Institutionen för Kliniska Vetenskaper, Danderyds Sjukhus (KI DS)

ASPECTS OF DIVERTING STOMA AND ERAS IN RECTAL CANCER SURGERY

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ASPECTS OF DIVERTING STOMA AND ERAS IN RECTAL CANCER SURGERY

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”Gi mej en jordglob men helst en mä bare Värmland på”

Elis i Taserud

CONTENTS

ABSTRACT

Annually, nearly 2000 patients are diagnosed with rectal cancer in Sweden. To date, the only known curative treatment is surgery and low anterior resection (LAR) is the operation of choice for tumours in the middle rectum. However, LAR has a high risk for short and long-term morbidity where one of the most severe complications is anastomotic leakage (AL). Since a diverting loop ileostomy has been shown to reduce the risk of early AL after LAR, nearly all patients in Sweden are currently diverted. Yet, a stoma, even temporary, is also associated with significant morbidity. Enhanced Recovery After Surgery (ERAS) is a perioperative care program with the aim to reduce surgical stress and thereby improve postoperative outcome after surgery. The aim of this thesis was to evaluate and optimise the treatment for patients with a diverting stoma following surgery for rectal cancer and to assess if compliance with ERAS influenced clinical outcome after primary diversion in LAR.

In **paper I**, short-term morbidity after LAR in relation to a diverting stoma and ERAS was evaluated. All 287 patients operated on for LAR at Ersta Hospital, Sweden, between 2002-2011, were included. Out of those, 139 had a diverting stoma (S+) at LAR and 148 patients had not (S-), whereas all were treated according to an ERAS program. Most of the diverted patients underwent surgery after 2007 due a change in practice at our institution. Data were prospectively collected in the ERAS database. Postoperative morbidity, including clinically apparent AL, was similar between the two groups, S+ and S-. Total rate of re-laparotomy was comparable but significantly more patients in the S- group underwent re-laparotomy due to AL. However, the total frequency of reinterventions due to AL did not differ. Postoperative recovery was faster among the patients in the S- group but this did not influence the length of stay.

In **paper II**, long-term morbidity within 3 years after LAR depending on whether or not a diverting stoma was fashioned was evaluated. The cohort was the same as in paper I, but data regarding long-term morbidity and permanent stoma were retrospectively collected. Late AL, unexpected readmissions in the late postoperative course, rate of permanent stoma and oncological outcome were comparable between S+ and S-. AL was an independent predictor for a permanent stoma and patients in the S+ group had longer hospital stay during the 3 year follow up.

In **paper III**, complications after closure of a loop ileostomy in relation to the type of anastomosis (hand-sewn or stapled) were analysed. The cohort consisted of 351 patients, operated on for stoma closure, 1999-2006, at three different Swedish hospitals. Data were collected retrospectively. In patients with a stapled anastomosis, the risk of small bowel obstruction after surgery was reduced by 50 percent, operation time was 10 minutes shorter and length of hospital stay was reduced by 1.5 day, compared with patients who received a hand-sewn anastomosis.

In **paper IV**, a total of 29 patients, undergoing rectal cancer surgery between 2008-2013 at Ersta Hospital, were randomised either to oral nutritional supplements (ONS) and rectal enema before surgery or no preoperative nutritional intervention and mechanical bowel preparation with polyethylene glycol (PEG). Bowel cleansing, postoperative morbidity and patients' nutritional and physiological status were assessed. The bowel was less clean in the right and mid colon but similar in the sigmoid and rectum in the ONS-group. In the interventional arm (ONS), patients gained in percent body fat, from randomisation to 3 days after surgery, and lost less in weight, from randomisation to 4 weeks after surgery, compared to the PEG-group. Postoperative morbidity did not differ.

In conclusion, we did not find any benefit of a diverting stoma regarding short and long-term morbidity after LAR among patients treated within an ERAS program. However, there may be an increased risk of symptomatic anastomotic leakage requiring re-laparotomy in those patients who were not diverted. Nonetheless, overall complication rates were similar with and without diversion, which suggests that routine diversion for all patients, undergoing LAR in Sweden, may be called into question. Moreover, a stapled anastomosis during the closure procedure seems preferable, resulting in a reduced frequency of postoperative small bowel obstruction and shortening operative time. Finally, oral nutritional supplements and local rectal cleansing prior to rectal cancer surgery may be a safe alternative to traditional bowel cleansing and in addition improve patients' nutritional status.

LIST OF PUBLICATIONS

I K. Anderin, U.O. Gustafsson, A. Thorell, J. Nygren

The effect of diverting stoma on postoperative morbidity after low anterior resection for rectal cancer in patients treated within an ERAS program

(European Journal of Surgical Oncology, 2015; 41: 724-730)

II K. Anderin, U.O. Gustafsson, A. Thorell, J. Nygren

The effect of diverting stoma on long-term morbidity and risk for permanent stoma after low anterior resection for rectal cancer

(Accepted for publication in European Journal of Surgical Oncology, April 2016)

III K. Gustavsson, U. Gunnarsson, P. Jestin

Postoperative complications after closure of a diverting ileostoma - differences according to closure technique

(International Journal of Colorectal Disease, 2012; 27: 55-58)

IV K. Anderin, A. Thorell, J. Nygren, U.O. Gustafsson

Oral nutritional supplements before rectal cancer surgery - hitting two birds with one stone? Results of a randomized controlled trial

(Submitted)

LIST OF ABBREVIATIONS

AL	Anastomotic leakage
ASA	American Society of Anaesthesiologists
ASIS	Abdominal Surgery Impact Scale
BMI	Body Mass Index
CI	Confidence interval
CT	Computer tomography
EDA	Epidural analgesia
EORTC	European Organisation for Research and Treatment of Cancer
ERAS	Enhanced Recovery after Surgery
ESD	Endoscopic sub mucosal dissection
ET	Enterostomal therapist
HS	Hand-sewn anastomosis
IBD	Inflammatory bowel disease
ICU	Intensive care unit
IE	Immune-enhancing diet
IMA	Inferior mesenteric artery
LAR	Low anterior resection
LE	Local excision
LOS	Length of hospital stay
LOS+	Total length of hospital stay
MBP	Mechanical bowel preparation
MRI	Magnetic resonance imaging
NIR	Near infra red light
NS	Not significant
ONS	Oral nutritional supplements
OR	Odds ratio
PEG	Polyethylene glycol
PME	Partial mesorectal excision
RCT	Randomised controlled trial
RDI	Recommended daily caloric intake
RT	Radiotherapy
S	Stapled anastomosis
S+	Stoma present
S-	No stoma present
SBO	Small bowel obstruction
SD	Standard deviation
SGA	Subjective Global Assessment
Ta TME	Transanal Total mesorectal excision
TEM	Transanal endoscopic microsurgery
TME	Total mesorectal excision
TNM	Tumour Nodes Metastasis
TPN	Total parenteral nutrition
Vs.	Versus

THESIS AT A GLANCE

PAPER	AIM	PATIENTS & METHODS	RESULTS	CONCLUSION
I	To assess short-term morbidity after LAR in relation to a diverting loop ileostomy and ERAS.	Patients operated on for LAR (N=287), +/- diverting stoma and treated according to ERAS, Jan 2002-Dec 2011 at Ersta Hospital. Prospective cohort comparing stoma (S+) and no stoma (S-) at LAR.	Postoperative morbidity was 53% vs. 43% (p 0.116), rate of AL 19% vs. 24% (p 0.316) and acute re-laparotomy 8% vs. 15% (p 0.065) in S+ and S-, resp. In S+ 2% had acute relaparotomy due to AL, vs. 14% in S- (p<0.001). Patients in S- had a faster postoperative recovery.	A diverting loop ileostomy at LAR did not improve postoperative short-term morbidity but was associated with a delayed recovery compared to those without diversion.
II	To assess long-term morbidity (>30 days-3 years) after LAR in relation to a diverting loop ileostomy.	Patients operated on for LAR (N=287), +/- diverting stoma and treated according to ERAS, Jan 2002-Dec 2011 at Ersta Hospital. Retrospective cohort comparing S+ and S- at LAR.	Late AL (6% vs. 5%), late readmission (16% vs. 15%), permanent stoma (17% vs. 14%) and oncological outcome (22% vs. 24%, over-all re-currence) did not differ, S+ and S-, resp. LOS+ was 7 days in S+ vs. 4 days in S- (p<0.001).	A diverting loop ileostomy at LAR did not reduce long-term morbidity or oncological outcome but was associated with a longer total LOS compared to those without a stoma constructed at LAR.
III	To evaluate postoperative complications after closure of a diverting loop ileostomy in relation to type of anastomosis.	Patients operated on for stoma closure (N=351), Oct 1999-Dec 2006, at Uppsala University Hospital, Karolinska University Hospital, Huddinge and Karlstad Hospital. Retrospective cohort, comparing hand-sewn (HS) and stapled (S) anastomosis at stoma closure.	Total rate of AL was 3% and SBO was 13% (36% of those required re-operation). In the HS-group SBO was 16% vs. 8% in S. In the S-group the risk of SBO was decreased by 56% (OR 0.44, 95%CI 0.21-0.93), operation time 10 minutes shorter (p 0.015) and LOS 4 days vs. 5.5 days in the HS-group (p<0.001).	A stapled anastomosis after closure of a diverting loop ileostomy was associated with decreased operation time, lower rate of postoperative SBO and shorter LOS compared to a hand-sewn anastomosis.
IV	To evaluate if bowel preparation can be safely achieved by oral nutritional supplements (ONS) and if this regimen affect postoperative morbidity, nutritional and physiological status in patients operated on for rectal cancer.	Patients planned for rectal cancer surgery (N=29), between June 2008- Feb 2013, were randomised to ONS or MBP with polyethylene glycol (PEG). Randomised controlled trial comparing ONS and PEG before rectal cancer surgery.	In ONS 77% reached their recommended daily intake (RDI) before surgery, vs. 19% in PEG (p 0.003). The bowel was less clean in right and mid-colon but similar in sigmoid and rectum after ONS. Weight loss was -1.6 kg in ONS and -4.6 kg, in PEG, from randomisation to 4 weeks after surgery.	ONS prior to rectal cancer surgery may be a safe alternative to traditional bowel cleansing. In addition, patients in the ONS-group gained in nutritional status and lost less in weight compared to patients treated with PEG.

INTRODUCTION & BACKGROUND

This thesis, "Aspects of diverting stoma and ERAS in rectal cancer surgery", examines morbidity after low anterior resection in relation to a diverting stoma and the use of ERAS in rectal cancer surgery. In this section, background to the main topics - rectal cancer, diverting stoma and ERAS - will be presented.

RECTAL CANCER

Epidemiology

Worldwide perspective

With an incidence of 1 361 000 new cases every year, colorectal cancer (CRC) is the third most common malignancy worldwide, whereas rectal cancer[1] constitutes approximately one third of cases.

The incidence varies 10-fold across the world and the highest numbers are seen in Australia and New Zealand (incidence rate 45 and 32/100 000 inhabitants, men and women, respectively) and the lowest are found in the Western Africa (incidence rate 5 and 4/100 000 inhabitants, men and women, respectively).[1] For unknown reasons, the prevalence of the disease is higher in men than in women.

Globally, overall mortality is decreasing slightly[1] and is clearly correlated to the stage of the tumour - the more advanced stage, the poorer survival.

National perspective

In Sweden, rectal cancer is the seventh most common cancer form and the median age at diagnosis is 72 years.[2] Between 2009-2013, 2147 new patients/year were diagnosed, 1234 men (57%) and 913 women.[3] The incidence has been relatively stable over the last decade with a tendency to increase, please see *Figure 1*.

Since 1970 the mortality has decreased slightly but has been unchanged over the past ten years, see *Figure 2*.[2] The 5-year relative survival in patients diagnosed between 2005-2009 was 61% in men and 64% in women, shown in *Figure 3*.[2]

Figure 1. *Age standardised incidence in rectal cancer per 100 000 inhabitants, Sweden, 1970-2010. Men, Women.*[2]

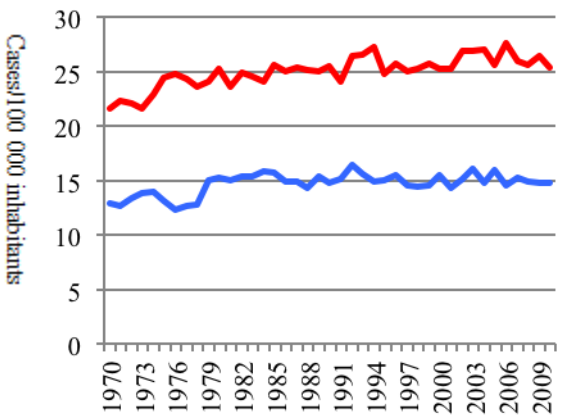


Figure 2. *Age standardised mortality in rectal cancer per 100 000 inhabitants, Sweden, 1997-2010. Men, Women.*[2]

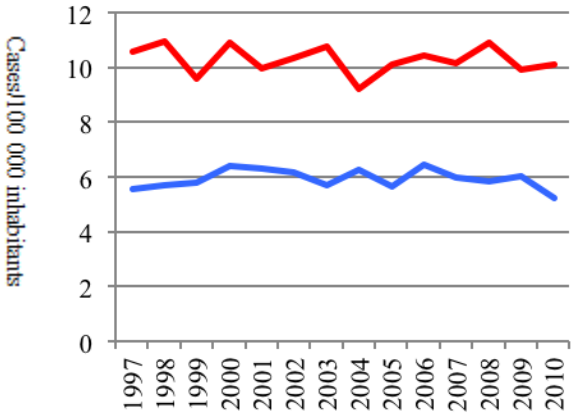


Figure 3. *Five-year relative survival in rectal cancer, Sweden, 1964-2003. Men, Women.*[2]

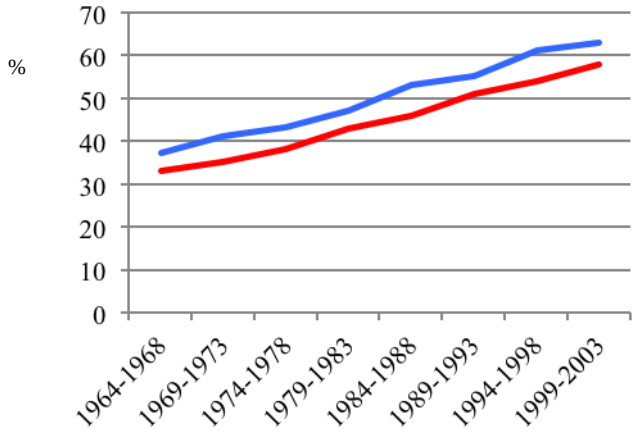


Figure 1-3 published with the permission from the Swedish rectal cancer registry.

Several factors over the last decades have contributed to the improved prognosis. Implementation of the total mesorectal excision (TME), a new surgical technique, has reduced local and overall recurrence and improved cancer-specific survival.[4, 5] Neoadjuvant radiotherapy (RT) in combination with TME has reduced local recurrence further and increased overall survival in radically resected stage III-tumours.[6] Moreover, neoadjuvant RT alone has been shown to reduce local recurrence[7, 8] and improve overall as well as cancer-specific survival.[8] Furthermore, RT in combination with chemotherapy decreases the frequency of local recurrence.[9]

Aetiology

Nearly all CRC is believed to arise from an intestinal adenoma through an accumulation of mutations called the adenoma-carcinoma sequence.[10, 11] The prevalence of adenomas, in a Swedish population, is around 10% and is higher in the elderly.[12] Accordingly, most of the adenomas do not proceed into CRC.

The mechanism behind the development of CRC is considered to be multifactorial. Lifestyle and environmental factors such as red meat,[13] low intake of fruits and vegetables,[14] physical inactivity,[15] obesity,[15] tobacco and alcohol use,[16, 17] diabetes,[18] male gender and increasing age[2] have been suggested to be involved.

Patients with inflammatory bowel disease (Ulcerative colitis and Chrons' disease) have a two to six times increased risk to develop CRC.[19] The duration, severity and extent of the disease as well as co-existing primary sclerosing cholangitis and a family history of CRC are confirmed significant risk factors in this group of patients.[19, 20]

Approximately 20% of all CRC is believed to have an underlying genetic factor, whereas two to four percent is monogenetic.[2] Syndromes described are Lynch syndrome (known as hereditary non-polyposis CRC (HNPCC) which accounts for 2-5% of all cases),[2, 21] familial adenomatous polyposis (characterised by development of hundreds to thousands of polyps in the gastrointestinal tract, mostly in duodenum, colon and rectum),[2, 21] MUTYH associated polyposis[2] and juvenile polyposis syndrome (JPS).[22]

TNM-classification and Staging

In 1932 the British pathologist Cuthbert Dukes presented a classification for colorectal cancer[21] severity, the so-called Dukes classification. This is divided into Dukes A, B and C. Dukes A represents invasion of the tumour into but not through the bowel wall, B invasion through the bowel wall but without affected lymph nodes and C, which includes affected lymph nodes. Later on Dukes D was added representing the presence of distant metastases.[21]

Over the years, there have been several different classification and staging systems, in addition to Dukes, for colorectal cancer. The most commonly accepted, currently used in Sweden, is the Tumour, Nodes and Metastasis (TNM) classification developed by the American Joint Committee on Cancer (AJCC) in collaboration with the Union Internationale Contre le Cancer (UICC). The first edition was presented in 1977[23] but the classification is revised every five years and has currently reached its seventh edition, in use since 2010.[24]

The TNM-classification is used both prior to surgery (by radiological and clinic examination, prefix "c" for clinical classification) and postoperatively (based on the pathological specimen, prefix "p" for pathological classification). It gives an indication of prognosis, aids the planning of treatment (neoadjuvant, surgical procedure, adjuvant), assesses treatment efficacy and aids comparing and exchanging information of treatment between different centres. It also determines entry into clinical trials and contributes to the research into CRC.[25]

Primary tumour (T), Regional lymph nodes (N) and Distant metastasis (M)

The T-stage represents the depth of invasion of the primary tumour into the bowel wall – Tx (primary tumour cannot be evaluated), Tis (carcinoma in situ), T0-T4.

Regional lymph nodes, affected or not, and the number of affected lymph nodes is described by the N-stage. This stage also includes tumour deposits (N1c).

The M-stage represents the occurrence of distant metastasis, confined to one or several organs.

The AJCC has also developed a staging system, according the different TNM-stages, where the stage, divided I-IV, correlates with the prognosis and is compared with the previous described Dukes classification.

Surgery

Until today, surgery is the only known curative treatment for rectal cancer. Various surgical approaches might be chosen depending on factors such as location of the tumour (upper, middle or lower part of the rectum), stage and growth of the tumour, patient co-morbidity and functional status.

Total mesorectal excision

In 1982, Heald *et al* presented the TME procedure for rectal cancer[26] and a new era of rectal cancer surgery began. Previously reported five-year local (14-25%) and overall (42-63%) recurrence rates decreased to five and 22%, respectively[4] and the five-year cancer-specific survival improved from 66 to 77% with the new technique.[5] In addition, this sphincter-preserving operation halved the frequency of permanent stomas.[5] Hence, the principles of the TME procedure are now standard in rectal cancer surgery.

In TME, mobilisation of the rectum and its associated mesorectum is performed with sharp dissection under direct vision along pre-existing embryological planes. The visceral fascia, enclosing the mesorectum, is divided from the pelvic parietal fascia and kept intact down to the pelvic floor. The hypogastric nerves are identified and preserved and the inferior mesenteric artery (IMA) is ligated approximately one centimeter from the aorta to ensure lymphatic clearance of upward spread in the mesocolon.[26]

Anterior resection

In Sweden, anterior resection (AR) is used in approximately 65% of all operations for tumours in the middle and upper rectum.[2]

The term anterior resection is imprecise in the literature. It includes both *High anterior resection/Partial mesorectal excision* (PME), for tumours in the upper rectum and *Low anterior*

resection (LAR) for lower tumours. Moreover, in some publications, even the sphincter-preserving surgical procedure performed before the introduction of TME is included.

In LAR, a complete TME is performed, down to the pelvic floor with an intact mesorectum. After the rectal excision the colorectal/anal anastomosis, often situated approximately four to five centimetres above the anal verge, is created using a double stapling technique.[27] More seldom, the anastomosis is hand-sewn by a trans-anal approach.

The stapled anastomosis can be constructed as a straight anastomosis or a neoreservoir, including a colonic J-pouch, end-to-side anastomosis or a transverse coloplasty. A neoreservoir has been shown to improve functional outcome compared to a straight anastomosis,[28-32] where an end-to-side construction is superior in that it is easier to perform, decreases operation time and lessens the number of staples lines used.[29] The functional outcome between the different types of neoreservoir is similar.[28, 31, 33, 28, 34] Compared with the colonic J-pouch and end-to-side anastomosis, transverse coloplasty is associated with an increase in anastomotic leakage (AL) which has led to a reduction in its usage in rectal cancer surgery.[29, 34]

Regardless of the type of neoreservoir, a low anastomosis in the lesser pelvis is associated with a higher risk of AL.[35, 36] Due to this, a temporary diverting loop ileostomy has been suggested to protect the anastomosis and to attenuate the severity of septic complications from a leakage.[35-40]

Since distal spread in the mesorectum is rarely seen more than 2 cm below the distal margin of the tumour,[41] high AR/PME has been advocated for tumours in the recto-sigmoid junction and upper part of the rectum.[42]

PME is performed using the same principle as in TME surgery except for a transection of the mesorectum four to five centimetres below the distal part of the tumour. It has been shown that this technique results in a reduction in operation time, reduced incidence of AL, shorter length of hospital stay and a lesser need for diverting stoma compared with LAR, without compromising oncological outcome.[42]

Abdominoperineal excision and Extralevator abdominoperineal excision

Before the implementation of TME surgery, abdominoperineal excision, APE, was the golden standard for tumours in the middle and lower rectum.[42, 43] Today, APE is considered for low rectal cancer, zero to five centimetres above the anal verge, when sphincter-preserving surgery cannot ensure distal margin. Moreover, it may be suitable for selected cases to avoid poor bowel function after surgery or when patients are not assumed to be able to manage an AL.

In Sweden, approximately 90% of all patients with a tumour in the lower rectum undergo APE.[2] However, APE has a higher risk for local recurrence and poorer five-year overall survival compared to LAR,[44] mainly due to an increased risk for intraoperative bowel perforation and involved CRM+ combined with this procedure.[43, 44]

In APE, the principles of TME are used during the abdominal part of the surgery but instead of an intestinal anastomosis, a permanent colostomy is constructed. The specimen, along with the anal canal and the anus, is then removed through a perineal approach. This may create a waist

of the specimen in the junction between the rectum and the anal canal, close to the rectal muscle tube.[45, 46]

In an attempt to improve oncological outcome, a modified APE, extralevator APE (ELAPE), has been introduced.[45] In ELAPE, the abdominal part follows the same general approach as in APE but the intraabdominal dissection is ended when the levator ani muscles are reached.[45] The specimen is then removed together with the levator muscles en bloc, resulting in a more cylindrical specimen compared to the 'waisted' specimen commonly occurring as a result of traditional APE.[45]

In a recently published meta-analysis comparing ELAPE and APE, the former procedure was associated with a lower rate of intraoperative bowel perforations, involved CRM+ and local recurrence compared to APE while operation time, LOS and postoperative complications remained similar.[46]

Hartmann's procedure

For tumours in the upper rectum where restoration of bowel continuity is not feasible, Hartmann's procedure is an option. The principles are the same as for PME but instead of a colorectal anastomosis, an end colostomy is created and the remaining rectal stump is closed.[21]

In Sweden, Hartmann's procedure is used in approximately 10% of cases.[2] It is often performed on patients with high co-morbidity, poor bowel function and/or other factors increasing the risk of AL.[21]

Local excision

The implementation of national screening programmes for CRC has led to an increased detection of stage I tumours.[47] For early rectal cancer, i.e. T1-tumours where the risk for nodal metastasis is low, local excision (LE) can be an option.[21, 48] Moreover, it can be considered in the palliative setting or when conventional surgery leads to a high risk of mortality or morbidity.

LE can be performed either by transanal excision, transanal endoscopic microsurgery (TEM) or endoscopic sub mucosal dissection (ESD). The major advantages, compared to abdominal surgery, are the reduced surgical trauma with lower morbidity, faster postoperative recovery and shorter LOS.[48] The limitations are the increased risks of local and overall recurrence when comparing with TME for T1-tumours.[48, 49] Hence, further research into long-term results and preferably randomised trials to determine the efficacy of LE compared to abdominal surgery are needed.

Laparoscopy and robotic surgery

Laparoscopic surgery for rectal cancer has become increasingly popular and has gained acceptance worldwide as studies have shown that it is associated with improved postoperative recovery, decreased LOS, peroperative bleeding and wound infection compared with open surgery.[50-55]

Still, for tumours in the middle and lower rectum, i.e. when a complete TME should be performed, there has been doubt regarding oncological safety after laparoscopic surgery.[56-58]

Laparoscopic LAR is considered technically challenging to perform with a long learning curve. Conversion rate to open surgery is high, varying between 0 to 34 percent[57, 59] and those converted have been found to have a worse oncological outcome and increased postoperative morbidity.[57] Operating in a deep and narrow pelvis may lead to difficulties in adequate exposure, the retraction needed can cause rupture of the mesorectal fascia and an incorrect identification of the distal resection margin. Moreover, the currently available laparoscopic stapling devices give a suboptimal angle when the distal part of the specimen is removed.

Recently published data, including a Cochrane review,[54] meta-analysis[55] and three and five-year follow-up from two large RCT's,[51, 52] have concluded that cancer-specific and overall survival as well as local and distant recurrences are similar between open and laparoscopic surgery for rectal cancer. Moreover, the frequency of CRM+ and number of resected lymph nodes are equal. Hence, in the three-year follow-up from the COLOR II-trial,[51] where patients with T3-T4 tumours with threatened CRM were excluded, it should be noted that for tumours in the middle rectum, local recurrence rates were higher in the laparoscopic group (6.5% vs. 2.4%) while for low tumours the recurrence rate was lower in the laparoscopic group (4.4% vs. 11.7%).

In an attempt to improve oncological outcome for those tumours suitable for LAR, a new laparoscopic procedure is under development, transanal TME (Ta TME). To facilitate the dissection of the most distal part of the rectum this mobilisation is performed by a transanal approach in a minimal invasive fashion. The laparoscopic abdominal part can be performed simultaneously, enhancing the operation for both teams by providing traction and counter traction and by guiding each other to the correct dissection plane.[59, 60] The specimen is removed trans-anally and the anastomosis can either be stapled or hand-sewn. The potential benefits of this procedure regarding oncological outcome and anorectal function are still unclear. Currently, there is an on-going international multicentre RCT comparing Ta TME with laparoscopic TME surgery for mid and low rectal cancer, the COLOR III-trial.[61]

As technology continues to advance, robotic surgery has become the next step in minimally invasive rectal cancer surgery. In addition to the improved short-term outcome with laparoscopy, robotic surgery gives a stable three-dimensional view, reduces surgeon tremor, increases the range of movement of instruments and improves surgeon ergonomics.[62] The technique has been suggested to be superior for surgery in the lesser pelvis, especially in obese men and it may also improve urogenital functions due to less damage to the autonomic plexus and has a lower conversion rate[63] compared with traditional laparoscopic surgery. Nonetheless, there has not been any robust evidence in favour of robotic surgery compared to laparoscopy

regarding short-term outcome.[62, 63] Moreover, long-term outcome, including oncological results, is still unknown.[63]

Both robotic and laparoscopic surgery has a longer operation time and increased costs compared to open surgery.[50, 54, 55, 57, 63]

Diverting stoma in rectal cancer surgery

The earliest stomas, (*Gr.* Mouth or opening) were unintentional enterocutaneous fistulas from penetrating abdominal injuries or complications of intestinal diseases such as diverticulitis or incarcerated hernias.[64] In the 16th and 17th centuries the first surgical stomas were described.[21] The series were small and patients died in the early postoperative period. It was not until 1793 that Duret, a French military surgeon, constructed the first successful stoma - a colostomy on a 3-year old infant with anal atresia. The patient lived until 45 years of age.[64]

Abdominal trauma, bowel obstruction and anal atresia were treated by loop colostomies and later on, in the late 19th, end stomas were constructed. End colostomies became popular through the introduction of Hartmann's procedure in the early 20th century. Subsequently, end ileostomies were first described by the German surgeon Baum in 1879, and were used in the treatment of ulcerative colitis.[64]

In 1961, Turnbull described the first loop ileostomy for patients with a short or fat mesentery or in the obese patient where the blood supply of an end stoma might become compromised.[21] The distal end of the ileum was closed and a loop of the proximal ileum was constructed. Later on, in 1974, Alexander-William realised that a loop ileostomy could be constructed as a temporary solution.[21]

Currently, the indications for faecal diversion, either through an ileostomy or a colostomy, include surgery for CRC, IBD, diverticulitis, trauma, pelvic sepsis, ischemic bowel, faecal incontinence, fistulae, obstetric complications, paediatric intestinal malformations and bowel obstruction.[64]

The stoma can be temporary or permanent and constructed as an end or loop stoma (*Figure 4* and *5*). Compared with an end stoma, a loop stoma is often easier to close, preferable at the stoma site without the need for laparotomy, and it also creates a diversion for the distal limb in cases of obstruction of the bowel distal to the stoma.

After introduction of the first successful stomas, postoperative care was hampered by the lack of appropriate stoma appliances, causing serious skin complications and serositis from the liquid content of the ileum. The serosal damage led to stricture formation and bowel obstruction at the stoma site. In 1952, Brooke developed a new method of suturing the intestinal mucosa to the skin, reducing the rate of these complications.[21] In addition, the introduction of enterostomal therapists (ET), specially trained stoma nurses, and specialised stoma appliances for correct bandaging of the stoma improved the results and care of the stoma furthe

Enterostomal therapists

The ET plays a central role in the care of the stoma patient. Preoperatively, in the elective setting, the ET educates, informs and helps patients to overcome the fear associated with the procedure and also marks a proper site for stoma creation, taking into consideration patient ergonomics. Marking of the site is done in the upright position, preferably in the left or right lower quadrant at the peak of the infraumbilical fat mound. One should avoid placing the stoma close to a bony prominence, the waistline, a scar, the umbilicus, the groin or skinfolds, which may all interfere with appliance management. For obese patients or those in wheelchairs, placing the stoma in one of the upper quadrants may be superior.[64]

Suboptimal stoma location can cause difficulties with stoma handling and appliances, which can result in leakage and skin irritation thereby increasing patient discomfort and embarrassment. Therefore, the correct marking is essential.

Patient education and training starts as soon as possible postoperatively. This includes stoma bandaging, emptying the pouch and caring for the parastomal skin. After discharge, follow-up by the ET is mandatory for further help with appliance and any stoma-related complications.[64]

Indications

In rectal cancer surgery, a permanent end colostomy is performed in APE and Hartmann's procedure (the latter one can, if possible, be reversed later on). In LAR, the majority of the patients are currently diverted either with a loop ileostomy or a loop transverse colostomy. When there are risk factors for AL such as patient co-morbidity, low serum albumin, steroid use or peroperative difficulties, a diverting loop ileostomy can be used even following a high AR/PME.

In case of intestinal obstruction due to the tumour, a diverting stoma can be constructed in the emergency setting, prior to definitive surgery. This loop stoma should be placed as distally as possible, without interfering with the tumour area. Hence, both loop ileostomy and loop colostomy can be an option.

Moreover, if not constructed at primary surgery, a diverting stoma can be used in both emergency and elective treatment for AL as well as in the palliative setting.

Figure 4. *End stoma*

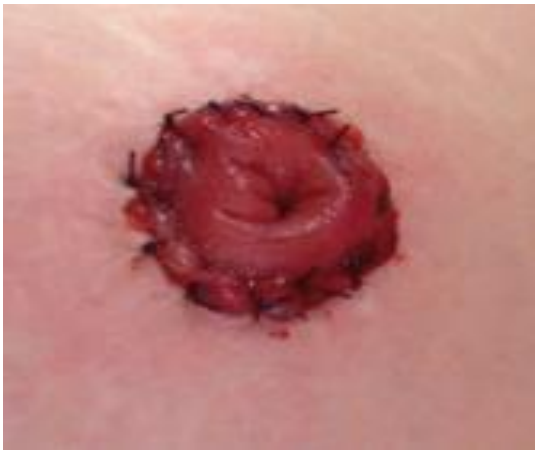
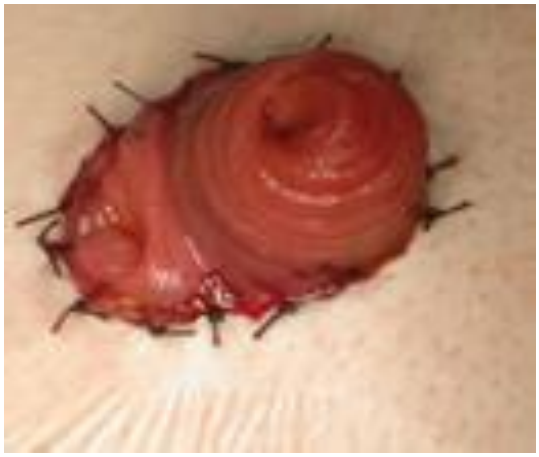


Figure 5. *Loop stoma*



Loop ileostomy

In Sweden and the United Kingdom, nearly all patients undergoing LAR are diverted by a loop stoma[2, 65] in an attempt to protect the low anastomosis. Except for rectal cancer surgery, a loop ileostomy is most often used in IBD surgery after proctocolectomy with ileal-pouch anal anastomosis.

Many surgeons consider loop ileostomy as the preferred diversion in LAR, instead of a loop transverse colostomy. A loop ileostomy is considered to have less bulky content and less odour, requiring fewer appliance changes and is easier to perform compared to a loop transverse colostomy.[64] Moreover, the risk of stoma prolapse and parastomal hernias is reduced and after stoma closure, postoperative complications such as wound infections and incisional hernias are decreased in favour of loop ileostomy.[21, 66] A Cochrane review, comparing the two types of stomas for faecal diversion of colorectal anastomosis, showed a lower frequency of stoma prolapse among loop ileostomies but with regards to other outcome measures, larger RCT are warranted to clarify which stoma is preferable in LAR.[67]

Construction and closure

At the preoperatively marked stoma site, a trephine is made by excision of skin and subcutaneous tissue. When reaching the anterior rectus sheath, a cruciate incision is performed and the muscles are split longitudinally. The posterior fascia is opened and a loop of the terminal part of the ileum, as close to the ileocaecal valve as possible, is delivered through the abdominal wall without tension. The trephine in the abdominal wall should be straight and admit two fingers. The ileum can either be rotated so that the afferent limb is placed caudally or left without rotation and a rod or a catheter can be used to support the loop. However, most important is to remember the orientation of the loop when closing the abdominal wall.

Once the abdominal wall is closed, a transverse incision is made in the distal to the middle part of the intestinal limb, at the antemesenteric border. The afferent and the efferent limbs are everted and sutured with absorbable interrupted mucocutaneous sutures, and when possible including the serosa at the antemesenteric portion. [64] Depending on type of primary procedure, the stoma can be constructed by laparotomy or laparoscopy [21, 64].

Closure of the loop ileostomy is usually performed within 3-6 months after creation, when the patient has recovered, the inflammation and oedema in the abdomen and surrounding the stoma has resolved and the adhesions are less fibrotic.[64, 68] Time between construction and closure vary, depending on the reason for construction, postoperative complications, co-morbidity and adjuvant therapy.[64] The closure procedure is not high-priority and may be postponed.

Before closure, a rectal examination, including both rectoscopy and CT with rectal enema, should be performed to ensure integrity of the anastomosis and to exclude stenosis or recurrence of the disease.

A peristomal skin incision is made and the serosa of the two limbs is freed from the sub-cutaneous fat, the rectus sheath and the peritoneum. The ileum must be completely freed so that it easily can be replaced into the peritoneal cavity. Normally, this procedure can be done at the stoma site, but in three to five percent, due to severe adhesions, a laparotomy may be necessary. [68, 69]

The new anastomosis is created in a hand-sewn or stapled fashion. If hand-sewn, the everted limbs of the ileum are turned back, eventually skin edges are excised and the opening in the ileum is sewn with a seromuscular continuous suture (*Figure 6*). If the limbs are affected or perforated during the closure procedure, a short small bowel resection is performed before the end-to-end anastomosis is constructed.

Using a linear staple, a stapled side-to-side anastomosis is created by putting the staple advices through the two bowel openings or by creating an incision just below the open edges. Thereafter, a linear staple is used, below the bowel openings, to close the remaining enterotomy (*Figure 7*). The enterotomy can also be closed in a hand-sewn manner.

After the construction of the anastomosis, the bowel is inserted back in the peritoneal cavity and the fascia is closed. The skin is most often left partially open with the use of a subcuticular purse-string suture, since this has been shown to decrease the frequency of wound infections compared with primary closure.[64]

Hand sewn versus stapled anastomosis

Currently, there is no consensus regarding the best surgical technique for closure of a loop ileostomy. Surgeon preference and local practice dictate the choice of anastomosis constructed.

It has been suggested that a stapled anastomosis creates a larger intestinal lumen and forces the surgeon to free the ileum more extensively in the peritoneal cavity in order to be able to insert the linear staple in a correct manner.[70, 71] This may decrease the risk of SBO compared to a hand-sewn anastomosis.

Nonetheless, the biggest RCT (N=328) comparing these two techniques published to date, the HASTA-trial[72] failed to demonstrate a reduction in SBO following a stapled anastomosis. On the other hand, two recently published meta-analyses, including the HASTA-trial, confirmed that a stapled anastomosis reduced the frequency of SBO by nearly 50%,[71, 73] in accordance with other reports.[70, 74, 75] Additionally, a stapled anastomosis was associated with a shorter operation time and LOS but the frequency of AL from the new anastomosis was not influenced.[71-74]

Figure 6. *Hand-sewn anastomosis*

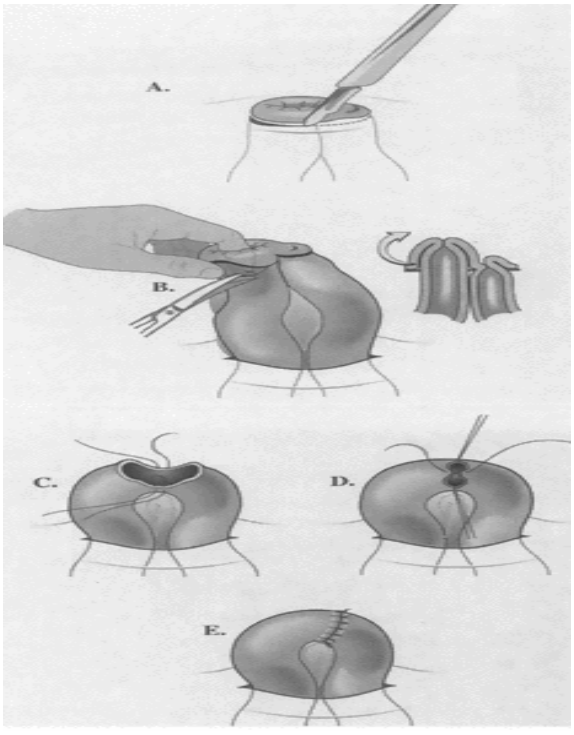


Figure 7. *Stapled anastomosis*

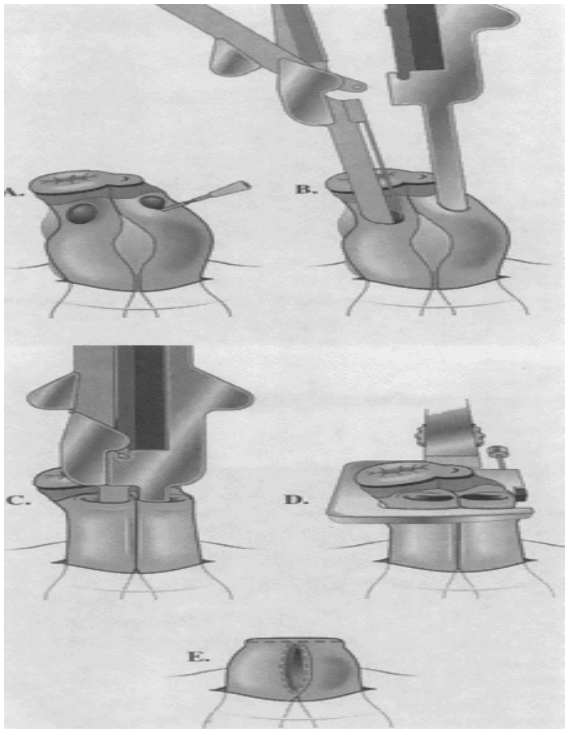


Figure 6 and 7 published with the permission of Wolters Kluwer Health, Inc.

Mortality and morbidity after low anterior resection and diverting stoma

In recent publications, postoperative 30-day mortality after LAR has been reported to be around two percent (0-8%).[2, 35, 76] In Sweden, postoperative mortality has decreased slightly over the past 20 years.[2]

Differences in defining surgical procedures and outcome measures make comparisons of morbidity between different studies and centres more difficult. In a meta-analysis regarding AL after LAR, the 22 studies included used 12 different definitions of AL.[76] Moreover, neoadjuvant treatment, demographic data, perioperative care, follow-up and registration of postoperative morbidity differ between centres. It has been shown that surgeons in training markedly under-report complications compared with trained study nurses, highlighting the issue of information bias.[77]

A summary of mortality and morbidity after LAR and diverting stoma is shown in *Figure 8.*

Short-term morbidity after low anterior resection

Short-term morbidity after LAR (within 30 days after surgery or the initial hospital stay) has been reported to be between 20-50%.[2, 78-83]

Risk-factors described for postoperative morbidity *other* than AL are male gender, age >70 years, co-morbidity, perioperative blood transfusion, growth of circumferential tumour, a history of deep venous thrombosis and previous abdominal surgery.[2, 80, 81, 83]

Non-surgical morbidity affects approximately 15-20% of all patients,[78-83] where infectious complications (e.g. pneumonia and urinary tract infections) and cardiac complications are most common.[79-81]

Surgical morbidity varies between 15-25%.[2, 79, 80, 83] AL, (see section "Anastomotic leakage" below) is the most common, most feared and therefore the most discussed complication following LAR. However, ileus (1-12%), urinary retention (3-9%), wound infection (1-7%), bleeding (1-2%) and wound dehiscence (1%) may also occur.[79, 80, 82-84] Approximately one in ten patients requires emergency reoperation[2, 79] and the frequency of unexpected readmissions in the early postoperative period is around 15%.[2, 78, 79]

Figure 8. *Mortality and morbidity after low anterior resection and diverting loop ileostomy.*

Functional outcome after low anterior resection

Bowel dysfunction, due to resection of the rectum, damage of the autonomic nerves in the pelvis and the sphincter muscles, is common after LAR and has been described in up to 60% of all patients.[29, 85]

The combination of urgency, faecal and/or flatus incontinence and frequent bowel movements occurring after LAR is referred to as the Low Anterior Resection Syndrome, LARS.[86] The LARS score, described by Emmertsen et al in 2012, is a commonly used scale to assess LARS after LAR.[86] The questionnaire includes items regarding incontinence for flatus and liquid stools, urgency, frequency and clustering (the need of defecate within one hour from the last bowel opening) and has been internationally validated.[87] LARS has been shown to have a negative impact on quality of life.[88] Even though LARS is most common the first year after surgery,[31] approximately 40% still suffer from significant LARS more than two years after LAR.[85]

Construction of a neoreservoir when creating the colorectal anastomosis, regardless of type, has been shown to reduce the risk and severity of LARS.[29] Risk factors, on the other hand, are TME surgery, neoadjuvant RT, AL and female gender.[85]

Urinary dysfunction is mainly caused by nerve damage during surgery, even though pelvic inflammation and fibrosis following AL, sutures and RT can be contributing factors.[89] With regard to sexual dysfunction, RT seems to have an additional role. Moreover, the presence of a stoma have also been associated with a worse sexual outcome for both genders.[89] Long-term follow-up has reported urinary incontinence in 38%, sexual dysfunction in 60% of female patients (dyspareunia and vaginal dryness) and in 75% of men (erectile dysfunction and problems with ejaculation).[89] However, a majority of patients undergoing surgery for rectal cancer are older; urogenital function decreases with age, but data suggest that 79% of men and 52% of women are sexually active at time of rectal cancer diagnosis.[89]

Complications to construction and closure of a diverting stoma

After construction of a diverting loop ileostomy nearly 50% (3-100%) of the patients have been described to suffer from at least one stoma-related complication.[64, 69, 90] The two most common complications are skin irritation (2-41%) and high stoma-flow (18-29%).[69, 90, 91] The latter can lead to severe electrolyte imbalance and renal failure with the need for readmission, reported in some studies to be as high as 15%.[64, 69, 90] Strictures, stoma prolapses and retractions, fistulas, parastomal hernias, small bowel obstruction and stenosis can also occur and, in some cases, necessitate reoperation.[64, 69]

Risk-factors that have been suggested to predispose for complications after stoma construction are obesity, IBD, increasing patient age, absence of preoperative marking of stoma site and evaluation of ET.[64]

After stoma closure, overall morbidity ranges from two to 40%[64, 68, 69, 90, 91] and postoperative mortality is around 0.5%.[64, 68]

SBO (6-23%), and wound infection (0-18%), are the most common complications.[64, 68, 73, 90] If postoperative SBO does occur, approximately one in three patients require reoperation.[70, 90] The incidence of wound infection has been reported to be significantly lower, 1-5%, if the wound is left open or partially open.[64, 68]

The frequency of AL after stoma closure varies between 0-8% and most instances of AL require relaparotomy. Other complications such as fistulas (0-7%) and incisional hernias (1-12%) have also been described.[64] LOS after stoma closure is around two to five days.[64]

Permanent stoma

A temporary diverting stoma created at LAR ends up as a permanent stoma in 15-25% of cases[92-94] where AL is the biggest risk factor for a permanent stoma.[92-94] A 6-year follow-up study stated that 56% of the patients with AL had a permanent stoma compared to 10% in those without a leakage.[94]

Other risk-factors include increasing age (>65-75 years), secondary constructed stomas, postoperative infectious complications, local recurrence, stage IV tumours and co-morbidity.[92-94]

The permanent stoma could be either a diverting loop ileo/colostomy or an end colostomy.[93, 94] It has been suggested that an end colostomy is preferable as a permanent stoma, due to the advantages in stoma handling and a reduced risk of high stoma flow.[94]

Quality of life

Studies assessing quality of life (QoL) after rectal cancer surgery report differing results due to differences in questionnaires used, in type of patients included and outcome measures, making interpretation of these results difficult.[88, 95, 96]

It is suggested that LARS decreases QoL in patients undergoing LAR.[88] Patients' body image and sexual function are worse compared to before surgery and women have poorer self-reported social well-being compared to men.[95] Despite this, global QoL is generally improved after surgery, probably due to patients' satisfaction that they could possibly be cured from their malignancy.[95]

Besides dealing with the underlying disease and the potential risk of cancer recurrence, stoma patients have to face several other challenges such as discomfort, embarrassment and altered body image. Simple tasks such as dressing, social activities and swimming may become significant obstacles affecting daily life. Even though patients having undergone LAR have a better self-reported social function and body image compared to those having undergone APE,[96] these improvements might be counterbalanced by the high risk for bowel dysfunction after LAR.[29] A Cochrane review, comparing APE with AR, revealed no difference in global QoL.[97]

Regarding temporary diversion, such as a diverting loop ileostomy, the decreased social function and body image correlated with the stoma is not always reversed after stoma closure.[98]

Anastomotic leakage in low anterior resection

Despite advances in surgical technology and attempts to define risk-factors for AL there has been no dramatic change in the incidence of leakage over the last decade.[2, 84, 99] AL, the most feared surgical complication after LAR, seems difficult to predict in the individual patient and it has been shown that the surgeon's prediction of the development of AL has extremely low sensitivity and specificity.[100]

The frequency of AL varies between 3-28%,[76, 84] likely in part due to differences in the definition of AL but also due to actual differences in surgical performance. In an attempt to clarify the definition of AL, the International Study Group of Rectal Cancer has suggested a definition and grading in rectal cancer surgery (*Table 1*).[101] It is noteworthy that this classification also includes abscesses close to the anastomosis without radiological verification of AL.

Table 1. *Definition and grading of AL by the International Study Group of Rectal Cancer*

Definition	Defect of the intestinal wall integrity at the colorectal or colo-anal anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments. A pelvic abscess close to the anastomosis is also considered as anastomotic leakage.
Grade A	Anastomotic leakage requiring no active therapeutic intervention
Grade B	Anastomotic leakage requiring active therapeutic intervention but manageable without re-laparotomy
Grade C	Anastomotic leakage requiring re-laparotomy

AL causes approximately one third of the early postoperative mortalities, (0.7%; 0-5%) after LAR.[76, 102]

Apart from immediate clinical consequences, such as intra abdominal abscess, peritonitis, sepsis and fistulas, with the risk of surgical and radiological re-intervention, AL also increases LOS as well as the risk for other complications. In a large cohort study, including more than 70 000 patients, Kang *et al*. showed a higher risk of postoperative ileus, wound infection, renal failure, urinary tract infections, pneumonia and deep venous thrombosis if AL was present.[102]

Regarding long-term outcome, AL increases the risk for a permanent stoma[94] and a worse functional outcome.[103]

It has been suggested that viable cancer cells that remain in the bowel lumen, close to the anastomosis, may become extra-luminal following AL, which may lead to local recurrence.[104] Moreover, immunosuppression caused by the inflammatory response and delayed adjuvant chemotherapy due to AL, could increase the risk for systemic recurrence and cancer-specific death.[104] However, the influence of AL on the risk for disease recurrence and cancer specific survival is debated in the literature and a consensus has not yet been reached.[105, 106] Changes in the use of neoadjuvant treatment and implementation of TME surgery over time causes difficulties interpreting studies concerning the influence of AL on oncological outcomes.

Risk-factors for anastomotic leakage

Patient, tumour and therapy-related parameters as well as a disturbed microcirculation have found to be risk factors for AL. A recently published meta-analysis, including over 90 000 patients operated on for CRC, stated that preoperative RT, low rectal anastomosis (≤5 cm from the anal verge) and male gender increased the risk for AL in rectal cancer.[107] In concordance, in the 2014 annual report of the Swedish rectal cancer registry, men and irradiated patients had a higher risk for AL.[2]

Preoperative RT initiates local inflammation, fibrosis and micro vascular changes with the risk of impaired wound healing. A low anastomosis is sometimes technically demanding to perform, and even more so in men where the pelvis is more narrow, leading to local tissue trauma and increased tension in the anastomosis as a consequence. In addition, possible poor blood supply in the middle and lower rectum could explain the increased risk for AL.[108] However, even though human and animal models have confirmed decreased blood flow in the anastomosis after vascular ligation,[104, 109] it still remains unclear what percentage of normal blood flow that is required for intestinal tissue healing.[110]

Other possible risk-factors for the development of AL are preoperative weight loss and malnutrition,[102] smoking, high consumption of alcohol,[111] obesity,[112] intra-operative adverse events, prolonged operation time,[113] absence of pelvic drainage[114] and the use of non steroidal anti-inflammatory drugs after surgery.[115]

High versus low-tie of the IMA has also been discussed. A high-tie could reduce blood supply to the anastomosis by dividing the IMA close to the aorta, including both the superior rectal artery and the left colic artery. On the other hand a low-tie has the risk of tension in the anastomosis due to a shorter length of the proximal colonic segment. Thus, no difference in AL has been found between these two methods.[116]

Diverting stoma and anastomotic leakage

Several studies have demonstrated a reduction in the frequency of clinically apparent AL if a diverting stoma - most often a loop ileostomy - is constructed at LAR.[35-40] Even though other cohort studies have failed to establish this correlation, their biggest limitation is the possible selection bias of high-risk patients in the stoma group.[117-122]

In a Swedish multicentre RCT published in 2007, comparing patients with or without a diverting stoma at LAR, the risk for AL was decreased from 28 to 10% in those diverted.[35] Hereafter, diverting loop ileostomies created at LAR have increased in Sweden from approximately 40% in 2002 to nearly 80% in 2014 (*Figure 9 and 10).*[2] Since PME is included in these numbers, it is to be assumed that nearly all patients operated on for LAR, with a complete TME, are diverted currently.

The marginal decrease in AL in the Swedish Rectal Cancer Registry during the same period (2002-2014) is difficult to interpret. The increasing use of diverting loop ileostomies could be one explanation, but as previously mentioned, both PME and LAR are included in these numbers and the frequency of AL is not reduced in men and in patients with preoperative RT.[2] A report from Snijders *et al*, from the Dutch Colorectal Surgical Audit (DCSA), did not reveal a lower frequency of AL in LAR despite an increased use of diverting stomas.[99]

In tandem with the increased risk for anastomotic leakage, the need of acute abdominal reoperation due to AL is augmented in those without a diverting stoma.[35, 37-39] A Cochrane report from 2010 showed a 77% risk reduction (RR 0.23; 95% CI 0.12-0.42) for acute reoperation if a diverting stoma was present.[36]

Figure 9. *Use of diverting loop ileostomy at anterior resection in Sweden among men.*[2]

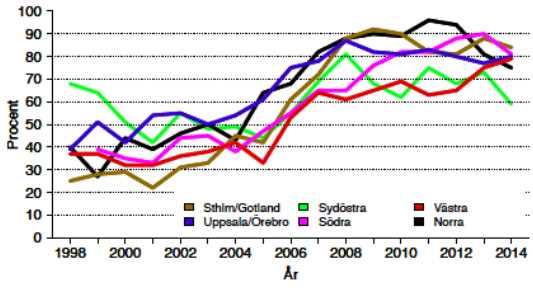


Figure 10*. Use of diverting loop ileostomy at anterior resection in Sweden among women.*[2]

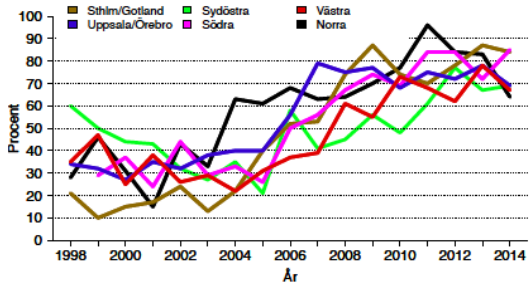


Figure 9 and 10 published with the permission from the Swedish rectal cancer registry.

Surprisingly, none of the RCT's or meta-analyses published[35-39] have found increased mortality, longer LOS or higher readmission rate among patients without a stoma compared to those who have been diverted. On the contrary, except for clinical AL and frequency of reoperation, other

postoperative morbidity is comparable[79, 123] and LOS is significantly reduced in those without a diverting stoma in some reports.[35, 117, 120]

Considering long-term morbidity, neither functional nor oncological outcomes have found to be influenced by a diverting stoma at LAR.[106, 124]

Late anastomotic leakage

Late AL, diagnosed after discharge or >30 days after primary surgery, is well known but less well described. In the few studies examining this issue, late AL seems to appear in approximately six to eight percent of all patients operated on for LAR irrespective of the use of a primary diverting stoma or not.[125-127] Time to diagnosis of late AL ranges between 22-99 days after surgery[125-127] and suggested risk-factors are female gender, low anastomosis and neoadjuvant chemo radiation.[127]

Patients with late AL have been described to have an initial uneventful postoperative course, similar to those without a leakage[128] and a lower rate of relaparotomy[126] compared with those suffering from early AL. Moreover, it has been suggested that late AL treated with a diverting stoma has a lower proportion of successful stoma reversal compared with those who suffer an early AL.[127]

Experimental treatment for anastomotic leakage

Several attempts have been made to find alternative treatments to diverting stomas as prevention of AL after LAR and to avoid or successfully manage an anastomotic dehiscence. The drawbacks with all of these studies are small case-series, selection bias and lack of reporting of long-term outcomes. In this section some of the actual treatment options are described.

Percutaneous ileostomy

A jejunal probe introduced in the distal ileum, a percutaneous ileostomy, has been suggested to be comparable with a diverting loop ileostomy with regard to the risk of AL in LAR, without any increase in other morbidity.[129] In addition to the advantages of less discomfort for the patients and the absence of a stoma, early removal without another surgical procedure may be performed. Currently, there is an on-going Italian multicentre RCT, the ALPPI trial, comparing these two strategies for diversion in LAR for rectal cancer.[130]

Ghost stoma

As an alternative to a diverting stoma, some surgeons advocate the use of a ghost stoma. A tube, drain or vessel loop is placed around the distal ileum and exteriorised to the abdominal wall. If

AL occurs, a loop ileostomy can easily be performed at the site of the tube without the need of a relaparotomy.[131]

Intraoperative micro perfusion

Adequate blood supply to the anastomosis is required for anastomotic healing. Traditionally, this is measured by visual lack of decolouration of the dissected colon, palpable pulses in the supplying arteries and active bleeding from the resection lines when dividing the intestine. However, this macroscopic evaluation may not always correlate with the presence of adequate microcirculation in the area. Fluorescence angiography with near-infrared light (NIR) technology can be achieved through intraoperative intravenous administration of a fluorescent agent. This may give a more objective assessment of the microcirculation along the planned resection lines and help guide the decision whether to divide the bowel at the intended site and if a diverting stoma is necessary or not.[132, 133]

Perioperative supplemental oxygen

To improve local oxygenation and perfusion in the anastomosis perioperative supplemental oxygen by increased fraction of inspired oxygen ($Fi0_2$) has been investigated. Although convincing evidence is lacking, improved outcome concerning wound infection and lower rate of AL have been observed.[134]

Endo-sponge and early closure

Vacuum-assisted treatment for different wounds are used to accomplish wound healing. An endo-sponge, inserted trans-anally in the cavity that arises after a leakage, and connected to a low-vacuum suction bottle has been suggested as a treatment option for AL.[135, 136] Treatment with endo-sponge in the sinus cavity after AL has been successful if the sponge is placed early in the postoperative course.[135] Moreover, initial treatment with endo-sponge followed by closure of the anastomotic dehiscence has resulted in healing in some patients.[136] However, except for small series and selected cases, long-term results are lacking.

Transanal tube

A transanal tube, inserted after the formation of the anastomosis, and kept in place for approximately 5 days postoperatively, has been shown to significantly reduce clinical AL even in patients without a diverting stoma.[137] The rationale behind this treatment option is decreased intraluminal pressure and improved evacuation of liquid stool proximal to the anastomosis.

Fibrin glue

Some studies have shown that application of fibrin glue over stapled anastomotic lines reduced the rate of clinical AL.[138] Currently, there is an on-going multicentre RCT evaluating this topic where preliminary results suggest a lower frequency of leakage in the experimental arm (ClinicalTrials.gov number, NCT02046278).

Probiotics and Intestinal microflora

The role of the intestinal microflora in anastomotic healing and development of AL is largely unexplored. Intestinal flora interacts with intestinal tissue and with intestinal healing.[104] A recently published RCT showed a reduction in overall morbidity (49% vs. 29%) and AL, specifically (9% vs. 1%), after colorectal cancer surgery if a combination of probiotics were given the day before surgery until 15 days after surgery.[139]

RT has been shown to reduce the amount of bacteria per gram of stool[140] and to affect potentially pathogenic microbes, leading to an enhancement of their virulence causing bacterial induced AL. Olivas *et al.* developed a model, where rats underwent distal colonic resection with a colorectal anastomosis.[141] Some of the rats were preoperatively radiated with 5x5 Gy and underwent surgery a week later on and some were inoculated with P. aeruginosa at the end of surgery. Rats with both preoperative RT and P. aeruginosa had a higher risk of AL compared to those who only were radiated and those who had P. aeruginosa, alone. Moreover, in animal models of colonic anastomosis and vessel ligation causing intestinal ischaemia, animals that received antibiotics had a decreased risk of AL.[104] Taken together, the role of intestinal microbes in either protecting against or inducing/aggravating AL remains unclear.

ENHANCED RECOVERY AFTER SURGERY

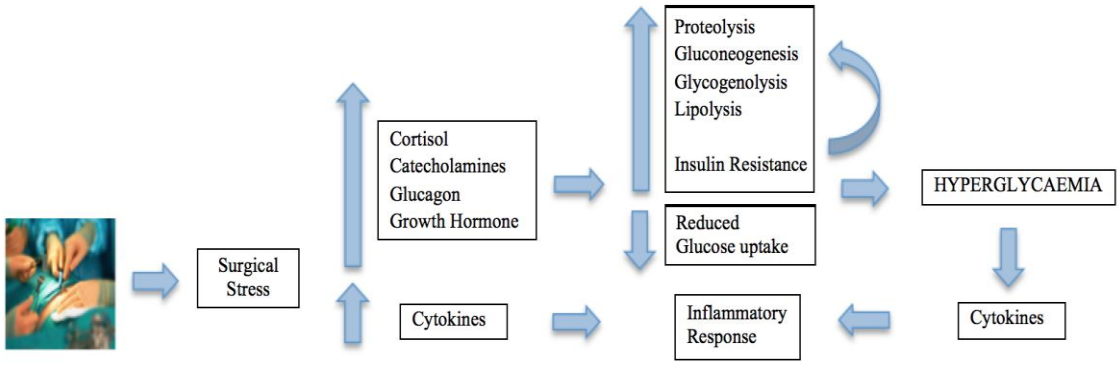
Surgical stress, insulin resistance and hyperglycaemia

Any physical injury, including surgery, induces a metabolic and inflammatory response, which disrupts normal homeostasis (*Figure 11*).

Cuthbertson first described the metabolic response to injury in 1942 and introduced the concept of ebb and flow phase after injury.[142] The ebb phase begins with a general fuel mobilisation, lasting for approximately 24 hours.[142] Thereafter the flow phase takes place with an initial catabolic state. The energy expenditure is elevated and a breakdown of body tissues occur. Finally, an anabolic state follows which eventually leads to recovery.

The stress response is characterised by an elevation of the stress hormones cortisol, catecholamines (noradrenaline and adrenaline), glucagon and growth hormone (also known as the counter-regulatory hormones) induced by the activation of the hypothalamic-pituitary-adrenal axis. Moreover, elevation of cytokines generates an inflammatory response.[142]

Figure 11. *Metabolic and inflammatory response to surgery*



The counter-regulatory hormones stimulate the breakdown of protein, glycogen and fat and induce formation of glucose from non-carbohydrate sources (gluconeogenesis) in order to ensure supply of energy to vital organs.[142] In addition, a high level of these hormones leads to an insulin resistance, i.e. when a normal concentration of insulin produces a subnormal biological response even in non-diabetic patients.[142-144]

Normally, insulin is released after intake of carbohydrates, protein and fat and acts as an anabolic hormone to ensure energy storage and to maintain normal glucose levels.[143] Even though the role of insulin is most studied with regard to glucose metabolism, where it stimulates the glucose uptake in insulin-sensitive tissues and suppresses gluconeogenesis in the liver, it also plays a role in the storage of fat and protein.[143, 145] Therefore, in insulin

resistance, the inhibitory effects of insulin on gluconeogenesis, glycogenolysis, lipolysis and proteolysis is reduced, resulting in hyperglycaemia. Insulin resistance also impairs glucose uptake, mainly in skeletal muscle and to some extent also in adipose tissue.[143] Thus, insulin resistance is a key response in the catabolism occurring after surgery.

Blood loss, type and magnitude of surgery as well as operation time have been found to correlate with changes in insulin sensitivity after surgery.[143, 144] Moreover, a significant association between the degree of postoperative insulin resistance, LOS and the development of postoperative complications has been shown.[143]

Hyperglycaemia, caused by the catabolic response and insulin resistance is associated with a worse clinical outcome.[144, 146] Van der Berge *et al.* conducted an RCT on 1548 surgical intensive care unit (ICU) patients, randomised to either receiving intensive insulin therapy (blood glucose between 4.4-6.1 mmol per liter) or to conventional treatment (blood glucose <10-11.1 mmol per liter).[146] Mortality was significantly lower in the experimental arm (4.6%) compared with the control arm (8%). Furthermore, blood stream infections were reduced by 46%, acute renal failure by 41%, number of blood transfusions by 50% and critical-illness polyneuropathy by 44% in the experimental arm.

However, intensive insulin treatment can cause hypoglycaemia and may be difficult to control outside the ICU. Thus, there is an on-going debate as to what should be the desired level of blood glucose control, both in the ICU and on the general ward, in order to balance the risk of hyperglycaemia and its attendant risks of morbidity with that of the development of hypoglycaemia.

The pathogenesis behind hyperglycaemia and the observed increased postoperative mortality and morbidity is not fully understood. It has been suggested that hyperglycaemia enhances the inflammatory response by increasing the expression of proinflammatory cytokines[147] and that it has a negative effect on the immune system by decreasing the function of neutrophils.[148]

The ERAS study group, ERAS protocol and ERAS database

Although surgery by itself induces a stress response, several other peroperative factors contribute to the metabolic alterations leading to insulin resistance and hyperglycaemia. The concept behind Enhanced Recovery After Surgery, ERAS, is to prevent surgical stress by interaction on all of these factors using a standardised evidence-based protocol for perioperative care.[149] ERAS has been shown to attenuate the metabolic response to surgery[150] and thereby improving recovery, shortening hospital stay and decreasing postoperative morbidity.

The pioneer behind fast track surgery (the concept that is now known as ERAS) is the Danish surgeon Henrik Kehlet. Professor Kehlet demonstrated that a multimodal approach to reduce surgical stress (focusing mainly on controlling postoperative pain with as little opiate use as possible, to encourage early mobilisation and early oral feeding) shortened LOS after colonic surgery.[151]

Influenced by Kehlet et al, the ERAS study group was established in the year of 2000,[152] including six European centres, representing five different countries; Ersta Hospital, Sweden, Tromsö University Hospital, Norway, Royal Infirmary and St Mark's Hospital, United Kingdom, Maastricht University Hospital, Netherlands and Charité University Hospital, Germany. The ERAS Society, established in 2011, involves a large number of institutions from all continents.

All of the participating centres use the same fast recovery protocol, the ERAS protocol, carried out by a multidisciplinary team of surgeons, anaesthetists, nurses and physiotherapists.[149] Over 20 evidenced-based perioperative interventions with the aim to reduce surgical stress are included.[152]

To compare outcomes and to measure the effect of the ERAS protocol and the effect of different ERAS items on specific outcomes, an international web-based ERAS database has been developed. Approximately 140 variables are prospectively collected in the ERAS database, from admission to hospital until 30 days after surgery.[152] Research nurses at each centre collect the data, since clinicians have been shown to underreport postoperative morbidity.[77]

The variables, except of the key-components in the ERAS protocol, consist of demographic data, perioperative findings and recovery items. Since 2011, postoperative morbidity is classified according to Clavien-Dindo[153] (*Table 2*, shown in section "*Patients & Methods*").

The effect of ERAS in colorectal surgery

The principles of ERAS, compared with traditional perioperative care in colorectal surgery, have been shown to half postoperative overall morbidity, reduce LOS with two to three days and to improve postoperative recovery without any increase in readmissions.[78, 154-157] The reduction in postoperative morbidity has been found to be mainly due to a reduction in non-surgical complications.[78, 154]

Furthermore, better adherence to the ERAS protocol (compliance over 70%) improves postoperative outcome, with reduction in overall morbidity, readmissions and LOS, compared with compliance less than 50%.[78, 158]

The impact of ERAS in rectal surgery, specifically, as opposed to colorectal surgery in general has not been thoroughly evaluated. As previously mentioned, grade and severity of postoperative insulin resistance is correlated to length and magnitude of the surgical procedure and degree of perioperative blood loss.[143] Although laparoscopy for rectal cancer has been suggested to be oncologically safe,[51, 52] the majority of cancer operations are still being performed as open procedures[2] where tissue damage and blood loss is larger. Thus, patients operated on for rectal cancer are likely to suffer from a more severe insulin resistance compared to patients with colonic cancer operated on laparoscopically, but can safely be treated according to an ERAS program.[149, 159-161] However, there are some differences in the ERAS protocol for rectal/pelvic surgery compared to colonic surgery, especially regarding

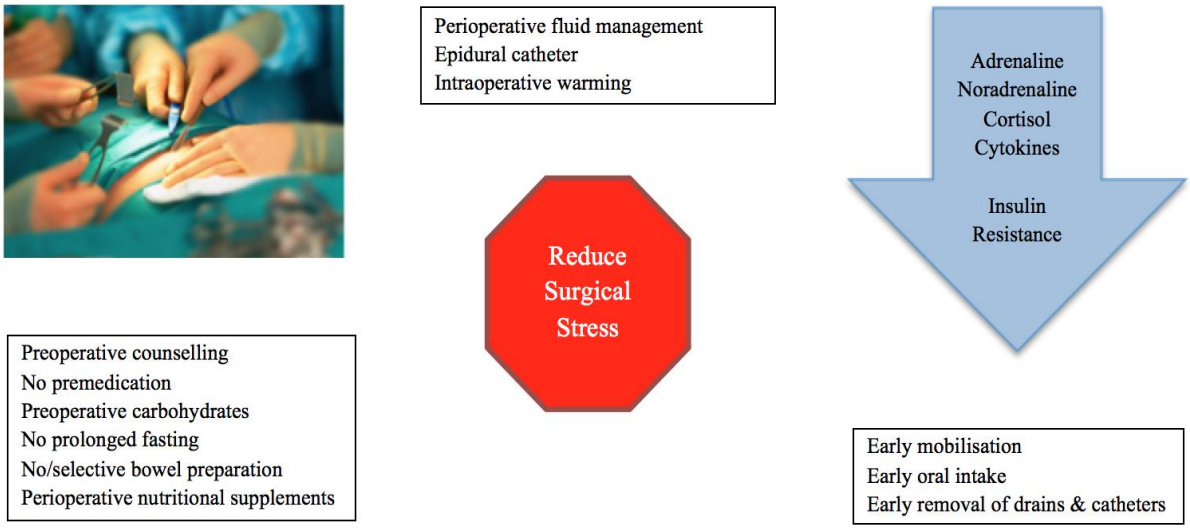
use of mechanical bowel preparation (MBP), stoma training and early mobilisation (in case of reconstruction of the pelvic floor).[149]

Despite the enhancements, the ERAS concept has been difficult to implement in clinical practice. Some of the interventions, such as avoiding drains and MBP in colonic surgery, early removal of nasogastric tubes, early mobilisation and oral feeding have to some extent been implemented in traditional care. The whole ERAS concept, however, is considered complex and resource-demanding. Moreover, the effect of each specific element on postoperative outcome remains unclear and studies published so far differ in adherence to the protocol and items used.

ERAS interventions

The aim of each key-component in the ERAS protocol is to reduce surgical stress. In this section the ERAS items used in the thesis are described from a rectal surgery perspective (*Figure 12*).

Figure 12. *ERAS-interventions used in the thesis*



Preoperative counselling

Preoperative information regarding the surgical and anaesthetic procedure and postoperative care can reduce fear and anxiety and thereby improve postoperative recovery.[162] Encouraging patients to fulfil different tasks after surgery and involving them in their own treatment may facilitate compliance to the ERAS protocol concerning perioperative feeding, early postoperatively mobilisation and pain control.

For patients planned for a temporary or permanent stoma, preoperative training with stoma devices and information from the ET have been shown to reduce delayed discharge from hospital due to the need for stoma training.[163]

Premedication

In general, preoperative medication with long-acting sedatives should be avoided as they may impair psychomotor function which can make immediate postoperative participation in the ERAS protocol difficult.[164] Although preoperative counselling may reduce fear, many patients waiting to undergo rectal cancer surgery still suffer from anxiety. Short-acting benzodiazepines can facilitate insertion of epidural and arterial catheters. However, this may not be recommended among the elderly, >60 years of age, due to an increased risk of postoperative cognitive dysfunction.[165]

No prolonged fasting and Preoperative carbohydrate supplementation

Traditionally, overnight fasting prior to surgery has been standard practice in order to reduce the risk of aspiration pneumonia on induction of general anaesthesia. However, more recent data has shown equal rates of aspiration and volumes of gastric content in traditionally fasted patients and those allowed intake of clear fluids until two hours before surgery.[166, 167]

During the night, when sleeping, a state of normal fasting occurs. Before breakfast, when there is a lack of circulating substrates and insulin levels are low, glycogenolysis and gluconeogenesis are induced in order to maintain normal blood glucose. However, when the fasting ends, i.e. breakfast, substrates are freely available, insulin levels increase rapidly and the body changes from a catabolic to an anabolic state.[166]

If surgery is performed after an overnight fast, surgical stress, with its hyper metabolic state and insulin resistance, becomes more pronounced. However, postoperative insulin resistance may be reduced by about 50% if patients are given oral carbohydrate treatment up until two hours before surgery (400 ml, 50 g carbohydrates)[166, 168, 169] and this may also improve control of postoperative blood glucose levels.[170] In addition, the treatment also results in reduced losses of nitrogen and proteins,[171] which results in improved maintenance of lean body mass[172] and muscle strength.[173] Furthermore, sense of hunger, thirst and anxiety before surgery are decreased.[166] Moreover, preoperative carbohydrate treatment has been shown to be an independent predictor of improved postoperative outcome.[78, 158, 168, 169, 174]

Bowel preparation

Mechanical bowel preparation (MBP) has been standard of care prior to colorectal surgery since the majority of postoperative abdominal infections are caused by colonic flora.[175] In Sweden, it is performed either with polyethylene glycol (PEG, Laxabon®, 4 litres the day before surgery) or oral sodium phosphate (NaP, Phosporal®, 45 ml x 2, the day before surgery).

When MBP is used prior to colonoscopy, adequate bowel cleansing is achieved in approximately 70% of patients. [176] However, many of patients (50-80%) need help with the administration regardless of the type of preparation.[177, 178] Even though NaP has been suggested to have a higher tolerability,[179] this regime is contraindicated in patients with heart and kidney failure due to the higher risk of electrolyte disturbances.[178]

In colonic surgery, MBP has been abandoned because studies have failed to reveal advantages compared with no cleansing.[180-182] It has been suggested that bowel preparation can lead to a more liquid content in the bowel, increasing the risk of spillage during surgery and thereby increasing the risk of intra-abdominal infections.[183, 184] Moreover, MBP causes fluid and electrolyte disorders,[185] a proposed risk-factor for AL,[102] where dehydration increases the need for intravenous infusions.[158] Furthermore, the procedure is stressful and has been shown to prolong postoperative ileus.[177]

In rectal cancer surgery, MBP is still being performed regularly.[149, 186] There are no proven benefits for mechanical cleansing in high anterior resection or in APE,[180, 181, 184, 187] but regarding LAR with diversion, further studies are required.

The GRECCAR III trial[188] compared MBP with no MBP in sphincter-preserving rectal cancer surgery where 80% of the patients had a temporary stoma. Significantly higher rates of overall and infectious morbidity were found in the non-MBP group as well as a trend towards a higher risk of AL and peritonitis. However, in this trial patients without MBP did not receive a rectal enema.

A Cochrane review by Guenaga *et al*. included a separate subgroup analysis for LAR (n=846) and showed a comparable risk for AL in those with and without MBP. They also compared MBP with rectal enema (n=195) in LAR, which yielded similar results in both groups.[181]

Due to inconclusive evidence, MBP is recommended in LAR with a diverting stoma according to the current ERAS-guidelines.[149]

Perioperative nutritional supplements

Fifty percent of patients planned for major gastrointestinal surgery suffer from weight loss and malnutrition,[189, 190] which have been shown to increase the risk of postoperative mortality and morbidity.[102, 191-194]

In rectal cancer, malnutrition can develop secondary to malignancy-related cachexia and intestinal obstruction caused by the tumour. Despite this, there is no consensus regarding type, regimen and duration of treatment with nutritional supplements as well as to whom it might be given.

There are different ways to measure malnutrition and it still remains unclear which screening instrument that best predicts the postoperative risk for nutrition-related complications.[189] One way to measure malnutrition is the Subjective Global Assessment (SGA) questionnaire, graded A-C, where grade A represents <5% weight loss, grade B 5-10% weight loss and grade C >10% weight loss during the last 6 months.[195]

If possible, enteral nutritional supplements should be given instead of parenteral supplements. Enteral nutrition maintains the intestinal mucosa structure and its barrier function. It is also less expensive and does not require vascular access with its attendant risks compared to parenteral administration.[189, 196] However, in certain situations, such as severe sepsis, malabsorption, intestinal obstruction or when multiple enterocutaneous fistulae are present, TPN might be the only way to improve nutritional status.[189]

So far, the major benefit of perioperative nutritional intervention has been seen in severely malnourished[191-194, 197] patients treated with perioperative TPN. However, administration of TPN in well-fed patients has been proven harmful with a higher rate of infectious complications.[191, 196, 197]

Preoperative treatment with ONS has not been proven to affect postoperative outcome[197-199] but some studies indicate a lower rate of weight loss and morbidity if given peri-[200] and postoperatively.[201, 202]

The ERAS protocol recommends ONS as a complement to normal oral intake to reach the recommended daily intake (RDI).[149] In cases of severe malnutrition, i.e. patients in the SGA-C category, nutritional support for 7-10 days pre- and postoperatively should be given.[203]

Immunonutrition

The amino acid arginine, naturally ingested, becomes deficient in plasma within hours after surgery.[204] Normally, arginine plays a role in nitric oxide (NO) production and T- lymphocyte function. As a consequence of arginine depletion, vasodilatation and microcirculation is impaired (due to absence of NO) and T-lymphocyte dysfunction is induced.[204] Glutamine, another amino acid, has been shown to aid preservation of small bowel function and the function of T-lymphocytes after major surgery[189] and omega-3 fatty acid reduces the inflammatory response.[205]

Oral nutritional treatment enriched with immune-modulating substrates such as arginine, glutamine and omega-3 fatty acid, called immune-enhancing diets (IE), has gained acceptance as a modulator of surgical outcome. Perioperative IE, even when given to well-fed patients, has been associated with improved postoperative outcome by reduction of infectious complications and LOS.[189, 197, 204, 206]

Still, there is no consensus regarding standard dosage of these immune modulating substrates, i.e. which component is the most important, and the timing of administration.[204, 205] Several ONS regimes contain immune modulating substrates in lower dosage and a recently published meta-analysis, found no benefit of IE over ONS in the preoperative setting.[205]

Perioperative fluid management

Several factors may influence fluid balance in rectal cancer surgery, such as preoperative dehydration caused by malnutrition and/or MBP, open surgery or excessive blood loss.

Additionally, intraoperative hypothermia, use of EDA and anaesthetic drugs can cause vasodilatation leading to haemodynamic instability.

Perioperative fluid overload can cause tissue oedema leading to impaired tissue-oxygenation and delayed recovery of gastrointestinal function.[207] A liberal fluid management, i.e. no restriction regarding intravenous infusions, is associated with an increased risk of postoperative complications and LOS after major abdominal surgery.[208-210] However, hypovolaemia may impair organ perfusion and oxygen delivery and thereby cause gastrointestinal dysfunction.[211]

Thus, individualised fluid replacement therapy to maintain the patient in a normovolaemic, balanced fluid state seems to be preferable.[209, 210, 212]

To optimise cardiac stroke volume, peroperative cardiac output can be measured with an oesophageal doppler, and the right amount of infusions and inotropic drugs can be titrated to enhance oxygen delivery. This goal-directed therapy has been suggested to improve postoperative outcome.[211] Yet, recently published trials have failed to show any benefit of this intervention versus restrictive fluid treatment conducted in an ERAS setting.[213] Moreover, a balanced fluid approach, resulting in a maintained postoperative body weight, has been found comparable to oesophageal doppler.[212]

Epidural catheter

Afferent nerves from the site of injury are of major importance for activation of the metabolic stress response.[214] A continuous EDA, inserted before initiation of surgery, blocks the afferent nerves and attenuates the increase in counter regulatory hormones and insulin resistance.[214]

Sufficient analgesia, to allow early mobilisation and oral feeding while avoiding opioids, is one of the corner stones in the ERAS concept. An EDA, kept in place for two to three days after surgery, reduces pulmonary complications, rate of postoperative ileus and allows early mobilisation.

In the era of minimal invasive surgery spinal anaesthesia may be sufficient with regard to pain-relief and has been shown to enhance gastrointestinal motility and reduce hospital stay compared to EDA.[215]

Intraoperative warming

Mild hypothermia (a 1-3°C fall in core temperature) is common during surgery. Operating rooms are cold while anaesthetic drugs interfere with normal thermoregulation.[216, 217] The skin is the dominant source of heat loss but evaporation from large skin incisions can also contribute to hypothermia.[217]

Even mild hypothermia increases the stress response and is associated with adverse outcomes after surgery.[216] Higher rates of wound infections, development of coagulopathy, cardiac events as well as a prolonged LOS have been reported.[217]

With administration of warm (37°C) intravenous fluids during surgery, use of laparoscopic technique when suitable and by covering the skin with forced-air heated warming blankets, the core temperature can be maintained and the stress response diminished.[149, 217]

Early mobilisation

After surgery, bed-rest increases insulin resistance,[218] muscle loss and impairs pulmonary function.[151] Early mobilisation may decrease the risk for thromboembolic events and pulmonary complications.[151] Thus, mobilisation for more than two hours the day of surgery and thereafter more than six hours per day until discharge are warranted according to the ERAS-protocol.[149] However, patients with flap reconstruction of the pelvic floor are excluded, as they require a special physiotherapy regime.

Early oral intake

Oral intake, within the first 24 hours after surgery, may decrease postoperative insulin resistance[218] and nitrogen losses.[170] Improved surgical outcome without any differences in rate of AL has been reported with this regime.[219, 220]

Early removal of drains and catheters

By early removal and avoidance of unnecessary drains, compliance with early oral intake and mobilisation can be improved.

Nasogastric decompression increases time to first bowel movement, LOS, discomfort for the patients and is combined with a higher risk for respiratory infections.[221, 222] The routine use of nasogastric tubes should therefore be avoided. If inserted during surgery, removal should take place before reversal of anaesthesia.[149]

Traditionally, a pelvic drain is placed near the rectal anastomosis to evacuate blood and serous collection to prevent AL. A Cochrane review has failed to show any benefit of pelvic drainage after elective rectal surgery and therefore, this routine is not recommended.[149, 223]

If EDA is used in open rectal cancer surgery, a urinary bladder catheter - placed through the urethra or suprapubic - is inserted to avoid urinary retention. In patients without risk-factors for prolonged urinary retention, early removal (day one after surgery) seems not to increase the risk of urinary retention, even if the EDA is left in place.[224] Moreover, a reduction in urinary tract infections and LOS has been reported.[224] When risk-factors for urinary retention are present, a suprapubic catheter is preferable. Compared with transurethral catheterisation, the suprapubic route is associated with less urinary tract infections and patient discomfort.[225]

RATIONALE FOR FURTHER RESEARCH

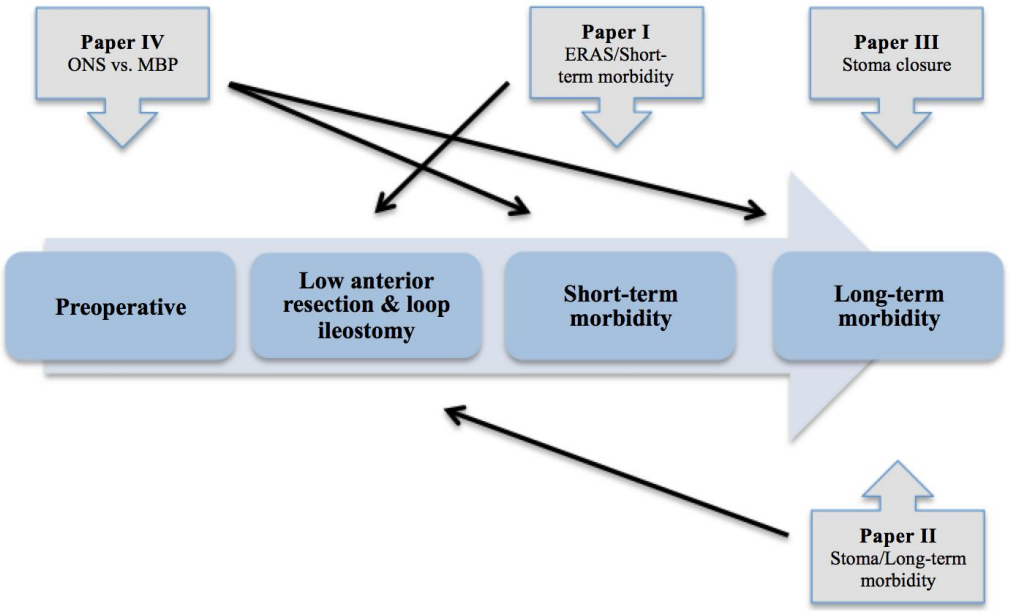
During the last decades, two main interventions aiming to prevent or reduce morbidity in rectal cancer surgery have been introduced; the use of a diverting loop ileostomy in LAR and perioperative fast track programs, such as ERAS.

Even though a diverting stoma has been reported to decrease clinical anastomotic leakage, no dramatic change in leakage rate over time has been noticed parallel with the increased stoma use. Moreover, stoma-related complications are added to the existing morbidity after LAR.

Previous studies on AL and diverting stomas have been designed in a traditional perioperative care setting and the main focus has been on short-term morbidity.

It is still unknown if ERAS (known to improve outcome after colorectal cancer surgery), influences the effects of a diverting stoma in LAR and if long-term results are affected by a temporary diversion. Furthermore, it is unclear if the type of anastomosis affects the incidence of SBO, one of the major complications after stoma closure.

Despite unclear evidence, MBP is often used in rectal cancer surgery due to the colonic diversion. This type of bowel cleansing can cause fluid shifts and electrolyte imbalance, suggested risk factors for AL and a worse postoperative outcome. If ONS can be an alternative to traditional MBP, the negative side effects with this procedure may be avoided and perhaps the postoperative course could be improved further.



AIMS OF THE THESIS

The ***overall*** aim of this thesis was to optimise and evaluate the treatment for patients with a diverting loop ileostomy in rectal cancer surgery.

The ***specific*** aims were to evaluate:

- Short-term morbidity after low anterior resection in relation to a diverting loop ileostomy and ERAS

  (Paper I)

- Long-term morbidity after low anterior resection in relation to a diverting loop ileostomy

  (Paper II)

- Postoperative complications after closure of a diverting loop ileostomy in relation to type of anastomosis.

  (Paper III)

- If bowel preparation can be safely achieved by nutritional supplements and if this routine affects postoperative morbidity, nutritional and physiological status in patients operated on for rectal cancer

  (Paper IV)

PATIENTS & METHODS

The regional ethics committee approved each of the four studies. A summary of patients and methods, paper I-IV, is shown in *Table 2.*

Table 2. *Summary of Patients and Methods, paper I-IV*

Paper	Design	Number of patients	Data collected	Exposure/Outcome
I	Prospective cohort study	287	Jan 2002-Dec 2011	Diverting loop ileostomy or not at LAR and ERAS / Short-term morbidity
II	Retrospective cohort study	287	Jan 2002-Dec 2011	Diverting loop ileostomy or not at LAR / Long-term morbidity
III	Retrospective cohort study	351	Oct 1999-Dec 2006	Type of anastomosis at closure of diverting loop ileostomy / Postoperative complications
IV	Randomised controlled trial	29	June 2008-Feb 2013	ONS or PEG before rectal cancer surgery / Bowel cleansing, nutritional and physiological outcome and short-term morbidity

PAPER I

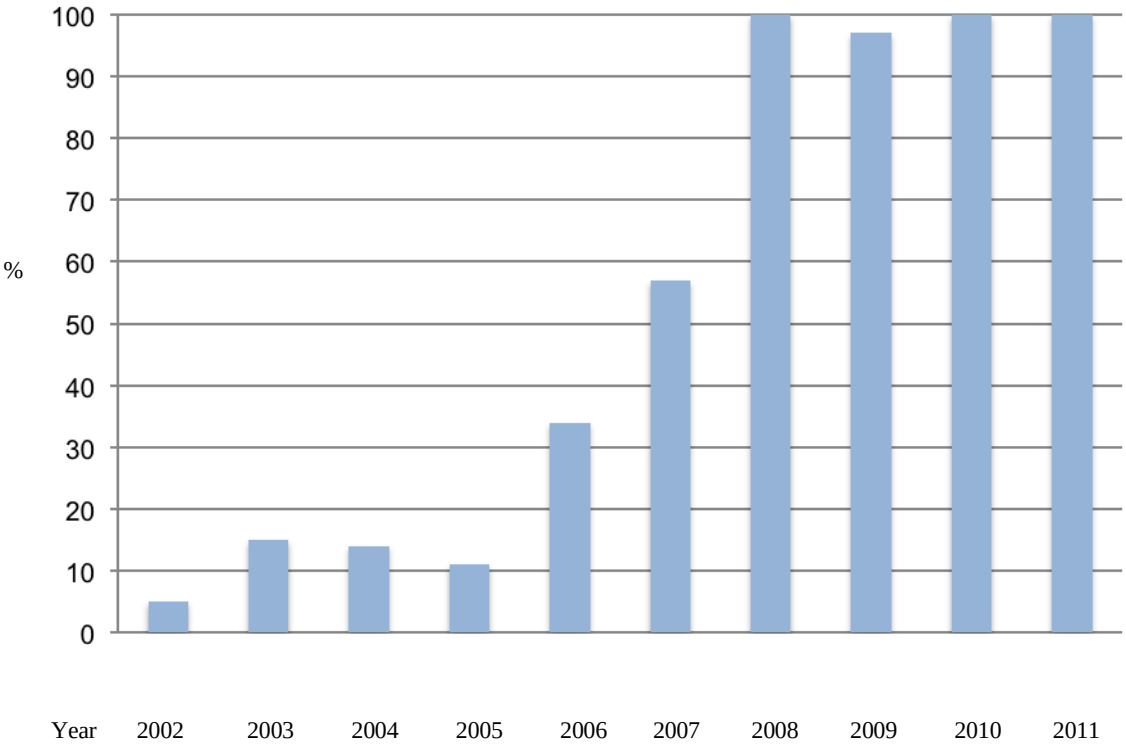
A prospective cohort study was conducted. The cohort consisted of all patients who underwent LAR (complete TME) for rectal cancer at Ersta Hospital, between 8th of January 2002 and 27th of December 2011. All patients were treated according to the ERAS protocol and were prospectively registered in the ERAS database. There were no exclusion criteria.

Between 2002-2006, 15% of the patients included had a diverting loop ileostomy during LAR, compared to 91% during 2007-2011 (*Figure 13*). Except for the increased use of

diverting loop ileostomies, there were no other major differences in surgical techniques, perioperative care or participating surgeons during the study period.

Data on patient characteristics, operative and postoperative outcomes were collected from the ERAS database. The Clavien-Dindo classification of postoperative morbidity was performed retrospectively.

Figure 13. *Use of diverting loop ileostomy in LAR, 2002-2011, paper I and II*



Definitions

LAR was defined as a complete TME according to the medical records.

Postoperative morbidity was classified according to the Clavien-Dindo classification,[153] (*Table 3*). The category "Other" included renal failure and uncontrolled hyperglycaemia.

Table 3. *The Clavien-Dindo classification of postoperative morbidity*

Infectious	Pneumonia	
	Septicaemia	
	Other	
Cardio/ Pulmonary	Acute cardiac infarction	
	Congestive heart failure	
	Cardiac arrhythmia	
	Deep venous thrombosis	
	Other	
Neurological	Cerebral vascular injury	
	Other	
Surgical	Wound infection	
	Intraabdominal infection	
	Wound dehiscence	
	Bleeding	
	AL	
	Stoma problems	
	Urinary catheter in situ on discharge from hospital	
	Other	
Other		
Grade 1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: antiemetics, antipyretics, analgetics, diuretics and electrolyte supplementation and physiotherapy. This grade also includes wound infections opened at the bedside.	
Grade 2	Complications requiring pharmacological treatment with drugs other than those allowed for grade I. Blood transfusions and total parenteral nutrition are also included.	
Grade 3	Complications requiring surgical, endoscopic or radiological intervention.	
	Grade 3a	Intervention not under general anaesthesia
	Grade 3b	Intervention under general anaesthesia
Grade 4	Life-threatening complication requiring ICU-management.	
	Grade 4a	Single organ dysfunction
	Grade 4b	Multi-organ dysfunction
Grade 5	Death of the patient.	

Clinical AL was defined as symptoms (abdominal pain with elevated CRP, peritonitis, faeces/air to vagina or urinary bladder, faeces/pus from abdominal drainage, pelvic abscess) in combination with radiological or operative findings confirming the diagnosis.

Moreover AL was *graded A-C*, according to the classification proposed by the International Study Group for Rectal Cancer,[101] table 1. Grade A; AL results in no change in patients'

management, grade B; AL requires active therapeutic intervention but no relaparotomy and grade C; AL requires relaparotomy.

Acute reoperations included conditions requiring general anaesthesia; relaparotomy, endoscopic evaluation of neorectum and pelvic drainage.

The *Recovery items* used in the ERAS database were assessed on the first postoperative day when the patient:

- Ate full meals of *solid food*
- Had no intravenous infusion, *drip down*
- Was *out of bed >6 hours*
- EDA catheter was removed, *EDA stop*
- Urinary catheter was removed, (in paper I named *KAD drawn)*
- Had their *first flatus*
- Had their *first stool*
- *Fulfilled all* of the included recovery items

To measure *ERAS compliance,* several key components in the ERAS protocol were analysed. The items were divided into pre-and postoperative items and compliance rate was calculated in percent.

Preoperative ERAS items (compliance if "yes"):

- Preadmission counselling
- Preoperative bowel preparation
- Carbohydrate drink
- No premedication
- EDA
- Intraoperative warming (using a Bairhugger® blanket)
- Oral fluids on the day of surgery
- Less than 3500 ml of intravenous fluids on the day of surgery

Postoperative ERAS items measured at postoperative day 1 (compliance if "yes"):

- No intravenous infusion
- Out of bed >6 hours
- Intake of >600 ml of ONS
- Intake of solid food

Exposure was a diverting loop ileostomy or not at LAR. *Primary outcome* was postoperative morbidity, including AL, within 30 days after surgery and *secondary outcomes* were postoperative recovery and LOS.

PAPER II

A retrospective cohort study was conducted. The cohort was the same as described in Paper I, i.e. all patients operated on for LAR, with or without a diverting loop ileostomy at Ersta Hospital, Sweden. The study period was between 8th of January 2002 and 27th of December 2011 and all patients were prospectively registered in the ERAS database.

All patients had repeated follow-up (4-6 weeks, then one, two and three years) after surgery with clinical examination, pelvic MRI and CT scan of the thorax and abdomen according to an oncological protocol. In addition, before closure of the stoma, a CT scan with rectal contrast and a flexible sigmoideoscopy to assess integrity of the anastomosis was performed.

Data on long-term morbidity and permanent stoma was collected from medical records. Follow-up time was until 3 years after LAR.

Definitions

Long-term morbidity was defined as late AL, *late readmissions* (>30 days until 3 years after LAR, due to late AL, stoma problems and/or ileus), postoperative complications after stoma closure, oncological outcome and permanent stoma.

Late AL was leakage occurring more than 30 days until 3 years after LAR. Symptoms (abdominal pain with elevated CRP, air/faeces from bladder or vagina and abdominal abscess) in combination with radiology were mandatory.

A stoma was considered *permanent* when a decision not to reverse the stoma was documented in the medical records. This included stomas created at LAR, stomas created later on and any *secondary stomas* constructed due to AL.

Repeated surgery was planned surgery for stoma closure and unplanned surgery for AL, stoma formation or ileus, 30 days to 3 years after LAR.

In the variable *LOS+*, all LOS (from 30 days to 3 years after LAR) due to late readmissions, formation of first or secondary stomas and stoma closure were combined.

Exposure was a diverting loop ileostomy, or not, at LAR. *Primary outcome* was long-term morbidity within 3 years after surgery and *secondary outcome* was LOS+.

PAPER III

A retrospective cohort study was conducted. The cohort consisted of all patients operated on for closure of a diverting loop ileostomy at Uppsala University Hospital, Karolinska University Hospital, Huddinge and Karlstad Central Hospital, between 1st of October 1999 and 31th of December 2006. Exclusion criteria were stoma constructed during cytoreductive surgery and incomplete available information in the medical record (14 patients).

Data regarding demography, previous surgery, type of anastomosis, postoperative complications within 30 days after surgery and LOS were collected from medical records.

Definitions

Type of anastomosis for closure of the diverting loop ileostomy was divided into two groups, hand-sewn (HS) and stapled (S) anastomosis. The HS-group was also divided into HS with or without a small bowel resection. Surgeon preference and local traditions dictated the choice of anastomosis.

Previous abdominal surgery was defined as at least one previous abdominal surgical procedure, stoma construction not included.

The *surgeon experience* was divided into four categories, A-D. Grade A represent Surgical registrar, B; General surgeon, C; Senior registrar (colorectal surgery) and D; Consultant surgeon (subspecialist accreditation in colorectal surgery).

Postoperative complications were divided into SBO, AL and need of acute reoperation.

SBO was defined as symptoms (nausea, vomiting, abdominal pain and absence of bowel movements, either gas or stool) in combination with radiology - plain abdominal x-ray or abdominal CT scan followed by water-soluble contrast.

AL was either confirmed with radiology and/or intraoperative findings.

Exposure was type of anastomosis during the closure procedure and *outcome* was postoperative complication within 30 days after surgery.

PAPER IV

A single-centre randomised controlled trial was conducted at Ersta Hospital, between 11th of June 2008 and 5th of February 2013 (ClinicalTrials.gov number, NCT00687570).

All patients planned for rectal cancer surgery, without severe dementia, distant metastases at diagnosis or symptoms of acute intestinal obstruction were asked to participate. Informed consent was mandatory.

Randomisation took place 4-6 weeks before surgery and was stratified for type of surgical procedure (open/laparoscopic) and the absence or presence of tumour-induced stricture. Sealed envelopes were used with information on group allocation. Patients were randomised to one of the two treatments arms, Oral Nutritional Supplements (ONS)-group or Polyethylene Glycol (PEG)-group.

ONS-group

From randomisation until one week before surgery 50% of the RDI of energy (30 kcal/kg/day) was provided as ONS (Fresubin®, residue free, 300 kcal/200 ml). The last week before surgery, ONS provided the entire RDI of energy ensuring a residue free diet. The evening before and the day of surgery two rectal enemas (Klyx®, 240 ml) were given and no further MBP was used.

PEG-group

Patients in this group had no change to their normal diet during the same period. The day before surgery MBP was given with 4 L of PEG (Laxabon®).

Prior to randomisation, 1 day before surgery, 3 days and 4 weeks after surgery, measurements of nutritional status (SGA, weight, BMI, upper arm circumference, percent total body and subcutaneous fat) and physiological tests (spirometry and handgrip strength) were performed and quality of life was assessed (European Organisation for Research and Treatment of Cancer (EORTC QLQ-30)[226] and Abdominal Surgery Impact Scale (ASIS)).[227]

Physical activity was determined with a pedometer, three weeks before until five days after surgery and patients also registered their daily intake of calories from randomisation to the day before surgery (one weekday and one day during the weekend).

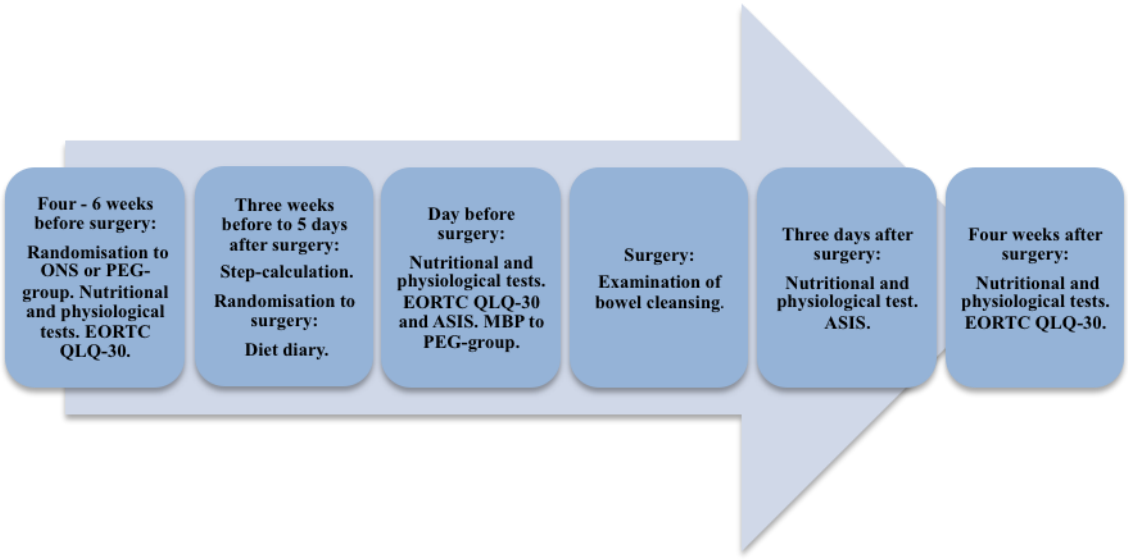
Peroperatively, surgeons examined the degree of colonic and rectal cleansing according to a standardised protocol (“empty”, “half full”, “full”).

All patients were treated according to the ERAS protocol and data on patients’ characteristics and postoperative outcome were collected from the ERAS database. Postoperative morbidity was classified according to Clavien-Dindo (*Table 2*) and the same recovery items as in Paper I were used.

A flow-chart of the different steps in the study is shown in *Figure 14*.

Exposure was ONS without MBP or preoperative MBP with PEG before rectal cancer surgery. *Outcome measures* were peroperative degree of bowel cleansing, perioperative nutritional and physiological outcome and postoperative morbidity.

Figure 14. *Flow-chart, paper IV*



STATISTICAL ANALYSES, PAPER I-IV

All values are presented as mean±SD, median with range and OR with 95% CI, where appropriate. For comparison of categorical variables, Pearson's X^2 test or Fisher's exact test was used. A two-tailed t-test or the Mann-Whitney U-test was used for comparison of continuous variables.

Baseline characteristics were analysed to determine the unadjusted association between the univariate predictors and the outcome variables clinical AL (Paper I), late AL and permanent stoma (Paper II) and postoperative complication (Paper III). A p-value <0.15 was considered relevant for the univariate predictor to be included in the multivariate analysis.

Multiple logistic regression was performed to determine the adjusted association between the different predictors and the outcomes. In Paper I and II the variables included in the multivariate analysis were age, BMI, gender, ASA score, preoperative radiotherapy and chemotherapy, stage of the tumour, type of anastomosis and diverting loop ileostomy at LAR. In Paper III, adjusting variables were gender, ASA score, BMI, previous abdominal surgery, surgeon experience and the reason for diverting loop ileostomy.

For calculation of repeated measurements in Paper IV (i.e. physiological and nutritional data) one-way ANOVA and paired t-tests were conducted.

A p-value <0.05 was considered statistically significant.

Power calculation

In Paper IV, the study hypothesis was that 25% of the patients in the ONS group would lose two kilograms in four weeks preoperatively, compared to 75% in the PEG-group. With 80% power and a one-sided 95% CI, the number of patients needed in each group for detecting a difference in preoperative weight loss was 18 patients. The data were analysed according to the intention-to-treat principle.

All statistical analyses were calculated with Stata® version 10.0 (StataCorp, College Station, Texas) in Paper I-II and IV.

In Paper III, all statistical analyses were made using Statistica® software (Stat soft, Tusla, USA).

RESULTS

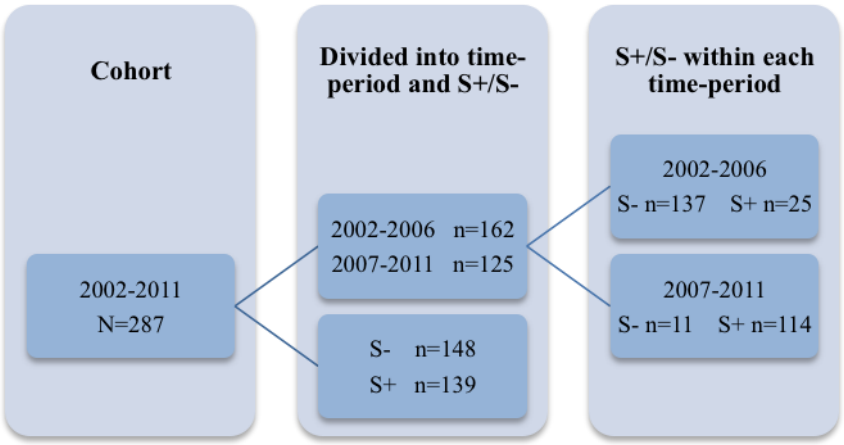
PAPER I

Demographic and preoperative data

During the study period 2002-2011, a total of 287 patients underwent LAR for rectal cancer, 139 with a diverting loop ileostomy (S+) and 148 patients without a diversion (S-).

Between 2002-2006, 162 patients underwent LAR, 15% with a diverting loop ileostomy. During 2007-2011, 125 patients underwent surgery, 91% with a diverting loop ileostomy. The cohort was divided into S+ and S- and into groups depending on the time period (2002-2006 and 2007-2011) as shown in *Figure 16.*

Figure 16. *Cohort divided in S+/S- and time-periods*



The groups, S+ and S-, were comparable regarding demographic data, preoperative MBP, tumour level and stage of the tumour (*Table 4*).

In each group, 113 patients (81% in S+ and 76% in S-, P=0.306) had preoperative RT. Nineteen (14%) patients received preoperative chemotherapy in the S+ compared to none in the S-, P<0.001.

Table 4. *Patient characteristics and preoperative data divided in S-/S+ and time-periods*

	S- n=148	S+ n=139	p-value	2002-2006 n=162	2007-2011 n=125	p-value
Age (median)	65(29-86)	62(30-84)	0.097[2]	64(29-86)	63(30-84)	0.484[2]
Gender M/F	85/63 (57/43)	87/52 (63/37)	0.373[1]	93/69 (57/43)	79/46 (63/37)	0.321[1]
ASA I/II/III	40(27) 99(67) 9(6)	32(23) 94(68) 13(9)	0.481[1]	44(27) 106(66) 12(7)	28(22) 87(70) 10(8)	0.653[1]
BMI (median)	25(19-42)	25(16-35)	0.554[2]	25(19-42)	25(16-35)	0.868[2]
Preoperative MBP	130(89)	117(84)	0.227[1]	142(89)	103(82)	0.093[1]
Preoperative RT	113(76)	113(81)	0.306[1]	121(75)	103(84)	0.056[1]
Preoperative chemotherapy	0	19(14)	<0.001[1]	2(1)	17(14)	<0.001[1]
Tumour level (from anal verge)						
Group 0=0-5 cm Group 1=6-10 Group 2≥11 cm	4(3) 89(61) 53(36)	3(2) 102(73) 34(25)	0.082[1]	4(2) 100(63) 56(35)	3(2) 91(73) 31(25)	0.173[1]
Stage I/II/III/IV	50(34) 47(32) 44(30) 6(4)	46(33) 33(24) 55(40) 5(3)	0.295[1]	59(37) 43(27) 53(33) 6(3)	37(30) 37(30) 46(37) 5(3)	0.666[1]

Percentage in brackets unless indicated otherwise. [1] Pearson's X^2 test, [2] t-test

In concordance, when the two time-periods (2002-2006 and 2007-2011) were compared regarding demography and preoperative data, preoperative chemotherapy was the only significant difference between the groups (*Table 4*).

In the following, only S+ and S- are compared.

Operative data

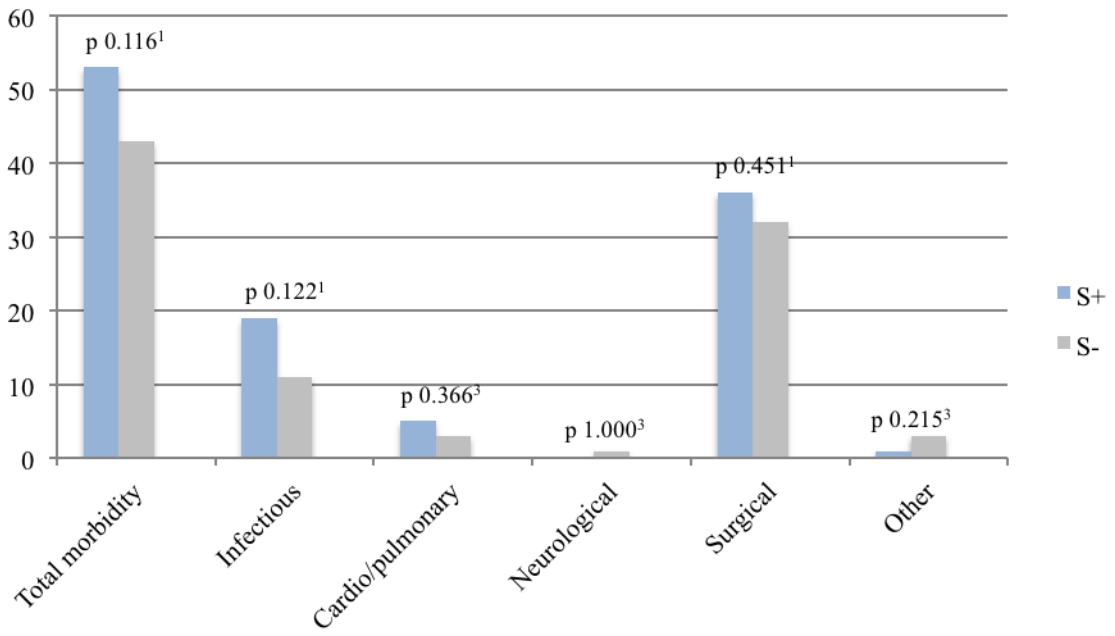
Two hundred eighty three out of 287 operations were performed as open procedures, while four patients underwent a laparoscopic resection. End-to-side anastomosis was most common and performed in 254 patients (S+ 99%, S- 79%, P<0.001). The level of anastomosis, from the anal verge, was in median 4 cm in both groups, P=0.200.

Operation time was longer in the S+ group compared to S- group (median 222 and 185 minutes, respectively; P<0.001).

Postoperative data

Postoperative morbidity occurred in 48% of all patients, 53% in S+ and 43% in S- (P=0.116) and did not differ between the groups (*Figure 17).*

Figure 17. *Postoperative morbidity classified according to Clavien-Dindo*



Number presented as percentage. [1] Pearson's X^2 test, [3] Fisher's exact test

Pneumonia and urinary tract infection were the most common infectious complications in both groups.

The frequency of surgical complications and acute reoperations are shown in *Table 5*. There was no significant difference in the frequency of clinical AL in the univariate analysis, 19% (27 patients) in S+ and 24% (36 patients) in S- (P=0.316) or in the multivariate analysis (OR 0.64; 95% CI 0.34-1.19).

The need for acute relaparotomy, due to AL and other causes, did not differ between the groups (S+ 11 patients, S- 22 patients, P=0.065).

Twenty patients underwent reoperation due to grade B and C AL in the S+ group compared with 31 patients in S- (P=0.146). Acute relaparotomy due to AL, grade C, was significantly more common in the S- group (21/148 or 14% vs. 3/139 or 2%, P<0.001)

***Table 5**. Surgical morbidity and acute reoperations*

	S+ n=139	S- n=148	p-value
Surgical morbidity	50(36)	47(32)	0.451[1]
Clinical AL	27(19)	36(24)	0.316[1]
Ileus	3	1	
Hematoma		1	
Intra abdominal abscess		1	
KAD at discharge	4	6	
Wound infection	2	2	
Bleeding	1		
High stoma flow	9		
Wound dehiscence	3		
Ischemia of a part of the stomach	1		
Acute relaparotomy	11(8)	22(15)	0.065[1]
Acute relaparotomy, AL (Grade C)	3(2)	21(14)	<0.001[1]
Acute reoperations, AL (Grade B, C)	20(14)	31(21)	0.146[1]

Percentage in brackets. [1] Pearson's X^2 test

Time until patients were mobilised (out of bed >6 hours), had no intravenous infusion and fulfilled all discharge criteria were significantly longer among S+ compared to S-, while other variables measured in postoperative recovery were comparable (*Table 6*).

Total compliance with pre- and postoperative ERAS items was 65% in the entire cohort, slightly higher in S+ (69%) compared to S- (61%), P<0.001. Preoperative compliance was also higher in S+ (77%) vs. S- (68%), P<0.001, whereas postoperative compliance did not differ (S+ 46%, S- 47%, P=0.994). In a multivariate analysis, compliance to ERAS did not influence the frequency of clinical AL.

There was no difference in readmissions (S+ 17%, S- 14%, P=0.472) within 30 days after surgery or in LOS (in median (range), S+ 11(4-53) days and S- 9(3-68), p NS) between the groups.

Table 6. *Postoperative recovery.*

	S+ n=139	S- n=148	p-value
Solid food	1(0-14)	1(0-11)	0.162[4]
Drip down	3(0-48)	2(0-42)	0.038[4]
Out of bed >6 h	3(1-28), mean 6 days	3(1-68), mean 4 days	0.006[4]
EDA stop	4(1-17)	4(2-27)	0.418[4]
Urinary catheter removed	5(2-23)	5(2-29)	0.865[4]
First flatus	2(0-13)	2(0-16)	0.591[4]
First stool	3(0-13)	3(1-19)	0.125[4]
Fulfil all	8(2-52)	5(2-68)	<0.001[4]

All values are presented as median (range) in days after surgery. [4] Wilcoxon rank sum test

Time-periods

All calculations were performed between the two time-periods, 2002-2006 and 2007-2011. In accordance with the above results, preoperative chemotherapy, operation time, type of anastomosis and compliance to the ERAS protocol were the only variables that differed significantly between the two periods.

Moreover, when the 36 patients that differed in surgical approach within each time-period (i.e. 25 patients with a diverting loop ileostomy 2002-2006 and 11 patients without a diverting loop ileostomy 2007-2011) were excluded, the same results were found.

PAPER II

For ***demography, preoperative*** and ***operative data*** see Paper I, *Table 4*. The cohort consisted of 287 patients, 139 in S+ and 148 in S-, all operated on with LAR for rectal cancer.

Long-term morbidity

A total of 17 patients (6%) developed late AL in the entire cohort, with no difference between the groups (S+ 6%, S- 5%, P=0.701). In a multivariate analysis, a diverting loop ileostomy at LAR did not reduce the risk for late AL (OR 0.84; 95% CI 0.28-2.46).

The median time to diagnosis of late AL was 83 (range 34-1021) days in S+ compared to 184 (34-802) days in S- (P=0.531). Of the 17 patients with late AL, 14 were diagnosed within the first year after LAR.

The frequency of late readmission due to AL, stoma problems or ileus was 16% (22 patients) in S+ and 15% (22 patients) in S-, P=0.808. AL and ileus were the most common cause for late readmission in both groups (*Table 7*).

LOS was significantly longer in S+ compared to S-, (mean LOS 7 and 4 days), respectively, P<0.001 (15 vs. 10 days if LOS within 30 days after LAR was included, P<0.001).

Table 7. *Late readmissions*

	S+ n=139	S- n=148	p-value
Late readmission	22(16)	22(15)	0.808[1]
Anastomotic leakage	8(36)	17(77)	0.085[1]
Ileus	9(41)	5(23)	0.224[1]
High stoma flow	5(23)	0	0.020[1]

[1] Pearson's X^2 test

The overall frequency of postoperative complications after stoma closure was 9% (SBO; 5 patients, bleeding from anastomosis; 2 patients, wound dehiscence; 1 patient). There was no AL from the new anastomosis and no postoperative mortality.

Total recurrence (systemic and loco-regional) and cancer specific death within 3 years after LAR did not differ between S+ and S-, 22% vs. 24% (P=0.786) and 10% vs. 8% (P=0.709), respectively. One patient in S+ had local recurrence compared to 3 patients in S-. AL did not increase the risk for total recurrence or cancer-specific death.

Twenty-three patients (17%) in S+ and 20 patients (14%) in S- had a permanent stoma during the 3-year follow up (P=0.742), (*Table 5*). In S+, in presence of AL, 47% had a permanent stoma compared to 39% in S- (NS) and in a multivariate analysis, AL was the only factor increasing the risk for a permanent stoma (OR 20.98; 95% CI 8.55-51.43).

Repeated surgery and permanent stoma

In the S+ group, 86% (120/139 patients) had their stoma closed. In the S- group, 35 patients (24%) had a diverting stoma constructed after LAR, 86% (31/35) due to AL. Forty-nine % (17/35) of those were closed (P<0.001) compared to closure of S+ (*Table 8*).

Table 8. *Construction and closure of primary/first stoma and permanent stoma*

	S+ n=139	S- n=148	p-value
Primary stoma at LAR	139	0	
First stoma not at LAR	0	35(24)	
Closure of primary/first stoma	120(86)	17(49)	<0.001[1]
Secondary stoma	4(3)	2(1)	
Closure of secondary stoma	0	0	
Permanent stoma	23(17)	20(14)	0.472[1]

Percentages shown in brackets. [1] Pearson's X^2 test

In total, 137 patients in the cohort underwent stoma closure. In patients with AL where the diverting stoma were reversed (n=37), 5 patients required a secondary permanent stoma (14%). In addition, in patients without a diagnosed anastomotic leakage at the time of reversal (n=100), only one patient (1%) required a secondary permanent stoma (due to an AL diagnosed 2 years later).

Time from construction to stoma closure was significantly shorter in S+; 188 (16-992) days in median, compared to 271 (123-482) days in S- (P=0.027). In patients with AL, time from construction to closure was similar between the groups (S+ 268 (137-814), S- 276 (151-482), days in median).

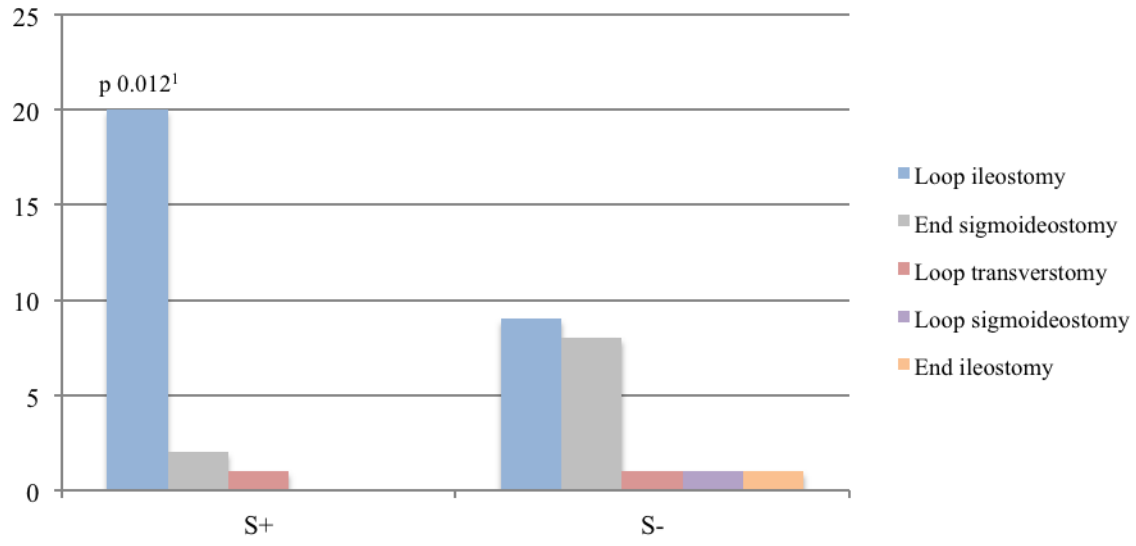
The median number of further operations including stoma closure was 1 (range 0-2) in the S+ group compared with 0 (0-3) in the S- group, P<0.001.

Type of permanent stoma

Sixty-seven % (29/43) of the permanent stomas were loop ileostomies (*Figure 18*). In S+, 87% were loop ileostomies compared with 45% in S- (P=0.012). Two patients in S+ had an end sigmoideostomy compared to eight patients in S- (P=0.105).

AL was the major cause for a permanent stoma in both groups (S+ 74% and S- 85%; P=NS).

Figure 18. *Type of permanent stoma*



[1] Pearson's X^2 test

PAPER III

Demography and preoperative data

A total of 351 patients were included; 219 in the HS-group (70 patients with a small bowel resection, 149 without) and 132 in the S-group.

There were no differences between groups regarding gender, age, BMI, ASA classification or previous abdominal surgery (*Table 9*).

Colorectal cancer and inflammatory bowel disease were the main reasons for having a diverting loop ileostomy, 55% and 25%, respectively, with no difference between the groups.

Table 9. *Patients' characteristics*

Type of anastomosis	Hand-sewn (HS) n=219	Stapled (S) n=132	p-value
Gender (M/F, (%))	126/93 (58/42)	76/56 (58/42)	0.994[1]
Age (median)	58	58	0.536[2]
ASA (median, (range))	2(1-4)	2(1-3)	0.289[2]
BMI (median, (range))	25(14-39)	25(16-38)	0.831[2]
Previous abdominal surgery (%)	118(54)	70(53)	0.877[1]

[1] Pearson's X^2 test, [2] t-test

Operative data

Operation time was in median (range), 80 (20-470) minutes in the HS-group compared to 70 (25-335) in the S-group, P=0.015.

A surgical registrar was the operating surgeon in 117 (33%) of the closure procedures and a consultant colorectal surgeon performed 91 (26%) operations.

Postoperative data

SBO occurred among 44 patients (13%) in the entire cohort of which 16 patients (36%) required reoperation. In the HS-group, the frequency of SBO was 16% compared with 8% in the S-group, P=0.029 (univariate analysis). In a multivariate analysis, there was a 56% risk reduction for SBO if a stapled anastomosis was constructed (OR 0.44; 95% CI 0.21-0.93).

There was no difference in the number of reoperations due to SBO between the groups (P=0.309) or in the frequency of AL (seven patients in the HS-group vs. three patients in the S-group, P=0.614).

LOS was significantly longer in the HS-group (median 5.5 (range 1-194) days) compared with the S-group (median 4 (range 1-72) days; P<0.001).

PAPER IV

Demography, preoperative and operative data

A total of 29 patients were randomised and included in the study, 13 patients in the ONS-group and 16 patients in the PEG-group. The median time from randomisation to surgery was five weeks (range 1-11) and three weeks (range 2-11) in the ONS and PEG groups respectively, P=0.142.

All of the patients were classified as SGA-A (i.e. not malnourished). The groups were comparable regarding demography, co-morbidity, neoadjuvant treatment, tumour stage and type of surgical procedure (*Table 10*).

During the time period from inclusion to the day before surgery, the ONS-group had a higher preoperative caloric intake compared to the PEG-group (median 34 (24-65) vs. 26 (14-37) kcal/kg/day, P=0.005) and significantly more patients in the ONS-group reached their RDI; 77% versus 19% in the PEG-group (P=0.003).

Grade of bowel cleansing differed between the groups. In the ascending colon, seven patients in the ONS-group compared with 13 patients in the PEG-group had an empty bowel (P=0.015). In the transverse and the descending colon, six patients in the ONS group compared with 15 patients in the PEG group had an empty bowel (P=0.003). No difference was seen in the degree of cleansing of the sigmoid and rectum, (P=0.444) and spillage of faecal content when constructing the anastomosis (P=0.481).

Postoperative data

Postoperative morbidity was comparable, 23% (three patients) in the ONS-group and 38% (six patients) in the PEG-group, P=0.454.

Infectious morbidity in the form of urinary tract infection was found in two patients in the ONS group and four patients in PEG-group (P=0.663).

Frequency of surgical morbidity (i.e. some patients had more than one complication) was 8% in the ONS-group and 31% in the PEG-group (P=0.183) (see *Figure 19*).

There was no difference in the recovery items measured.

Table 10. *Patient characteristics and preoperative data*

	ONS n=13	PEG n=16	p-value
Age: years ± SD	66.2 ± 9.2	62.4 ± 9.6	0.292[4]
Gender: Male/Female	8/5	10/6	0.958[1]
BMI ± SD	24.9 ± 4.2	26.6 ± 3.4	0.091[4]
SGA-A: n (%)	13(100)	16(100)	
ASA			1.000[3]
ASA 1: n	1	1	
ASA 2: n	12	14	
ASA 3: n	0	1	
Smoker: n	0	0	
Comorbidity: n			1.000[3]
Heart failure	0	0	
Hypertension	6	7	
Pulmonary dysfunction	0	0	
Diabetes	0	0	
Cortisone treatment	0	0	
Neoadjuvant treatment: n	10	13	1.000[3]
Radiotherapy: n	9	12	
Chemo/Radiotherapy: n	1	1	
Stage: n			0.207[3]
T-stage I	5	6	
T-stage II	5	2	
T-stage III	3	8	
T-stage IV	0	0	
Tumor level: median (range)	10(3-18)	9(6-15)	0.707[4]
Procedure: n			0.553[3]
LAR with loop ileostomy	7	12	
APR	2	2	
AR	4	2	
Stoma: n (%)	9(69)	14(88)	0.228[3]
Laparoscopic/open	1/12	3/13	0.606[3]

[1] Pearson's X^2 test, [3] Fisher's exact test, [4] Wilcoxon rank sum test

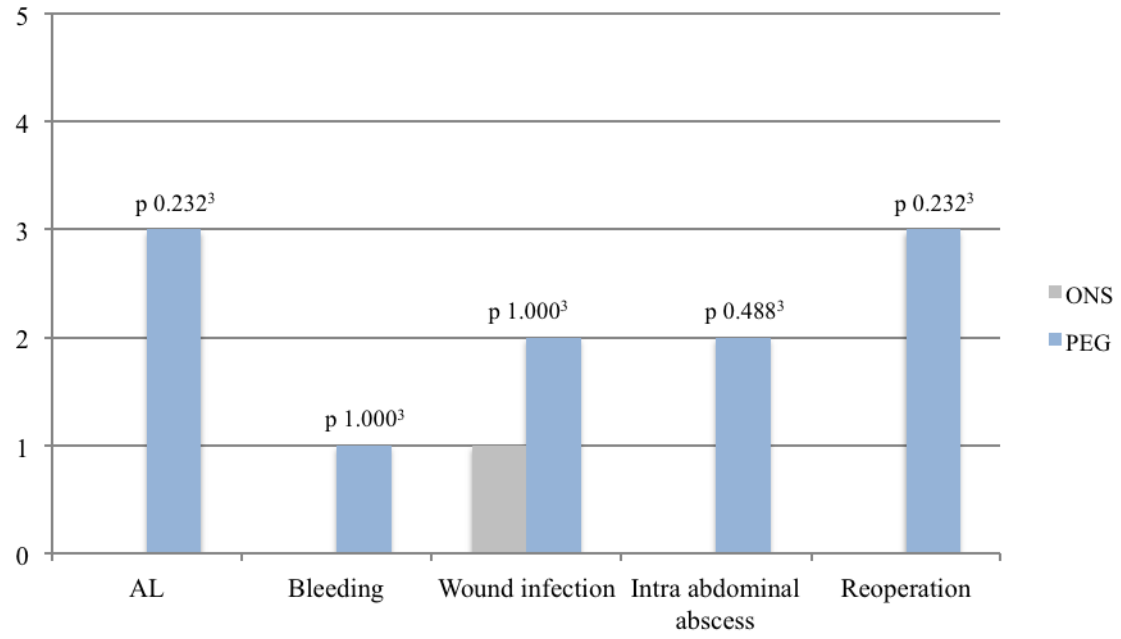
Nutritional and physiological data

Patient in the ONS-group lost less in weight (mean -1.6 kg vs. -4.6 kg; P=0.028) compared with the PEG-group, from randomisation to four weeks after surgery.

In the ONS-group, patients gained 1.9% in body fat, from randomisation until three days after surgery (P=0.041), while the PEG-group remained unchanged. Regarding subcutaneous fat, the PEG-group had a significant decrease, -1.6 mm from randomisation to surgery (P=0.019), whereas the ONS group gained 0.5 mm during the same period.

There were no other significant differences in nutritional and physiological measurements or in quality of life between the groups.

Figure 19. *Surgical morbidity*



[3] Fisher's exact test

DISCUSSION

The data from the current thesis suggest that morbidity after low anterior resection, among patients treated within an ERAS program, seems not to be affected by a diverting loop ileostomy. Even though the number of patients requiring an acute relaparotomy (<30 days from LAR) for anastomotic leakage was higher in those not diverted, the overall frequency of acute relaparotomy and length of hospital stay was not influenced. Moreover, patients without a loop ileostomy at LAR had a faster postoperative recovery. In the longer term, those diverted at LAR had a longer total LOS and a higher risk for repeated surgery, without any differences in risk of late AL, late readmissions, oncological outcome or permanent stoma.

When closing a diverting loop ileostomy, a stapled anastomosis was associated with a shorter operation time, LOS and a lower rate of postoperative small bowel obstruction.

Finally, we have demonstrated that oral nutritional supplements in combination with rectal enema before rectal cancer surgery might be a safe alternative (in terms of surgical complications) to mechanical bowel preparation and may, in addition, improve patients' nutritional status.

With improved oncological outcomes after rectal cancer surgery, more attention has been given to other aspects of postoperative outcome. Despite recent advances and attempts to optimise perioperative care, both short and long-term morbidity after low anterior resection is considerable.[2, 81, 85, 94, 123]

Anastomotic leakage, a severe surgical complication after LAR, increases early postoperative mortality,[102] other morbidity,[102] bowel dysfunction[103] and the risk for a permanent stoma.[94] In addition, oncological outcome has been suggested to be worse in patients suffering from AL.[105]

In 2007, a randomised multicentre controlled trial showed a reduction in clinical AL from 28% to 10% and a lower rate of relaparotomy for leakage if a diverting stoma was constructed at LAR.[35] Thereafter, several meta-analyses have confirmed similar results.[36-39] As a consequence, nearly all patients operated on for LAR in Sweden are currently being diverted.[2] However, despite the increased use of loop ileostomy, no dramatic change in rate of AL has been found in Sweden or other European countries.[2, 99]

Although a loop ileostomy is constructed in order to reduce the risk of AL, the morbidity associated with this diversion must be acknowledged when considering the overall morbidity after LAR. Nearly half of the diverted patients have some kind of complication associated with the stoma, where high stoma flow is common and may require readmission in some cases.[69, 90] Moreover, the risk for small bowel obstruction is significant after stoma reversal and sometimes surgery is required to resolve this condition.[64]

Another intervention to reduce morbidity after LAR, apart from diversion at primary surgery, is the introduction of ERAS pathways.[152] This evidence-based perioperative care program has been widely adopted due to its enhancement of postoperative outcome after colorectal surgery.[154, 155] The advantages have been found mainly in overall morbidity, while surgical morbidity has not been convincingly improved.[228] In addition, it has been shown that a higher compliance with the ERAS elements (>70%) correlates with an improved postoperative outcome, reduced postoperative morbidity[78, 158] and even five-year cancer specific survival in colorectal cancer.[229] Previous reports on diverting stomas and AL are based on data from traditional perioperative care settings.[35, 36] A diverting stoma might interfere with certain postoperative care elements such as intravenous infusions (due to high stoma flow), mobilisation and early oral feeding and thereby worsen the compliance to postoperative ERAS items.

A diverting stoma in LAR among patients treated within an ERAS programme was evaluated regarding short (Paper I) and long-term (Paper II) morbidity.

The rate of overall short-term morbidity and clinical AL in Paper I was somewhat higher compared with some previous studies[83, 84] which may be due to several different factors. Previous reports focus mainly on AL whereas overall morbidity is only rarely reported. In our study, all morbidity was included and classified according to Clavien-Dindo[153] in combination with a wide definition of AL. Previous studies have shown that surgeons are prone to underreport postoperative morbidity.[77] Therefore, in the current studies, information was prospectively collected and recorded by a trained study nurse. Furthermore, only LAR was included and not high anterior resections (PME), which are known to have a lower rate of AL.[42] Finally, nearly 80% of the patients had preoperative radiotherapy, which is higher than in most previously published reports and a known risk factor for AL[107] and worse functional outcome.[85]

Avoiding fluid overload has been demonstrated to be an independent predictor of improved outcome after colorectal surgery.[78, 158] In Paper I, patients without a stoma had a larger volume of intravenous infusions on the day of surgery (compliance with ERAS <3.5 litres on the day of surgery) and in general, a lower compliance with the ERAS protocol compared with those diverted (probably due to higher ERAS compliance over time). Nevertheless, short-term morbidity was 53% for patients with a stoma and 43% in those without. Yet, this apparent difference was not statistically significant, and neither was the difference in infectious complications (19% vs. 11%). It could be speculated that a higher pre and perioperative compliance with ERAS in the non-diverted group may have reduced complications further, thereby resulting in a significant difference.

After surgery, postoperative overall compliance to ERAS (measured on the first day after surgery) did not differ between the groups. However, patients without stomas were mobilised and free from intravenous infusions earlier.

The number of patients with a clinical AL, both within and after 30 days from surgery, did not differ between those with and without a diverting stoma at LAR. This is in contrast to a previous RCT[35] and meta-analyses (ranging from 648 to 11,429 patients included),[36-39] but in similarity with some other prospectively and retrospectively performed cohort studies.[121, 122]

Yet, some previous cohort studies have a risk of selection bias with high-risk patients among those diverted, which could have influenced the results.

However, more recent reports have showed similar results as those in Paper I. Bakker *et al.* compared 2 585 patients with or without a diverting stoma or end colostomy in rectal cancer surgery and found a lower rate of mortality, morbidity and LOS in those without a stoma. However, the rate of AL was significantly higher, 12% vs. 9%.[117] The second study by Snijders *et al.* compared patients undergoing anterior resection (N=3104) in hospitals with high stoma rates (88%) versus centres with low stoma rates (26%). Baseline characteristics were comparable between the groups and there were no differences in early AL or mortality. The authors concluded that the main reason for stoma construction was the strategic approach of the hospital rather than a systematic bias where centres with higher stoma rates had more high-risk patients compared with centres with lower stoma rates. In this study, it appeared that hospitals with low stoma rates were better at selecting high-risk patients[230] in which deviation was deemed necessary. Finally, Shiomi *et al.* used a grading system for selection bias to match 936 patients with or without a stoma. The rate of AL was similar between the groups (11% vs. 16%, with and without primary diversion, respectively) but frequency of relaparotomy due to AL was higher in those not diverted, also in accordance with our findings.[118] This could be explained by a more severe consequence of the leakage in the absence of a stoma or simply that a stoma remains necessary in the treatment of most patients following AL. However, in Paper I, the overall rate of acute relaparotomy and frequency of interventions due to AL, grade B and C-complications included, did not differ.

Neither in Paper I, nor in previously mentioned RCTs or meta-analyses, was a diverting stoma associated with decreased mortality, other morbidity, LOS or readmissions within 30 days after surgery.[35-39] In contrast, in some studies, diverted patients had a longer LOS, regardless of whether stoma closure was included or not.[35]

The impact of a loop ileostomy on long-term morbidity after LAR has been less explored. In previous reports, a diverting stoma has not been found to reduce the rate of late leakage,[128] permanent stomas[94] or oncological outcome,[106] similar to the findings in Paper II.

In addition to the outcomes reported in Paper II, QoL, incisional and parastomal hernias as well as functional outcome should be included in long-term morbidity. Approximately 40% have been reported to suffer from severe LARS more than two years after surgery[85] without any known correlation with diversion at LAR,[124] where major LARS has been suggested to correlate with worse QoL.[86] This is important to keep in mind since sphincter-preserving procedures have become the most common surgical approach for rectal cancer.[2]

Of all patients with AL, in Paper II, 43% ended up with a permanent stoma, irrespectively of primary diversion or early or late leakage. In comparison, only four percent of patients without AL had a permanent stoma at the end of the follow-up.

Among the patients with AL who underwent subsequent stoma closure, 14% required a secondary stoma compared with 1% of those without an AL.

Most of the permanent stomas, among those primarily diverted at LAR, were loop ileostomas. In contrast, nearly 50% of the patients that were diverted later on received a loop ileostomy or an end sigmoideostomy, respectively, as a permanent stoma.

An end sigmoideostomy has been suggested preferable as a permanent stoma due to advantages in stoma handling and less risk of high stoma flow.[94] Obviously, for those primarily diverted in our cohort, the loop ileostomy that became permanent was never closed compared to those diverted later on where a permanent solution was constructed more frequently.

In Paper III, a stapled anastomosis for closure of a loop ileostomy was associated with a 50% reduction in the risk of SBO compared with a hand-sewn anastomosis. Moreover, operation time and LOS was shorter in this group. These findings are in agreement with two published RCTs[74, 75] and two meta-analyses.[71, 73] The largest RCT by Löffler *et al.* (N=328), showed SBO in 10% vs. 17% (stapled vs. hand-sewn) and a longer operating time in the hand-sewn group [72]. However, the difference in SBO was not statistically significant between the groups.

In a stapled anastomosis, the new intestinal lumen is wider compared with a hand-sewn anastomosis and the intestines need to be more extensively dissected in order to enable correct positioning of the staple instrument. This might explain the decreased frequency of SBO following this procedure. Thus, some of the previous studies included a mixed study-population containing both rectal cancer and IBD patients and the hand-sewn anastomosis were performed in different ways.[68, 71, 73] Even though end-to-end anastomosis is the most common, side-to-side and end-to-side have been used. This might blur the results, since patients with different diagnoses and different types of hand-sewn anastomoses are not always comparable. Nonetheless, in Paper III, the influence of the underlying diagnosis in patients having a loop ileostomy (i.e. rectal cancer or IBD) was evaluated in a multivariate analysis and was not found to be a predictor for postoperative SBO.

Malnutrition and weight loss prior to surgery is associated with a worse postoperative outcome.[191, 193] Nearly 50% of the patients awaiting abdominal surgery for malignancy suffer from preoperative weight loss.[190] Despite this, there are no general recommendations or guidelines on how to approach this problem in rectal cancer surgery. Previous reports differ in administration of nutrition, type of nutritional supplement and duration of treatment and most often only patients with severe malnutrition are included.[191, 193]

The use of mechanical bowel preparation in colorectal surgery might increase the risk of fluid shift and electrolyte imbalance and also prolongs preoperative fasting.[158, 178]

The hypothesis in Paper IV was that oral nutritional supplements before rectal cancer surgery would improve the nutritional status of the patients. Thus, the risk for a catabolic state at the time of surgery would decrease and the stress response and degree of insulin resistance would be attenuated. In addition, due to its residue-free constitution, the bowel would be clean enough for rectal cancer surgery. Thereby, traditional MBP with PEG, with its potential side effects, could be avoided.

Even though only well-nourished patients were included, an improvement in patients' nutritional status was observed in the interventional arm, in which patients gained in percent body fat and lost less weight.

To our knowledge, there is only one previously published study showing the same correlation between preoperative treatment with ONS and weight loss. This RCT, by Smedley *et al*., found that perioperative ONS reduced weight loss and minor complications after colorectal surgery.[200] In Paper IV, postoperative ONS was given according to the ERAS protocol.[149]

The higher rates in both overall and surgical morbidity observed in the PEG-group did not reach statistical significance. However, the study was underpowered for the detection of any difference in this outcome.

Although the colon was less clean in those treated with ONS, the distal colon and rectum was similarly clean compared with the PEG-group, in accordance with previous findings in patients randomised to ONS or PEG as preparation before colonoscopy.[231] In addition, there was no difference in spillage when the bowel was opened. In fact, all three patients with AL had had traditional bowel cleansing. Undeniably, larger studies are warranted to confirm these novel findings and to detect a potential effect on postoperative outcome. However, ONS might be an option to avoid traditional MBP and thereby hitting two birds with one stone, considering the additional benefits with regards to nutritional outcome.

In summary, clinical anastomotic leakage, or at least its initial consequences, might be reduced by a diverting loop ileostomy at low anterior resection. However, early mortality, other morbidity and LOS are not influenced. Moreover, long-term morbidity, including oncological outcome and the risk of a permanent stoma are comparable between those primarily diverted and patients diverted due to anastomotic leakage. Due to this, and bearing in mind the significant stoma-related morbidity, current practice in which most patients are diverted during LAR, may have to be reconsidered. A more selective approach, with a diversion in high-risk patients and in those where the clinical consequences of an AL could postpone subsequent adjuvant treatment, may be a possible new strategy. Thus, future studies should focus on the identification of patients with a high risk of leakage, thereby leading to improved clinical decision-making and better patient outcomes.

In patients who are diverted, a stapled anastomosis might be preferred during the closure procedure, to diminish the risk of postoperative SBO. However, larger RCTs including only patients with rectal cancer and end-to-end anastomosis are needed to confirm this result.

Finally, adherence to the ERAS protocol decreases the overall morbidity after rectal cancer surgery. Thus, to enhance all patients' nutritional status (even in those without severe malnutrition preoperatively) the use of a residue free regimen seems to provide an alternative to traditional bowel cleansing before surgery, which might further improve postoperative outcome.

General methodological aspects and limitations of the thesis

Randomised controlled trials have many advantages. However, even RCTs can suffer from selection and information bias and unknown confounders, the three major limitations in a prospective or retrospective cohort study.

Studies examining different types of surgical procedure are made more difficult as it is not possible to blind the surgeon. Patients selected may be more suitable for inclusion and sometimes healthier persons are more prone to participate. Therefore, a well-conducted non-randomised cohort study should not be underestimated. If prospectively performed, the risk of information bias is reduced and a large number of variables can be collected to diminish the risk of confounding. In addition, the case-mix in a large cohort study, including all consecutive patients in a certain group, such as those undergoing rectal cancer surgery, may better represent the patients that are to be studied. Depending on the trial, all patients can be included and followed for a long time.

A retrospective cohort study has a higher risk for bias but can be performed quicker. In case of well defined exposure and outcome measures and if a large cohort of patients are evaluated, conclusions can still be made. Moreover, a RCT may not always be ethical and on those occasions, a non-randomised cohort study could be the only option available to the researcher.

Paper I

Due to the change in practice regarding primary diversion after 2007, the two surgical procedures where unequally distributed between two different time-periods (2002-2006 and 2007-2011). Thus, there is a risk that patients with diversion in the earlier time-period may have had a higher risk for leakage and vice versa. However, only 15% and 9% of the patients differed in strategy within the time-periods and when these 36 cases were excluded from the analysis, the results remained the same. Moreover, all calculations (comparison of demography, operative findings and postoperative morbidity and recovery) were performed between the two time-periods as well. In concordance with the results presented in Paper I, some differences regarding preoperative chemotherapy, type of anastomosis, operation time and ERAS compliance were found when comparing the two time-periods.

Certainly, there may still be unknown confounders in the cohort, but the known confounders have been adjusted for in a multivariate analysis (both between stoma and no stoma and the two time-periods). Moreover, the risk of selection bias regarding surgical procedure is low since all patients with a complete TME were included and the institutional indications for TME were the same during the study period. Furthermore, the data were prospectively collected and the participating surgical staff were the same during the entire study-period.

The high morbidity observed in the study and the impact of the ERAS programme should be discussed. The ERAS database gives the opportunity to compare several prospectively registered outcome measures regarding postoperative morbidity and recovery. As mentioned,

all patients with a complete TME were consecutively included and a study nurse performed the collection of data, including the recording of all complications. The majority of the patients had had preoperative RT and the definition of AL was wide. Nevertheless, the morbidity rate and the frequency of AL are comparable to previous studies, in which patients undergoing low as well as high anterior resection (known to have a lower rate of postoperative complications compared to a complete TME) were included.

Paper II

Systematic collection of data regarding functional outcome, urogenital and bowel dysfunction, quality of life, incisional and parastomal hernias was not performed. The risk of recall and information bias, from both patients and surgeons, and a select group of patients willing to answer questions regarding QoL make some of these data difficult to evaluate retrospectively. Nevertheless, one may assume that several of the patients in Paper II who had a permanent stoma due to AL, also had impaired bowel function.

There is a risk of missing data from patients referred to another emergency hospital than Ersta and for those who had their follow-up at another centre. Still, the majority (94%) of the patients (death excluded) had a complete three-year follow-up at our institution. Moreover, any complication/readmission revealed from another hospital was included in our analysis and most of the patients initially readmitted to a different hospital because of complications were sent to Ersta the following day.

Paper III

A multicentre RCT may have been preferable, including only patients operated on for LAR with a loop ileostomy to ensure enhanced external validity. However, compared with other trials on the subject, this retrospective cohort study is large (N=351) with well-defined outcome measures (SBO and AL) and three different Swedish hospitals were included.

The study was planned in 2007, due to a high observed complication rate after the increased use of diverting stomas. Since approximately 50% of the patients with LAR had a diversion between the study-period 1999-2006, all patients with stoma closure were included in order to gain study power. However, in 55% of the included patients, LAR was the primary procedure and in a multivariate analysis, the underlying diagnosis did not influence the rate of postoperative SBO.

Information regarding perioperative bleeding and type of incision (parastomal or laparotomy) are missing. These two variables could have had impact on postoperative morbidity. However, stoma closure is most often performed using parastomal access with only a small amount of blood loss.

It is sometimes difficult to separate normal postoperative paralysis from SBO. Therefore, the rate of SBO observed in the study might be somewhat high. However, the definition of SBO used in the study was both clinical and radiological.

Paper IV

Although the study was designed as an RCT, the cohort was small. The duration of the inclusion period was long, the patients included had low co-morbidity and were well nourished, representing only a fraction of the patients treated for rectal cancer at our institution. Despite these limitations, the calculated required sample size with 18 patients/group was almost reached and a difference in the primary outcome (nutritional status) was found. Moreover, compliance with the study protocol (registration of caloric intake, step-calculation, outcome variables measured) among the included patients was high and there were few missing data.

Certainly, the current data indicating a worse outcome in the PEG-group needs to be confirmed in a larger study. However, questions have arisen from the current trial regarding the value of preoperative treatment of all patients with ONS before rectal cancer surgery and whether mechanical bowel preparation may be avoided before small bowel diversion in these patients.

CONCLUSIONS

Overall conclusion

Morbidity after low anterior resection for rectal cancer is high, even in patients with a diverting stoma and perioperative treatment according to the ERAS protocol.

Specific conclusions

Clinical anastomotic leakage and other morbidity after low anterior resection for rectal cancer seems not to be reduced by a diverting loop ileostomy among patients treated according to an ERAS protocol.

A diverting loop ileostomy at low anterior resection decreases the need of acute relaparotomy due to anastomotic leakage but does not affect the total rate of acute reinterventions or length of hospital stay.

Among patients treated within an ERAS programme, postoperative recovery after low anterior resection seems to be slower in patients with a diverting loop ileostomy.

Long-term morbidity after low anterior resection (including readmissions, late anastomotic leakage, risk of permanent stoma and oncological outcome) seems not to be reduced by a diverting stoma at primary surgery. Instead, total length of hospital stay and number of surgical procedures required is higher in diverted patients.

After closure of a diverting loop ileostomy, occurrence of postoperative small bowel obstruction, operation time and length of hospital stay may be reduced by a stapled, compared with hand-sewn, anastomosis.

A residue-free diet before rectal cancer surgery using oral nutritional supplements in combination with rectal enema may be an alternative to traditional mechanical bowel preparation.

Oral nutritional supplements before rectal cancer surgery seem to improve patients' nutritional status and reduce weight loss after surgery.

FUTURE PERSPECTIVES

Recent published data suggest a more selective approach towards a diverting stoma in low anterior resection for rectal cancer.[79, 133, 230, 232] In order to change existing clinical protocols to a selective approach, it is important to re-evaluate the effect of a stoma on both short and long-term morbidity. It is also important to find new perioperative strategies for the prevention of AL. Identifying which patients who are at higher risk of AL and therefore require a diversion at LAR may be a key for improved postoperative outcome. Future studies should therefore focus on the role of a diversion in LAR among patients treated within a modern perioperative setting in order to define high-risk patients for AL. An algorithm for the risk of AL in individual patients, including all known risk factors, stage of the tumour and eventually neoadjuvant and adjuvant treatment, may help in this decision making framework.

Moreover, new approaches such as ghost stoma or a percutaneous ileostomy in combination with early radiology could be an alternative to stoma diversion and may even decrease the risk of relaparotomy in case of a leakage. Adjuncts, such as fluorescence angiography with near-infra red light technology, might detect impaired micro perfusion. This could contribute to the decision regarding where to divide the bowel, where to make the anastomosis and thereby, which patients would benefit from a loop ileostomy.

Furthermore, the effect of intestinal microflora and probiotics on postoperative morbidity, including anastomotic dehiscence, is also generally unexplored.

Few studies have addressed long-term morbidity after LAR in relation to a diverting stoma. Even though no current data suggest any benefit of a diversion, larger prospective cohort studies are warranted. These studies should also assess bowel dysfunction, quality of life and oncological outcome. If future reports confirm that a diversion at LAR do not benefit long-term outcome and morbidity this would add arguments for a selective approach.

Currently, except in the case of severely malnourished patients, there is no general recommendation regarding nutritional supplements before rectal cancer surgery. Further larger studies are required to ascertain whether ONS and rectal enema may safely replace mechanical bowel preparation before primary diversion at rectal cancer surgery and if the observed enhancement in patient nutritional status further influences postoperative morbidity and outcomes.

SAMMANFATTNING FÖR ICKE-KIRURGER

Till mamma

Årligen drabbas nästan 2000 personer i Sverige av ändtarmscancer, den sjunde vanligaste cancerformen för både kvinnor och män. Trots att sjukdomen blivit allt vanligare, överlever idag nästan 65 % - en avsevärd förbättring sett över en 50-årsperiod.

I dagsläget är kirurgi det som kan bota, men dessvärre är en operation inte ofarlig. En av de operationsmetoder som används innebär att ungefär 40 % får komplikationer direkt efteråt och en hög andel får även bestående men. Svårigheter med avföringen, urinen och det sexuella är vanligt, och nästan en av fem riskerar att få en livslång påse på magen, s.k. stomi.

En av de mest fruktade komplikationerna är anastomosläckage, att den nya tarmskarven läcker. Detta innebär i sig en ökad risk för tidig död, andra komplikationer, dålig tarmfunktion och att man får en livslång stomi.

En tillfällig stomi, samtidigt som själva ändtarmsoperationen, tros minska risken för läckage från den nya tarmskarven. I Sverige får därför en stor andel av de som opereras samtidigt en tillfällig stomi. Några månader efter operationen är tanken att den ska stoppas tillbaka ner i buken, s.k. stominedläggning.

Trots denna åtgärd får fortfarande många anastomosläckage. Dessutom riskerar stomin att ge ytterligare sjukvårdskrävande besvär, både genom att ha den och när man ska lägga ner den.

En riskfaktor för komplikationer efter operation är viktnedgång och näringsbrist. Nästan 50 % av de patienter som ska genomgå ändtarmskirurgi har gått ner i vikt innan operationen. Trots detta finns det inte något allmän strategi för hur man ska hantera problemet.

Att vårdas enligt ett speciellt vårdprogram, ERAS (Enhanced Recovery After Surgery), där man som patient inte ska fasta i onödan, vara ordentligt smärtlindrad, röra på sig och äta så fort som möjligt efter operationen har visat sig minska komplikationerna efter kirurgi. Däremot kan det praktiskt vara svårt att genomföra alla åtgärder som innefattas av ett ERAS-program, varför många sjukhus väljer att avstå helt eller bara använda delar utav programmet.

I detta avhandlingsarbete, uppdelat på fyra delarbeten, har nyttan av den tillfälliga stomin vid ändtarmscancerkirurgi utvärderats hos patienter som behandlats enligt vårdprogrammet ERAS. Dessutom har patienter som fått näringsdrycker innan ändtarmscancerkirurgi undersökts avseende komplikationer efter operationen och om denna metod även rengjort tjock och ändtarmen tillräckligt.

Arbete I

Gör den tillfälliga stomin vid operation av ändtarmscancer nytta om patienterna också behandlas enligt vårdprogrammet ERAS?

Alla 287 patienter som genomgått en viss operation för ändtarmscancer på Ersta sjukhus, mellan år 2002-2011, kontrollerades. Knappt hälften av dessa hade opererats *med* en tillfällig stomi och drygt hälften *utan*. Dessa två grupper jämfördes.

Det var ingen skillnad i antal eller typ av komplikationer efter ändtarmskirurgin mellan grupperna. Fler patienter som inte fått en stomi blev akutopererade för att tarmskarven läckte, men sett på antalet akutoperationer - oavsett orsak - så var det ingen skillnad.

Gruppen av patienter utan stomi återhämtade sig snabbare även om den faktiska tiden på sjukhus var lika.

Arbete II

Påverkar en tillfällig stomi vid ändtarmscancerkirurgi komplikationerna på lång sikt?

Här undersökte vi samma patienter som i arbete I, men jämförde grupperna avseende besvär som uppstått mer än 30 dagar fram till 3 år efter operationen.

Andelen patienter som fått läggas in på sjukhus igen, under denna tid, fått läckage från tarmskarven som hittats senare, fått tillbaka sin cancersjukdom eller dött i densamma var lika mellan grupperna. Det var inte heller någon skillnad i hur många som fått en livslång stomi. Däremot var antalet dagar på sjukhus, totalt sett under denna treårsperiod, fler hos de som fått stomi vid ändtarmsoperationen.

Arbete III

Är en tarmskarvsmetod bättre än en annan vid nedläggning av den tillfälliga stomin?

Vi undersökte 351 patienter som opererat tillbaka sin tillfälliga stomi vid tre olika svenska sjukhus - Uppsala, Huddinge och Karlstad. En del av dem hade fått sin nya tarmskarv handsydd och en del hade fått en staplad (häftad) tarmskarv.

Hos de som fått en staplad tarmskarv gick operationen fortare (10 minuter), hälften så många fick tarmvred (16 % jämfört med 8 %) och de kunde gå hem 1,5 dag tidigare från sjukhuset.

Arbete IV

Kan näringsdrycker innan operation för ändtarmscancer ersätta laxering för rengöring av tarmen och klarar sig de patienter som fått detta bättre efteråt?

Tjugonio patienter som skulle genomgå operation för ändtarmscancer lottades till att få näringsdrycker innan kirurgi (ca 4-6 veckor) eller äta som vanligt, efter eget bevåg, och dagen innan operation få dricka 4 liter tarmlaxering (standard i Sverige).

Vid lottningen till behandlingsgrupperna, dagen innan operationen, tre dagar och fyra veckor efter operationen gjordes undersökningar för att mäta patienternas näringstillstånd och fysiska förmåga.

Hos de patienter som fått näringsdrycker var tjocktarmen sämre rengjord men ändtarmen lika bra rengjord som hos de som fått tarmlaxering. Andelen komplikationer efter operationen var också lika. Däremot hade de som fått näringsdrycker lagt på sig mer underhudsfett fram till kirurgin och gått ner mindre i vikt, från lottningen till fyra veckor efter operationen.

Utifrån dessa fyra delarbeten blir slutsatsen att andelen läckage efter ändtarmscancerkirurgi fortsatt är många och besvären, såväl på kort som på lång sikt, tycks inte alltid påverkas av en tillfällig stomi. Dessutom tillkommer än mer komplikationer med själva stomin. Det finns därför skäl att ifrågasätta regeln att alla i Sverige, som genomgår en viss typ av ändtarmscancerkirurgi, samtidigt ska ha en tillfällig stomi. Att innan operationen väga argumenten för och emot hos den enskilde individen, i hopp om att hitta den grupp patienter som det gagnar mest, är ett möjligt framtida scenario. Vidare, har man väl fått en stomi är en staplad tarmskarv vid nedläggningsförfarandet att föredra.

Till sist, näringsdrycker innan ändtarmscancerkirurgi kan vara ett alternativ till tarmlaxering och samtidigt göra patienterna bättre förberedda, rent näringsmässigt, inför och efter kirurgi.

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