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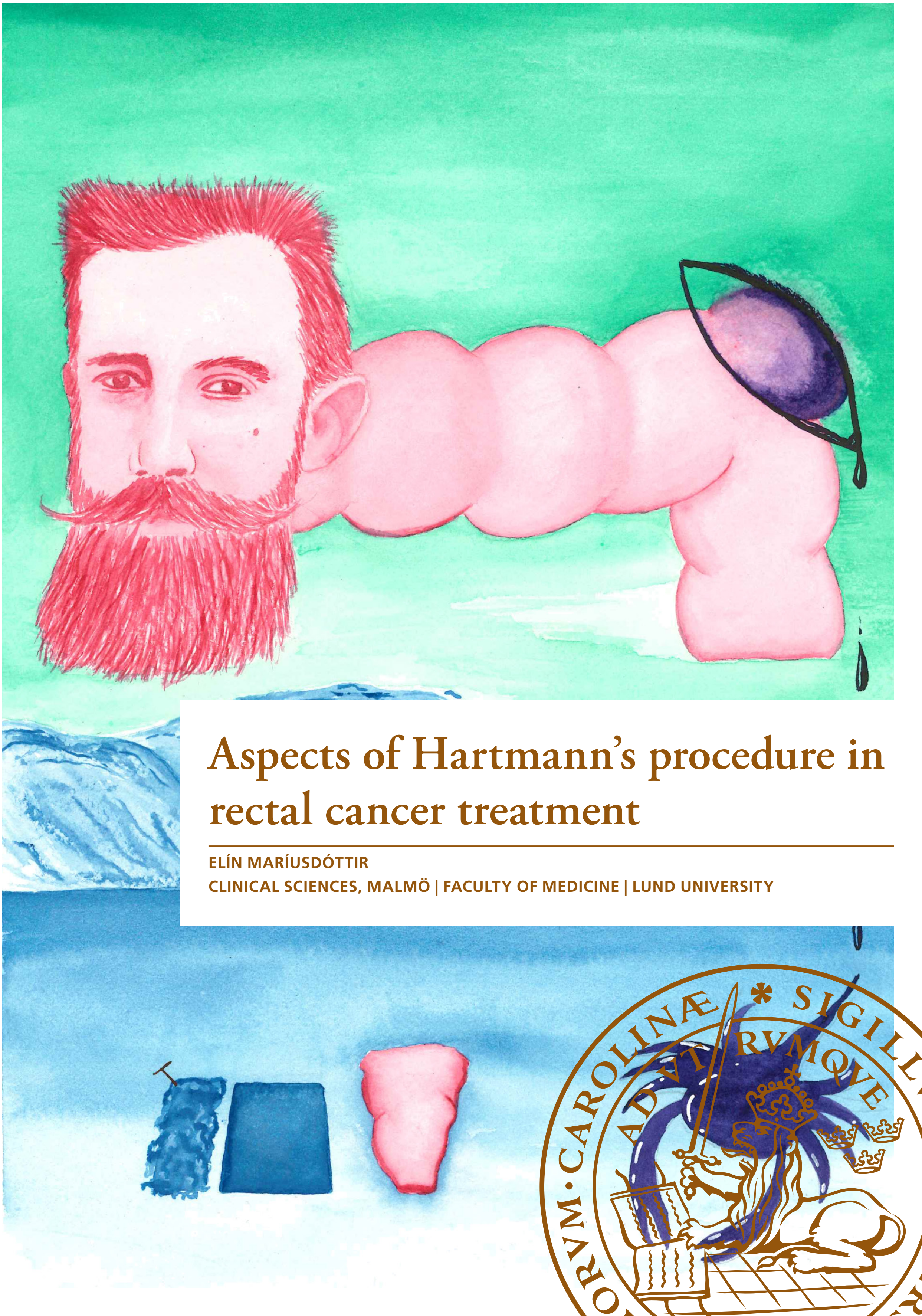

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Elín Maríusdóttir

LUND
UNIVERSITY

DOCTORAL DISSERTATION

By due permission of the Faculty of Medicine, Lund University, Sweden.
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**Title and subtitle:** Aspects of Hartmann's procedure in rectal cancer treatment

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**Material:** For papers I and II, data was sourced from the Swedish Colorectal Cancer Registry (SCRCR) from the southern part of Sweden. Regional data was further supplemented with information extracted from medical charts. In papers III and IV nationwide data from the SCRCR was used.

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Study II: The incidence of pelvic sepsis following HP was 11%. Risk factors for developing pelvic sepsis were neoadjuvant radiotherapy (OR 7.96, 95% CI 2.54-35.36) and BMI over 25 kg/m2 (OR 5.26, 95% CI 1.80-19.50). Median time from operation to diagnosis was 21 days (range 5-355) with 40% of patients diagnosed beyond 30 days postoperatively. The majority of cases (70%) were treated conservatively and none needed major surgery.

Study III: The study included 8476 patients with 1210 undergoing HP, 5406 undergoing AR and 1860 abdominal perineal resection (APR). The 30-day overall complication rate following HP was lower than after APR. A multivariable analysis revealed that undergoing HP did not increase the risk of overall or surgical complications. Patients undergoing APR had an increased overall risk of complications (OR 1.18 95% CI 1.01–1.40). The type of surgical procedure was not a risk factor for 30-day mortality.

Study IV: In this study 4741 patients were included, 614 undergoing HP, 3075 AR and 1052 APR. Multivariable Cox regression revealed that the type of operation was not a risk factor for local recurrence (LR) or distant metastasis. Overall survival was better following AR (OR 0.62, 95% CI 0.54-0.72) likely due to patient selection. Risk factors for LR were intraoperative bowel perforation, a pT4 tumor and a positive circumferential resection margin.

**Conclusion:** For patients not amenable for restorative surgery, HP represents a valid alternative with a favorable postoperative and oncological outcome.

**Key words:** Rectal cancer surgery, Hartmann's procedure, surgical outcomes, non-restorative surgery, pelvic sepsis, complications, oncological outcomes.

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*Jórunn, Auður og Unnur*
*- mínir fegurstu gimsteinar.*

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# Rationale

Rectal cancer is a common malignancy, every year around 2000 individuals are diagnosed in Sweden. Developments in rectal cancer treatment such as surgical technique, radiation therapy as well as systemic chemotherapy have improved outcomes substantially, but the constantly changing landscape has also made comparison of long-term outcomes challenging. This makes decisions regarding the optimal treatment difficult and calls for new studies.

Elderly and frail individuals in need of treatment for rectal cancer are a growing entity and these patients require special attention as the gold standard of restorative surgery does not always apply. Individualizing surgical treatment, aiming to provide tailored treatment, is the standard of care for example by multidisciplinary team conferences.

Patients with mid or high rectal cancer that are unfit for anterior resection (restorative surgery) may be offered a Hartmann's procedure with creation of a sigmoid stoma, leaving a rectal stump.

The use of Hartmann's procedure varies widely between countries. This suggests a lack of evidence regarding the best treatment for rectal cancer in patients who are unfit for restorative surgery. Previous studies have reported high risk of surgical complications following Hartmann's procedure, especially pelvic sepsis caused by breakdown of the rectal remnant causing blowout. This caused many surgeons to recommend abdominoperineal resection to avoid the complications caused by leaving the rectal stump. Another non-restorative option is the intersphincteric abdominoperineal resection. However, this procedure is not widely used in Sweden.

Recent studies have challenged previous findings regarding the surgical outcomes following Hartmann's procedure. Further research is necessary, particularly since many studies exclude patients undergoing Hartmann's procedure, as this group tends to be older and frailer.

Population based studies report that up to 25% of patients are unfit for restorative surgery which makes this patient group of particular interest to study. The optimal surgical treatment for this patient group is an important question and this thesis aims to provide valuable insights and potential answers.

# List of papers

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

**I.** **Mariusdottir E**, Jörgren F, Mondlane A, Wikström J, Lydrup ML, Buchwald P. Low incidence of pelvic sepsis following Hartmann's procedure for rectal cancer – a retrospective multicentre study. *BMC Surg. 2022 Dec 9 ;22(1) :421*

**II.** **Mariusdottir E**, Jörgren F, Saeed M, Lydrup ML, Buchwald P. Hartmann's procedure in rectal cancer surgery is often an intraoperative decision- a retrospective multicenter study. *Langenbeck's Archives of surgery. 2024 Feb 7;409(1):55*

**III.** **Mariusdottir E**, Jörgren F, Lydrup ML, Buchwald P. Post-operative morbidity following Hartmann´s procedure in comparison to anterior resection and abdominoperineal resection for rectal cancer – a population-based study. *Colorectal Dis. 2024 Jun;26(6):1250-7.*

**IV.** **Mariusdottir E,** Jörgren F, Lydrup ML, Buchwald P. Oncological outcome following Hartmann's procedure compared with anterior resection and abdominoperineal resection for rectal cancer – the type of procedure does not influence local recurrence or distant metastasis. A population-based study. *Colorectal Dis. 2024;00:1-9.*

# Abbreviations

| | |
|---|---|
| AL | Anastomotic leak |
| ANOVA | Analysis of variance |
| APR | Abdominal perineal resection |
| AR | Anterior resection |
| ASA | American society of anaesthesiologists |
| BMI | Body mass index |
| CEA | Carcinoembryonic Antigen |
| CRM | Circumferential resection margin |
| CT | Computed tomography |
| DFS | Disease free survival |
| DM | Distant metastasis |
| dMMR | Mismatch repair deficiency |
| DS | Diverting stoma |
| EMVI | Extramural vascular infiltration |
| FAP | Familial adenomatous polyposis |
| HP | Hartmann's procedure |
| iAPR | intersphincteric abdominal perineal resection |
| ICU | Intensive care unit |
| LAR | Low Anterior resection |
| LARS | Low anterior resection syndrome |
| LHP | Low Hartmann's procedure |
| LLN | Lateral lymph nodes |
| LR | Local recurrence |
| MIS | Minimally invasive surgery |
| MMR | Mismatch repair |
| MRI | Magnetic resonance imaging |
| OR | Odds ratio |
| OS | Overall survival |
| pCRM | Positive circumferential resection margin |

| | |
|---|---|
| QoL | Quality of life |
| RAPIDO | Radiotherapy and preoperative induction therapy followed by dedicated operation |
| RT | Radiotherapy |
| SCRCR | Swedish colorectal cancer registry |
| SD | Standard deviation |
| TD | Tumor deposits |
| TME | Total mesorectal excision |
| TNM | Tumor Node Metastasis |

# Abstract

**Background:** It is crucial to determine the optimal surgical treatment for the rising number of patients diagnosed with rectal cancer who are unsuitable candidates for restorative surgery. In this study, the use of Hartmann's procedure (HP) was examined, focusing on patients with mid or high rectal cancer, to clarify the role of HP in rectal cancer treatment.

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**Conclusion:** For patients not amenable for restorative surgery, HP represents a valid alternative with a favorable postoperative and oncological outcome.

**Keywords:** Rectal cancer, Hartmann's procedure, non-restorative surgery, pelvic sepsis, complications, oncological outcomes.

# Populärvetenskaplig sammanfattning

Årligen drabbas ungefär 2000 personer i Sverige av ändtarmscancer. Den åldersstandardiserade incidensen är 25/100.000 för män och 17/100.000 för kvinnor. Ändtarmscancer definieras som elakartad tumör <15 cm från anus. Den kurativa behandlingen är kirurgi, kombinerat med strålbehandling och/eller cytostatika-behandling ibland.

Val av operationsmetod styrs utifrån tumörhöjd från anus samt patientfaktorer;

Främre resektion är standardbehandling för ändtarmscancer belägen i mellersta och övre tredje delen av rektum. Operationen innebär att ändtarmen avlägsnas och en anastomos (koppling) mellan ändtarm och proximal tjocktarmsända med eller utan avlastande tunntarmsstomi (påse på magen) genomförs.

Abdominoperineal resektion utförs hos patienter med ändtarmscancer belägen <5 cm från anus. Abdominoperineal resektion innebär bortoperation av ändtarmen tillsammans med hela slutarmuskeln och ibland även bäckenbotten samt anläggande av tjocktarmsstomi.

Hartmanns operation väljs som behandling för tumörer belägna i mellersta eller övre tredjedelen av ändtarmen när anastomosförfarande inte bedöms lämpligt på grund av hög risk för anastomosläckage. Anastomosläckage innebär att kopplingen mellan tarmändarna inte håller tät och kan orsaka en alvarlig infektion. Hartmanns operation kan också vara ett alternativ vid hög risk för dålig funktion vid känd inkontinens, exempelvis tidigare skada på slutarmuskeln. Hartmanns operation används också när främre resektion inte bedöms vara lämplig under operationen exempelvis på grund av händelse eller fynd. Antalet patienter aktuella för Hartmanns operation kan förväntas öka med befolkningens stigande ålder. Hartmanns operation innebär att ändtarmen bortopereras, kvarvarande ändtarmsstump försluts, vilken lämnas i lilla bäckenet och tjocktarmen läggs upp som en påse på magen.

Inom Sverige varierar andelen Hartmanns operation vid ändtarmscancer stort, 10–40% på olika sjukhus. De stora skillnaderna avspeglar att kunskapen om såväl komplikationer och funktionella resultat samt i viss mån onkologiska data vid Hartmanns operation för ändtarmscancer är otillräcklig.

Det övergripande syftet med avhandlingen är att utröna Hartmanns operations roll i behandlingsarsenalen vid ändtarmscancer. Registeruppgifter från svenska kolorektalcancerregistret användes i alla delarbeten och data kompletterades med journaluppgifter för arbete I och II.

Den första studien syftade på att undersöka patientspecifika faktorer som förutsäger valet av Hartmanns operation. Studien visade att patienter som genomgick Hartmanns operation var betydligt äldre och hade oftare mer uttalad samsjuklighet jämfört med patienter opererade med främre resektion och abdominoperineal resektion. Beslutet att utföra Hartmanns operation togs intraoperativt i 23% av fallen, oftast på grund av svårigheter vid anastomosförfarandet eller onkologiska orsaker.

Den andra studien visade att incidensen av bäckensepsis, en Hartmann specifik komplikation var 11%, vilket är betydligt lägre än vad som tidigare beskrivits. Bäckensepsis är en infektion kring den kvarvarande ändtarmsstumpen som lämnas kvar vid en Hartmanns operation. Patienter som hade genomgått strålbehandling inför operationen samt patienter med övervikt (BMI >25 kg/m$^2$) hade ökad risk för att utveckla bäckensepsis.

Den tredje studien undersökte om val av operationsmetod påverkar risken att drabbas av komplikationer. Hartmanns operation var associerad med en ökad risk för infektion inne i buken jämfört med övriga ingrepp. Ingen signifikant skillnad observerades i frekvensen av reoperationer eller återinläggningar mellan operationstyperna och operationstyp var inte en riskfaktor för 30 dagars mortalitet. Resultaten indikerar att Hartmanns operation är ett bra behandlingsalternativ i de fall en koppling är olämplig.

Den fjärde rikstäckande studien fann att typen av ingrepp inte påverkar utvecklingen av lokalrecidiv eller fjärrmetastaser. Hartmanns operation är ett tänkbart alternativ med onkologiska utfall liknande abdominoperineal resektion för patienter där det inte är tillrådligt att koppla ihop tarmen.

Att klargöra Hartmann operations roll vid behandling av ändtarmscancer är kliniskt relevant särskilt med tanke på att antalet äldre patienter inom denna patientgrupp förväntas öka, vilket gör Hartmanns operation till ett alltmer aktuellt behandlingsalternativ. Våra resultat har tillfört ny kunskap om patienturval, bäckensepsis, postoperativa komplikationer och långtidsonkologiska resultat vid Hartmanns operation. Dessa fynd förtydligar rollen för Hartmanns operation vid behandling av ändtarmscancer. Studierna förväntas bli citerade vid uppdateringar av vårdprogram för ändtarmscancer.

# Introduction

## Rectal cancer

The rectum is in its lateral and posterior parts surrounded by the mesorectum. The mesorectum is the mesentery of the rectum, a perirectal fatty tissue that contains lymph nodes draining the rectum and arteries supplying the rectum. The mesorectum is enclosed by the mesorectal fascia (1).

Rectal cancer is defined as adenocarcinoma arising completely or partly within 15 cm from the anal verge (2). Tumors are divided into low, mid or high measuring the distance to the tumor from the anal verge with a rigid endoscope during withdrawal (Figure 1).

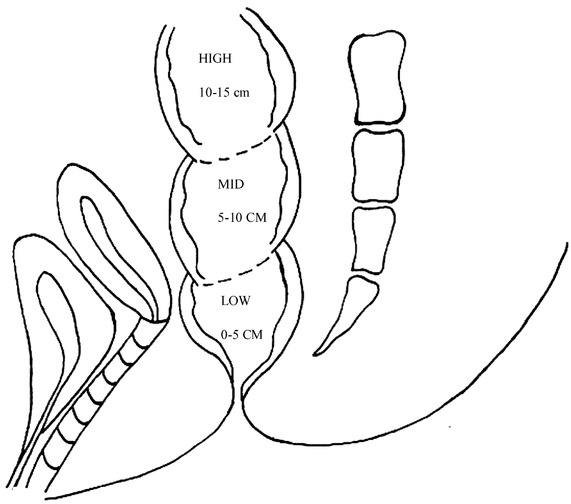


**Figure 1.** The rectum in relation to pelvic structures in a female.

### Epidemiology and risk factors

The incidence of rectal cancer varies widely with the highest incidence reported in Eastern Europe, Australia/New Zealand and Northern Europe. Africa and Southern Asia have the lowest incidence. Rectal cancer is the 10$^{th}$ most deadly cancer globally (3). Each year, around 2000 cases of rectal cancer are diagnosed in Sweden, 1200 men and 800 women. Median age at diagnosis is 73 years and around 21% of patients are over

80 years at diagnosis (2). Risk factors for developing rectal cancer include older age, male gender, sedentary lifestyle, smoking, obesity, heavy alcohol use and the consumption of red meat, especially processed red meat (2, 4). Inflammatory bowel disease, especially ulcerative colitis increases the risk of developing rectal cancer, likely due to chronic inflammation (5).

Rectal cancer is an uncommon disease among young persons with around 5% of rectal cancer patients diagnosed before 50 years of age. However, there has been an increase in rectal cancer among patients under 40 years in the last decades (3, 6). Among reasons suggested for this apart from a western lifestyle and diabetes are the increased use of antibiotics and the resulting changes in gut microbiology. Certain bacteria can potentially increase the risk for rectal cancer, however, the causal relationship is unknown (7, 8).

Around 2-3 % of rectal cancers are hereditary, most commonly due to Lynch syndrome and familial adenomatous polyposis (FAP). Lynch syndrome is due to mutations in the DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS. These genes code for MMR proteins that repair incorrect pairings of nucleotide bases during DNA replication. This causes microsatellite instability characterized by variations in length of repetitive DNA sequences and the resulting copy may not work properly leading to an increased risk for cancer (9). FAP is caused by a defect in the APC tumor suppressor gene and affected individuals develop a large number of adenomas at a young age. Hereditary cancers tend to be more aggressive and often have a worse prognosis (10). Similar genetic pathways are involved in sporadic rectal cancers. Most tumors are believed to arise from adenomas and the adenoma-carcinoma sequence typically takes ten to fifteen years to develop (Figure 2) (11).

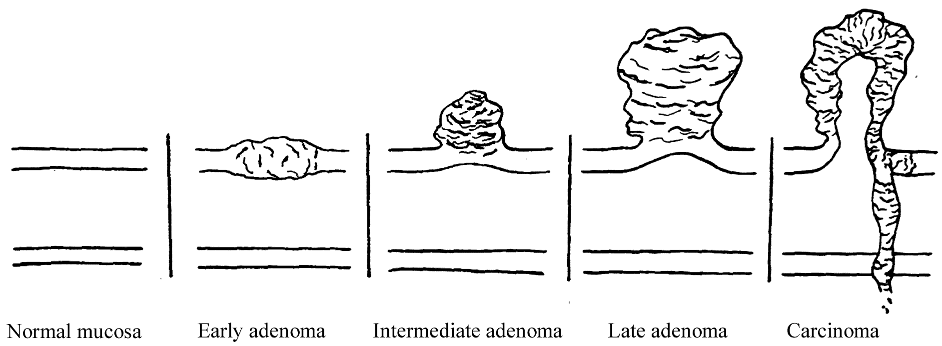


**Figure 2.** The adenoma-carcinoma sequence.

Not all adenomas progress to carcinomas and the malignant potential of adenomas is related to their size, growth pattern and degree of atypia (12). Early detection and removal of adenomas leads to a significant reduction in the incidence and mortality of rectal cancer (13, 14). Colorectal cancer screening increases the chance of detecting adenomas early and can be performed with tests for detecting blood in stool, endoscopic examinations or a computed tomography (CT) colonography. Since 2018 the Swedish national board of health and welfare has recommended screening with an immunochemical fecal occult blood test every other year in persons aged 60-74 years. A positive test should lead to a colonoscopy (2).

## Staging

The 8th edition of the tumor node metastasis (TNM) classification of rectal cancer is used in staging and is based on the primary tumor growth (T), local lymph node metastasis (N) and distant metastasis (M). Pelvic magnetic resonance imaging (MRI) is important for locoregional staging of rectal cancer and numerous factors regarding tumor location and growth are assessed to accurately determine the primary tumor growth (15, 16). Advancements in MRI have led to breakthroughs in staging patients, resulting in a more accurate diagnoses of locally advanced disease and improved treatment outcomes (16, 17). In particular, high-resolution MRI can detect tumor invasion into the mesorectal fascia, infiltration into the perirectal fat and extramural vascular infiltration (EMVI); factors that predict the risk of LR (15, 18-20).

The T stage represents the tumor growth through the bowel wall layers. Figure 3 shows the T stage of rectal cancer. If the tumor is solely growing in the submucosa it is classified as T1, whereas a T2 tumor invades the muscularis propria. A T3 tumor invades through the muscularis propria into the mesorectum and is subdivided into four stages according to depth of the invasion. A T4 tumor has grown through all layers of the rectum and into the visceral peritoneum (T4a) or adjacent organs (T4b).

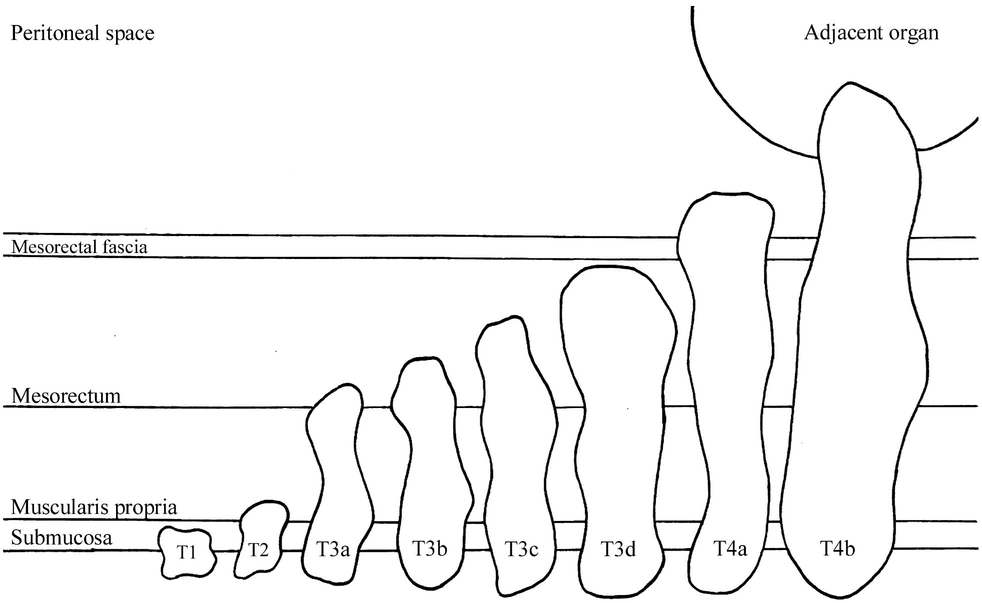


**Figure 3.** Tumor staging of rectal cancer with the layers of the bowel wall and growth of tumor into the bowel.

The N stage represents growth into lymph nodes, N0 indicates that no regional lymph node metastasis is present. N1 is assigned if there are metastases in up to three lymph nodes, while N2 is designated if there are metastases in four or more regional lymph nodes. Lymph node involvement increases the risk of LR and in rectal cancer surgery studies have shown improved survival rates with dedication to retrieving a higher number of lymph nodes with the specimen. Ideally, at least 12 lymph nodes should be removed when possible (21, 22).

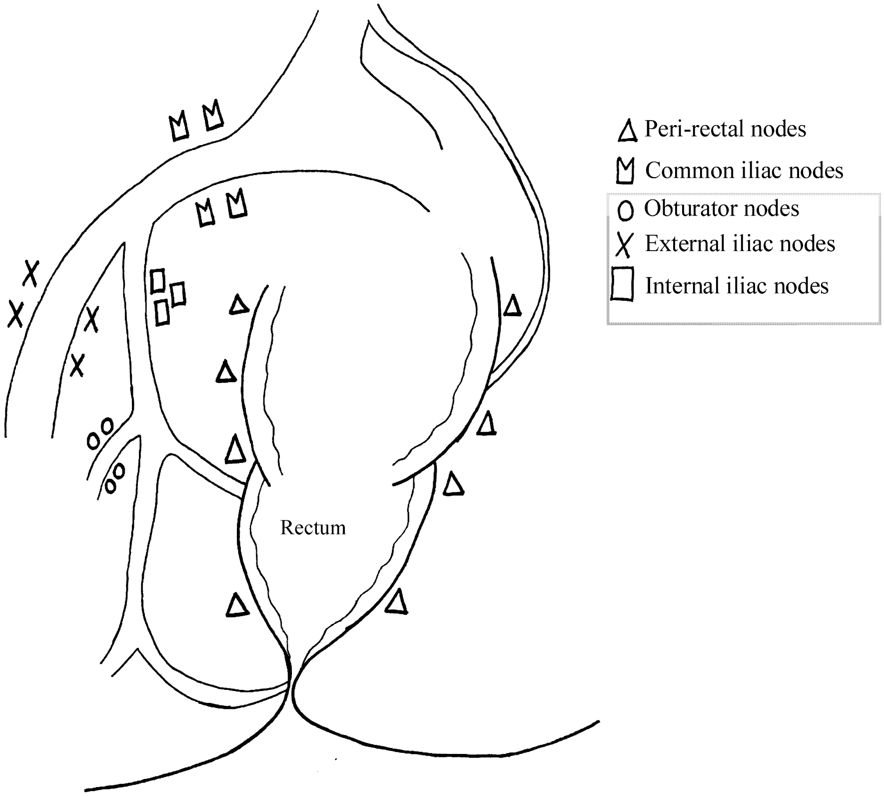


**Figure 4.** Illustration of the lymph nodes that drain the rectum. Lateral lymph nodes are dipicted in the box.

For mesorectal lymph nodes, malignancy is indicated by increased axial and/or longitudinal size as well as a round shape (not oval), irregular border, mucinous content and a mixed signal intensity (23). The use of MRI to accurately predict nodal involvement is constrained by the limited sensitivity and specificity of the results (24). This is especially true regarding lateral lymph nodes (LLN) as there are very few radiology-pathology correlated studies that can be used to confirm MRI findings. LLNs are not contained in the mesorectal fascia and are thus not resected in standard procedures. Currently, the only criteria for LLN malignancy is size, as other morphological features have not been conclusively validated by studies. Enlarged LLNs detected on MRI are considered a negative prognostic marker, associated with an increased risk of cancer recurrence and reduced survival (25, 26). For patients that have received neoadjuvant therapy interpretation of the MRI findings is difficult regarding restaging nodal status. Currently, lymph nodes > 5 mm after therapy are considered malignant (27).

A CT scan of the thorax and abdomen is used to determine if there are signs of DM. The M stage describes the occurrence of DM and includes metastasis in non-regional lymph nodes and parenchymatous organs.

Patients have stage I-II disease if the tumor is limited to the bowel, stage III if local lymph nodes are affected and stage IV disease if DM is observed (Table 1). The classification is important for determining prognosis and plays a significant role in guiding and evaluating treatment decisions (28, 29).

**Table 1.** Summary of the stages in rectal cancer according to the TNM classification.

| Stage | TNM classification |
|---|---|
| **0** | Tis |
| **I** | T1-T2, N0, M0 |
| **II** | T3-T4,N0,M0 |
| **III** | T1-4,N1-3,M0 |
| **IV** | M1 |

## Survival

Survival has improved in the last decades and in Sweden the five-year OS rate for rectal cancer is about 60% (Figure 4) (30, 31).

The most important predictor of survival is tumor stage at diagnosis as reflected in the fact that patients diagnosed with stage I rectal cancer have a five-year survival rate of 83% compared with 14 % in stage IV disease (28, 31).

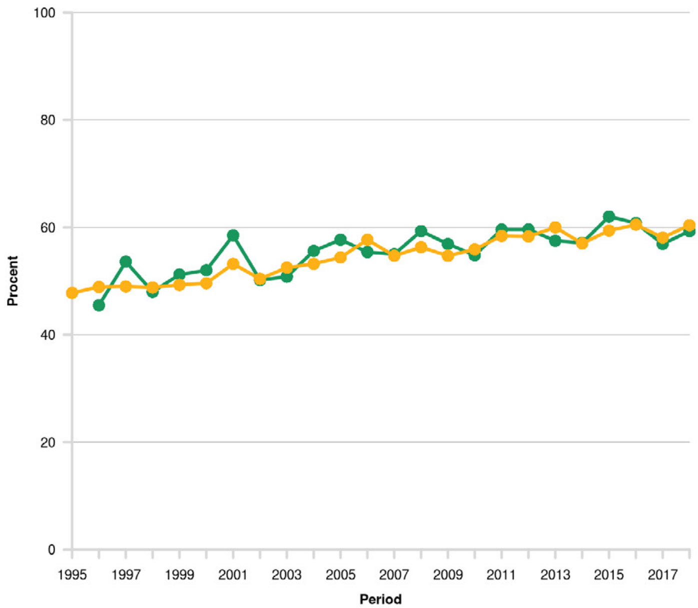


**Figure 5.** The five-year overall survival for patients diagnosed with rectal cancer in all of Sweden (yellow line) and the southen part of Sweden (green line)(31).

# Treatment

## Multimodal management

Preferably all patients are discussed at a multidisciplinary conference with surgeons, oncologists, radiologists, pathologists and specialist nurses present. The goal is to individualize the treatment and assess the need for neoadjuvant therapy. The treatment strategy is decided based on clinical findings including the patient's performance status and symptoms, the height of the tumor from the anal verge, and most importantly, tumor stage.

The level of serum carcinoembryonic antigen (CEA) is measured as part of the patient assessment. An elevated CEA preoperatively that does not normalize after surgery is an independent prognostic marker predicting higher risk of recurrence. CEA levels can also be used to predict response to neoadjuvant therapy as well as for postoperative surveillance (2, 32).

Microsatellite instability/mismatch repair deficiency (dMMR) testing is reflectively carried out although the incidence of dMMR in rectal cancer is only 5% and its prognostic value unknown. Testing is encouraged to detect Lynch syndrome and because there are ongoing trials aiming to determine if the favourable results observed with immunotherapy for dMMR colon cancer can be replicated in the treatment of rectal cancer (33-35).

Patients that present with signs of disseminated disease are evaluated to determine if downstaging treatment is recommended or the treatment is to be palliative. In such cases a complementary MRI of the liver or a F-Fluorodeoxyglucose Positron-emission tomography (PET)-CT scan is often used to complement previous imaging results (36).

## Neoadjuvant treatment

Advances in RT have improved the prognosis for rectal cancer patients (30, 37, 38). Preoperative short-course RT combined with surgery is superior to surgery alone in selected cases as RT reduces the likelihood of LR (38). The toxic effects of RT for those patients with a low risk of LR must be considered and careful preoperative staging to select the right patients to RT reduces LR (16, 38-40). Patients with a high tumor or early rectal cancer in the absence of risk factors have a low risk of LR and the recommendation is usually therefore immediate surgery. If the patient has a higher than 6-8% risk of LR such as patients with a T4 tumor or a low tumor without signs of mesorectal fascia involvement the recommendation is usually a short-course RT (5x5 Gy) followed by immediate surgery (optimal within 7 days) or a wait of 4-8 weeks and then surgery. Surgical complications are more common if the surgery is delayed beyond 10 days after RT (41).

In patients with locally advanced disease downsizing treatment is recommended with re-evaluation during and after treatment. Signs of locally advanced disease include signs of mesorectal fascia involvement, EMVI, LLN enlargement, N2 stage or T4b growing into an organ that is not easily resectable (2).

Breakthroughs in recent years have altered the treatment for patients with locally advanced rectal cancer. Previous regimes included preoperative chemoradiotherapy followed by surgery and adjuvant chemotherapy. Low compliance to adjuvant treatment presented a challenge as DM is the most common cause of cancer recurrence and it is important to administer chemotherapy to control micrometastasis and circulating tumor cells at latest 8 weeks after surgery (42). As surgery can safely be delayed 4-8 weeks following RT this creates a window to administer chemotherapy preoperatively instead. Trials with total neoadjuvant treatment have shown excellent results establishing this strategy as superior (43, 44). Consequently, total neoadjuvant treatment is now widely becoming standard of care for locally advanced rectal cancer (45). In Sweden the RAPIDO concept is used, the therapy consists of a short-course RT (5x5 Gy) followed by chemotherapy (six cycles of Capecitabin and Oxaliplatin) and thereafter surgery (2, 46). A variation of RAPIDO called LARCT-US which has two cycles less chemotherapy is also widely used in Sweden reducing the toxic effects of chemotherapy (47).

### Watch and wait

The quality of life is affected by side effects and long-term consequences of RT, chemotherapy and surgical resection for rectal cancer (48). This is particularly true in frail individuals, where complications are less tolerated (49). In patients with locally advanced rectal cancer that receive neoadjuvant therapy and achieve a complete response with no evidence of viable tumor cells the recommendation to proceed to major surgery has been questioned as the optimal treatment (50). As a result, the watch and wait strategy was developed, where no surgical resection is performed and the patients is closely monitored instead (50, 51). Although this strategy is controversial it should be considered in patients with a complete response, especially in patients with a high risk of morbidity following surgery. In Sweden this strategy is only offered as part of a national clinical trial (2). Although more research is needed, long-term data suggests that the risk of DM is not increased and most patients subjected to regrowth can undergo a surgical resection with a curative intent (51, 52). The psychological morbidity associated with rigid follow-up must be accounted for and not all patients are suited thus patient selection is vital (18, 53).

## Surgical treatment

Surgical resection is the cornerstone of curative therapy for rectal cancer. The treatment decision is based on the height of the tumor from the anal verge as well as patient comorbidity and preference. AR is the gold standard for rectal cancers as it involves restoring bowel continuity. For tumors in the lowest part of the rectum and tumors involving the sphincter APR is recommended. HP is reserved for old and frail patients where the risk of anastomotic leakage (AL) is unacceptably high and in patients with a history of incontinence. Alternatively, intersphincteric APR (iAPR) can be used in patients unfit for restorative surgery. For early rectal cancer (T1) local excision can be an alternative (2, 54). Minimally invasive surgery (MIS) has been shown to improve outcome and surgeons are recommended to use the technique preferably, but patient selection is essential (55-57).

### Total mesorectal excision

In 1982 Heald *et.al.* introduced the total mesorectal excision (TME) technique (58). TME entails removing the rectal cancer with its blood and lymphatic supply, the mesorectum, to ensure the complete removal of all cancer cells and lymph nodes. Rectal cancers often spread beyond the rectal wall, both distally and anteriorly into the surrounding mesorectum, where affected lymph nodes can be found randomly distributed and are not easily visible or palpable. With the refined surgical technique, the goal is to produce a surgical specimen containing the rectum and mesorectum dissected in the avascular plane surrounding the mesorectum. TME has improved the prognosis and is now considered the gold standard for surgical treatment of mid and low rectal cancers. For tumors higher in the rectum, a partial mesorectal excision is used in selected cases (38).

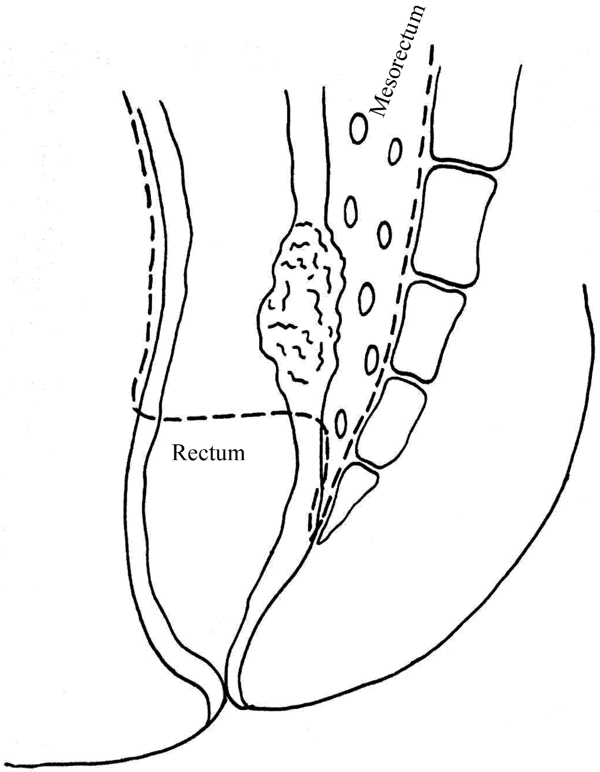


**Figure 6.** Total Mesorectal Excision.

## Anterior Resection

Restorative AR was first introduced in 1948 by Claude F. Dixon and was presented as a treatment for tumors in the proximal rectum and the distal sigmoid colon. The operation entails removal of the tumor bearing segment of bowel with TME and the creation of an anastomosis to restore bowel continuity.

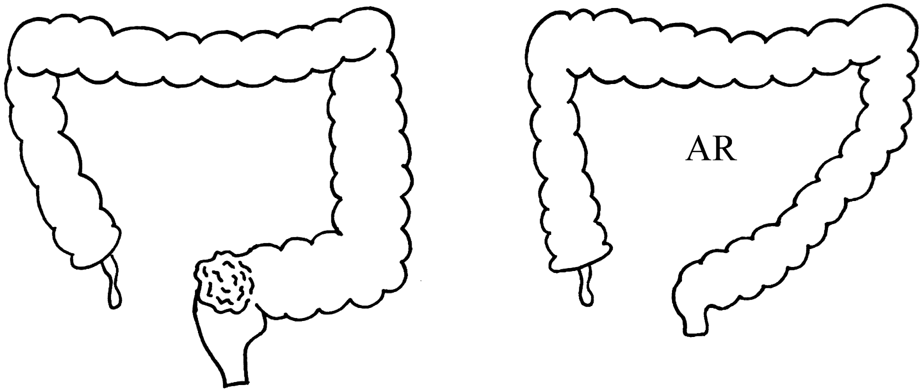


**Figure 7.** Anterior resection.

With the introduction and development of stapling devices this procedure can be used for mid and low rectal tumors as well (59).When AR is performed for low rectal tumors the term low anterior resection is used (LAR).

One of the most dreaded complications following AR is AL defined as a breach in a surgical join between two bowel parts, sometimes causing pelvic sepsis. The rate of AL is 1-19%, depending on the location of anastomosis, neoadjuvant treatment, comorbidity and tumor stage among other things. Variations also reflect differing definitions within the literature (60-63). A diverting stoma (DS), usually a temporary loop ileostomy, has been proven to minimize the consequences of AL. In Sweden this is recommended especially when a LAR is performed and in around 75% of patients undergoing AR, a DS is constructed (64). AL has been shown to increase short term morbidity and has a negative impact on survival (65). The question of whether AL is linked to inferior long-term oncological outcome remains to be answered as studies have been inconclusive (66-68). Another complication linked to AR is low anterior resection syndrome (LARS) consisting of symptoms such as fecal incontinence, urgency or incomplete evacuation. The frequency of LARS has been reported in up to 80% of patients following LAR and has a negative impact on the quality of life (69, 70).

## Abdominal perineal resection

APR was first described by Sir William Ernest Miles in 1908 and involves the complete removal of the distal colon, rectum, and anal sphincter complex through both anterior abdominal and perineal incisions with TME. This procedure results in a permanent colostomy (71).

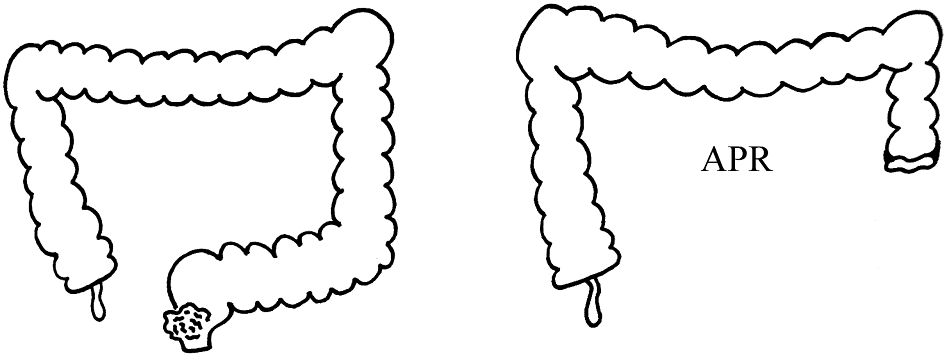


**Figure 8.** Abdominal perineal resection.

With advances in neoadjuvant therapy and surgical technique the use of APR has declined in favour of AR and APR is today indicated in patients with an advanced low tumor as well as tumors involving the sphincter (72). APR is associated with a worse oncological outcome when compared to AR, particularly due to a higher risk of LR. APR is a technically demanding procedure and a higher rate of intra-operative bowel perforation and CRM involvement has been reported, factors that increase the LR risk. Patient selection is also a significant factor as more advanced tumors and tumors not responding to neoadjuvant therapy are selected for APR (73, 74). Surgical morbidity is high following APR. The most common complication is intraabdominal abscess or pelvic abscess. Complications can also derive from nerve injury or urologic injury. Lastly the perineal wound is a common cause of morbidity with delayed healing and wound infections (71, 75).

## Hartmann's procedure

HP was first described in 1921 by Henri Hartmann, a French surgeon, his approach was later extended to treat cancer in the lower rectum not involving the sphincter. The procedure was presented as an alternative to APR claiming lower rates of complications (76). The operation consists of removal of the tumor bearing segment of bowel with TME leaving a rectal stump and the creation of a colostomy.

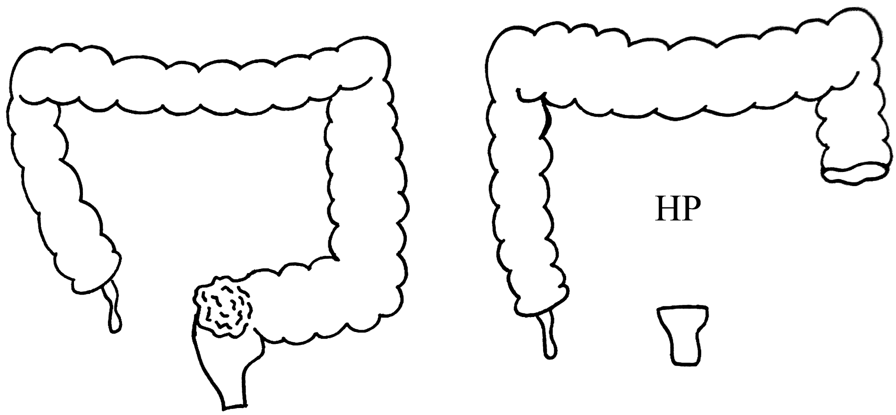


**Figure 9.** Hartmann's procedure.

HP is often used in the emergency setting for diseases in the left colon such as perforated diverticulitis or abdominal trauma where creation of an anastomosis is precarious. HP is also an alternative in rare cases of emergency rectal cancer operations (77). HP can be reversed to restore bowel continuity, this is however a complicated procedure associated with a significant morbidity and evidence regarding HP reversal is limited. The closure rate is much lower if HP is performed due to malignancy than benign conditions and in almost all cases the stoma is considered permanent in cancer patients (78).

HP is considered in rectal cancer treatment for patients with a mid or high rectal tumor not suitable for restorative surgery due to comorbidity, advanced disease or high risk of AL. HP can also be performed to avoid the poor bowel function that often results from performing AR in patients with incontinence (2).

HP may also be employed in the palliative treatment of unresectable rectal cancer to alleviate associated symptoms such as bleeding, tenesmus, diarrhea, or pain (79).

The reported percentage of patients undergoing HP for rectal cancer varies widely. While large studies often exclude patients undergoing HP, population-based data indicates that approximately 10-25% of patients in Europe undergo HP with rates closer to 5% in the USA and Canada (39, 80-84). In Sweden around 20 % of patients undergo HP with regional variations ranging from 10% to 40 % in different parts of the country (31).

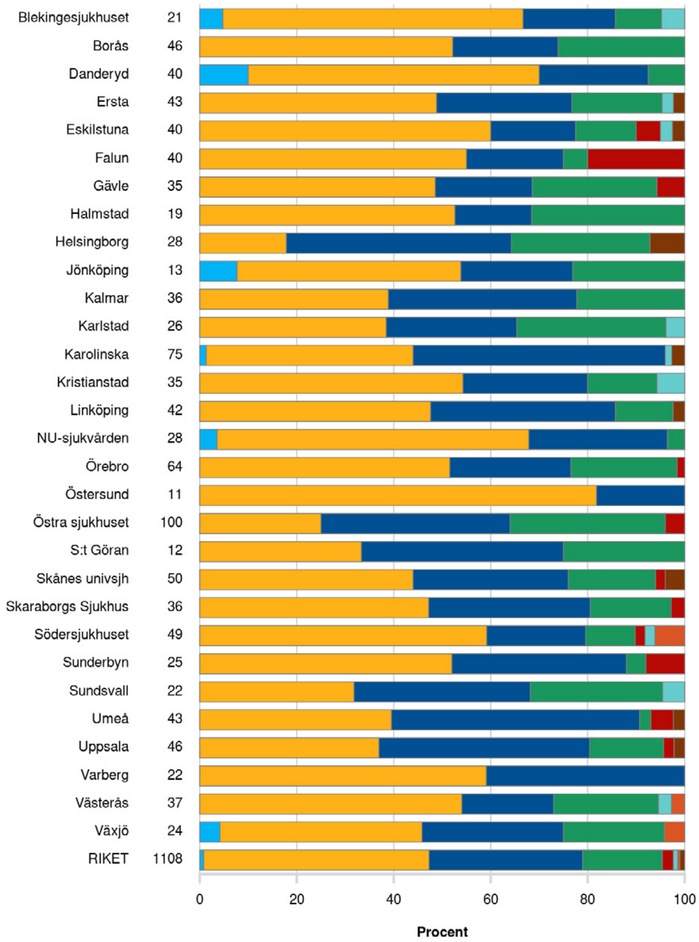


**Figure 10.** The proportion of patients treated with Hartmann's procedure (green) in different parts of Sweden in 2023 (31).

These large variations in the use of HP reflect the fact that the role of HP in rectal cancer treatment is still debated. Several previous studies have reported a high post-operative morbidity, especially pelvic sepsis following HP (85). Pelvic sepsis after HP is thought to occur if the staple line in the remaining rectum breaks down. Rates from 17- 33% have been reported with the highest risk if the rectal stump was shorter than 2 cm as the risk of staple line breakdown is considered higher when a low HP (LHP) is performed. Pelvic sepsis requiring surgical intervention results in a higher reoperation rate and prolongs the hospital stay (86, 87).

The perception that HP is linked to a high risk of pelvic sepsis has been challenged in recent studies with lower incidence of pelvic sepsis reported. The rate of reoperations and postoperative complications is also lower despite the fact that HP is reserved for older patients with comorbidities and often a more advanced cancer (81, 88-90). This suggests that HP may be a good alternative although the uncertainty regarding outcome has not been resolved.

Very few studies report on the oncological outcome following HP, partly due to the fact that larger studies often exclude patients undergoing HP. Previous studies suggest that the outcome may be inferior but the results are subjected to selection bias as patients undergoing HP often have a more advanced disease, consequently more studies are needed (84, 91).

## Intersphincteric APR

With iAPR the anus is removed with an intersphincteric dissection, thus preserving the external sphincter. This method allows for closure of the perineal wound with more muscle tissue to improve wound healing when compared to the traditional APR. As with APR this procedure results in a permanent colostomy. This procedure can be offered to patients with a mid or high rectal tumor not suitable for restorative surgery and may be used as an alternative to HP as symptoms related to the rectal remnant are diminished. The most common complications following iAPR are pelvic sepsis as well as delayed wound healing in the perineum (92, 93). The question of whether HP or iAPR is superior has not been definitively answered (94-96). The evidence is very limited as the use of iAPR for rectal cancer is rarely discussed in the surgical literature. Studies comparing HP and iAPR have reported similar complication rates, suggesting that either procedure is acceptable (92-95).

The HAPIrect study is a randomized clinical trial designed to compare HP and iAPR in terms of post-operative morbidity with the aim to assess which method is associated with less morbidity. The study was launched in Sweden in 2016 (97). Results from the study show that both procedures can be used with smaller differences in complication rates than anticipated (98). In Sweden, HP is the preferred non-restorative procedure at most hospitals and the use of iAPR is limited (31).

## Considerations in non-restorative surgical treatment

The number of elderly patients and patients with comorbidity in need of treatment for rectal cancer is expected to increase with the aging population as well as increased use of neoadjuvant therapy. This calls for re-evaluation of current guidelines to offer the best non-restorative treatment available (99). There is a division among surgeons regarding the preferred method.

Surgeons in favour of HP prefer this procedure because it avoids the perineal dissection and wound complications following APR. HP is a quicker to perform and the surgical trauma is diminished when compared to APR. Surgeons that prefer APR point to studies linking HP to a high risk of pelvic sepsis as well as inferior oncological outcome. Others favour iAPR as there is less perineal morbidity when compared to conventional APR and problems regarding pelvic sepsis related to the rectal remnant are excluded (94).

Determining which patients are suitable candidates for a non-restorative procedure is important. Elderly patients frequently present with increased comorbidities that can impact treatment decisions, and there is often a tendency to offer less aggressive treatment to older patients. At the same time the definition of an older patient varies in studies, ranging from 65-80 years and several studies have demonstrated that older age by itself is not a risk factor for post-operative complications (99, 100). Factors such as neoadjuvant RT, low tumor and more advanced tumor all impact the decision and need to be taken into account as studies have shown an increased risk of AL in these situations if AR is the decided procedure (101). Another factor to consider when counselling patients regarding treatment options is the fact that a large proportion of patients undergoing AR receive a DS, especially if a LAR is performed. Around 20% of patients never undergo a second operation to reverse the stoma (90). Risk factors for non-closure of DS include older age, higher ASA score, comorbidities and AL (90, 102). A DS is most often an ileostomy which carries the risk of high output with subsequent challenges in managing fluid balance. This can be particularly problematic in frail individuals, increasing the risk of complications such as renal failure and increasing the length of hospital stay (103). With this consideration in mind, certain patients may benefit more from planning a permanent colostomy from the beginning.

When advising patients on treatment alternatives the quality of life (QoL) following surgery must also be considered. Patients report worse QoL before start of treatment for rectal cancer with most patients returning to baseline in 12-24 months (104). A study comparing patients undergoing HP to AR and APR revealed no differences in QoL overall. Patients undergoing HP scored worse on certain variables such as mobility and self-care but that may be explained by the fact that the patients undergoing HP were older and frailer (105).

# Follow-up and prognostic factors

At the postoperative multidisciplinary conference, the pathology report is reviewed and risk factors evaluated to select patients that might benefit from adjuvant treatment and importantly decide upon a follow-up strategy. The tumor stage and the number of lymph nodes harvested are reported as well as whether there was metastasis in lymph nodes. In addition, the histopathological examination gives valuable information about several prognostic factors.

The circumferential resection margin (CRM) is the distance from the leading edge of the tumor or malignant cells to the nearest edge of surgically dissected margin. A CRM <1 mm is described as CRM positive, which is a known risk factor for LR, DM as well as OS (106-108). As distal tumor extension along the rectal wall is limited, a distal margin of 2 cm is considered adequate. Tumor grade is reported, low grade tumors have well differentiated cells and are associated with lower risk of DM. High grade tumors are on the other hand poorly differentiated and confer a higher risk of DM, as these are considered more aggressive. Perineural and lymphovascular invasion as well as EMVI have prognostic value as they represent invasive growth patterns. This occurs primarily in stage T3 or T4 tumors and has negative impact on LR and DM (2, 109). The presence of tumor deposits (TD) has also a negative impact on the prognosis with increased risk of LR and DM if present (110).

A macroscopic evaluation of the quality of the TME of the specimen is presented, graded into three groups, complete (mesorectal), nearly complete (intramesorectal) or incomplete (muscularis propria). This evaluation gives important information about the quality of the surgical resection and has prognostic value. It also serves as a quality indicator of the surgeon, providing feedback on the quality of the surgical resection (111-113).

The aim of follow-up is to detect LR or DM in a timely manner (2). Patients with stage I disease that have undergone a radical resection have a very low risk of LR or DM and follow-up is therefore usually not recommended. For most patients with a stage II or III disease the follow-up consists of a measurement of blood CEA and a CT scan of the thorax and abdomen at 1 year and 3 years postoperatively (114). A colonoscopy is usually performed at three years after surgery and thereafter every fifth year until the patient turns 75 years of age.

For stage IV patients the follow-up depends on the treatment received and their response to treatment. Patients that undergo curative resection of lung or liver metastasis require high frequency follow-up the following two years consisting of CT imaging and CEA measurements every six months.

# Adjuvant treatment

The evidence supporting the use of adjuvant treatment after surgery for rectal cancer is limited. Many studies on this topic include patients with colon cancer as well, which may lead to conflicting results, because colon cancer responds differently to chemotherapy (115). In Sweden the national guidelines recommend that patients with stage III disease as well as stage II disease and the presence of risk factors should be evaluated for adjuvant chemotherapy. Risk factors presented in the pathology report such as stage 4 tumor, CRM involvement, EMVI, low differentiation grade, fewer than 12 lymph nodes harvested as well as tumor perforation, emergency surgery and elevated CEA postoperatively have been shown to increase the risk of cancer relapse (2, 21, 22, 32). In patients treated with preoperative RT, adjuvant treatment can be offered to selected patients. There is, however, little evidence supporting the decision (116). For patients who have undergone neoadjuvant chemotherapy, the use of adjuvant chemotherapy is not recommended in Sweden (2). This recommendation is based on studies that have demonstrated conflicting results about the potential benefits of adjuvant chemotherapy in this population (2, 45, 116, 117).

# Local recurrence

Historically, LR after surgery for rectal cancer was a major concern. With the introduction of TME and advances in RT the LR rates are less than 10% today (38, 118). In Sweden around 5% of patients are diagnosed with LR, with the median time to diagnosis being 21 months. Patients are diagnosed outside of follow-up more commonly than at scheduled follow-up visits and the most frequent symptom is pain (31, 119, 120). The most important risk factor for LR is tumor stage. As the stage advances, the risk of LR increases. CRM involvement and the number of positive lymph nodes also increase the LR risk as well as rectal perforation and the occurrence of intraoperative adverse events (107, 121-124). Furthermore, tumor height influences risk of LR, with low rectal cancers conferring a 40–50% increased risk of LR compared to high tumors (123, 125). It is not clear whether the choice of surgical procedure affects LR (126, 127).

Intraoperative rectal washout can help minimize the number of viable cancer cells in the bowel and reduce the risk of LR. Studies on the impact of rectal washout have been conflicting regarding the benefit when HP is performed (128-130). Rectal washout is recommended in Sweden as it is not associated with any complications and has been proven to reduce the risk of LR when AR is performed (2, 131).

LR can manifest in various locations within the pelvis (Figure 10), and the location of recurrence holds prognostic significance, as it is associated with the potential success of curative surgery. Patients with anastomotic or anterior recurrence tend to have a more favourable prognosis compared to those with posterior or lateral recurrence (123).

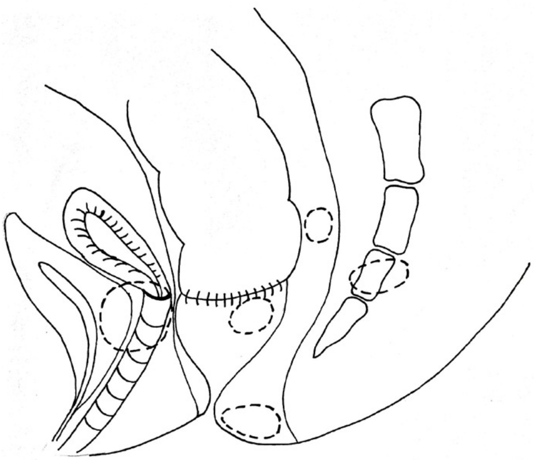

**Figure 11.** Examples of local recurrence locations.

Although rates of LR have decreased significantly LR is a significant clinical concern as the prognosis is poor with few patients eligible for curative treatment (120, 126). Pelvic exenteration is possible in selected cases of recurrent rectal cancer and advances in recent years have increased the chances of cure (132). This procedure entails radical multi-visceral resection and the goal is to achieve complete oncological resection (R0). This operation is performed at specialised centres as it is technically challenging with considerable morbidity (133, 134).

# Distant metastases

DM remains the leading cause of rectal cancer related death (37). With improvements in imaging, metastasis is more often detected at the time of diagnoses (synchronous metastasis). Around 20% of patients develop DM after radical resection of rectal cancer (metachronous metastasis). The majority (19%) are detected within three years from diagnosis (31). Metastasis occurs through lymphatic and venous routes and circulating tumor cells are also thought to contribute to DM.

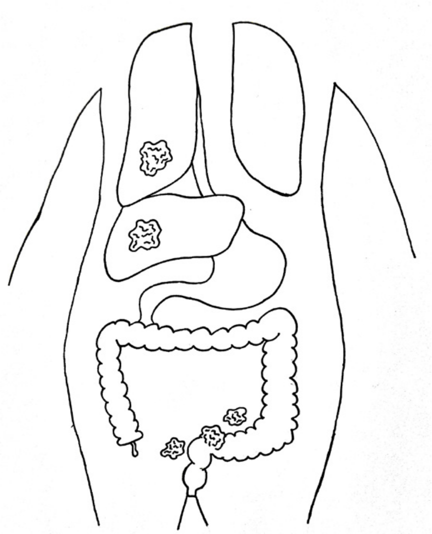

**Figure 12.** The most common sites for distant metastasis in rectal cancer.

Studies have suggested that in order to more accurately assess the risk of DM in patients a distinction should be made between local tumor spread and venous tumor spread. The risk of DM correlates with depth of tumor invasion, lymph node involvement and tumor size as well as CRM involvement, all factors predicting local tumor spread. Low tumors also have a higher risk of DM. Factors predicting venous tumor spread include EMVI and the presence of tumor budding (106, 135).

The most common site of metastasis from rectal cancer is the liver followed by the lung and the peritoneum. Uncommonly metastasis to the brain or skeleton occurs (136).

Changes in the treatment of DM in recent years such as improvements in chemotherapy and an increase in pulmonary and liver metastasis resections have improved survival for patients with stage IV disease (136-138).

# Aims of the thesis

This thesis describes aspects of HP and aims to define the role of HP in rectal cancer treatment in a cohort of patients that could theoretically undergo either HP, AR or APR.

## Specific aims

### Paper I

To investigate patient-related factors predicting the selection of rectal cancer patients to HP as well as to investigate how often and on what grounds, AR is intraoperatively changed to HP.

### Paper II

To evaluate the incidence of pelvic sepsis following HP in rectal cancer patients within one year postoperatively. Secondary aims include exploring risk factors for pelvic sepsis as well as the time to diagnosis and the treatment used.

### Paper III

To compare the 30-day postoperative morbidity and mortality following HP with that for AR and APR.

### Paper IV

To compare LR after surgery following HP with that for AR and APR. Secondary aims include comparing DM, disease-free survival (DFS) and OS at five years as well as assess risk factors for LR.

# Patients and Methods

## Swedish ColoRectal Cancer Registry

Since 1995, all patients undergoing resection of rectal cancer in Sweden are registered in the SCRCR. Data on patient and tumor characteristics, diagnostics, treatment and postoperative morbidity 30 days after surgery are registered. Oncological outcomes (LR and DM) and deaths are reported at 3 and 5 years after the primary registration. The SCRCR has a coverage of >99% of patients with rectal cancer and has a high internal validity (30, 139-143). There are however limitations that need to be considered. Data from the SCRCR can include registration errors but the effect of these random errors is minimal due to the large sample size. Missing data occurs, most often due to incomplete registration. Studies aiming to validate results in the SCRCR have revealed that some variables such as preoperative staging, complications and operative factors are subjected to interpretation and their validity is therefore lower. Furthermore, surgical complications as well as general complications are underreported. This may be related to a broad definition and registration problems (144). A study on AL after AR found this variable underreported in the SCRCR. That may be due to a lack of consensus regarding the definition of AL (145). Perioperative bowel perforation is also poorly registered which is a problem as this variable is important to assess surgical quality and risk of LR (140).

## Study population

For this thesis, data from the SCRCR was collected for patients undergoing HP, APR or AR with newly diagnosed rectal cancer. According to the Swedish national guidelines, the recommended procedure for tumors ≤ 5 cm is APR. HP is used in rare cases regarded as exceptions for tumors 0-4 cm from the anal verge, thus all patients with a tumor < 5 cm were excluded from the analysis.

Papers I and II included data from the SCRCR for the southern part of Sweden (Region Skåne) from January 1, 2007 through June 30, 2017. Data from the SCRCR were expanded with further information from medical charts regarding cardiovascular disease, diabetes, pulmonary disease, immunosuppression and smoking as well as preoperative blood tests including albumin, CEA and creatinine.

For paper I the preoperative reasons for choosing HP as documented from the outpatient notes and multidisciplinary team conference notes were registered. The reasons for intraoperatively changing the procedure were collected from the operation notes.

For paper II information regarding morbidity associated with the rectal stump, complications within one year postoperatively and treatment received was gathered from medical charts.

Papers III and IV included patients undergoing elective HP, AR and APR using population-based data from the SCRCR.

Paper III included patients operated on from January 1, 2010 through December 31, 2017.

Paper IV included patients with a TNM stage I-III disease, who underwent R0/R1 surgery between 1, January 2013 and December 31, 2017.

# Outcomes of interest

Paper I: Patient-related factors predicting the selection of rectal cancer patients to HP as well as how often, and on what grounds, AR is intraoperatively changed to HP.

Paper II: The incidence of pelvic sepsis within one year after HP in rectal cancer patients. Risk factors for pelvic sepsis as well as the time to diagnosis and the treatment used.

Paper III: The risk of overall 30-day complications following HP compared to AR and APR, respectively. Surgical complications including intra-abdominal infections, reoperations, readmissions, length of stay as well as 30-day mortality.

Paper IV: 5-year LR after HP compared to AR and APR as well as 5-year DM, OS, DFS and risk factors for LR.

# Definitions

Rectal cancer is defined as adenocarcinoma located within 15 cm from the anal verge measured with a rigid sigmoidoscopy on withdrawal.

HP is defined as removal of the rectum leaving an anorectal stump.

Emergency rectal resection is defined as a procedure performed during an emergency setting often due to bowel perforation, bleeding or bowel obstruction.

A colorectal surgeon is defined as a surgeon specialized in colorectal surgery and trained in the TME technique.

If the planned operation according to the outpatient notes was AR and the surgeon decided intraoperatively to perform HP, this was registered as an intraoperative decision.

Pelvic sepsis was defined as abscess formation in the pelvis demonstrated on a CT scan and/or purulent discharge from the anus.

Surgical complications were defined as significant intra-abdominal bleeding, intra-abdominal abscess, wound dehiscence, necrosis of a stoma, AL or wound infection requiring treatment.

LR was defined as tumor recurrence occurring below the promontory, including intraluminal, perirectal, lateral lymph node, vaginal, urinary bladder, or perineal recurrence. This was documented through clinical, radiological, or pathological examination, or during surgery or autopsy, detected more than 3 months after the primary surgery.

DM was defined as presence of tumor growth outside the pelvis not present at the time of diagnosis detected more than 3 months after primary surgery

DFS was defined as the proportion of the patients that were alive at 5 years that were without signs of LR or DM.

OS was defined as the proportion of patients alive at 5 years.

## Statistical methods

Statistical analyses were conducted by the author following discussions with a statistician, who also reviewed the results.

All calculations were performed in R (paper I-III in versions 3.6.1 and paper IV in 4.2.3) and $p < 0.05$ was considered significant. Continuous variables were presented as median with an interquartile range or mean with standard deviation, and categorical data were described using frequencies of counts with associated percentages. For papers I and II a comparison between groups was performed using Fisher's exact test for nominal variables and a Mann-Whitney test for continuous variables. For papers I, III and IV patients were divided into groups based on the operation performed i.e. HP, AR or APR. A Shapiro-Wilks test was performed to assess normality. A one-way ANOVA test was used to compare means between the groups in terms of continuous variables and the chi-square test for categorical variables. A Dunnett's post Hoc test for ANOVA was used to identify the means that differ from the reference group (HP). Patients undergoing HP were used as a reference group and the date of surgery was the starting point for all endpoints.

In paper I, II and III a logistic regression was used to investigate risk factors. A univariable logistic regression was performed and significant factors included in the multivariable logistic regression analysis.

**Paper I**: A comparison between patients undergoing HP after an intraoperative decision to those in whom the procedure was planned was conducted to investigate risk factors for intraoperative change of plans.

**Paper II**: To identify risk factors for pelvic sepsis, a comparison was conducted between patients who experienced pelvic sepsis and those who did not.

**Paper III**: A multivariable regression model was developed to evaluate the differences in post-operative morbidity between the groups. A subgroup analysis was performed to investigate risk of complications after surgery for patients with a tumor 5-7 cm from the anal verge as well as patients older than 75 years.

**Paper IV**: A Kaplan-Meier survival analysis was employed to compare time to LR, DM and DFS as well as OS between the groups. A log rank test was utilized to test significance. Uni-and multivariable Cox regression analysis was performed to investigate odds ratios (OR) for LR, DM, DFS and OS.

## Ethics

The study was approved by the Swedish Ethical Review Authority (Dnr 2019-01262 and 2022-06047-02) and followed the Declaration of Helsinki guidelines.

# Results

## Paper I

### Demographics of the study cohort

A total of 1141 patients were included in the study: 275 (24%) HP, 491 (43%) AR and 375 (33%) APR. When comparing the HP group to the AR and APR groups, patients undergoing HP were significantly older ($p < 0.001$), more frequently reported a history of cardiovascular disease and diabetes and had a higher ASA score ($p < 0.001$). The median tumor height was lower in the APR group, 7 cm compared to 10 cm in the HP group and AR group ($p < 0.001$) and 222 patients with a tumor height of 6-10 cm underwent APR. Neoadjuvant RT was used less frequently in the HP group.

### Preoperative reasons for performing HP

The decision to perform HP was made preoperatively in 209 patients (76%). The reasons are presented in Table 2.

**Table 2.** The preoperative reasons to perform HP as stated in the multi-disciplinary team conference note and the preoperative outpatient visit.

| Preoperative reasons to perform Hartmann's procedure | n = 209 (%) |
|---|---|
| Comorbidity | 57 (27) |
| Oncology-related | 53 (25) |
| Advanced tumor – planned adjuvant treatment | 28 |
| Advanced tumor – locally advanced | 22 |
| Advanced tumor – palliation | 3 |
| High age | 24 (11) |
| Patient preference | 17 (8) |
| High age and comorbidity | 16 (8) |
| Emergency surgery | 7 (3) |
| Low tumor | 6 (3) |
| Comorbidity and incontinence | 6 (3) |
| Incontinence alone | 5 (2) |
| High age and incontinence | 5 (2) |
| Reason not clearly stated | 13 (6) |

## Intraoperative decision to perform HP

In altogether 64 patients (23%) planned for AR, the decision was changed to HP during the operation (Table 3).

**Table 3.** The reasons for intraoperative decision to change from AR to HP according to the surgeon.

| Intraoperative reasons to perform Hartmann's procedure | n = 64 (%) |
|---|---|
| Anastomosis related | 38 (59) |
| Technical difficulties | 14 |
| Anastomosis too low | 12 |
| Radiotherapy tissue damage | 8 |
| Diminished blood flow to the bowel | 4 |
| Oncology related | 14 (22) |
| Advanced tumor – planned adjuvant treatment | 12 |
| Advanced tumor – palliation | 2 |
| Major bleeding | 5 (8) |
| Bowel perforation | 5 (8) |
| Reason not clearly stated | 2 (3) |

A comparison of patients who were intended to undergo AR but this changed to HP intraoperatively and those undergoing preoperatively planned HP revealed that patients in the unplanned HP group were younger than those undergoing planned HP (71 years compared to 77 years; $p = 0.002$), more often male gender (73% vs 55%; $p = 0.01$), and had a significantly lower ASA score. A higher rate of neoadjuvant RT was observed in the unplanned HP group (63% vs 46% $p = 0.02$). No significant differences were seen in tumor height and the preoperative T stage was similar between the groups.

Results from the multivariable analysis showed that male gender increased the likelihood of intraoperative changes: OR 2.45 (95% CI:1.31–4.79) as well as ASA score I and II: OR 2.07 (95% CI:1.10–4.01). Neoadjuvant RT was not a significant risk factor after correcting for age, gender and ASA score.

## Intraoperative decisions regarding APR

Two patients (1%) were planned for APR but this was changed to HP during the operation because the tumor was higher than suspected. No patient underwent APR because of an intraoperative change from AR.

# Paper II

## Demographics of the study cohort

After exclusions, complete data from 252 patients were included in this study. Twenty-seven patients were diagnosed with pelvic sepsis, the incidence of pelvic sepsis was 11%. Demographic data are displayed in Table 4.

**Table 4.** Patient, tumor and treatment characteristics of patients undergoing Hartmann's procedure.

| | All patients<br>n = 252 | Pelvic sepsis<br>n = 27 | No pelvic sepsis<br>n = 225 | p-value |
|---|---|---|---|---|
| Age (years) at surgery* | 75 (20-92) | 69 (50-85) | 76 (20-92) | 0.002 |
| Male gender | 149 (59) | 18 (67) | 131 (58) | 0.53 |
| BMI >25 (kg/m$^2$) | 130 (52) | 22 (82) | 108 (48) | 0.001 |
| Medical history | | | | |
| Cardiovascular disease | 148 (59) | 15 (56) | 133 (59) | 0.68 |
| Diabetes mellitus | 40 (16) | 7 (26) | 33 (15) | 0.27 |
| Pulmonary disease | 27 (11) | 1 (4) | 26 (12) | 0.32 |
| Immune suppression | 13 (5) | 0 | 13 (6) | 0.30 |
| Smoking history | | | | |
| Never | 142 (59) | 15 (56) | 127 (60) | 0.80 |
| Former | 67 (28) | 9 (33) | 58 (27) | |
| Current | 31 (13) | 3 (11) | 28 (13) | |
| ASA score 3 or 4 | 107 (42) | 7 (26) | 100 (44) | 0.07 |
| Albumin (g/L)* | 36 (11-48) | 37 (23-45) | 36 (11-48) | 0.47 |
| CEA (µg/L) * | 4 (1-465) | 10 (1-72) | 4 (1-465) | 0.35 |
| Creatinine (µmol/L) * | 78 (34-235) | 81 (47-143) | 78 (34-235) | 0.38 |
| Tumor height * | 10 (5-15) | 10 (6-15) | 10 (5-15) | 0.38 |
| Low 5 cm | 6 (2) | 0 | 6 (3) | |
| Mid 6-10 cm | 131 (52) | 19 (70) | 112 (50) | |
| High 11-15 cm | 115 (46) | 8 (30) | 107 (47) | |
| TNM stage | | | | |
| I | 35 (14) | 2 (7) | 33 (15) | 0.52 |
| II | 86 (34) | 12 (44) | 74 (33) | |
| III | 90 (36) | 8 (30) | 82 (36) | |
| IV | 39 (15) | 5 (19) | 34 (16) | |
| Neoadjuvant radiotherapy | 128 (51) | 22 (81) | 106 (47)) | < 0.001 |
| Chemoradiotherapy | 46 (20) | 7 (26) | 39 (19) | 0.36 |
| Neoadjuvant chemotherapy | 6 (2) | 1 (4) | 5 (2) | 0.47 |

Values in parenthesis are % unless *median with range. Abbreviations: BMI body mass index, CEA carcinoembryonic antigen. ASA American Society of Anaesthesiologists. TNM Tumour Node Metastasis staging system

## Surgical outcome

Patients diagnosed with pelvic sepsis had a longer operation time; 323 min vs. 250 min ($p = 0.005$) and the blood loss was greater; 750 mL vs. 400 mL ($p = 0.003$). The 30-day overall complication rate, including both medical and surgical complications was 67% in the pelvic sepsis group compared to 38% in patients without ($p = 0.006$). The reoperation ($p < 0.001$) and readmission ($p < 0.001$) rates were higher in the pelvic sepsis group as well as the length of stay ($p = 0.04$).

## Risk factors for pelvic sepsis

In the multivariable logistic regression analysis neoadjuvant radiotherapy was identified as a risk factor for pelvic sepsis; OR 7.96 (95 % CI: 2.54-35.36) as well as BMI over 25 $kg/m^2$; OR 5.26 (95 % CI: 1.80-19.50). Older patients had a lower risk of developing pelvic sepsis; OR 0.95 (95 % CI: 0.90-0.99).

## Diagnosis and treatment of pelvic sepsis

The median time from the operation to the diagnosis of pelvic sepsis was 21 days (range 5-355 days) with 11 patients (40%) diagnosed beyond 30 days postoperatively. In 19 patients (70%) the diagnosis was made with a CT scan. In the majority of patients, the abscess was located above the stapled rectum and a rectal defect could be palpated with pus draining from the rectum. In 19 patients (70%) the treatment was conservative, with passive rectal drainage and irrigation. Re-operation was needed in 8 patients (30%), with the placement of an active transrectal drainage. No patient underwent re-laparotomy or perineal proctectomy

## Morbidity and mortality after HP

Altogether 39 patients (15%) reported symptoms from the rectal stump, including secretion in 32 patients (13%), rectal bleeding in 6 (2%) and proctitis in 4 (2%). These symptoms were diagnosed during follow-up and no patient required readmission or received in hospital treatment for these symptoms. The 30- and 90-day mortality were 2.8% and 4.7% respectively. None of the patients that developed pelvic sepsis died within 90-days postoperatively.

# Paper III

## Demographics of the study cohort

A total of 8476 patients were included in this study with 1210 (14%) undergoing HP, 5406 (64%) undergoing AR and 1860 (22%) undergoing APR. The median age in patients undergoing HP was 77 years compared to 67 years in the AR group and 70 years in the APR group ($p < 0.001$) and patients undergoing HP had significantly more often an ASA score of 3 or 4 (49%) compared to patients undergoing AR (18%) and APR (30%). The proportion of patients with TNM stage IV disease was highest in the HP group and patients in this group more often proceeded direct to surgery without neoadjuvant treatment.

## Surgical outcome

Table 5 displays the postoperative complications following surgery in relation to the treatment groups.

**Table 5.** Data on 30-day postoperative complications and outcome.

| | All patients n = 8476 | HP n = 1210 | AR n = 5406 | APR n = 1860 | p-value |
|---|---|---|---|---|---|
| Overall complications | 3321 (39) | 493 (41) | 1969 (36) | 859 (46) | < 0.001 |
| Medical complications | | | | | |
| Infectious | 684 (8) | 129 (11) | 400 (7) | 155 (8) | < 0.001 |
| Cardiovascular | 281 (3) | 71 (6) | 137 (3) | 73 (4) | < 0.001 |
| Neurological | 30 (0.4) | 4 (0.3) | 19 (0.4) | 7 (0.4) | 0.96 |
| Surgical complications overall | 1809 (21) | 248 (21) | 1083 (20) | 478 (26) | < 0.001 |
| Wound infection | 495 (6) | 74 (6) | 192 (4) | 229 (12) | < 0.001 |
| Intra-abdominal infection | 382 (5) | 74 (6) | 222 (4) | 86 (5) | 0.009 |
| Wound dehiscence | 166 (2) | 40 (3) | 84 (2) | 42 (2) | < 0.001 |
| Intra-abdominal bleeding | 72 (0.8) | 15 (1) | 35 (0.6) | 22 (1) | 0.031 |
| Stoma complications | 200 (2) | 25 (2) | 122 (2) | 53 (3) | 0.27 |
| Reoperation | 779 (9) | 128 (11) | 472 (9) | 179 (10) | 0.09 |
| Unplanned ICU stay | 438 (5) | 87 (7) | 234 (4) | 117 (6) | < 0.001 |
| Length of stay in days, mean (SD) | 9 (4) | 10 (4) | 8 (4) | 10 (4) | 0.009 |
| Readmissions | 1191 (14) | 150 (12) | 799 (15) | 250 (13) | 0.06 |
| 30-day mortality | 91 (1) | 26 (2) | 42 (0.8) | 23 (1) | < 0.001 |
| 90-day mortality | 168 (2) | 49 (4) | 80 (2) | 39 (2) | < 0.001 |
| Alive at end of follow up | 5938 (70) | 610 (50) | 4241 (78) | 1197 (64) | < 0.001 |

Values in parenthesis are percentages unless mean with standard deviation. HP Hartmann´s procedure, AR Anterior resection, APR Abdominoperineal resection, ICU intensive care.

## Multivariable analysis

A multivariable analysis was conducted to investigate the impact of type of surgery on postoperative morbidity and the results are displayed in Table 6.

**Table 6.** Multivariable regression analysis of the impact of type of surgical procedure on 30-day complications and outcome.

| | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | p-value | Odds ratio (95% CI) | p-value |
| Overall complications | | | | |
| HP | 1.00 | | 1.00 | |
| AR | 0.83 (0.73–0.94) | 0.004 | 0.93 (0.81–1.07) | 0.31 |
| APR | 1.24 (1.08–1.44) | 0.003 | 1.18 (1.01–1.40) | 0.043 |
| Surgical complications | | | | |
| HP | 1.00 | | 1.00 | |
| AR | 0.97 (0.83–1.13) | 0.71 | 1.01 (0.85–1.21) | 0.84 |
| APR | 1.34 (1.13–1.60) | < 0.001 | 1.15 (0.95–1.40) | 0.15 |
| Intra-abdominal infection | | | | |
| HP | 1.00 | | 1.00 | |
| AR | 0.66 (0.50–0.87) | 0.002 | 0.59 (0.44–0.81) | < 0.001 |
| APR | 0.74 (0.54–1.03) | 0.07 | 0.57 (0.41–0.82) | 0.002 |
| 30-day mortality | | | | |
| HP | 1.00 | | 1.00 | |
| AR | 0.36 (0.22–0.59) | < 0.001 | 1.02 (0.58–1.81) | 0.94 |
| APR | 0.56 (0.32–1.00) | 0.05 | 1.26 (0.66–2.42) | 0.48 |

A multivariable logistic regression adjusted for age, sex, ASA score, tumor height, TNM stage, preoperative radiotherapy, preoperative chemotherapy, minimally invasive surgery, local radical resection, surgical competence and intraoperative bowel perforation.

## A subgroup analysis of patients with a tumor height 5-7 cm

A subgroup analysis of 2334 patients with a tumor 5–7 cm from the anal verge revealed that 245 (10%) underwent HP, 764 (33%) underwent AR and 1325 (57%) underwent APR. Patients undergoing HP were older and had more often a higher ASA score. In the HP group 67% received preoperative RT compared to 79% following AR and 82% after APR ($p < 0.001$). The proportion of patients undergoing HP with a tumor at 5 cm was 21% compared to 15% in the AR group and 53% in the APR group ($p < 0.001$). The risk for overall complications following surgery and surgical complications in this subgroup was not significantly higher following HP. The risk was increased following APR compared to HP and AR ($p = 0.008$).

The results of the multivariable analysis showed that HP was not associated with a higher risk of developing complications following surgery and the type of surgical procedure was not a risk factor for 30-day mortality. APR was associated with a higher risk of overall complications and surgical complications.

## A subgroup analysis of patients older than 75 years

A multivariable analysis was conducted to explore whether the choice of surgical procedure influenced the 30-day outcome in patients older than 75 years and the results are shown in table 7. The analysis showed that the type of surgical procedure was not a risk factor for 30-day morbidity or mortality in patients over 75 years.

**Table 7.** Multivariable regression analysis of the impact of type of surgical procedure on 30-day complications and outcome in patients older than 75 years.

| | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | p-value | Odds ratio (95% CI) | p-value |
| Overall complications | | | | |
| HP | 1.00 | | 1.00 | |
| AR | 1.06 (0.79-1.43) | 0.69 | 1.10 (0.80-1.52) | 0.55 |
| APR | 1.57 (1.18-2.09) | 0.002 | 1.17 (0.90-1.52) | 0.23 |
| Surgical complications | | | | |
| HP | 1.00 | | 1.00 | |
| AR | 1.25 (0.87-1.82) | 0.24 | 1.23 (0.83-1.84) | 0.30 |
| APR | 1.58 (1.13-2.26) | 0.009 | 1.14 (0.82-1.57) | 0.42 |
| Intra-abdominal infection | | | | |
| HP | 1.00 | | 1 | |
| AR | 1.37 (0.68-3.06) | 0.40 | 0.68 (0.40-1.19) | 0.82 |
| APR | 1.31 (0.68-2.86) | 0.46 | 0.73 (0.38-1.37) | 0.80 |
| 30-day mortality | | | | |
| HP | 1.00 | | 1.00 | |
| AR | 0.74 (0.21-3.48) | 0.67 | 1.12 (0.62-2.40) | 0.21 |
| APR | 0.80 (0.25-3.52) | 0.73 | 1.36 (0.63-2.91) | 0.77 |

A multivariable logistic regression adjusted for age, sex, ASA score, tumor height, TNM stage, preoperative radiotherapy, preoperative chemotherapy, minimally invasive surgery, local radical resection, surgical competence and intraoperative bowel perforation.

# Paper IV

## Demographics of the study cohort

A total of 4741 patients were included in the study with 614 (13%) undergoing HP, 3075 (65%) AR and 1052 (22%) APR. A flow chart of the study inclusion is shown in figure 13.

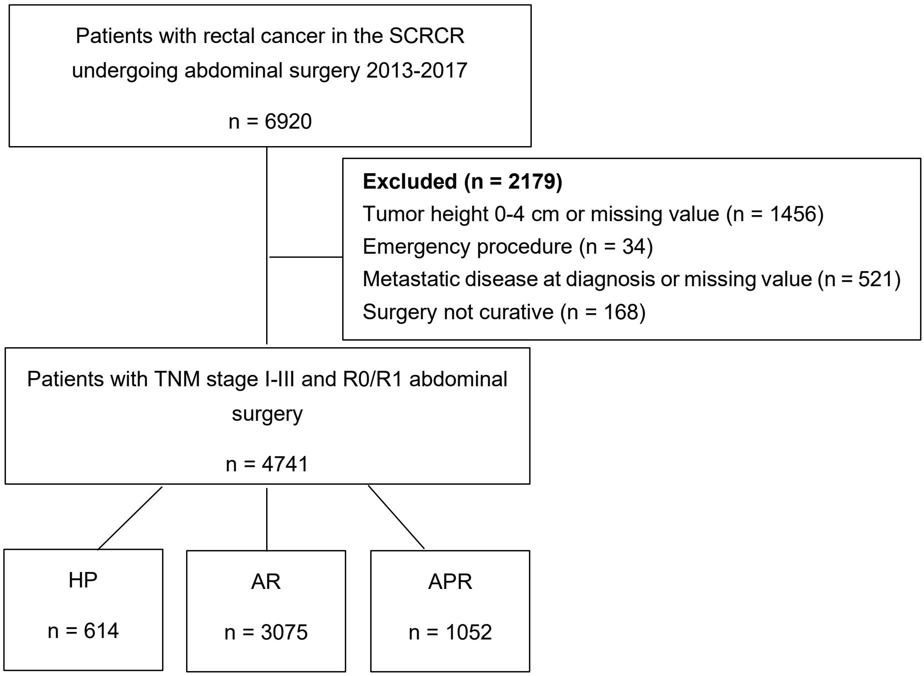


**Figure 13.** Flow chart of the study inclusion. Abbreviations: HP Hartmann´s procedure, AR anterior resection, APR abdominoperineal resection, SCRCR Swedish ColoRectal Cancer Registry, TNM Tumor Node Metastasis classification.

Patients in whom HP was performed were significantly older and had more frequently an ASA score of 3 or 4. The proportion of cT4 tumor was 14 % in the HP group, 11% in the AR group and 16% in the APR group ($p < 0.001$). The median tumour height was 10 cm in HP and AR groups compared to 6 cm in the APR group. Altogether 64% of patients undergoing APR had a tumor situated above 5 cm from the anal verge. Preoperative RT was administered to 52% of patients undergoing HP compared to 43% undergoing AR and 76% undergoing APR.

## Postoperative outcome

Table 8 displays the surgical details and postoperative outcomes in relation to the different operations.

**Table 8**. Surgical details and postoperative outcomes.

| Variable | All patients n = 4741 | HP n = 614 | AR n = 3075 | APR n = 1052 | p-value |
|---|---|---|---|---|---|
| Surgical approach | | | | | < 0.001 |
| Minimally invasive | 1784 (38) | 161 (26) | 1213 (40) | 410 (39) | |
| Of those robot assisted | 906 (50) | 84 (52) | 628 (52) | 194 (47) | |
| Conversion to open surgery | 315 (18) | 40 (25) | 224 (18) | 51 (12) | 0.02 |
| Intra-operative bowel perforation | 168 (4) | 24 (4) | 61 (2) | 83 (8) | < 0.001 |
| Overall complications | 1855 (39) | 250 (41) | 1130 (37) | 475 (45) | < 0.001 |
| Surgical complications | 985 (21) | 123 (20) | 614 (20) | 248 (24) | 0.04 |
| Intra-abdominal infection | 218 (5) | 36 (6) | 127 (4) | 55 (5) | 0.09 |
| Major Bleeding | 35 (0.7) | 7 (1) | 18 (0.5) | 10 (1) | 0.22 |
| 30-day reoperation | 420 (9) | 60 (10) | 265 (9) | 95 (9) | 0.62 |
| 30-day mortality | 49 (1) | 15 (2) | 20 (0.7) | 14 (1) | < 0.001 |
| pT stage | | | | | 0.01 |
| pT0 | 167 (4) | 16 (3) | 101 (3) | 50 (5) | |
| pT1 | 476 (10) | 55 (9) | 304 (10) | 117 (11) | |
| pT2 | 1384 (29) | 163 (26) | 920 (30) | 301 (29) | |
| pT3 | 2440 (52) | 333 (54) | 1582 (52) | 525 (50) | |
| pT4 | 257 (5) | 47 (8) | 157 (5) | 53 (5) | |
| pTx | 12 (0.2) | 0 | 7 (0.2) | 5 (0.4) | |
| pN stage | | | | | 0.11 |
| pN0 | 2988 (63) | 385 (63) | 1921 (62) | 682 (64) | |
| pN1 | 1227 (26) | 167 (27) | 810 (26) | 250 (24) | |
| pN2 | 506 (11) | 58 (9) | 336 (11) | 112 (11) | |
| pNx | 18 (0.3) | 3 (0.4) | 7 (0.3) | 8 (0.7) | |
| pCRM < 1mm | 121 (3) | 18 (3) | 51 (2) | 52 (5) | < 0.001 |
| Number of lymph nodes examined | | | | | |
| Median* | 18 (7) | 18 (7) | 18 (7) | 17 (7) | < 0.001 |
| > 12 examined | 3882 (82) | 517 (84) | 2587 (84) | 779 (73) | < 0.001 |
| Adjuvant chemotherapy | 924 (19) | 88 (14) | 650 (21) | 186 (18) | < 0.001 |

Values in parenthesis are percentages or * median with IQR. Abbreviations: HP Hartmann´s procedure, AR anterior resection, APR abdominoperineal resection, pCRM positive circumferential resection margin.

## Long term oncological outcome

LR was observed in 144 cases or 3% of the study population. LR was more common after HP and APR (4%) than after AR (3%) (p = 0.02). An unadjusted Kaplan-Meier analysis demonstrated that the LR free survival was higher following AR (Figure 14).

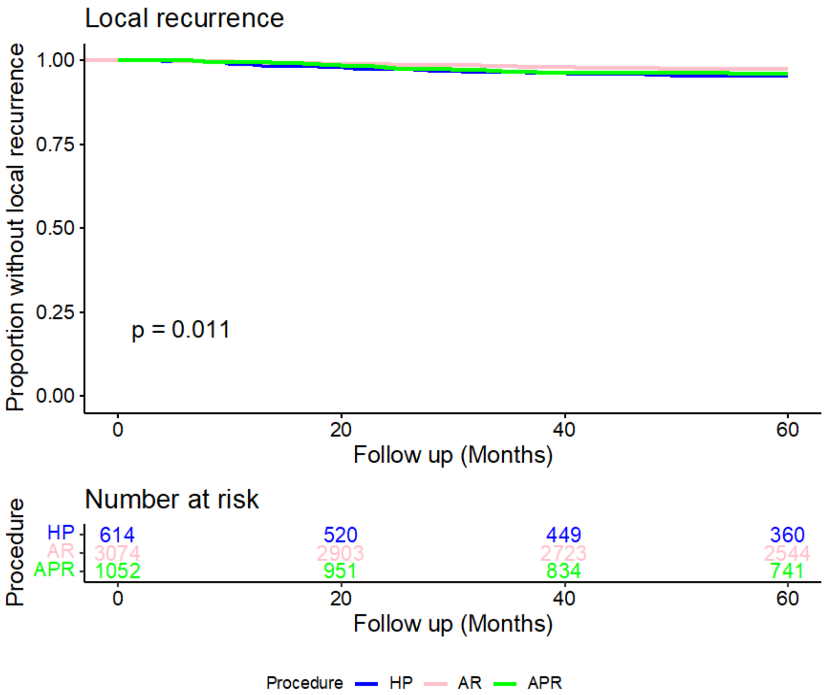


**Figure 14.** Kaplan-Meier curves for unadjusted 5-year local recurrence free survival. Abbreviations: HP Hartmann´s procedure, AR anterior resection, APR abdominoperineal resection.

A multivariable Cox regression analysis revealed that the type of operation was not associated with LR. Risk factors for LR were intraoperative bowel perforation; OR 2.41 (95% CI 1.33-4.40), pT4 tumor; OR 1.93 (95% CI 1.11-3.40) and pCRM < 1mm; OR 5.62 (95% CI 3.28-9.61). Female gender decreased the risk; OR 0.67 (95% CI 0.46-0.99).

DM was observed in 802 cases or 17% of the study population. The rate was highest following APR or 22% compared to 16% after HP and AR (p < 0.001). The unadjusted Kaplan-Meier analysis showed that the DM free survival was lowest in the APR group, log rank test p < 0.001 (Figure 15). The type of procedure was not associated with DM in the multivariable Cox analysis.

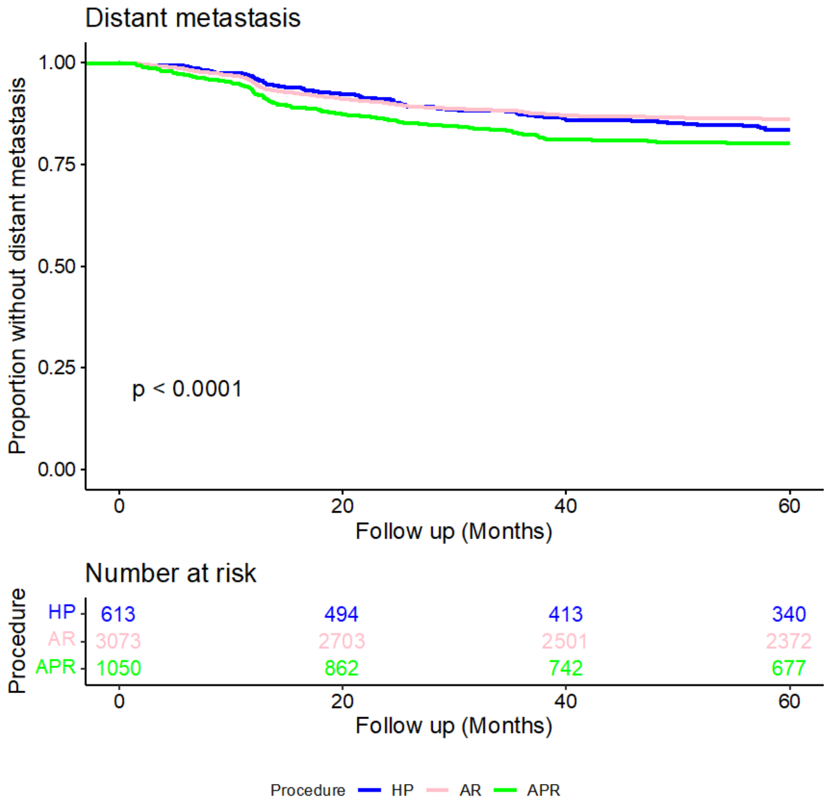


**Figure 15.** Kaplan-Meier curves for unadjusted 5-year distant metastasis free survival. Abbreviations: HP Hartmann´s procedure, AR anterior resection, APR abdominoperineal resection

## Survival

The proportion of patients that were disease-free at five years was higher following AR 81% compared to 71% following HP and 68 % after APR ($p < 0.001$). A Kaplan-Meier survival analysis showed that the unadjusted 5-year DFS was significantly better following AR. A multivariable Cox analysis demonstrated that the type of procedure did not have a significant effect on DFS.

OS at follow-up was lower following HP 59% compared to 85% after AR and 72% after APR ($p < 0.001$). A Kaplan-Meier survival analysis demonstrated that the unadjusted 5-year OS was superior following AR compared to HP and APR, log rank test $p < 0.001$ (Figure 16). A multivariable Cox analysis showed that undergoing AR improved survival; OR 0.62 (95% CI 0.54-0.71).

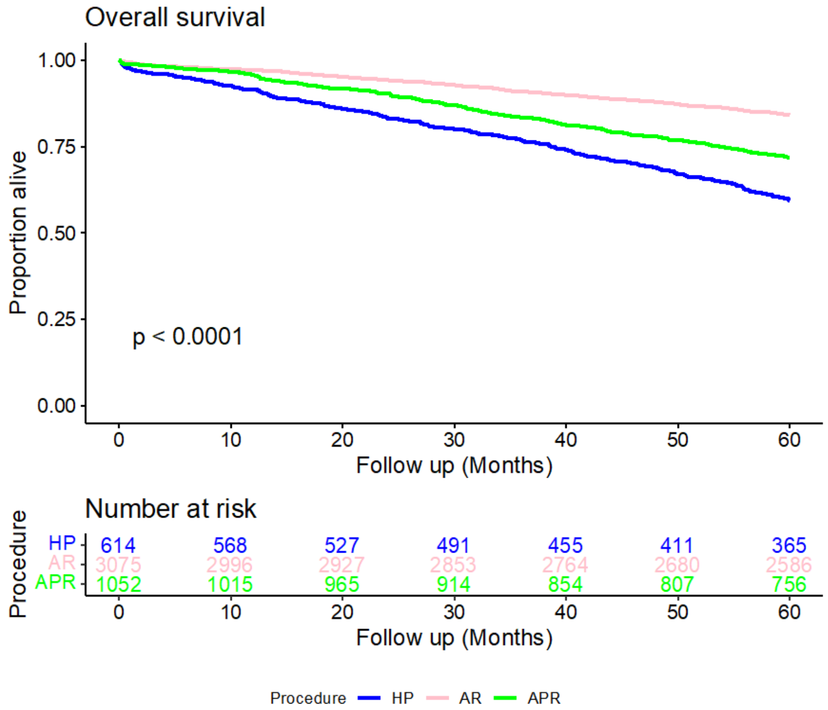


**Figure 16.** Kaplan-Meier curves for unadjusted 5-year overall survival.
Abbreviations: HP Hartmann´s procedure, AR anterior resection, APR abdominoperineal resection.

# Discussion

In this thesis various aspects regarding the use of HP and outcome after surgery were studied in a cohort of patients that could theoretically undergo either HP, AR or APR. The use of HP (non-restorative AR) varies widely internationally and within regions in Sweden reflecting uncertainties regarding the role of HP in rectal cancer treatment. The perception of high postoperative morbidity associated with HP also remains (95). Tradition is partly to blame, APR is the preferred non-restorative option in some countries such as the USA with HP hardly mentioned in published articles (39). Recently iAPR is employed more often although its use is still limited in most countries. On the other end of the spectrum HP is selected in up to 25% of patients undergoing surgery for rectal cancer in parts of Sweden and the Netherlands (146).

As patients with rectal cancer unfit for restorative surgery are a growing group the optimal management is a prioritized question. Randomized studies comparing different procedures are unlikely to be conducted and therefore the most effective approach to compare different procedures is through a large population-based study. It is also important to mention that large population-based data reflects real world medical scenarios that represent a wider selection of patients. This makes the results applicable to a broader clinical setting. Although HP, AR, and APR have different indications and specific complications, comparing patients in a large database enables a comprehensive evaluation.

In paper I and II data from the SCRCR was expanded and information extracted from medical charts in order to gather details regarding the use of HP in a clinical setting. For papers III and IV a nationwide cohort was used and included a large number of patients to assess whether the type of operation influences 30-day postoperative morbidity as well as long term oncological outcomes following rectal cancer surgery.

In paper I a comparison of patients undergoing HP with patients undergoing AR and APR revealed that the reasons for performing HP are multifactorial, including higher age and ASA score, lower preoperative albumin and more frequently a history of cardiovascular disease and diabetes. A more advanced disease was reported as the reason for choosing HP in a quarter of cases. These findings are in line with other studies with older and frailer patients undergoing HP. Furthermore, a higher ASA score and a less aggressive course regarding neoadjuvant and adjuvant therapy in spite of more advanced disease is often observed in patients undergoing HP (81, 82, 91). These findings were verified in papers II, III and IV with frailer patients undergoing HP. This causes a selection bias that needs to be taken into consideration when interpreting results from studies regarding HP.

Intraoperative difficulties resulting in a change of plan from AR to HP possibly represent part of the increased risk of complications following HP shown in most studies. Intraoperative changes are however infrequently reported and very few studies have investigated the intraoperative change of plan from AR to HP. Understanding the factors that can contribute to increased surgical difficulties is important, as it enables surgeons to anticipate challenges and provide informed guidance to patients accordingly. Intraoperative changes are not registered in the SCRCR and therefore data was extracted from medical charts to investigate this question. Altogether 23% of patients were planned for AR and this was changed to HP during the operation (paper I). The most common reasons for intraoperative change were related to difficulties creating an anastomosis or in 59% of cases. As AL is a detrimental complication following AR with considerable morbidity and mortality surgeons aim to minimize the risk as much as possible and a non-restorative option is sometimes the best if the risk is presumed too great (65, 101). Males were overrepresented in the group undergoing unplanned HP or 73%. This was possibly due to anatomical reasons as the male pelvis is narrower, known to cause intraoperative challenges such as difficulties using a surgical stapler (60, 61, 101).

The risk of AL is increased if the anastomosis is close to the anal verge and tumor height is a predictor of AL occurrence (61, 62). In cases where the anastomosis was deemed too low, a change of plan to HP was frequently reported. However, such decisions were made at the discretion of the responsible surgeon, making comparisons challenging as it is difficult to define what constitutes a too low anastomosis. Technical difficulties and diminished blood flow to the bowel as well as tissue damage caused by previous RT also prompted surgeons not to construct an anastomosis. A more advanced tumor than previously suspected accounted for a number of cases of intraoperative changes. This may be related to the anticipation that adjuvant treatment may be needed. In such cases every effort to minimize the risk of postoperative complications, especially AL must be undertaken as the window to administer adjuvant therapy closes. The fact that advanced tumor stage is also a risk factor for AL must also be considered (60).

Obesity has been shown to increase the risk of AL although BMI may not be the optimal marker as visceral fat is probably more related to AL (60, 147). In our cohort no significant difference in BMI was noted in relation to intraoperative change of plan.

When counselling patients regarding treatment options, it is vital to possess knowledge of what to expect and to anticipate potential complications as well as the expected outcome following surgery (148). This knowledge provides surgeons with confidence when advising and informing patients.

A higher overall risk of complications following APR was observed or 46% compared to 41 % following HP and 36 % after AR (paper III). Furthermore, the multivariable analysis showed that undergoing APR increased the risk of overall complications (OR 1.18, 95% CI 1.01–1.40). This contradicts studies that report a higher risk of complications following HP (85, 87). Performing HP also took shorter time and there was significantly less bleeding both of which can affect the postoperative outcome. As the cohort in paper III consisted of patients with a tumor at 5 cm or higher the decision to perform APR due to tumor height was not a significant factor. Nevertheless 22% of patients underwent APR, certainly in some instances due to technical reasons but uncertainties regarding HP as well as tradition probably influence the decision.

The rate of intraoperative bowel perforation was highest following APR or 9% compared with 6% following HP and 2% after AR (paper III). This is in line with previous studies and technical difficulties linked to the perineal phase of the procedure likely account for most cases. Intraoperative changes from a planned AR due to adverse events have also been mentioned as a possible culprit (121, 122, 149). Interestingly data from paper I showed that no patient undergoing APR did so as a result of an intraoperative change from AR. Bowel perforation was however mentioned as a reason to change to HP from AR intraoperatively in 5% of cases. This indicates that the higher rate of bowel perforations following APR may reflect the procedure itself as it seems surgeons rather perform HP in cases of adverse intraoperative advents. These findings should be interpreted with caution as they may also reflect a small sample size or regional tradition in the southern part of Sweden.

Our results suggest that patients undergoing HP have superior outcomes compared to those undergoing APR in terms of 30-day morbidity, making HP a better non-restorative alternative in most cases. Recent studies comparing HP, APR or iAPR also indicate a favourable outcome following HP (92, 94, 95).

A particular complication often associated with HP is pelvic sepsis mainly thought to be caused by breakdown of the staple line in the rectal remnant with formation of an intra-abdominal infection and abscess. Pelvic sepsis occurs following AR or APR as well but earlier reports suggested that this was more common following HP (85, 86). Recent studies contradict these findings, with conflicting reports regarding the high risk of pelvic sepsis following HP (80, 89, 94). In the published literature different definitions of pelvic sepsis have been employed and the follow-up time ranges from 30 days to one year making comparison difficult (89, 92, 93).

The rate of pelvic sepsis within 30 days postoperatively was 6% after HP in paper III, which harmonizes with a rate of 11% seen after a follow up time of one year in paper II and is in line with recent studies (80, 88, 89). Extending the follow-up time gives more accurate results regarding the true incidence as almost half of the patients were diagnosed after 30 days.

The multivariable analysis in paper III revealed that undergoing HP increased the risk of developing pelvic sepsis (OR 1.7, 95% CI 1.26–2.28). As the rates of reoperations and readmissions were comparable across all groups, with no discernible difference in 30-day mortality, the clinical significance of this complication may not be as pronounced as previously suggested. Results from paper II showed that the consequences of pelvic sepsis were not as detrimental as often stated, with most patients treated conservatively and none needed major surgery. None of the patients that developed pelvic sepsis died within 90-days postoperatively. Jonker *et.al*. compared HP to AR with or without a DS and observed a higher rate of complications and reoperations following AR alone and undergoing HP was significantly associated with a lower risk of postoperative complications (81). Furthermore, Lazzaron *et al*. demonstrated that when comparing AR with or without a DS to HP a lower rate of complications and reoperations was seen after HP compared to AR alone (82). When considering the fact that a significant proportion of patients with a DS do not undergo stoma reversal, resulting in a permanent ileostomy, surgeons should carefully consider HP in frailer individuals unfit for restorative surgery. While fewer patients were diagnosed with pelvic sepsis after AR, this complication is frequently attributed to AL and can be considerably more challenging to manage (63, 82).

In paper II a closer look at risk factors for developing pelvic sepsis revealed that patients diagnosed with pelvic sepsis had signs of intraoperative difficulties such as longer operation time and greater bleeding. Neoadjuvant RT increased the risk of pelvic sepsis after HP (OR 7.96, 95 % CI 2.54-35.36) consistent with prior research indicating that RT can impair wound healing, thereby elevating the risk of pelvic sepsis (80, 83, 89, 150).

Patients with a BMI over 25 kg/m$^2$ had a five times higher risk of developing pelvic sepsis compared to patients with a BMI under 25 kg/m$^2$. Similar findings have been reported although studies on the effects of obesity on the risk of complications have been somewhat conflicting (81, 89). Obesity can cause technical difficulties resulting in a higher risk of complications, it is also associated with comorbidities such as insulin resistance and diabetes, which are risk factors for postoperative infections. The relationship between BMI and complication risk is however somewhat complex as underweight patients (BMI below 18.5 kg/m$^2$) have an increased risk of complications as well (151). BMI was not a significant risk factor for pelvic sepsis development in the analysis in paper III, partly explained because three procedures were compared and no significant difference in BMI was noted between procedures.

Tumor height is often mentioned as a risk factor for pelvic sepsis and studies have identified lower tumors as having an increased risk of intra-abdominal infection following HP, likely attributable to a shorter rectum stump as well as preoperative RT (86, 87). Low tumors were excluded from the present study most likely explaining why tumor height was not a significant risk factor for developing pelvic sepsis.

Increased postoperative surveillance with suspicion of pelvic sepsis is warranted when intraoperative difficulties occur, especially in patients with low tumors, history of RT, heightened BMI or a combination of factors.

One of the reasons mentioned for removing the rectum are the benefits of not having symptoms related to the rectum remnant. This is however rarely reported in studies and the scope of this problem is understudied. In paper II, 15% of patients reported symptoms from the rectal stump, secretion was the most common symptom. Rectal bleeding and proctitis were uncommon. These symptoms were diagnosed during follow-up and no patient required readmission or received in-hospital treatment for these complaints. Similar findings are reported by Popiolek *et.al.*(93).

Few studies have specifically addressed the optimal treatment of tumors located in the lower mid rectum. Lower tumors carry a higher risk of AL, which may in some cases compromise the patients' eligibility for receiving adjuvant treatment. The use of DS is more prevalent with lower tumors which results in a permanent ileostomy in some cases. Additionally, low tumor height and consequently low anastomotic height are associated with an increased risk of developing LARS leading to a diminished quality of life (69, 101). These factors are crucial considerations when discussing treatment options with patients. The subgroup analysis (paper III) of patients with tumors located 5–7 cm from the anal verge revealed that those undergoing HP did not have a significantly higher risk of complications or mortality following surgery. Interestingly, the sub-analysis showed no significant differences in the rate of pelvic sepsis despite tumor height and the fact that a larger proportion of patients received preoperative RT, a finding that contradicts previous studies (80, 86).

Many surgeons think of higher age as a factor linked with inferior outcome following surgery for rectal cancer and less aggressive treatment is often offered as a result (99, 146). Furthermore, the use of HP is more prevalent in older patients (146). At the same time, the definition of high age is variable making comparison difficult (100). In paper III a subgroup analysis of patients older than 75 years revealed that the choice of operation did not significantly affect the risk of complications, reoperations or 30-day mortality. Our results indicate that age in itself does not exclude patients from being eligible for AR, the decision to perform non-restorative surgery is multifactorial. However, the consequences of complications for the patient can be more severe with older age and should be taken into consideration when choosing the treatment strategy. Of note, older age is a risk factor for non-closure of DS making HP an attractive alternative in this population (102). Furthermore, AL leads to a more pronounced increase in the risk of death with older age (65).

The oncological outcome following HP is understudied as many larger studies exclude patients that undergo HP or the percentage of patients undergoing restorative surgery is much larger than the broader clinical setting (41, 66). The multivariable analysis in paper IV demonstrated that the choice of procedure was not significantly associated with

LR. Only a few studies have investigated the risk of LR following HP and previous studies have been conflicting on the matter (91, 127, 152).

Two recent Dutch studies reported worse oncological outcomes following HP when compared to AR, with HP significantly associated with LR after correcting for confounding factors. Roodbeen *et.al*. compared the oncological outcome following HP to AR and reported a LR rate of 8 % following HP (127). This is difficult to compare with our findings of a 4% LR rate given that patients with low tumors were excluded in our study. Tumor height is an important risk factor where low tumors are more prone to LR (152). In their study 20% of HP patients had a tumor height of <3 cm making comparison unreliable. They found that undergoing HP significantly increases the risk of LR in the multivariable analysis, contrary to our findings. The authors suggest that technical challenges associated with a lower tumor height could contribute to an incomplete TME dissection. Additionally, the adoption of a non-restorative approach, influenced by perioperative adverse events, may account for the elevated LR rate observed following HP (127).

Hol *et.al*. compared AR, APR and HP and reported a 14.6% LR rate after HP with a lower OS and they conclude that undergoing HP might be associated with a worse oncological outcome after correcting for confounding factors. Tumor stage is a very important factor when assessing risk of LR and the fact that T stage was significantly higher in the group undergoing HP suggests that a confounding bias might have influenced their results. Of interest, the rate of pCRM was similar in all groups and the rate of pelvic sepsis lower following HP compared to AR, both of which can influence LR (91).

Our findings are consistent with those of a Swedish study conducted by Anderin *et.al*. (149). Similar to our study, they found that inadvertent bowel perforation and a positive CRM of less than 1 mm were more common following APR, potentially leading to a higher LR rate, although the multivariable analysis did not demonstrate significant differences in LR rates related to the procedure chosen (149).

Several factors can contribute to a higher rate of CRM positivity in the APR group in the present study. A larger percentage of patients undergoing APR were male and subsequent technical difficulties with a narrower male pelvis may play a role. The T stage was also higher in the APR group and the tumor height was lower as 37% of patients had a tumor at 5 cm compared to 2% in the AR group and 5% in the HP group probably influencing our results.

Paper IV showed that intraoperative bowel perforation, T4 tumors, and a pCRM of <1 mm were risk factors for LR and our findings concur with previous studies (121, 123). Female gender was associated with a decreased risk of LR, a similar finding was reported in a study by Martling *et.al.* However, in their study, the gender effect on LR risk was no longer significant after adjusting for differences in RT between men and women. The fact that RT was offered less frequently to women in their study indicated that LR rate may be lowered if RT was offered more often to women. (153). Although our cohort excluded the lowest tumors making direct comparisons difficult, our multivariable analysis adjusted for RT and found that the significance remained.

In paper IV the rate of DM following HP and AR was 16 %, in line with the DM rate reported in large trials comparing laparoscopic with open TME (154, 155). The DM rate was higher following APR, diagnosed in 22% of patients. Patients undergoing APR had lower tumors, which may explain the higher DM rate. A similar finding was reported in a Swedish study by Doroudian *et.al*. with a DM rate of 20% for patients undergoing APR and 15% following HP. Tumor height had a significant impact on the DM risk (152).

After correcting for confounding factors in the multivariable analysis the type of procedure had no significant impact on DM. The type of procedure chosen may affect the risk of developing DM and inferior oncological outcome following HP has been reported (91). The present study could not confirm these findings, the outcome following HP was similar although tumor stage was significantly higher in patients undergoing HP compared to AR.

In paper II the 30-day mortality following HP was 2.8%, similar to the 30-day mortality of 2% following HP seen in paper III. The mortality rate following HP is higher than the 0.8% 30-day mortality rate following AR and 1% following APR. This aligns with previous studies reporting inferior survival after HP (81, 91, 156). As previously mentioned, patients undergoing HP were older and frailer explaining a higher mortality post-operatively.

Furthermore, the Cox regression analysis in paper IV revealed superior OS following AR, even after adjusting for several factors. However, the inherent health advantage of patients undergoing AR may not be fully accounted for, leading to the question of whether the difference in outcomes is due to the procedure itself or patient selection. Without a randomized trial, this question remains unanswered.

# Strengths and Limitations

An influential limitation to our studies is the retrospective nature of our data, although the data in the SCRCR is prospectively gathered. A well-defined study population and the high validity and coverage of the SCRCR are on the other hand a major strength (140, 141). Furthermore, data from the SCRCR were complimented with chart reviews (paper I and II) performed by the author.

When comparing different surgical procedures, it is essential to consider the selection bias that arises from surgeons choosing procedures based on patient characteristics. Consequently, some of the benefits observed with AR may be attributed more to patient selection than to the procedure itself.

iAPR was first recorded in the SCRCR in 2018, which means that information regarding patients in the present studies who were registered as having undergone APR, may actually have undergone iAPR. However, the proportion of iAPR procedures is likely very low for the study period, as only 120 iAPR procedures were performed across Sweden in 2018.

Certain variables were not registered in the SCRCR during the study periods such as transanal TME or transanal transection with single-stapled anastomosis and could therefore not be assessed in the studies. EMVI was not registered during the study period and could therefore not be included in the studies.

A potential weakness to our study is the fact that height was used to define rectal tumors. That may affect the generalizability of our findings as many researchers use the sigmoid take-off as the anatomical landmark that defines the termination of the rectum (157-159).

# Conclusions

The main reasons for choosing HP are frailty causing a significant risk of AL and locally advanced tumor planned for adjuvant treatment. A significant number of patients undergo HP as a result of an intraoperative decision. Male gender, a distal transection line close to the anal sphincter and a more advanced tumor may increase the risk of anastomotic difficulties leading to an unplanned HP.

The incidence of pelvic sepsis following HP for rectal cancer is relatively low (11%) after a one-year follow-up. Neoadjuvant RT was the most significant risk factor for pelvic sepsis. Surgeons should be aware that almost half of patients are diagnosed beyond 30 days postoperatively. The majority of patients were managed conservatively and no patient required major surgery due to pelvic sepsis.

HP has a more favourable surgical outcome when compared to APR. Although a higher risk of intra-abdominal infection was noted following HP no differences were seen in rates of reoperations, readmissions or 30-day mortality. Undergoing APR increased the risk of overall complications.

The type of procedure chosen was not a significant risk factor for LR or DM. OS was superior following AR although this may be related to patient selection. Risk factors for LR were intraoperative bowel perforation, T4 tumor and a positive CRM. Female gender decreased the risk.

For patients with a tumor in the mid or upper rectum unfit for restorative surgery HP stands as a valid alternative with favourable surgical and oncological outcome.

# Future perspectives

This thesis investigates the use of HP in rectal cancer surgery in Sweden. The articles add new information regarding the use of HP and show that HP has a favourable outcome when compared to APR regarding postoperative morbidity and oncological outcome. As the number of patients unsuitable for restorative surgery is expected to grow with aging population and increased neoadjuvant therapy our findings are of value and can be used when updating national guidelines.

The restoration of bowel continuity is an important goal but not always a realistic choice. The problem lies in the difficulties deciding which patient benefits from choosing a non-restorative procedure. One of the research questions that would complement our findings is the rate of stoma reversal in the group undergoing AR with DS as well as assessing risk factors for non-closure of DS using a large nationwide cohort.

Another important factor to consider when recommending treatment is the quality of life after surgery. The quality of life after HP compared with AR and APR or iAPR has not been assessed in a large population-based cohort and this would be of great interest for further studies.

The use of iAPR is halted by lack of studies demonstrating its safety, especially in terms of long-term oncological outcome. A large population-based study comparing HP and iAPR after 2018 when this variable was introduced to the SCRCR would be of interest for further studies.

EMVI has been recognised as an important prognostic marker both for LR and DM. As EMVI is not registered in the SCRC during the study period a follow-up study investigating if the type of procedure affects oncological outcome with the possibility to assess this variable would be interesting.

The rate of MIS has increased dramatically in Sweden during the study period and this may affect the generalizability of the current findings. An updated study investigating the effects of performing HP with MIS is of great value as current guidelines emphasize the use of MIS.

Healthier patients are more likely to be selected for AR, leading to an uneven distribution of procedure allocation and, without a randomized trial, an uneven distribution of confounders. This poses a particular problem when investigating rare events such as LR. One potential solution is to use propensity score matching, which is more effective in adjusting for confounders in smaller datasets where there are few events per variable (160, 161). This is particularly relevant since patients with comorbidities have a higher likelihood of undergoing HP, and propensity score matching can address the issue of unequal chances of receiving a specific procedure. It would be intriguing to investigate if this method alters the results regarding the risk of LR.

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