömmer du tarmen	
☐	Mer än 7 gånger per dygn	4
☐	4-7 gånger per dygn	2
☐	1-3 gånger per dygn	0
☐	Mer sällan än en gång per dygn	5
	Finns det tillfällen då du behöver tömma tarmen igen inom en timma efter senaste tarmtömningen	
☐	Nej, aldrig	0
☐	Ja, mer sällan än en gång i veckan	9
☐	Ja, minst en gång i veckan	11
	Finns det tillfällen då du är i så stort behov av att tömma tarmen att du måste rusa till toaletten?	
☐	Nej, aldrig	0
☐	Ja, mer sällan än en gång i veckan	11
☐	Ja, minst en gång i veckan	16

Ifylls av läkare / sjuksköterska:

☐ 0-20: No LARS ☐ 21-29: Minor LARS ☐ 30-42: Major LARS

EORTC QLQ-C30 (version 3)

Vi är intresserade av några saker som har med Dig och Din hälsa att göra. Besvara alla frågor genom att sätta en ring runt den siffra som stämmer bäst in på Dig. Det finns inga svar som är "rätt" eller "fel". Den information Du lämnar kommer att hållas strikt konfidentiell.

Var vänlig fyll i Dina initialer: |_|_|_|_|
När är Du född? (Dag, Månad, År): |_|_|_|_|_|_|
Dagens datum (Dag, Månad, År): 31 |_|_|_|_|_|_|

		Inte alls	Lite	En hel del	Mycket
1.	Har Du svårt att göra ansträngande saker, som att bära en tung kasse eller väska?	1	2	3	4
2.	Har Du svårt att ta en lång promenad?	1	2	3	4
3.	Har Du svårt att ta en kort promenad utomhus?	1	2	3	4
4.	Måste Du sitta eller ligga på dagarna?	1	2	3	4
5.	Behöver Du hjälp med att äta, klä Dig, tvätta Dig eller gå på toaletten?	1	2	3	4

Under veckan som gått:

		Inte alls	Lite	En hel del	Mycket
6.	Har Du varit begränsad i Dina möjligheter att utföra antingen Ditt förvärvsarbete eller andra dagliga aktiviteter?	1	2	3	4
7.	Har Du varit begränsad i Dina möjligheter att utöva Dina hobbys eller andra fritidssysselsättningar?	1	2	3	4
8.	Har Du blivit andfådd?	1	2	3	4
9.	Har Du haft ont?	1	2	3	4
10.	Har Du behövt vila?	1	2	3	4
11.	Har Du haft svårt att sova?	1	2	3	4
12.	Har Du känt Dig svag?	1	2	3	4
13.	Har Du haft dålig aptit?	1	2	3	4
14.	Har Du känt Dig illamående?	1	2	3	4
15.	Har Du kräkts?	1	2	3	4
16.	Har Du varit förstoppad?	1	2	3	4

Fortsätt på nästa sida

Under veckan som gått:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
17. Har Du haft diarré?	1	2	3	4
18. Har Du varit trött?	1	2	3	4
19. Har Dina dagliga aktiviteter påverkats av smärta?	1	2	3	4
20. Har Du haft svårt att koncentrera Dig, t.ex. läsa tidningen eller se på TV?	1	2	3	4
21. Har Du känt Dig spänd?	1	2	3	4
22. Har Du oroat Dig?	1	2	3	4
23. Har Du känt Dig irriterad?	1	2	3	4
24. Har Du känt Dig nedstämd?	1	2	3	4
25. Har Du haft svårt att komma ihåg saker?	1	2	3	4
26. Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Ditt familjeliv?	1	2	3	4
27. Har Ditt fysiska tillstånd eller den medicinska behandlingen stört Dina sociala aktiviteter?	1	2	3	4
28. Har Ditt fysiska tillstånd eller den medicinska behandlingen gjort att Du fått ekonomiska svårigheter?	1	2	3	4

Sätt en ring runt den siffra mellan 1 och 7 som stämmer bäst in på Dig för följande frågor:

29. Hur skulle Du vilja beskriva Din hälsa totalt sett under den vecka som gått?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

30. Hur skulle Du vilja beskriva Din totala livskvalitet under den vecka som gått?

1	2	3	4	5	6	7
Mycket dålig						Utmärkt

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Funktionella långtidsresultat efter främre resektion för rektalcancer, LOAR-studien

Initaler	Stud nr

EORTC QLQ – CR29

Patienter berättar ibland att de har följande symptom. Markera i vilken utsträckning som Du har haft dessa symptom under Den senaste veckan. Svara genom att ringa in Den siffra som bäst passar in på Dig.

Under veckan som gått:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
31. Urinerade Du ofta under dagen?	1	2	3	4
32. Urinerade Du ofta under natten?	1	2	3	4
33. Har Du haft urinläckage?	1	2	3	4
34. Har Du känt smärta eller sveda i samband med urinering?	1	2	3	4
35. Har Du haft buksmärtor?	1	2	3	4
36. Hade du ont i skinkorna/runt analöppningen/ändtarmen?	1	2	3	4
37. Har Du känt Dig uppsvälld I magen?	1	2	3	4
38. Har du haft stomipåse (kolostomi/ileostomi)? (Var vänlig ringa in rätt svar)	**Ja**	**Nej**		

Under veckan som gått:	**Inte alls**	**Lite**	**En hel del**	**Mycket**
39. Har du haft ofrivillig gasavgång/gasbildningar från ändtarmen eller stomipåsen?	1	2	3	4
40. Har avföringen läckt (från ändtarmen eller stomipåsen)?	1	2	3	4
41. Har Du haft blod i avföringen?	1	2	3	4
42. Har du haft slem i avföringen?	1	2	3	4
43. Har huden varit öm runt stomin eller området runt analöppningen?	1	2	3	4
44. Förekom frekventa tarmrörelser/påsbyten under dagen?	1	2	3	4
45. Förekom frekventa tarmrörelser/ påsbyten under natten?	1	2	3	4

Besvara dessa frågor endast om du har stomipåse. Om så inte är fallet, var snäll fortsätt på nästa sida.

46. Har Du haft problem att sköta din stomi?	1	2	3	4
47. Kände Du dig besvärad av din stomi?	1	2	3	4

Fortsätt på nästa sida

Under veckan som gått:	Inte alls	Lite	En hel del	Mycket
48. Har du oroat dig över din vikt?	1	2	3	4
49. Har Du varit torr i munnen?	1	2	3	4
50. Har ditt hår varit torrt och livlöst på grund av din sjukdom eller behandling?	1	2	3	4
51. Har du haft problem med smaksinnet?	1	2	3	4
52. Har Du varit orolig för din framtida hälsa?	1	2	3	4
53. Har Du känt Dig mindre attraktiv på grund av sjukdomen eller behandlingen?	1	2	3	4
54. Har Du känt dig mindre kvinnlig/manlig på grund av din sjukdom eller behandling?	1	2	3	4
55. Har Du känt Dig missbelåten med din kropp?	1	2	3	4

Under de senaste fyra veckorna:	Inte alls	Lite	En hel del	Mycket
Endast för män				
56. I vilken utsträckning har Du varit intresserad av sex?	1	2	3	4
57. Har Du haft svårt att få eller bibehålla en erektion?	1	2	3	4
Endast för kvinnor				
58. I vilken utsträckning har Du varit intresserad av sex?	1	2	3	4
59. Kände du smärta eller obehag vid samlag?	1	2	3	4