Rectal cancer

Aspects of post-operative complications

INGVAR SVERRISSON
Abstract

Aim: The overall aim of this thesis was to study post-operative complications in patients with rectal cancer.

Methods: Post-operative complications in patients operated for rectal cancer was retrospectively analyzed in three prospective registers; the local rectal cancer registry in the Västmanland County, Sweden, the Swedish Colorectal Cancer Registry (SCRCR) and the National Prostate Cancer Registry (NPCR). In Papers I and II, the focus was on the complication pattern after Hartmann’s procedure (HP). In Paper III, the incidence of parastomal hernia was assessed during a period when no prophylactic mesh was used (1996-2006) compared with a period when a prophylactic mesh was routinely used (2007-2012). In Paper IV, the anastomotic leakage (AL) rate after anterior resection (AR) for rectal cancer patients who had previously received RT for prostate cancer was assessed with combined data from the SCRCR and the NPCR.

Results: In Paper I, patients operated with a HP were significantly older, had a higher ASA-score, a poorer WHO performance score and lower serum albumin levels. Few developed pelvic complications. In Paper II, the intra-abdominal infection rate was 8% and the re-laparotomy rate was 10%. Multi-variable logistic regression analysis identified pre-operative radiotherapy as a risk factor for intra-abdominal infections. In Paper III, we found no difference in the rate of parastomal hernia between patients with and without a prophylactic stoma mesh. In Paper IV, we identified 59 out of 188 patients who had undergone previous radiation therapy for prostate cancer who had been operated with AR. Twelve (20%) developed an AL, of whom only one underwent re-laparotomy and there was no 90-day mortality.

Conclusion: The rate of serious post-operative complications was low after HP and it seems to be a safe and appropriate alternative in old and frail patients. Pre-operative radiotherapy was a risk factor for intra-abdominal infections in rectal cancer patients operated with a HP. A prophylactic stoma mesh did not reduce the rate of parastomal hernias. In patients that had previously been irradiated for prostate cancer, a minority underwent an AR. These patients were healthy with early cancer stages and, in this selected group of patients, the AL rate was much lower than previously reported.

Keywords: Rectal cancer, Complications, Anastomotic leakage, Abscess, Parastomal hernia, Prostate cancer, Radiation therapy

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This book is dedicated to
my wonderful boys,
Ingólfur Hrafn and Sverrir Þór
This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


   *Int J Colorectal Dis.* 2018;33:327-332

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   *Int J Colorectal Dis.* 2015;30:1217-22

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### Abbreviations

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<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AL</td>
<td>Anastomotic leakage</td>
</tr>
<tr>
<td>APE</td>
<td>Abdominoperineal excision</td>
</tr>
<tr>
<td>AR</td>
<td>Anterior resection</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>C.I.</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CRM</td>
<td>Circumferential Resection Margin</td>
</tr>
<tr>
<td>CRT</td>
<td>Chemoradiotherapy</td>
</tr>
<tr>
<td>DI</td>
<td>Diverting ileostomy</td>
</tr>
<tr>
<td>ELAPE</td>
<td>Extralevator abdominoperineal excision</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray</td>
</tr>
<tr>
<td>HAPIrect</td>
<td>The Hartmann’s Procedure or Abdominoperineal Excision With Intersphincteric Dissection in Rectal Cancer Patients</td>
</tr>
<tr>
<td>HP</td>
<td>Hartmann’s procedure</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>LAR</td>
<td>Low anterior resection</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>OR</td>
<td>Odds’ Ratio</td>
</tr>
<tr>
<td>PSH</td>
<td>Parastomal hernia</td>
</tr>
<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>SCRCR</td>
<td>Swedish Colorectal Cancer Registry</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for Social Services</td>
</tr>
<tr>
<td>TME</td>
<td>Total Mesorectal Excision</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
Introduction

History

Diseases of the rectum have been recognized and treated for thousands of years. Hemorrhoids and fistula-in-ano were treated by the ancient Egyptians and Greeks. The fifth century Greek historian Herodotus commented on the body of knowledge of ano-rectal diseases while studying at the Library of Alexandria, and, though recognized, rectal cancer was considered incurable (1).

Only sporadic cases of stoma surgery can be identified before the 18th century. The earliest stomas were actually fistulas that developed spontaneously following bowel perforation. In the late 18th century, the first successful colostomy was performed by Duret in a child with anal atresia. The mortality was high after these operations due to fecal contamination. During the 19th century, following the development of anesthesia, surgery became a realistic treatment option for managing bowel obstruction by using a diverting colostomy (2). An extraperitoneal lumbar approach was introduced in 1841. These stomas were difficult to manage due to their location on the flank and the rate of stenoses was high. The modern-day colostomy with mucosa sutured to the skin was first performed by Allingham in 1887 (3).

Jean Faget is credited with the first attempt to resect the rectum because of rectal cancer in 1739. The first successful bowel resection of rectal cancer was performed in 1826. The operation was a rectal amputation with a subsequent perineal colostomy, performed by Jacques Lisfranc in Paris. Ernest Miles performed in 1907 the first combined abdominal and perineal operation for rectal cancer that resulted in an abdominal colostomy, today called an abdominoperineal excision (1). The French surgeon Henry Albert Hartmann described in 1923 what is still known as the Hartmann’s procedure (4). In 1948, an operation for more proximal tumours was described by C.F. Dixon, the anterior resection performed with an anastomosis and without a stoma (1).

The first reported use of a mesh for preventing the development of a parastomal hernia is described in 1986 (5).

In 1853, the first case of prostate cancer was described by J. Adams, a surgeon at The London Hospital. He described it as “a very rare disease”. Surgery for prostate cancer was initially performed to relief symptoms from urinary obstruction. In 1904, Hugh Hampton Young performed the first radical perineal prostatectomy at the Johns Hopkins Hospital. In the 1940’s
Charles Huggins discovered that prostate cancers respond to androgen therapy. The first reports on the use of radiation treatment in prostate cancer patients came at the beginning of the twentieth century. Radiation sources were introduced into the urethra and rectum and this was used as a palliative alternative to surgery. External Beam Radiotherapy was initially used as an adjunct to interstitial radium and, in the late 1950’s, Malcolm Bagshaw and colleagues revealed the possibility of radiation curability of prostate cancer. In 1983, H. Holm reported a technique of implanting the prostate with radioactive “seeds” under the guidance of transrectal ultrasound which has become a common method for treating localized prostate cancer (6).

**Definition/ incidence/ symptoms**

Rectal cancer is usually defined as a tumour with its most proximal margin within 15 cm from the anal verge but also as a tumour with its most proximal margin below the sacral promontory.

In 2016, the incidence of rectal cancer in Sweden was 25/100,000 for men and 15/100,000 for women, which meant that more than 1,200 men and 800 women were diagnosed with rectal cancer. Together with colon cancer, rectal cancer is the second most frequent cancer diagnosis in men after prostate cancer and in women after breast cancer. Rectal cancer is a rare disease in young people with only 4 % of all rectal cancers diagnosed in patients under 50 years of age (7).

The single, most important risk factor is age. Heredity with one or more first grade relatives with rectal cancer is also of importance. Life-style and environmental factors play an important role in the etiology of colorectal cancer even though no single component can explain the international variation in its incidence. Modifiable life-style factors, such as smoking, physical inactivity, obesity, alcohol intake and diet have been implicated as risk factors. Physical activity, fruit and vegetable intake are believed to have protective effects (8-11). Diabetes mellitus has been shown to increase the risk of cancer by 30 % (12) and long-standing inflammatory bowel disease also increases the risk significantly (13, 14).

Rectal bleeding and alterations in bowel habits are the most common symptoms of rectal cancer. Weight reduction, loss of appetite, abdominal pain, anemia and signs of intestinal obstruction may also be presenting symptoms.

The prognosis for colorectal cancer has improved in the last decades. The relative 5-year survival of rectal cancer patients in Sweden 2011-2017 was 66 % in men and 68 % in women (7).
Diagnosis and Histopathological staging

The diagnosis of a rectal cancer is based on endoscopy with a biopsy from the tumour and subsequent microscopic analysis. A colonoscopy is performed, if possible, to detect synchronous colonic malignancies that occur in 5% of colorectal cancer patients (15, 16). A computed tomography (CT) of the thorax and abdomen is performed to detect distant metastases and an MRI or a rectal ultrasound is performed to stage the tumour locally. The MRI is mostly used to predict the TN stage (Table 1) and in particular to obtain very important information about the distance of the tumour to the mesorectal fascia (MRF) (17).

The World Health Organization (WHO) classification divides ano-rectal cancer into adenocarcinoma (>90%), adenosquamous carcinoma, spindle-cell carcinoma, squamous cell carcinoma and undifferentiated carcinoma. The most common clinico-pathological classification system is TNM (Tumour, Node, Metastases), that was developed by the American Joint Committee on Cancer (AJCC) (18) and the International Union Against Cancer (UICC), see Table 1.
Table 1a Tumour classification (TNM)

<table>
<thead>
<tr>
<th>Primary tumour (T)</th>
<th>Regional lymph nodes (N)</th>
<th>Distant metastases (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>no evidence of primary tumour</td>
<td>no distant metastases by imaging; no evidence of tumour in other sites or organs</td>
</tr>
<tr>
<td>T0</td>
<td>primary tumour cannot be assessed</td>
<td>distant metastases</td>
</tr>
<tr>
<td>Tis</td>
<td>carcinoma in situ, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)</td>
<td>metastases confined to 1 organ or site without peritoneal metastasis</td>
</tr>
<tr>
<td>T1</td>
<td>tumour invades submucosa (through the muscularis mucosa but not into the muscularis propria)</td>
<td>metastases to 2 or more sites or organs is identified without peritoneal metastasis</td>
</tr>
<tr>
<td>T2</td>
<td>tumour invades muscularis propria</td>
<td>metastases to the peritoneal surface is identified alone or with other site or organ metastases</td>
</tr>
<tr>
<td>T3</td>
<td>tumour invades through the muscularis propria into the pericolorectal tissues</td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>tumour invades through the visceral peritoneum (including gross perforation of the bowel through tumour and continuous invasion of tumour through areas of inflammation to the surface of the visceral peritoneum)</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>tumour directly invades or adheres to other adjacent organs or structures</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>no regional lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>metastases in 1 - 3 regional lymph nodes</td>
<td></td>
</tr>
<tr>
<td>N1a</td>
<td>metastasis in 1 regional lymph node</td>
<td></td>
</tr>
<tr>
<td>N1b</td>
<td>metastases in 2 - 3 regional lymph nodes</td>
<td></td>
</tr>
<tr>
<td>N1c</td>
<td>no regional lymph nodes are positive but there are tumour deposits in the subserosa, mesentery or non-peritonealized pericolic or perirectal / mesorectal tissues</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>metastases in 4 or more regional lymph nodes</td>
<td></td>
</tr>
<tr>
<td>N2a</td>
<td>metastases in 4 - 6 regional lymph nodes</td>
<td></td>
</tr>
<tr>
<td>N2b</td>
<td>metastases in 7 or more regional lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>TNM</td>
<td></td>
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<td>-------</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>Tis</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>T1-T2 N0</td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>T3 N0</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>T4a N0</td>
<td></td>
</tr>
<tr>
<td>IIC</td>
<td>T4b N0</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-T2 N1/N1c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T1 N2a</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>T3-T4a N1/N1c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2-T3 N2a</td>
<td></td>
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<tr>
<td></td>
<td>T-T2 N2b</td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>T4a N2a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3-T4a N2b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4b N1-N2</td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>Any T Any N</td>
<td></td>
</tr>
<tr>
<td>IVB</td>
<td>Any T Any N</td>
<td></td>
</tr>
<tr>
<td>IVC</td>
<td>Any T Any N</td>
<td></td>
</tr>
</tbody>
</table>

After a diagnosis has been made, the patient is informed about the disease and the different oncological and surgical treatment methods with their respective complication patterns, so that the patient can be a part of the decision-making about which treatment strategy is most suitable. A specialist nurse is present during the consultation and acts as the patient’s subsequent contact-person. The patient is encouraged to bring a close relative to the consultation. It is very important to assess the patient’s nutritional and functional status. Many patients are old, frail and co-morbid, and this has to be taken into consideration when choosing neo-adjuvant oncological treatment and planning the type of surgery. The time from the first visit to the start of treatment can be used to optimize the patient’s nutritional status with the help of a dietician/nutritionist, to give mental support through a social counselor and to improve functional status by consulting other medical expertise. The patient is given information about an eventual stoma by a specialist stoma nurse.
A helpful and simple clinical classification, that can aid in the choice of management, is to categorize the tumours into “good”, “bad” and “ugly”, depending on prognostic factors identified on the MRI. The “good” tumours without bad prognostic factors (mid/upper rectum: T1-T3b; low rectum: T1-2, T3a; N0; no involvement of MRF), “bad” tumours with an increased risk of distant metastases (mid/upper rectum: T3c/d; low rectum: T3b-d; T4 with peritoneal or vaginal involvement only; N1/N2; no involvement of MRF) and “ugly” tumours with a high risk of local recurrence and distant metastases (T4 with overgrowth to the prostate, seminal vesicles, base of urinary bladder, pelvic side walls or floor or sacrum; positive lateral lymph nodes; involvement of MRF) (19).

The information gathered in the pre-operative investigations is then presented at the pre-operative multidisciplinary team meeting (MDT) and a decision is taken on eventual neo-adjuvant oncological treatment.
Treatment

Pre-operative oncological treatment

Several trials have shown that neo-adjuvant radiation therapy for patients with rectal cancer clearly reduces the risk for local recurrence and increases survival (20-22). A large randomized trial showed that pre-operative radiotherapy reduced local recurrence but did not affect survival when TME surgery was performed (23).

Patients with “good” tumours and a low risk of local recurrence, should not receive pre-operative radiation therapy in addition to TME surgery according to the Swedish national guidelines. Patients with “bad” tumours, where there is an increased risk of recurrence, mostly receive short-course radiation therapy with immediate surgery (5 Gy x 5 times in one week) (22, 24, 25). Data from the Stockholm III trial, however, indicate that a short course of radiotherapy with surgery delayed for 4-8 weeks might have some advantages over immediate surgery, especially in elderly and co-morbid patients. The oncological results are similar but post-operative complications are fewer. Short course radiotherapy with a delay provides an opportunity to optimize the patient before surgery (26) and opens up the possibility of a “watch and wait” approach for these patients.

Patients with “ugly” tumours are recommended to receive pre-operative chemoradiotherapy (CRT) (19). Previously, patients received CRT as a long course of RT (1.8–2 Gy x 25–28 in 5–6 weeks) delivered together with chemotherapy (27-29). Recently, a short-course radiation schedule combined with chemotherapy has had a breakthrough in Sweden following the RAPIDO trial (30). Preliminary data from the RAPIDO trial showed that a large proportion of patients completed the neo-adjuvant treatment, indicating low treatment-related morbidity and in 19% of patients there was a complete tumour remission (31).

The adverse effects depend on the irradiation dose and the volumes treated. Acute adverse effects of irradiation usually appear within 3 months of starting the radiotherapy and entail mainly genito-urinary problems and gastrointestinal problems such as diarrhoea, abdominal pain, nausea and vomiting, bloating, rectal bleeding and urgency (32, 33). Pre-operative radiotherapy has been shown to be a likely risk factor for anastomotic leakage and perineal wound infections (34, 35). The chronic radiation toxicity usually presents a few months or even years after the irradiation. It influences the vascular endothelial cells and fibroblasts causing thrombi and occlusion of arterioles and fibrosis in the rectum (36). The chronic adverse effects comprise a decrease in anal sphincter function after anterior resection, decreased sexual function in both men and women, urgency, rectal bleeding, flatulence,
abdominal pain, late bowel obstruction and an increased risk of secondary malignancies, mainly after radiation treatment for prostate cancer and cervical cancer (33, 37-40).

Radiation treatment for prostate cancer
The main goal of radiation treatment in prostate cancer is to deliver a high, tumoricidal dose to the tumour while keeping the dose to the surrounding normal structures below tolerance. Overall treatment decisions are determined according to the stratification of patients into risk groups; low-, intermediate- and high-risk. Radiotherapy is rarely given in the low-risk group but if they do, the RT can be given with either external beam radiotherapy (EBRT) or brachytherapy. For intermediate risk disease, the use of RT is often combined with short-term androgen deprivation therapy (ADT). In the high-risk patients, RT is combined with ADT which is administered during 2-3 years (41). The most common curative radiotherapy regime for prostate cancer implemented in Sweden has been external beam radiotherapy with a total dose of 78-80 Gy in 2 Gy/fractions (42).

Surgery
In the 1960’s and 1970’s, very high local recurrence rates were observed after rectal cancer surgery; these resulted in the introduction of neo-adjuvant radiotherapy to try to minimize the rate of local recurrence (43-45). Sub-optimal surgical techniques were later considered to play an important role in the high recurrence rates (46-49). In 1982, Heald (50) introduced the so-called total mesorectal excision (TME), which means that the rectum and its surrounding fat tissue including lymph nodes and vessels are removed. The surgeon uses a sharp dissection technique and the dissection takes place in the embryological avascular plane outside the mesorectal fascia that encloses the perirectal fat with its lymph nodes. The hypogastric and sacral nerves are preserved. Since the introduction of TME and neo-adjuvant radiotherapy for patients operated for rectal cancer, survival has improved and local recurrence rates have decreased (20, 51). Several workshops demonstrating the TME technique were held in Sweden (52) and, at the same time, rectal cancer surgery was centralized to larger colorectal units in each county. (53).

Three different types of abdominal bowel resections are employed in patients with rectal cancer; anterior resection, Hartmann’s procedure and abdominoperineal excision. They are all performed using the mesorectal excision technique and, in recent years, there has been an increasing trend in performing the operations with a laparoscopic approach, either traditional laparoscopy or robot-assisted, in order to facilitate faster post-operative recovery and possibly decrease the complication rate without worsening the treatment results. The same dissection technique is used in the laparoscopic
TME surgery, as described above. These methods can even be combined with a trans-anal approach, trans-anal TME (54).

Before surgery, all patients must have a potential stoma site marked. Oral colon cleansing is given to those who will be operated with an anterior resection, especially if a diverting stoma is planned (55). A rectal enema is enough for those who will be operated with a Hartmann’s procedure or an APE.

The most common approach is the anterior resection, which is selected for tumours located in the middle and upper rectum. A ligation of the inferior mesenteric artery is performed proximally, or just after the origin of the left colic artery and a proximal division of the large bowel, usually on the descending colon, is performed. The splenic flexure is taken down and the inferior mesenteric vein is divided just below the pancreas to avoid tension in the anastomosis. The pelvic nerve plexus is identified and preserved if no suspicion of tumour invasion is present. A TME is performed down to the pelvic floor. The bowel is clamped distally to the tumour with margin and the rectum is washed out with 500 ml of an alcoholic solution. A circular stapler device is used to perform the anastomosis and an end-to-side anastomosis is performed. Many patients receive a temporary diverting loop-ileostomy because of the risk of anastomotic leakage after a low anterior resection (56). For some tumours in the upper rectum, a high anterior resection can be performed with partial mesorectal excision (PME) and a colo-rectal anastomosis (57).

Figure 3. Bowel stapler used to staple the rectum below the tumour
Since patients are often old and frail with co-morbidities and weak sphincter functions, the so-called Hartmann’s procedure (HP) is often performed to avoid the formation of an anastomosis and thereby eliminate the risk of life-threatening anastomotic leakage. The proportion of patients undergoing HP has increased in recent years from approximately 10% to 15% (58) and up to 30% in patients with metastases (59). The whole operation, including the TME, is performed in the same way as an anterior resection except that no anastomosis is performed. Instead, the distal rectum is stapled off, leaving a short ano-rectal stump and an end-colostomy is constructed by taking the stoma out through the rectus abdominis muscle. If a mesh is used prophylactically, it is placed between the rectus abdominis muscle and the posterior rectus sheath. The opening is made just to let the bowel pass through the mesh through a cross-cut at its centre. The lateral corners are fixed to the posterior rectus sheath with absorbable stitches. The medial corners of the mesh are grasped with a stitch of the running suture closing the midline incision (60). A prophylactic stoma mesh can also be placed with the laparoscopic technique, intraperitoneally (61) or retromuscularly (62), however, the ideal location has not yet been delineated.

For the lowest tumours (at or below 5 cm from the anal verge), an abdominoperineal excision (APE) is often necessary. The rectum is only covered by fat and mesorectal fascia in the upper two-thirds and below that, the levator muscle and the prostate/vagina lie directly against the rectal wall. This means that a low rectal cancer can develop into a locally advanced tumour with invasion of the surrounding nerves, muscles, prostate, vagina and even bony pelvis.

A TME is performed in the same manner as in a standard LAR and, additionally, the whole anus is excised in the perineal phase of the operation with the patient in a jack knife or prone position and an end-colostomy is created in the same manner as that described for the Hartmann’s procedure above. If needed, a multiorgan en-bloc resection of invaded adjacent organs (63-65) or a partial en-bloc resection of the posterior vaginal wall or prostate is performed (66). If the tumour adheres to the levator or the sphincter muscles, a so-called extralevator APE (ELAPE) is performed where the levator muscles are resected en-bloc to achieve a radical resection (67). The APE creates a large perineal wound that is difficult to close, as it is mostly fatty tissue that has to be adapted. A common practice in Sweden is to reconstruct the defect in the pelvic levator muscles either with a biological implant or to cover it with a gluteus maximus muscle flap (68).

The large perineal wound can possibly be avoided by removing the ano-rectal stump through an alternative procedure, abdominoperineal excision with an intersphincteric dissection (ID) (69). This means that the pelvic floor and the external sphincter are left intact resulting in stronger and better vascularized
muscular tissue to suture, thus avoiding blood/fluid cavities in the perineal fat which further increase the risk of infection. This results in better wound healing than with the traditional APE. The on-going HAPIrect trial can hopefully clarify if APE with ID is a safer alternative than the Hartmann’s procedure regarding post-operative complications in rectal cancer patients with tumours more than 5 cm from the anal verge, where an AR is not an option (69).

Surgical complications

Post-operative complications after bowel resections for rectal cancer are common. The overall complication rate after TME surgery has been reported in up to 51 % of cases and surgical complications in up to 32 % of cases (70). The most common surgical complications are abdominal wound infections, anastomotic leakage (after AR) that can be life-threatening, intra-abdominal infections (pelvic abscesses) and perineal wound infections (after APE).

Figure 4. CT image of an anastomotic leakage. The arrow shows the extravasation of contrast that is administered via the rectum.
The literature on post-operative complications after HP in rectal cancer is, on the other hand, limited. The relevant studies are retrospective with small cohorts (71-74). The results have indicated a relatively high post-operative morbidity with a pelvic abscess rate of up to 33% in patients who have undergone a low transection of the rectal stump in a study from Denmark (72), and 17% in a study from New Zealand (71).

Figure 5. Endoscopic view of a defect in the staple line 4 weeks after Hartmann’s operation
The local experience from the Västmanland county, Sweden, was that the complication frequency was not as high as that seen in previously published reports. This raised our interest in extracting data from our local colorectal cancer registry in Västmanland in order to describe the post-operative complication pattern in patients operated with Hartmann’s procedure. In this registry, comprehensive pre-, per- and post-operative data have been prospectively gathered since 1996. In order to be able to explore a much larger cohort, we have also analyzed the Swedish Colorectal Cancer Registry (SCRCR) with regard to post-operative complications.

Parastomal hernias
Parastomal hernias (PSH) are a common complication after stoma formation with a reported incidence of up to 78% (3, 75-77). Numerous risk factors have been proposed, such as an elevated BMI, increased age and smoking (78). Clinical symptoms associated with PSH have been reported in up to 76% of cases. Symptoms include: pain due to bulging, difficulty with stomal appliance, leakage, skin irritation and difficulty with irrigation (79). Most often, the parastomal hernias are evident on clinical examination with sensitivity rates reported between 66 and 94% and specificity rates as high as 100%. There is no “gold standard” for the diagnosis of parastomal hernia but the use of CT has been recommended when there is clinical uncertainty (80). The use of a prophylactic mesh to prevent the occurrence of a parastomal
hernia has been proposed and a number of randomized clinical trials have been published (60, 81-86). Before 2007, a mesh was never used as a prophylactic measure in Västmanland but, since most of the earliest RCT’s showed promising results in favour of the mesh, the colorectal unit in Västmanland started placing a mesh prophylactically in all rectal cancer patients, planned to be equipped with a permanent stoma (APE and HP). This gave us the opportunity to compare the PSH rate with and without the mesh using prospectively collected data in our local rectal cancer registry. There is still no concrete evidence for PSH prevention by using the mesh. However, the European Society of Hernia supports the use of prophylactic mesh during the construction of a permanent end colostomy (80), even though the largest to-date RCT on the subject did not show any benefit using a prophylactic mesh (87).

Figure 7. CT image of a parastomal hernia. A small bowel (dotted arrow) can be seen bulging out through the defect between the stoma-forming bowel and the fascia. We can even see a ventral hernia (whole arrow).
General and specific aims

The general aim of this thesis was to describe certain post-operative complication patterns in patients whose bowel was resected because of rectal cancer and to define risk factors for the development of these complications.

The specific aims of the studies were:

Paper I
To describe the selection of rectal cancer patients operated with Hartmann’s procedure and the post-operative pelvic complications by analyzing population-based comprehensive data from the local prospective rectal cancer data-base in the county of Västmanland, Sweden.

Paper II.
To describe the complication pattern in rectal cancer patients operated with Hartmann’s procedure on a national level, using the Swedish Colorectal Cancer Registry (SCRCR). Risk factors for developing different types of post-operative surgical complications were analyzed.

Paper III.
To evaluate the risk of parastomal hernias in rectal cancer patients operated with and without a prophylactic mesh based on prospectively collected data from the local rectal cancer data-base in the county of Västmanland, Sweden.

Paper IV
To assess the rate of anastomotic leakage after anterior resection in men with rectal cancer who were previously irradiated for prostate cancer, using the SCRCR and the National Prostate Cancer Registry (NPCR).
Methods

Paper I.
The local rectal cancer registry in the county of Västmanland, Sweden, with a catchment area of 270,000 inhabitants, was established in 1996. All patients diagnosed with a rectal cancer in the county are treated at the colorectal unit in Västerås. All rectal cancer patients are registered and patients operated with a tumour resection are monitored prospectively with clinical, endoscopic and radiological examinations. Data regarding demographics, radiology, surgery, laboratory parameters, histopathology, complications, clinical course and oncology were prospectively gathered on all rectal cancer patients operated with a bowel resection in Västmanland between 1996 and 2012. Data were retrospectively analyzed. The registry is comprehensive with data on ASA, laboratory data such as s-albumin, smoking, WHO performance status, cardiovascular disease, tumour tethering, pre-operative radiotherapy, type of operation and en-bloc resection.

Even though the three different operation techniques (AR, APE and HP) are not directly comparable, due to different levels of complexity and complication patterns, we made a comparison to describe the selection of HP patients and the complication patterns.

To ensure that all post-operative complications were included after HP, we also performed a review of the medical records and the complications were also classified according to the Clavien-Dindo score of post-operative complications (Table 2).

Paper II.
The Swedish Colorectal Cancer Registry (SCRCR), originally launched as the rectal cancer registry in 1995, has a coverage of more than 99% of all patients diagnosed with an adenocarcinoma of the rectum. The data-base is continuously validated (88-90). Between 2007 and 2014, all patients that were operated for rectal cancer with a bowel resection were included in the study. Co-morbidity is only registered as ASA and there are no laboratory parameters or data on functional status in the SCRCR. The Clavien-Dindo score was not available in the SCRCR until 2013 and, therefore, not included in Paper II. Emergency HP’s were excluded.
Both Papers I and II

The most common RT regime during the study periods was a short course treatment (5 Gy x 5 times in one week) followed by immediate surgery. In patients receiving chemo-radiotherapy (CRT), a long course of RT (1.8–2 Gy in 25–28 fractions administered in 5–6 weeks) was delivered together with chemotherapy (usually peroral capecitabine).

Paper III

All patients who were operated with an APE or HP at the colorectal unit, Västmanlands hospital, between 1996 and 2012, were included. The local rectal cancer registry in Västmanland was used (see details above). As a part of the routine, in the one-year cancer control, a computerized tomography (CT) was performed. A radiologist blinded for the presence of a mesh re-evaluated all available CT scans to detect the presence of a parastomal hernia.

Two groups were defined, those who had their stoma with a prophylactic mesh and those without. Between 1996 and 2006, all permanent colostomies were created without a prophylactic mesh and between 2007 and 2012, a prophylactic mesh was used for all patients after APE and HP.

All patients were followed with clinical examinations (annually for 5 years) and a CT of the chest and abdomen (at 1- and 3-years post-operatively) according to the follow-up routine for rectal cancer patients. The data were prospectively registered.

Paper IV

The National Prostate Cancer Registry (NPCR) was linked to a number of other registries in 2010 to form the Prostate Cancer data Base Sweden (PCBaSe). All men in the SCRCR who were treated with bowel resection due to rectal cancer between 2000 and 2016 and received RT for prostate cancer before the rectal cancer diagnosis were identified in the PCBaSe. Two groups were identified: patients who underwent bowel resection for rectal cancer and who had previously been administered RT for prostate cancer (RT-prost) and patients who were bowel-resected for rectal cancer after neo-adjuvant RT with or without a previous prostate cancer diagnosis, without receiving RT for prostate cancer (RT-rect), Figure 8.

Medical records were reviewed for all patients operated with an AR for rectal cancer in the RT-prost group. The presence of anastomotic leakage up to 90 days after the operation was graded according to International Study Group of Rectal Cancer (ISGRC) (91).
Figure 8. The flow chart in Paper IV

RC = rectal cancer, PC = prostate cancer, RT = radiotherapy, w/ = with, w/o = without

Definitions

Rectal cancer is defined as an adenocarcinoma of the rectum within 15 cm from the anal verge.

In Paper I, we defined “pelvic-perineal complication” as anastomotic leaks after AR (including colovaginal fistula), pelvic hematoma, abdominal or pelvic abscess, perineal wound infection (APE) and urinary catheter at discharge from hospital. Post-operative complications were defined as those that occurred within 30 days of the primary operation.

Post-operative complications listed as “others” included prolonged small bowel obstruction, stoma complications (necrosis, peristomal infection, stenosis and stoma re retractions), pancreatitis, bile leakage, abdominal wound infections and deep wound dehiscence.

The Clavien-Dindo grading (92) was used to define the severity of the surgical post-operative complications (Table 2). In the low Hartmann’s procedures, the transection of the rectum was just above or at the pelvic floor.
In Paper II, post-operative complications were defined as those that occurred within 30 days of the primary operation.

In Paper III, any intra-abdominal content protruding beyond the peritoneum or the presence of a hernia sac at least one year after operation on the CT images, was defined as a parastomal hernia (93, 94).

In Paper IV, the ISGRC defines an anastomotic leakage as a defect of the intestinal wall at the anastomotic site leading to a communication between the intra- and extra-luminal compartments. Grade A requires no active therapeutic intervention, Grade B requires active therapeutic intervention but manageable without re-laparotomy and Grade C requires re-laparotomy (91).

Table 2. Clavien-Dindo Classification of Surgical Complications

<table>
<thead>
<tr>
<th>Grades</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I:</td>
<td>Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.</td>
</tr>
<tr>
<td>Grade II:</td>
<td>Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.</td>
</tr>
<tr>
<td>Grade III:</td>
<td>Requiring surgical, endoscopic or radiological intervention</td>
</tr>
<tr>
<td>Grade IIIa:</td>
<td>intervention not under general anaesthesia</td>
</tr>
<tr>
<td>Grade IIIb:</td>
<td>intervention under general anaesthesia</td>
</tr>
<tr>
<td>Grade IV:</td>
<td>Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management</td>
</tr>
<tr>
<td>Grade IVa:</td>
<td>single organ dysfunction (including dialysis)</td>
</tr>
<tr>
<td>Grade IVb:</td>
<td>Multi-organ dysfunction</td>
</tr>
<tr>
<td>Grade V:</td>
<td>Death of a patient</td>
</tr>
</tbody>
</table>

‡ brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit

www.surgicalcomplication.info

(92)
Surgery

Paper I

In Paper I, patients were discussed pre-operatively at a multidisciplinary meeting. A clear surgical intention was to restrict the number of rectal cancer surgeons to no more than three experienced surgeons in the TME technique and one of the surgeons either performed or supervised 94% of the operations during the study period. A clear aim was to deliver a specimen with a complete and undamaged mesorectal fascia. A multi-organ en-bloc resection of invaded adjacent organs (63) or partial en-bloc resection of the posterior vaginal wall or prostate was performed, as has been previously described (66). The decision to perform HP was made pre-operatively. The indications for an HP were patients with severe co-morbidities, and/or poor functional status, malnutrition and/or the presence of metastases, where a HP was considered to be a procedure with less severe post-operative complications compared with an APE and AR. Another indication was impaired sphincter function in order to avoid poor function.

In HP, the TME was performed as in patients who underwent an AR and, in the majority, the ano-rectum was divided at the level of the levator ani muscle. In all HP and AR, the ano-rectum distal to the tumour was rinsed with at least 500 ml of an alcoholic solution before transection. All patients underwent open surgery.

Papers II and IV

TME was introduced in Sweden during the 1990’s (58) and there has been a clear shift to centralization of rectal cancer surgery to larger hospitals in most counties, where TME surgery is performed. In the beginning, TME was registered in the SCRCR, but for some years now, it has not been registered. To be able to assess the level of transection of the rectum, we have looked at the height of the tumour from the anus. According to the Swedish national guidelines, transection of the rectum in patients requiring a partial mesorectal excision is recommended 5 cm distal to the tumour. If the tumour was at 10 cm or less from the anus, we have classified it as TME (low HP or a low AR), which in turn is defined as transection of the rectum below the peritoneal reflection just above the levator ani.

There are regional differences in the rate of HP’s performed in Sweden, but the majority of rectal cancer resections during the study period were performed or supervised by a colorectal surgeon.
Paper III

Between 1996 and 2006, no prophylactic meshes were used when the permanent colostomies were created. The use of a prophylactic mesh gained popularity in Sweden following the publication of a few small randomized controlled trials, which is why a prophylactic stoma mesh was placed in all elective, permanent colostomy operations in Västerås from 2007 onwards. A standard trephine technique was used to get the end stoma through the rectus muscle. When a mesh was used, it was placed between the rectus abdominis muscle and the posterior rectus sheath and an opening was made just so the bowel could pass through the mesh as described by Israelsson (95).

Statistical analysis

Papers I and II
Differences in proportions were calculated using the chi-square test or the t-test for independent samples. Fisher’s exact test was used for low numbers. Data were normally distributed according to a histogram. Binary multivariable logistic regression analysis for risk factors for pelvic-perineal complications in Paper I and for intra-abdominal infections and re-operations with laparotomy within 30 days in patients operated with HP in Paper II, was performed. Data are reported as odds ratio (OR) and 95% confidence intervals (c.i.). Data were analyzed using Statistical Package of Social Services (SPSS tm), version 19 and 22.

Paper III
Differences in proportions were calculated using the chi-square test or the t-test for independent samples. Fisher’s exact test was used for low numbers. A Cox’s proportional hazard regression model was performed to identify risk factors for developing parastomal hernia. A p-value of < 0.05 was considered statistically significant. Data were analyzed using Statistical Package of Social Services (SPSS tm), version 21.

Paper IV
Differences in proportions were calculated using the Chi-square test for categorical variables and the Mann-Whitney U-test for continuous ones. Difference in absolute risk of any complication after surgery between groups was evaluated by type of surgery and in total, using Fischer’s exact test. Logistic regression models were employed to evaluate risk factors for anastomotic leakage in AR patients. Data were reported as OR and 95% confidence intervals. A two-sided significance level of 5% was set for all
hypothesis tests, the null hypothesis was always one of equal distribution. R version 3.4.4 was used for all statistical analysis.

Ethical considerations

All studies were approved by The Regional Ethics Review Board in Uppsala (Dnr. 213/467 (Paper I and III), 2012/558 (Paper II) and 2014/207 (Paper IV)) and followed the Declaration of Helsinki guidelines.
Results

Paper I

Of the 624 patients included, 396 (64 %) had undergone an AR, 159 (25 %) an APE and 69 (11 %) a HP. Of the 396 patients operated with an anterior resection, 290 (73 %) received a diverting loop-ileostomy. Patients that were operated with a HP were older, had a higher ASA score, a poorer WHO performance score and lower serum albumin levels. There were no differences in the inflammatory response (C-reactive protein and white blood cell count), body mass index or frequency of smokers between the groups (data not shown).

In all groups, the surgery was performed with the intent of local radicality, but the rate of metastases was higher in patients who underwent a HP (25%) when compared with those undergoing an APE (16%) and LAR (9%). A low Hartmann procedure was performed in 90% of HP patients. Operative time for HP lasted for a median of 49 minutes less than for AR and 99 minutes less than for APE. There was also less operative bleeding after a HP.

Overall complications are listed in Table 3. In total, 34 complications occurred in the 69 patients that were operated with HP. The majority of the complications were minor and could be managed pharmacologically. There were three patients with Clavien-Dindo 3b (intervention under general anaesthesia), two abdominal wound infections and one stoma complication.
Table 3. Overall complications in rectal cancer patients after elective abdominal resection in the county of Västmanland between 1996-2012.

<table>
<thead>
<tr>
<th></th>
<th>AR n=396</th>
<th>HP n=69</th>
<th>APE n=159</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic-perineal complications</td>
<td>37 (9)</td>
<td>9 (13)</td>
<td>51 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Others</td>
<td>25 (6)</td>
<td>7 (10)</td>
<td>18 (11)</td>
<td>0.157</td>
</tr>
<tr>
<td><strong>Non-surgical complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>39 (10)</td>
<td>16 (23)</td>
<td>23 (14)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>16 (4)</td>
<td>2 (2)</td>
<td>8 (5)</td>
<td>0.764</td>
</tr>
<tr>
<td>Re-operation</td>
<td>17 (4)</td>
<td>3 (4)</td>
<td>11 (7)</td>
<td>0.438</td>
</tr>
<tr>
<td>Re-operation (laparotomy)</td>
<td>11 (3)</td>
<td>2 (3)</td>
<td>6 (4)</td>
<td>0.829</td>
</tr>
<tr>
<td><strong>30-day mortality</strong></td>
<td>2 (1)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>0.074</td>
</tr>
<tr>
<td><strong>Death during hospital stay</strong></td>
<td>2 (1)</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td>0.132</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. AR (Anterior Resection), HP (Hartmann’s Procedure), APE (Abdominoperineal Excision)

Complications related to the pelvic-perineal dissection are presented in Table 4. The frequencies of these complications were 9%, 13% and 32%, p<0.001 for AR, HP and APE, respectively. Twenty-three percent of the pelvic-perineal complications in APE patients were due to perineal wound infections. In patients who were operated with HP, two (3%) developed a pelvic hematoma (Clavien-Dindo 3a) and two (3%) a pelvic abscess (Clavien-Dindo 3a). Two patients operated with HP died within 30 days of surgery.
Table 4. Pelvic-perineal complications in all rectal cancer patients after elective abdominal resection in the county of Västmanland between 1996-2012.

<table>
<thead>
<tr>
<th></th>
<th>AR  n=396</th>
<th>HP  n=69</th>
<th>APE n=159</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastomotic insufficiency</td>
<td>25 (6)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pelvic hematoma</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Pelvic abscess</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Perineal wound infection</td>
<td>-</td>
<td>-</td>
<td>36 (23)</td>
<td></td>
</tr>
<tr>
<td>Urinary catheter on discharge</td>
<td>12 (3)</td>
<td>5 (7)</td>
<td>14 (9)</td>
<td></td>
</tr>
<tr>
<td>Overall pelvic-perineal</td>
<td>37 (9)</td>
<td>9 (13)</td>
<td>51 (32)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. AR (Anterior Resection), HP (Hartmann’s Procedure), APE (Abdominoperineal Excision).

The median post-operative stay in hospital was 12 days for patients who had undergone an HP and 13 days after an APE. The post-operative hospitalization was longer for both of these interventions, compared with 9 days after an AR (p<0.001).

At the one-year follow-up, there were no patients found with late symptomatic abscesses or fistulae after HP. In the binary multivariable logistic regression analysis, the only factors associated with less pelvic-perineal complications was operation with a HP (OR 0.31; 95% confidence intervals 0.12–0.81) and AR (OR 0.26; 95% confidence intervals 0.14–0.48).

Paper II

Of 10,940 patients, bowel resected for rectal cancer, 1,452 (13%) underwent HP. A low HP was performed in 62% of the patients.

An accredited colorectal surgeon or a surgeon with a special interest in colorectal surgery performed or supervised 97% of the operations. The post-operative complication rates are listed in Table 5.
Table 5. Post-operative complications in patients with rectal cancer after abdominal resection in Sweden between 2007 and 2014

<table>
<thead>
<tr>
<th>Complication</th>
<th>hp n = 1452</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall complications</td>
<td>594 (41)</td>
</tr>
<tr>
<td>Overall surgical complications</td>
<td>372 (26)</td>
</tr>
<tr>
<td>Intra-abdominal infections</td>
<td>122 (8)</td>
</tr>
<tr>
<td>Unplanned ICU stay</td>
<td>138 (10)</td>
</tr>
<tr>
<td>Re-laparotomy</td>
<td>146 (10)</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>53 (4)</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>87 (6)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages. HP, Hartmann's procedure; ICU, intensive care unit.

The multivariable logistic regression analysis on patients operated with HP identified pre-operative RT (OR 1.78; 95% CI, 1.14–2.77), intra-operative bowel perforation (OR 1.99; 95% CI, 1.08–3.67), T4 tumours (OR 1.68; 95% CI 1.04–2.69) and female gender (OR 1.73; 95% CI, 1.15–2.61) as risk factors for intra-abdominal infections. Elevated body mass index (BMI) (OR 1.05; 95% CI 1.02–1.09), female gender (OR 2.06; 95% CI 1.41–3.00) and higher ASA score (OR 1.62; 95% CI 1.12–2.34) were associated with an increased risk of re-laparotomy.

**Paper III**

During the study period, 206 patients were operated for rectal cancer with a permanent stoma, 145 (70%) had undergone an APE and 61 (30%) a HP. There was no statistical difference between patients with and without a mesh regarding, age, gender, pre-operative albumin levels, ASA score, body mass index (BMI), smoking, cardiovascular and diabetic disease. There was a small difference concerning WHO performance scale with fitter patients in the mesh group. There were no mesh-related complications (abscess, fistula, intestinal
erosion or obstruction) and 71 (34%) developed surgical complications where 5 (2%) needed a re-laparotomy with no difference between the groups. At the 12-months follow-up, 187 were alive and available for analysis of a parastomal hernia. The median follow-up time was 31 (12-202) months. CT scans were available in 141 (75%) patients. No difference was seen in the parastomal hernia frequency diagnosed on clinical examination or on CT scans regarding the use of prophylactic stoma mesh or not (Table 6). Even with combined clinical and CT scan results, no difference was observed. Four patients were operated electively for parastomal hernia with no difference between the groups. The presence of a prophylactic stoma mesh did not affect the risk of parastomal hernia formation in a Cox regression analysis. An elevated BMI was an independent risk factor for parastomal hernia formation when either clinically detected and/or CT-verified. When only using clinical examination in the Cox model, the risk factors for parastomal hernia formation were smoking and BMI.

Table 6. Parastomal hernia in rectal cancer patients operated with and without a prophylactic stoma mesh in the county of Västmanland between 1996-2012.

<table>
<thead>
<tr>
<th></th>
<th>No Stoma mesh</th>
<th>Stoma mesh</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically verified parastomal hernia (n=187)</td>
<td>31/124 (25)</td>
<td>16/63 (25)</td>
<td>0.869</td>
</tr>
<tr>
<td>CT-verified parastomal hernia (n=141)</td>
<td>43/81 (53)</td>
<td>32/60 (53)</td>
<td>0.176</td>
</tr>
<tr>
<td>CT and/or clinically verified parastomal hernia (n=187)</td>
<td>49/115 (43)</td>
<td>34/66 (52)</td>
<td>0.247</td>
</tr>
<tr>
<td>Follow-up (months)*</td>
<td>36 (12-202)</td>
<td>24 (12-89)</td>
<td></td>
</tr>
<tr>
<td>Re-operation due to parastomal hernia</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses are percentages unless otherwise indicated *Values are median (range)

Paper IV

A total of 13,299 men were operated for rectal cancer during the study period. A previous diagnosis of prostate cancer was found in 1,122 of these men, of whom 188 received RT for prostate cancer. A total of 63 patients were registered to have been operated with AR after having previously received RT for prostate cancer. After reviewing patient records, 59 were found to have been operated with AR. The surgical complication rate was 22% for the RT-prost group and 27% for the RT-rect group. The post-operative AL rate for
those operated with AR in the RT-prost group was 10% and 15% in the RT-rect group. After reviewing the patient records for those operated with AR in the RT-prost group, the AL rate rose to 20%. No mortality was found within 90 days (Table 7).

Table 7. Clinical characteristics and post-operative complications in patients operated with anterior resection who had previously received radiotherapy for prostate cancer after review of medical records.

<table>
<thead>
<tr>
<th></th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td>59 (100)</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>42 (71)</td>
</tr>
<tr>
<td>3-4</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Missing data</td>
<td>10 (17)</td>
</tr>
<tr>
<td><strong>Rectal cancer stage</strong></td>
<td></td>
</tr>
<tr>
<td>Stage 1-2</td>
<td>36 (61)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>14 (24)</td>
</tr>
<tr>
<td>Stage 4</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Missing data</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Mean (SD) delay between RT for prostate cancer and rectal cancer surgery (months)</strong></td>
<td>64.4 (49.1)</td>
</tr>
<tr>
<td><strong>Level of rectal tumour</strong></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>6 (10)</td>
</tr>
<tr>
<td>6-10</td>
<td>27 (46)</td>
</tr>
<tr>
<td>11-15</td>
<td>26 (44)</td>
</tr>
<tr>
<td>&gt;15</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Missing data</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Pre-operative RT</strong></td>
<td>3 (5)</td>
</tr>
<tr>
<td><strong>Pre-operative CRT</strong></td>
<td>3 (5)</td>
</tr>
<tr>
<td><strong>Pre-operative chemotherapy</strong></td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Diverting stoma</strong></td>
<td>50 (85)</td>
</tr>
<tr>
<td><strong>Overall surgical complications</strong></td>
<td>24 (41)</td>
</tr>
<tr>
<td><strong>Clavien-Dindo &gt;= 3b</strong></td>
<td>8</td>
</tr>
<tr>
<td><strong>Anastomotic leakage</strong></td>
<td>12 (20)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>6</td>
</tr>
<tr>
<td>Grade 2</td>
<td>5</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Re-laparotomy</strong></td>
<td><strong>5 (8)</strong></td>
</tr>
<tr>
<td><strong>Mortality within 30 days</strong></td>
<td><strong>0 (0)</strong></td>
</tr>
<tr>
<td><strong>Mortality within 90 days</strong></td>
<td><strong>0 (0)</strong></td>
</tr>
</tbody>
</table>

AR = anterior resection, ASA = American Society of Anesthesiologists, SD = standard deviation, RT = radiotherapy, CRT = chemoradiotherapy
Discussion

The management of rectal cancer has seen dramatic changes in the past 3 decades. Not only have diagnostic methods evolved but also surgical and perioperative management have changed so that survival has improved. Rectal cancer surgery is afflicted with life-threatening complications that have been studied thoroughly throughout the years. With an aging population, we are faced with new dilemmas regarding complication patterns and selecting the appropriate treatment strategy for our patients. This thesis studies the postoperative complication patterns in rectal cancer patients.

Post-operative complications

The frequency of intra-abdominal infections in patients operated with Hartmann’s procedure was low, despite their high age, more co-morbidities and more severe disease. In Paper I, there was no difference in the relaparotomy rate when compared with AR and APE and the operation time was shorter. Pre-operative radiation therapy was administered in fewer HP patients compared with AR and APE patients. The multivariable logistic regression analysis in Paper I showed that both HP and AR were the only risk factors associated with fewer pelvic-perineal complications. In Paper II the multivariable logistic regression analysis identified RT, T4 tumours, intra-operative bowel perforation and female gender as risk factors for developing intra-abdominal infections. An ASA score of 3 or 4, female gender and BMI were identified as risk factors for being re-operated with laparotomy. The level of transection of the rectum was not identified as a risk factor for developing intra-abdominal infections in the multivariable analysis.

The intra-abdominal infection frequency of 8% (Paper II) and the pelvic abscess rate of 3% (Paper I) are clearly lower than the pelvic infection rates of 12-33% seen in the previously published small retrospective cohort studies (71-73). The rates are, however, consistent with a recently published Dutch study that compared post-operative complications after HP with and without RT (96). An intra-abdominal abscess requiring re-intervention was seen in 7% of those who underwent HP after RT and in 3% in those who only underwent HP. In the Dutch study, some risk factors differed from those observed in Paper II. The median age was lower (72 vs. 77) and stage IV patients were excluded in the Dutch study, which strengthens our findings that HP is a
relatively safe operation in the old and frail. The Dutch group recently published another study where low HP was compared with LAR with and without diverting ileostomy in rectal cancer patients who had received pre-operative RT (97). The results showed that the HP was associated with fewer intra-abdominal infectious complications and fewer re-operations compared with LAR. In this study, they excluded 31 % of the patients because of T4 tumours, emergency surgery, no RT or missing values. Of the mentioned variables, our study (Paper II) only excluded emergency surgery and still the rate of intra-abdominal complications was not high, again strengthening the validity of HP as the method of choice among the established types of surgery.

The increased risk for anastomotic leakage in patients operated with LAR after receiving RT is known (34). In the same manner, the healing of the stapled rectal stump in HP patients may be impaired after the patient has received pre-operative RT, possibly explaining the higher risk of intra-abdominal infections after pre-operative RT. The number of cartridges used to divide the rectum has been proposed as a risk factor for AL in laparoscopic AR (98-101). However, almost all operations in Papers I and II were open procedures, which probably means that a fewer staplers were used. The size of the cartridges used could also be a risk factor. Unfortunately, those two variables were not registered in our registries. In Paper I, we used the broadest possible transverse stapler that can be fitted in the pelvis, mostly 45 or 60 mm. As a routine, we also used 2 pelvic drains that were removed two days post-operatively. Another proposed risk factor is the low level of transection since this has been described as risk factor for AL in patients undergoing AR (34, 101, 102). However, the multivariable analysis in Paper II found no association between the level of the tumour and an increased risk for intra-abdominal infections. Male gender has, in some studies, also been associated with higher post-operative pelvic complications after HP (72, 97). In the Västmanland cohort (Paper I), the male gender was not identified as a risk factor for developing pelvic-perineal complications but to our surprise the female gender was identified as a risk factor for intraabdominal complications in Paper II. Nothing in the literature supports this and we have no explanation for this finding.

In Paper II, we found that the intra-operative perforation rate was relatively high in patients operated with HP (8%). The reason for this finding might have been conversion to HP from AR when the surgeon experiences bowel perforation or other technical difficulties. Another theoretical explanation might be different surgical experiences but, since 97% of all the HP were performed or supervised by an accredited colorectal surgeon or surgeon with special colorectal interest, that explanation is less probable.

In Paper I, we also reviewed all medical records of patients operated with HP, identifying all complications and their severity. The Clavien Dindo scale was not introduced until 2013 in the SCRCR and, therefore, not analysed in Paper II. Only 50% of patients that underwent a HP in Paper II received pre-
operative RT. The relatively low number of HP patients that received neo-adjuvant RT is a concern due to the beneficial effects on local recurrence (20). However, we have shown that the HP patients that receive neo-adjuvant RT are at a higher risk of developing intra-abdominal infections. Additionally, there might be an underestimation of the amount of intra-abdominal infections since we have not accounted for the complications that could appear later than 30 days post-operatively. Furthermore, late complications, such as secretion and bleeding from the remaining rectum, have not been analysed in these studies. The extent of these sometimes crippling problems with secretion/bleeding and incontinence is totally unknown.

Even though all registries used in this thesis gather data prospectively and have almost complete coverage, there are some limitations to the studies. A study by Gunnarsson et al. (88), on the validation of post-operative complications in the SCRCR, showed that the validity is acceptable for the more serious complications while the less serious ones are underestimated. This means that the results from the SCRCR probably underestimate the frequency of wound infections which is why we did not analyze those. Data regarding potential late re-admissions in the national registry were not retrieved, which may have led to an underestimation of the rate of intra-abdominal infections in Paper II.

The strength of Paper I is the comprehensive data-base including patient-related variables such as smoking, albumin levels, co-morbidities and functional performance status. However, the large number of included patients and the national population-based design is the strength of Paper II.

The studies in Paper I and II might seem very similar and one might speculate as to why one should perform both studies, since all patients in the local population-based study are also registered in the national registry and hence part of Paper II. The local rectal cancer registry in the Västmanland county (Paper I) is a comprehensive data base including numerous details regarding the demographics, blood tests, comorbidity, WHO scores, radiology, surgery, histology, clinical course and oncology. The registry was validated with a thorough review of medical records of patients operated with HP and it describes a single centre experience where one surgeon has performed or supervised the majority of the operations. The good results from the local study inspired us to proceed to the much larger national cohort for exploring the risk profile after HP. There are some uncertainties regarding the validity of the SCRCR, the data on smaller pelvic abscesses and suture line insufficiencies are probably higher than those reported, when compared with the data in the local registry that were validated. Despite this, the finding in the national registry of an intra-abdominal infection rate of less than 10 %, supports that HP is an appropriate surgical method in the old and frail.
**Parastomal hernia**

Prophylactic stoma mesh did not prevent the occurrence of parastomal hernias and the only risk factor for parastomal hernia formation on the multivariable analysis was BMI.

The study on PSH (Paper III) is one of the largest studies on the subject with 206 included patients. Most of the randomized studies are small and heterogenous with varying ages, indications for stoma, type of stoma, type of mesh, placement of stoma and outcome measures (60, 81, 82, 86). In our study, the mesh was in all cases placed in the retromuscular plane and only a small number of experienced colorectal surgeons operated according to standardized techniques. A parastomal hernia rate of 53% in patients without a prophylactic mesh, when diagnosed on CT was high but comparable to previous small randomized trials. However, a parastomal hernia rate of 53% in the group with a prophylactic mesh is much higher than reported in previous randomized trials (81, 103). A recent RCT from Sweden, which to date is the largest RCT on this subject, did not find any difference in the rate of parastomal hernia between the mesh (32%) and non-mesh (34%) groups after a one year follow-up (87). In a recent Cochrane review, where 10 randomized trials with a total of 844 patients were included, a significant reduction in the risk of parastomal hernias was shown in patients receiving a prophylactic mesh compared with the standard stoma formation. There was no difference in re-operation rate at 12 months, operative time, length of stay and stoma- or mesh-related infections. They concluded, however, that despite the significant reduction in the rate of parastomal hernia, their confidence in that estimate is low due to the presence of a large degree of clinical heterogeneity as well as high variability in follow-up duration and techniques of parastomal herniation detection (104).

There were no differences between the groups regarding re-operation rate for parastomal hernia, 2% for the no mesh group and 1% for the mesh group. This low re-operation rate could indicate that the presence of parastomal hernia rarely causes discomfort for the patients, even though the majority of the parastomal hernias contained intestinal loops or omentum. It was noteworthy that the group with meshes had hernias containing higher rates of intestinal loops or omentum, indicating that these hernias were actually larger but the difference was not statistically significant.

The number of patients and its retrospective, non-randomized design are the main limitations. Furthermore, the detection of parastomal hernia on CT is difficult and some false negative cases might have been identified, especially since none of the CT scans were done during the Valsalva manoeuvre. However, the radiologist was blinded to the presence of a mesh and there was no difference between the groups in the parastomal herniation rate at clinical examination.
Anastomotic complications

The selected group of patients that were operated with an anterior resection for rectal cancer, previously irradiated for prostate cancer, had an anastomotic leakage rate of 20% which is lower than previous reports have shown. The majority of these patients were healthy, had a diverting stoma and early tumour stages. Most patients are, however, operated with non-restorative surgery, probably reflecting the surgeon’s awareness of the increased risk for anastomotic complications.

Only two small cohort studies have addressed the issue of anastomotic leakage after anterior resection for rectal cancer in patients that have previously received irradiation for prostate cancer. Both studies, with a total of 20 patients previously receiving radiotherapy for prostate cancer, reported over 50% leakage rate after anterior resection (105, 106). In our cohort, the patients previously irradiated for prostate cancer had an anastomotic leakage in 20% of the cases, after validation by a review of the medical records.

Four patients were identified with wrong type of operation after reviewing patient records. The review was performed only on men that were operated with AR in the RT-prost group. The ISGRC definition of AL was used grading the AL which was not used in the SCRCR and the AL were registered at 90 days while the SCRCR registers AL at 30 days. This can partly explain the increase from 10% to 20% in AL frequency before and after the medical record review since the leaks that were missed were minor leaks (Grade A).

Paper IV is the largest study to date on the subject with 188 patients operated for rectal cancer after radiation treatment for prostate cancer. The two registries, SCRCR and NPCR, have both been validated and have almost complete coverage and register data prospectively.
In an attempt to improve the post-operative complication pattern, a multi-centre, randomized controlled trial, The Hartmann’s Procedure or Abdominoperineal Excision With Intersphincteric Dissection in Rectal Cancer (HAPIrect trial- NCT01995396) (69) has been launched. An APE with an intersphincteric dissection is a possible alternative for patients with rectal cancer unsuitable for an anastomosis but deemed suitable for both APE and HP. An intersphincteric dissection means that the external sphincter is left intact which makes it easier to suture the perineum and the risk of infections in the perineum will decrease and, in that way, the problem with the ano-rectal stump will also disappear. Patients are randomized between an intersphincteric APE or HP with the aim of identifying the optimal surgical method for this patient group.

It is still unclear how the frequency of parastomal hernia is affected with minimal invasive surgery and the different types and locations of the prophylactic mesh. Even though our study has not demonstrated better effect with the usage of mesh, the high frequency of PSH is still a clinical problem and further studies are needed on this matter, primarily with focus on minimal invasive surgery and the types and location of the mesh.
Conclusions

Despite higher age, more co-morbidities and more advanced disease in patients operated with HP, as seen in papers I and II, the frequencies of post-operative intra-abdominal infections were low. A low HP is not a risk factor for intra-abdominal infections but pre-operative RT is a risk factor. HP is a valid alternative in the old and frail patients with rectal cancer.

A parastomal hernia occurs in half of the patients who receive a permanent stoma, regardless of whether a prophylactic mesh was placed during the index operation or not. The placement of a prophylactic mesh is not recommended at our department until further randomized controlled trials have shown a clear benefit of its use.

The rate of anastomotic leakage after anterior resection for rectal cancer in men that were previously irradiated for prostate cancer was much lower than previously reported and the leaks rarely required re-laparotomy and there was no mortality. These patients were healthy with early cancer stages and in this selected group of patients, anterior resection is a viable alternative.
Rektalcancer drabbar årligen ca 2 000 personer i Sverige och tillsammans med koloncancer utgör denna den näst vanligaste cancern hos både män och kvinnor. Vid rektalcancer är en bukopoperation i form av en så kallad låg främre resektion (LFR) med total mesorektal excision (TME) gyllene standard. Operationen innebär att man tar bort ändtarmen med sin fettkudde, som innehåller lymfkörtlar, men lämnar kvar sista centimetrern av ändtarmen samt analkanalen dit tjocktarmen sen kopplas med en anastomos (tarmskarv). Drygt hälften av alla patienter är opererade med denna metod. För de lågt belägna tumörerna är en abdominoperineal excision (APE) nödvändig, vilket innebär att man även tar bort anus och lägger upp en permanent kolostomi (påse på magen). Ett tredje alternativet är en så kallad Hartmann’s operation (HA) som ofta väljs för de äldre och sjukare patienterna för att minska risken för livshotande komplikationer såsom anastomosläckage (tarmskarven läker inte och avföring kan komma ut i bukhålan) eller funktionella besvär som till exempel avföringsinkontinens. Operationen innebär att man tar bort större delen av ändtarmen samt en del av tjocktarmen, försätter ändtarmsstumpen och sedan lägger upp en permanent kolostomi.

Dessa bukopoperationer kan efterföljas av svåra postoperativa komplikationer. Anastomosläckage efter LFR och abscesser (varansamlingar) i lilla bäcken kan förekomma hos samtliga. Svårbehandlade infektioner i perineala såret kan förekomma hos patienter opererade med APE. Några mindre studier har visat hög frekvens (12-33%) av bäckenabscesser hos rektalcancerpatienter opererade med HA. Parastomalt bråck är vanligt förekommande hos de som får stomi. För att minska risken för bråck har studier genomförts där ett nät placerats i samband med anläggande av stomin. Patienter som tidigare i livet fått strålbehandling för prostatacancer och som sedan opereras med främre resektion får anastomosläckage i mer än hälften av fallen enligt två små retrospektiva studier.

Syftet med avhandlingen är att beskriva postoperativa komplikationer hos patienter med rektalcancer.

Studie I

Studie I var en populationsbaserad analys av postoperativa komplikationer hos patienter med rektalcancer som opererats med HA där vi jämförde HA med
de två övriga bukoperationer för rektalcancer: APE och LFR. Vi identifierade
riskfaktorer för att utveckla postoperativa pelvic-perineala (bäcken-underlivs)
komplikationer. Detta var en retrospektiv (tillbakablickande) analys av
prospektivt insamlade data från det lokala rektalcancerregistret i
Västmanland. Samtliga patienter opererade med tarmresektion på grund av
rektalcancer i Västmanland mellan 1996 och 2012 inkluderades. Av 624
inkluderade patienter opererades 396 (64%) med AR, 159 (25%) med APE
och 69 (11%) med HA varav 90% av dessa operationer utfördes som en låg
HA (en liten anorektalstump lämnades kvar). Patienter opererade med HA var
ärldre, hade högre ASA grad (högre operationsrisk) och lägre WHO grad (ned-
satt funktionsförmåga). Operationstiden för HA var i median 49 respektive 99
minuter kortare än för LFR och APE och det blödde mindre. Bäcken-
komplikationer var vanligare efter APE jämfört med både LFR och HA (32% vs.
9% vs. 13%, p<0.001). Våra resultat visade att det var få patienter som
etter HA utvecklade postoperativa bäckenkomplikationer, trots högre ålder
och mer komorbiditet (sjuklighet), jämfört med LFR- och APE-ingrepp och
att HA är en lämplig operation för gamla och sköra patienter.

Studie II

Studie II var en nationell populationsbaserad retrospektiv analys av
prospektivt insamlade data. I denna samlade vi data från det Svenska
kolorektalcancerregistret som är rikstäckande och inkluderar över 99 % av alla
rektalcancer-patienter i Sverige. Mellan 2007 och 2014 opererades 10940
patienter för rektalcancer, varav 1452 (13%) opererades med en HA. Median-
åldern var 77 år och 43% hade ASA score 3 eller 4. Låg HA, dvs delning av
ändtarmen strax ovanför anus, utfördes hos 62% av patienterna. Den intra-
abdominella infektionsfrekvensen var 8%. Relaparotomifrekvensen (nytt
bukingrepp pga komplikation) uppgick till 10%. Multivariatet logistik
regressionsanalys identifierade preoperativ strålbehandling (OR 1.78; 95% CI
1.14-2.78), intraoperativ tarmperforation (OR 1.99; 95% CI 1.08-3.67), T4
tumörer (OR 1.68; 95% CI 1.04-2.69) och kvinnor (OR 1.73; 95% CI 1.15-
2.61) som riskfaktorer för att utveckla intraabdominell infektion. Förhöjdf BMI
(OR 1.05; 95% CI 1.02-1.09), kvinnor (OR 2.06; 95% CI 1.41-3.00) och ASA
grad 3/4 (OR 1.62; 95% CI 1.12-2.34) identifierades som riskfaktorer för re-
laparotomi. Trots äldre och sjuka patienter med avancerad cancer var
frekvensen allvarliga postoperativa komplikationer och relaparotomier låg hos
patienter som opererades med en HA i Sverige. Även denna studie bekräftar
att HA är en lämplig operation för äldre och sköra patienter med rektalcancer.
Studie III


Studie IV

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References


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)