Abstract

Survival among patients with stage IV rectal cancer is poor and surgical treatment for this disease is associated with morbidities such as small bowel obstruction, complications with a diverting loop ileostomy, and functional bowel disturbances. The overall aim of this thesis was to assess risk factors and morbidity after surgery for rectal cancer and to evaluate factors affecting survival in patients with stage IV rectal cancer.

**Paper I** a prospective study on patients with rectal cancer with loop ileostomy who underwent stoma closure in a 23-hour hospital stay setting. Results were compared with a group who underwent standard in-hospital stoma closure prior to the start of the study, selected retrospectively as controls. No differences were found in the number of complications or the frequency of re-hospitalization or re-operation, indicating that ileostomy closure in a 23-hour hospital stay setting in these selected patients was feasible and safe with high patient satisfaction.

**Paper II** a population-based study with data gathered prospectively. In total, 11% of the patients developed small bowel obstruction (SBO), mostly during the first year after rectal cancer surgery. Surgical treatment for SBO was performed in 4.2% of the patients, and the mechanism was stoma-related in one-fourth. Rectal resection without anastomoses, age, morbidity, and previous radiotherapy (RT) was not associated with admission to the hospital or surgery for SBO. Re-laparotomy due to complications after rectal cancer surgery was an independent risk factor for admission for treating SBO.

**Paper III** a population-based study with data gathered prospectively on bowel function at 1 year after anterior resection or stoma reversal. No associations were found between any defecatory dysfunction and the part of the colon used for anastomosis, the level of the vascular tie, or gender. An association was observed between higher anastomotic level and a lower risk of incontinence and clustering. At 1 year after loop ileostomy closure, the risks of incontinence, clustering, and urgency increased by up to fourfold.

**Paper IV** a case-control study aiming to identify patient-, tumor-, and treatment-related prognostic factors for 5-year survival in patients with rectal cancer with synchronous stage IV disease. Patient-related factors did not differ between groups. Among the tumor-related factors, multiple site metastases, bilobar liver metastases, and increasing numbers of liver metastases were associated with poor survival. Prognostic treatment-related factors were preoperative RT, metastasectomy, and radical resection of the primary tumor. The most important prognostic factor for long-term survival was metastasectomy.

**Keywords:** Loop ileostomy, Small bowel obstruction, Defecatory dysfunction, Stage IV rectal cancer

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To my wife Pernille and daughter Ellie
List of Papers

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


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### Abbreviations

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<td>AL</td>
<td>Anastomotic leakage</td>
</tr>
<tr>
<td>APE</td>
<td>Abdominoperineal excision</td>
</tr>
<tr>
<td>AR</td>
<td>Anterior resection</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CR</td>
<td>Complete response</td>
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<tr>
<td>CRC</td>
<td>Colorectal cancer</td>
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<tr>
<td>CRM</td>
<td>Circumferential resection margin</td>
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<td>CRT</td>
<td>Chemoradiotherapy</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DFS</td>
<td>Disease–free survival</td>
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<tr>
<td>DRM</td>
<td>Distal resection margin</td>
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<tr>
<td>EMVI</td>
<td>Extramural venous invasion</td>
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<td>ESMO</td>
<td>European Society for Medical Oncology</td>
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<tr>
<td>HP</td>
<td>Hartmann’s procedure</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>LARS</td>
<td>Low anterior resection syndrome</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of hospital stay</td>
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<td>LRT</td>
<td>Long-course RT</td>
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<td>LTS</td>
<td>Long-term survivors</td>
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<tr>
<td>LR</td>
<td>Local recurrence</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PET</td>
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<td>PME</td>
<td>Partial mesorectal excision</td>
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<td>MDT</td>
<td>Multidisciplinary team</td>
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<td>MRF</td>
<td>Mesorectal fascia</td>
</tr>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>RT</td>
<td>Radiotherapy</td>
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<td>SCRCR</td>
<td>Swedish Colorectal Cancer Registry</td>
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<td>SBO</td>
<td>Small bowel obstruction</td>
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<tr>
<td>SRT</td>
<td>Short-course RT</td>
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<tr>
<td>STS</td>
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<tr>
<td>TaTME</td>
<td>Transanal TME</td>
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<tr>
<td>TME</td>
<td>Total mesorectal excision</td>
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<td>TNM</td>
<td>Tumor/Node/Metastasis</td>
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</table>
Introduction

Epidemiology

Colorectal cancer (CRC) is the third most common type of cancer worldwide. There are geographical differences in CRC, with the highest incidence in Europe, Northern America, Australia, and New Zealand, and the lowest incidence in Africa, Asia, and the Middle East. Rectal cancer accounts for approximately 30% of all cases of CRC. In Sweden, about 2000 new cases are diagnosed annually, and of these, about 40% are women. Although the overall incidence of CRC is increasing, in Sweden, the age-standardized incidence rates have remained stable over the last 15 years, but mortality is decreasing (Figure 1). The overall 5-year survival rate is approximately 60% for both men and women (although men have slightly lower survival).

Etiology and risk factors

CRC develops through multiple mutational processes, from adenomas via activation of oncogenes and inactivation of tumor suppressor genes, but only 10% of adenomas become malignant. Sporadic tumors arise in 80% of all cases of CRC, with the remaining 20% caused by hereditary factors. About 5% of patients with CRC have cancer as a result of genes predisposing for colorectal syndromes such as Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis. Other well-known risk factors for the development of CRC include inflammatory bowel disease (Crohn’s colitis and...
ulcerative colitis\(^6\), obesity\(^7\), and high intakes of red and processed meat, tobacco, and alcohol\(^8\). Protective factors that has been suggested include high fiber intake\(^8\), dairy products\(^9\), physical activity\(^7\), and the long-term use of aspirin\(^10\).

Anatomy

The most distal part of the gastrointestinal tract is called the anal canal, and the rectum is considered as the distal 15 cm of the large bowel. The upper border begins at the sacral promontory from which the rectum extends down to the anal verge. The dentate line marks the transition of columnar glandular to squamous epithelium. According to the European Society for Medical Oncology (ESMO) guidelines, rectal tumors are defined as lesions up to 15 cm from the anal verge when diagnosed using a rigid rectoscope\(^11\).

The rectum is surrounded by fatty lymphovascular tissue called the mesorectum, which in turn, is enveloped with an avascular layer called the mesorectal fascia (MRF). The upper third of the rectum is covered anteriorly and laterally by the peritoneum down to the peritoneal reflection, and the distal part below the pouch of Douglas (in women) and the rectovesical pouch (in men) is completely retroperitoneal. Organs adjacent to the rectum are anteriorly the prostate, seminal vesicles, vas deferens, and urinary bladder in men, and the vagina and uterus in women. The rectum is limited laterally by vital structures such as the ureters, iliac vessels, and lateral pelvic wall, and posteriorly the sacrum, coccyx, and hypogastric nerve plexus.

Arterial blood supply to the rectum arises from the inferior mesenteric artery, which continues as the superior rectal artery and from the internal iliac artery, which continues as the inferior rectal artery; some individuals also have a middle rectal artery.

Lymphatic drainage follows the arteries, and knowledge of this is important because cancers can spread thorough this pathway\(^12\). There are three main lymphatic pathways: from the upper rectum along the superior rectal artery to the lymphatic nodes along the inferior mesenteric artery; from the lower rectum along the internal iliac artery to the lateral pelvic nodes; and from the anal canal to inguinal nodes.

Clinical presentation and preoperative investigations

Clinical symptoms and assessment of local tumors

Common symptoms of rectal cancer include altered bowel habits, incomplete bowel evacuation, and rectal bleeding. Symptoms of more advanced disease
include weight loss, fatigue, abdominal-, rectal-, and anal pain, anal inconti-
ence, and anemia. The clinical investigation includes digital palpation of a
distal tumor with a description of its relation to the anal sphincters and assess-
ment of its mobility. Using a rigid rectoscope, the distant border is measured
from the anal verge, but a flexible sigmoidoscope is typically used to assess
the tumor. Biopsies are taken to establish the diagnosis by histopathology.
Colonoscopy or computed tomography (CT)-based colonography is performed
to rule out synchronous CRC, which occur in 4%–7% of patients13,14. Accord-
ing to the ESMO guidelines, rectal cancers should be classified into three cat-
egories based on the lower border of the tumor: low (0–5 cm), median (6–10
cm), or high (11–15 cm)11.

Figure 2. Endoscopical view of a rectal cancer

Magnetic resonance imaging (MRI) is also used to stage rectal cancers accord-
ing to tumor stage/depth (T-stage), lymph node involvement (N-stage) based
on the morphologic criteria of the nodes15, possible tumor deposits, the tumor
and node distance to the MRF, and extramural venous invasion (EMVI). A
positive (+) or threatened MRF seen on MRI is considered in the guidelines
to be an indication for chemoradiotherapy (CRT)11. Patients with positive
EMVI findings are associated with an increased risk of having synchronous
or developing metachronous metastasis16, and tumor deposits have been re-
ported to have prognostic value17. This staging is important because it guides
physicians in the selection of neoadjuvant treatment18-20.
Assessment of metastases

At the time of diagnosis, about 25% of patients with CRC have synchronous metastases\(^\text{21}\), the most common locations for which are the liver (70%), followed by the lungs (24%), peritoneum (15%), and non-regional lymph nodes (16%). Metastases to the bones (4%) and brain (2%) are uncommon\(^\text{22}\). Synchronous colorectal metastases at a single site are seen in 14% of cases and at multiple sites in 8%\(^\text{21}\).

Contrast-enhanced CT of the thorax and abdomen is often used to detect synchronous metastases to the liver and lungs. Compared with chest X-rays, the introduction of CT to detect lung metastasis has led to the increased identification of lung lesions, but most (up to 42%) are too small and unspecific for diagnosis, and only about one-fourth of these are metastases\(^\text{20}\). For detecting liver metastasis with CT, the sensitivity and specificity are 74%–84% and 95%–96%, respectively, for smaller (<1 cm) and unclear lesions. MRI has almost equal specificity (93%–97%), but higher sensitivity (80%–88%)\(^\text{23,24}\). In some cases, positron emission tomography (PET) with \(^{18}\text{F}\)-fluorodeoxyglucose is used to detect extrahepatic metastasis or to diagnose potential metastases. The anatomic localization of a potential metastasis can be identified by combining PET with contrast-enhanced computed tomography (PET–CT). PET–CT is also useful to assess the effects of CRT in locally advanced or recurrent rectal cancers. However, in Sweden, it is not used routinely, but rather applied as a complement to routine preoperative investigations\(^\text{25}\).
Staging of rectal cancer

Different staging systems have been used over the years. The previously used Dukes classification has been replaced by the tumor/node/metastasis (TNM) classification system developed and revised by the Union for International Cancer Control and the American Joint Committee on Cancer. In the Swedish national guidelines for CRC, the 8th edition is recommended (Table 1). In addition to the staging classification, prefixes are used to indicate preoperative clinical stage with c and postoperative/pathological stage with p, and if neo-adjuvant (presurgical) treatment has been given, the prefix y is used.

T-stage
This stage describes the depth of invasion of the primary tumor. The prognosis deteriorates with higher T-stage tumors.

N-stage
The number of regional lymph nodes with possible metastatic involvement is the basis for the N-stage. Tumor deposits are also included in the N-stage and are metastatic foci in the perirectal fat.

M-stage
The M-stage is defined as the presence of metastatic foci in distant organs, nonregional lymph nodes, or peritoneal carcinomatosis.

Table 1a. Tumor classification by TNM staging

<table>
<thead>
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<tbody>
<tr>
<td>Tx</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>Tis</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
</tr>
<tr>
<td>T4a</td>
</tr>
<tr>
<td>T4b</td>
</tr>
<tr>
<td>Regional lymph nodes (N)</td>
</tr>
<tr>
<td>Nx</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N1a</td>
</tr>
<tr>
<td>N1b</td>
</tr>
<tr>
<td>N1c</td>
</tr>
<tr>
<td>N2</td>
</tr>
</tbody>
</table>

- Tx: Primary tumor cannot be assessed
- T0: No evidence of a primary tumor
- Tis: Carcinoma in situ, intramucosal
- T1: Tumor has invaded the submucosa
- T2: Tumor has invaded the muscularis propria
- T3: Tumor has invaded the subserosa or perirectal tissue
- T4a: Tumor has perforated the visceral peritoneum
- T4b: Tumor has invaded or adheres to other organs or structures
- Nx: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastases
- N1: Metastases in 1–3 regional lymph nodes
- N1a: Metastases in 1 regional lymph node
- N1b: Metastases in 2–3 regional lymph nodes
- N1c: No regional lymph node metastases, but tumor deposits in the subserosa or perirectal tissue
- N2: Metastases in ≥4 regional lymph nodes
<table>
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<tr>
<td>Tis</td>
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<tr>
<td>T1–T2</td>
<td>N0</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
</tr>
<tr>
<td>T4a</td>
<td>N0</td>
</tr>
<tr>
<td>T4b</td>
<td>N0</td>
</tr>
<tr>
<td>T1–T2</td>
<td>N1</td>
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<tr>
<td>T1</td>
<td>N2a</td>
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<tr>
<td>T3–T4a</td>
<td>N1</td>
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<tr>
<td>T2–T3</td>
<td>N2a</td>
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<tr>
<td>T1–T2</td>
<td>N2b</td>
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<td>T4a</td>
<td>N2a</td>
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<td>Any T</td>
<td>Any N</td>
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<tr>
<td>Any T</td>
<td>Any N</td>
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Postoperative histopathology staging

Postoperative histopathology staging after rectal cancer surgery means evaluation of the resected specimen macroscopically and thereafter microscopically. The pathologist examines the tumor (TN-stage), resection margins (circumferential resection margin [CRM] and distal resection margin [DRM]), and surgical quality (R-residual tumor). The quality of total mesorectal excision (TME) is judged complete, nearly complete, or incomplete, and this has been shown to influence the prognosis. In addition to these factors, the pathology report should also state tumor differentiation and tumor infiltration in venous and lymphatic vessels and nerves.

Resection margin

The resection surface examined is divided into the CRM and DRM. The CRM is defined as the distance between the lateral part of the rectal tumor, tumor...
deposit, or metastatic node and the lateral resection margin. Numerous studies have shown that a positive CRM, i.e., tumor cells within 1 mm\textsuperscript{30-36} or 2 mm\textsuperscript{37} from the margin, is a negative prognostic factor for local recurrence (LR)\textsuperscript{30-37}, systemic disease, and overall survival\textsuperscript{36,38}. However, some studies have reported no correlations with LR owing to modern surgical and oncological treatments\textsuperscript{39}. Today, a positive CRM is defined as ≤1 mm and a negative CRM as >1 mm. A DRM of 1 cm with a complete TME is accepted in middle-to-low rectal cancers, and a partial TME with a DMR of 5 cm is accepted in high rectal tumors\textsuperscript{40,41}.

Residual tumor status

The residual tumor (R) status depicts the involvement of a tumor at the CRM or DRM. The classification is R0 if no residual tumor is found, R1 if a microscopic residual tumor is present, and R2 if there is a macroscopic residual tumor in the margin. R status is correlated with distant metastasis, LR, and patient survival\textsuperscript{42}.

Vascular and perineural invasion

Vascular involvement is reported as venous and/or lymphatic. Venous invasion can be either intramural (within the submucosa or the muscularis propria, EMVI–) or extramural (beyond the muscularis propria, EMVI+). In a pathology report, V0 means the lack of venous involvement, V1 marks venous involvement detected only microscopically, and V2 marks venous invasion already detectable during the macroscopic assessment of the specimen. The absence (L0) or presence (L1) of lymphatic invasion is reported separately. Invasion of the lymphatic vessels might predict future lymph node metastasis, and venous involvement is associated with decreased survival and an increased risk of distant metastases\textsuperscript{43-45}. Perineural invasion has been defined as tumor growth in, around, and through peripheral nerves, and is a prognostic factor for inferior patient outcomes\textsuperscript{46,47}.

Differentiation

The most common type of CRC is an adenocarcinoma of epithelial origin. The second most common form of adenocarcinoma is the mucinous type, defined by >50% extracellular mucin, and thereafter, the more uncommon signet ring cell adenocarcinoma. Other types of CRC include neuroendocrine, adenosquamous, and medullar carcinomas\textsuperscript{48}. Adenocarcinomas were previously classified as well, moderately or poorly differentiated, and this was later changed, so that well and moderately differentiated tumors were classified as low grade and the poorly differentiated ones as high grade\textsuperscript{49}. Less well-differentiated carcinomas indicate poorer patient survival outcomes\textsuperscript{50}. 
Multidisciplinary team (MDT) conference

When the preoperative assessment is completed and all information is gathered, all patients with CRC should be discussed at an MDT conference. At these conferences, different specialties, including colorectal surgeons, oncologists, radiologists, pathologists, and nurses, gather together. Patients are often discussed both pre- and postoperatively and sometimes during treatment, when neoadjuvant treatment is given. In Sweden, it is mandatory to discuss all patients with CRC at an MDT conference, and at present, 98% of all such patients are discussed\textsuperscript{51}. After the implementation of MDTs, more patients were seen undergoing preoperative radiology assessment and reduced rates of positive CRM were observed\textsuperscript{52,53}. Patients with liver and lung metastases are discussed at a separate MDT conference with hepatic and thoracic surgeons.

Swedish ColoRectal Cancer Registry

The Swedish Rectal Cancer Registry was established in 1995 and the Swedish Colon Cancer Registry in 2007; these were later merged into the Swedish ColoRectal Cancer Registry (SCRCR). Data are gathered prospectively based on reports from surgeons, oncologists, and pathologists, and include information on pre- and postoperative staging, surgery, postoperative course, neoadjuvant-, adjuvant-, and palliative treatments, treatment of metastases, recurrence, and follow-up. The national coverage is estimated to be >97%\textsuperscript{54}.

The SCRCR has been validated on several occasions\textsuperscript{54-58}. Jörgren et al.\textsuperscript{56} reported overall high validity with <10% errors registered in 14 variables concerning the tumor, neoadjuvant treatment, surgery, radicality, TNM stage, anastomotic leakage, and local and distant recurrence. In a study of 130 variables, the accordance between medical charts and the registry was 90%\textsuperscript{58}. In 2003, postoperative complications were examined, with the results showing that the registration of serious complications was more valid than that of minor complications such as wound infections\textsuperscript{57}. In a study of registered anastomotic leakage (AL) in patients undergoing anterior resection (AR), there was substantial underreporting (29%) when the consensus definition of AL from the International Study Group of Rectal Cancer was used compared with the standard definition in the registry\textsuperscript{59}. In general, data from the registry are considered of high validity with good coverage, especially concerning the main variables such as patient, tumor, and treatment data; however, data on complications and follow-up are underreported\textsuperscript{54-58}. 

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The Swedish National Patient Registry

The Swedish National Patient Registry is maintained by the Swedish National Board of Health and Welfare. Registration started in 1964, but the information registered at that time covered only some hospitals in the country. Since 1987, registration became nationwide and included information on inpatient care from all hospitals in Sweden. Surgical procedures were registered from 1997 and outpatient visits from 2001. The codes used conform to the International Classification of Disease system; the register was validated in 2011 and showed positive predictive values of 85%–95% for diagnosis\textsuperscript{60,56}.

Local rectal cancer registry in Västmanland

Since 1996, a comprehensive registry covering a catchment area of 270,000 people has been set up at the Colorectal Unit, Västmanland’s Hospital, Västerås. All patients diagnosed with rectal cancer have been registered. Data regarding demographics, radiology, surgery, pathology, postoperative follow-up, oncological treatment, and bowel function are collected prospectively. All data are registered at each follow-up. All patients who have undergone surgery for rectal cancer were scheduled for follow-up at 1, 6, 12, 24, 36, 48, and 60 months after surgery. Preoperative screening for metastases is performed routinely. Until 2002, chest radiography and liver ultrasonography were used, and thereafter, CT of the thorax and abdomen. MRI of the pelvis was used for local staging in almost all patients. At the 12- and 36-month follow-ups, the patients underwent control CT scans of the thorax and abdomen.

The main differences between the local rectal cancer registry in Västmanland and the SCRCR is the minimal number of missing variables and more in depth information regarding preoperative factors, i.e., comorbidities, World Health Organization performance status, preoperative bowel symptoms and anorectal function, RT to any tumor in the abdomen prior to rectal cancer, type of palliative treatment offered to patients with rectal cancer who will not undergo surgery, and type of stoma deviation prior to rectal cancer surgery. The following surgical and perioperative details are collected: type of closure after abdominoperineal excision (APE) (with Permacole® or a gluteus maximus muscle flap), metastasis in the abdomen, nerve sparing during dissection, mobilization of the splenic flexure and potential damage to the spleen, type of anastomosis and height, part of the bowel used for anastomosis or stoma, anesthesia, perioperative complications, and macroscopic evaluation of the bowel specimen according to the surgeon. In addition, there is extensive information about the pathology and postoperative course, and at every outpatient visit, particular information is collected on oncological treatment and complications regarding the anastomosis, anorectal, urinary, sexual function, and stoma.
Incisional and parastomal hernias are observed and recorded through either a clinical examination during follow-up or CT scans. Small bowel obstruction (SBO) is registered if the patient had been admitted or received surgery for it. Anorectal function is registered as incontinence (if leakage of any of the following occurs more than once a week: gas, fluid, loose stool, or firm stool), evacuatory dysfunction (if defecating for longer than 15 min), clustering (if needing to defecate 30 min after prior defecation), frequency (number of defecations), and urgency (feeling an urgent need to defecate).

No validation study has been performed on the register, which up to January 2020, included 1345 patients diagnosed with rectal cancer; however, the internal validity is good because over the time, there have always been only three or four dedicated colorectal surgeons performing rectal cancer surgery in Västmanland. These surgeons have reached consensus on the definitions of different variables and also been responsible for outpatient follow-up and registration. A research nurse together with the head of the unit are responsible for the registry and the research nurse continuously registers data using IBM SPSS statistics software. Regarding external validity, there have been several publications based on the registry where the medical records have been scrutinized, confirming the validity of the data.

Neoadjuvant treatment and adverse effects

Neoadjuvant treatment is the treatment given to patients before surgery either as RT alone or in combination with chemotherapy, also called CRT. Blomqvist and Glimelius\textsuperscript{61} classified rectal cancer into three categories based on preoperative MRI scans: ‘good’, ‘bad’, and ‘ugly’. The proportions of patients in each group were: ‘good’ 20\%–40\%; ‘bad’ 40\%–60\%; and ‘ugly’ 10\%–20\%.\textsuperscript{61} This stratification remains a good basic tool in decision-making for neoadjuvant treatment (Figure 4). The purpose of preoperative treatment is to destroy potential tumor cells near the rectal tumor and outside the surgical dissection plane and to downstage/or shrink the tumor from being unresectable to resectable.
The Uppsala Trial\textsuperscript{62} randomized patients as either preoperative short-course RT (SRT) (5 × 5 Gy) or postoperative long-course RT (LRT) (total 60 Gy) and showed lower rates of LR in the SRT group, but no difference in survival. Later, in the Stockholm I trial\textsuperscript{63}, SRT followed by surgery was compared with surgery alone; the results showed that the LR rate was reduced by almost half when surgery was combined with SRT, although increased postoperative mortality was observed. Because of the mortality rate, the Stockholm II\textsuperscript{64} and Swedish Rectal Cancer trial\textsuperscript{65} were initiated with changed RT protocols and a limited target area; the results showed lower postoperative morbidity and mortality rates apart from the low LR rate. The Dutch TME trial\textsuperscript{66} compared preoperative SRT and surgery within 1 week with surgery alone; the results showed that the LR rates could be reduced to 5%. The hypothesis that changing the timing of surgery after RT could improve survival was explored in the Stockholm III trial\textsuperscript{67}. The results showed a reduced risk of postoperative complications after SRT with delayed surgery for 4–8 weeks, but similar oncological results. Since then, the RAPIDO trial\textsuperscript{68} has had a breakthrough in Sweden, showing that SRT in combination with chemotherapy instead of LRT with chemotherapy had low treatment-related morbidity in patients with advanced rectal cancer, and that 19% of patients had complete tumor remission.

\begin{figure}
\centering
\begin{tabular}{l}
\textbf{Favorable ‘Good’ Tumor} \\
Mid/Upper rectum > 5 cm \\
T1-T3b \\
Low rectum ≤ 5 cm \\
T1-T2, T3a \\
N0 \\
MRF clear
\\
\textbf{Intermediate ‘Bad’ Tumor} \\
Mid/Upper rectum > 5 cm \\
T3c/d \\
Low rectum ≤ 5 cm \\
T3b-d \\
T4 with peritoneal/vaginal involvement only \\
N1-2 \\
MRF clear
\\
\textbf{Advanced ‘Ugly’ Tumor} \\
T4 with overgrowth to prostate, seminal vesicles, base of urinary bladder, pelvic side wall or floor, sacrum \\
Positive lateral lymph nodes \\
MRF positive
\end{tabular}
\caption{Magnetic resonance imaging-based preoperative evaluation of rectal cancers for neoadjuvant treatment\textsuperscript{61}}
\end{figure}
Tumor response (downsizing and downstaging) with preoperative treatment has led to interest in an organ-preserving option to surgery named “watch and wait” in the literature. A pathological complete response (pCR) is based on an available resected specimen to verify that there are no tumor cells remaining. A clinical complete response (cCR) is based on three factors: digital rectal examination, endoscopic evaluation, and MRI. As the pCR and cCR are not always in accordance with each other, a diagnosis of cCR carries some uncertainty.

The Brazilian researcher Habr-Gama and colleagues were the pioneers of organ-preserving treatment. In 2004, a series of 265 resectable patients with rectal cancer treated with CRT were assessed for cCR at 8 weeks after CRT. As a result, 71 (27%) had cCR and entered an intense surveillance program. Patients with an incomplete clinical response underwent TME. The mean follow-up duration was 57.3 months and during that time, two patients had tumor regrowth and underwent successful salvage surgery, and three patients had metachronous metastases. Five-year overall survival was 100% and disease-free survival (DFS) was 92%. These results indicated that a nonsurgical alternative is safe in selected patients.

There is large heterogeneity in studies regarding patient selection, which makes assessment of the “watch and wait” strategy difficult. Older patients may benefit from this option. Hence, possible complications to surgery such as AL and low anterior resection syndrome (described later) can be avoided if AR is planned. For patients with distal tumors, APE can be avoided and the inherent morbidity that a stoma provides.

In Sweden, early rectal tumors (i.e., T1–T3a,b, N0, and MRF−) are supposed to be treated with surgery alone, and neoadjuvant CRT is given to patients with advanced rectal tumors (any cT or any cN and MRF+ and/or lateral lymph nodes). Therefore, including early tumors in a “watch and wait” program can lead to overtreatment. In locally advanced rectal cancers, cCR can be seen in 10%–20% and tumor regrowth in 15%–22%. A “watch and wait” trial including patients with locally advanced tumors who received neoadjuvant CRT or short-course RT with delayed surgery according to the Swedish guidelines, with the first evaluation of cCR status after 6–8 weeks, is ongoing in Sweden since 2017.

Treatment with RT is beneficial in patients with rectal cancers, but is associated with side effects. The acute adverse effects depend on the RT dose and target volume. Typical acute symptoms include urogenital and gastrointestinal symptoms such as diarrhea, urgency, bloating, abdominal pain, nausea, and vomiting. In a Cochrane systematic review including five trials, more acute toxicity symptoms were observed following LRT or CRT compared with SRT. The late adverse effects of RT include symptoms such as fecal incontinence and increased stool frequency and urgency. These symptoms are the same as those associated with rectal cancer surgery, but RT has an additive effect. Other described late effects of RT include increased rates of adverse
gastrointestinal symptoms such as bowel obstruction/ileus, symptoms of urinary dysfunction, and sexual dysfunction. The risk of RT induced cancers has been investigated in several studies, with conflicting results. No increased risk of secondary cancer was found in a recent Swedish study that included data from over 13,000 patients registered in the SCRCR.

**Surgical treatment**

In 1982, Heald introduced the TME technique—dissection along the MRF— to resect the rectum together with the whole mesorectum as an intact specimen without damaging the MRF. By using this technique, they were able to decrease the LR to 4% without RT, from previous LR rates of approximately 30%. Presently, the LR rate in Sweden is around 5%. TME is currently considered the “gold standard” for the surgical treatment of rectal cancer in the middle or low rectum. The same technique is used regardless of the surgical approach, whether it is AR, APE, or Hartmann’s procedure (HP), and whether it is open or minimally invasive. Regarding high rectal tumors, partial mesorectal excision (PME) is sometimes performed, meaning transecting the bowel 5 cm below the tumor to achieve better functional outcomes. Most patients who undergo AR will have oral colon cleansing and those treated with APE or HP will receive a rectal enema.

![Figure 5. Distribution of operations from 1995 to 2019 for all patients with rectal cancers. Key: AR (yellow), APE (purple), HP (green), local excision (red), laparotomy without resection (light blue), other interventions (light grey), or no surgery (dark grey). The figure is reprinted with permission from reference2](image-url)
Anterior resection

In Sweden, approximately 35% of patients with rectal cancer diagnosis undergo AR, which is the most common approach for rectal tumors located in the middle (6–10 cm) or upper (11–15 cm) rectum. It is termed AR because the approach is from the abdomen. In TME surgery, mesorectal excision is performed down to the pelvic floor while identifying and preserving the hypogastric nerves. In cases with overgrowth of the rectal tumor to other organs, these are resected together with the bowel specimen. A high ligation of the inferior mesenteric artery is performed just distally to the origin of the left colic artery. The splenic flexure is frequently taken down and the inferior mesenteric vein divided just below the pancreas to achieve a tension-free anastomosis. Before dividing the rectum, distally to the tumor, the distal part is washed out with an alcohol solution. Using a circular staple device, the colo-rectal or coloanal anastomosis is created as end-to-end, side-to-end, or a J-pouch configuration. AR can be subclassified into low anterior resection (LAR) with TME or high anterior resection with PME, depending on the level of rectal transection. Because of the high risk of AL and the severe consequences, most patients subjected to LAR receive a temporary diverting loop ileostomy (see below).

Hartmann’s procedure

Patients not fit for AR, with weak sphincter function, or in a palliative care situation are candidates for HP, which includes TME or PME without an anastomosis. These patients receive a permanent end-colostomy.

Abdominoperineal excision

In Sweden, APE is usually performed for rectal tumors measuring <5 cm. The procedure basically includes resection of the entire rectum and anal canal with TME and construction of an end-colostomy. There are four subtypes: intersphincteric, conventional, extralevator (ELAPE), and ischioanal.

Interesphincteric APE is an alternative to HP. In the latter, a stapled anorectal stump is left in the lower pelvis, but with the intersphincteric method, the anal canal is resected by an intersphincteric dissection. The benefit with this approach is that the risk a potential pelvic abscess can be reduced and later problems from the anorectal stump can be avoided. This is currently being explored in the so-called HAPIrect study.

In conventional APE, abdominal TME dissection is continued down to the pelvic floor. The perineal dissection involves both sphincters and the anal canal. This approach in low located advanced tumors is associated with high rates of CRM positivity, which is why ELAPE was introduced.
In ELAPE, dissection extends to the coccyx, keeping the mesorectum attached to the levator ani muscle. The perineal part of the dissection runs along the external sphincter, continues along the levator ani muscle to its attachment onto the pelvis, with or without excision to the distal coccyx, resulting in a cylinder-shaped specimen with wider lateral resection marginals. The defect in the pelvic floor is closed using either a musculocutaneous flap or biological mesh. Studies comparing conventional APE with ELAPE have shown lower rates of CRM positivity and bowel perforation\textsuperscript{100-102}.

Ischioanal APE is similar to ELAPE, but instead, the perineal dissection follows the fascia of the internal obturator muscle. This approach is used mainly for locally advanced tumors. The most challenging part of the surgery is the anterior dissection. In patients with anteriorly lying tumors, en bloc resection of a part of the prostate or vagina is indicated to increase the CRM and minimize the risk of tumor perforation\textsuperscript{103}.

Minimally invasive surgery

Open surgery was the only technique used up to the 1990s, when a laparoscopic approach entered colorectal surgery. In 2010, the first randomized multicenter trial comparing laparoscopic and open rectal cancer surgery—the COREAN trial\textsuperscript{104}—was initiated. This trial reported similar short-term outcomes between the two surgical techniques. In 2013, the COLOR II trial\textsuperscript{105} reported faster return of bowel function and a shorter length of hospital stay (LOS) for laparoscopic surgery. The 3-year follow-up studies of the trials showed that, for the former, noninferiority of the laparoscopic approach was met regarding DFS\textsuperscript{106} and for the latter, similar 5% recurrence rates\textsuperscript{107}. Two other trials, the ACOSOG\textsuperscript{108} and ALaCaRT\textsuperscript{109}, had clear margins as primary end points, but failed to demonstrate noninferiority when laparoscopic surgery was compared with open surgery. However, their 2-year follow up did not show differences in overall survival or DFS\textsuperscript{110,111}. In the early 2000s, robotic surgery was introduced to colorectal surgery. A large randomized multicenter trial—ROLARR—compared laparoscopic with robotic surgery and had conversion rates to open surgery as the primary end point\textsuperscript{112}. The trial could not prove significant differences between the two surgical techniques for rectal cancer surgery. No long-term outcomes are yet available. Due to its numerous advantages, including advanced three-dimensional vision with better nerve discrimination, lack of tremor, more complex movements with the instruments, reduced discomfort for the surgeon, and a lower learning curve, robotic surgery is expected to overcome the limitations of laparoscopic surgery\textsuperscript{113}.

In 2010, a new technique combining laparoscopic abdominal and transanal TME (TaTME) gained popularity for overcoming difficult pelvic dissections, especially for distal tumors in patients with a narrow pelvis and a high body mass index. A Dutch trial compared TaTME with laparoscopic surgery and reported equal CRM positivity, at 4%\textsuperscript{114}. In a multicenter study of TaTME and
robotic surgery, no overall difference was found in pathological margins\textsuperscript{115}. However, in a Norwegian trial comparing TaTME with established surgical techniques, higher AL and LR were reported, so TaTME is currently suspended in Norway\textsuperscript{116}. More evidence is needed to determine the benefits and safety of TaTME.

Temporary ileostomy

A temporary diverting ileostomy is usually established after an AR to minimize the consequence and reduce the frequency of AL, which occurs in up to 28% of patients after AR\textsuperscript{93}. In the Swedish RECTODES trial, the results showed a threefold increased risk of AL in patients without a diverting ileostomy\textsuperscript{93}. Leaks can be associated with devastating consequences, such as abscess formation, sepsis, peritonitis, a higher prevalence of LR, and poor subsequent neorectal function\textsuperscript{117-119}. However, disagreements remain regarding the routine use of a diverting ileostomy, and it is still being debated\textsuperscript{120,121}. Nevertheless, there are high-risk patients and situations that might benefit from a loop ileostomy, such as those with colorectal or coloanal anastomoses, those undergoing technically difficult operations, malnourished patients, and obese men\textsuperscript{120}. The benefit of creating a loop ileostomy is to avoid complications such as AL, which could delay or exclude adjuvant treatment. On the other hand, closure of a loop ileostomy is also associated with morbidity and mortality. In a systematic review including 6107 patients, overall morbidity following the closure of a loop ileostomy was 17.3%, with a total mortality rate of 0.4\textsuperscript{122}. Another review of complications after loop ileostomy closure demonstrated SBO in up to 15% of cases, wound infections in up to 18.3%, and AL in up to 8\textsuperscript{123}. Furthermore, having a stoma is associated with morbidity for patients such as those readmitted for dehydration and renal failure\textsuperscript{122,124,125}, as well as those with skin irritation, stomal prolapse retraction, or hernia\textsuperscript{126}.

It is well known that many patients live with stomas for a long time before reversal, and in a Swedish single-center study, up to 75% of stomas (in colostomy and ileostomy) were reversed after 4 months, usually because of adjuvant chemotherapy or surgical complications; however, in one third, no health reason was identified\textsuperscript{127}. In the same study, 18% of patients with a defunctioning stoma ended up with a permanent stoma, of which, 10% were loop ileostomies. Following the reversal of a loop ileostomy, most patients remain in hospital until bowel function returns, despite no evidence supporting this approach. The mean LOS in hospital was reported as 5.1 days after stoma closure\textsuperscript{122,127}. There have also been studies supporting early discharge following ileostomy reversal\textsuperscript{128-133}. Most studies have been retrospective, and to our knowledge, there are only four prospective studies with a total of 72 patients who were discharged within 23 hours, suggesting that this concept is safe and feasible\textsuperscript{129-131,133}. 

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Early closure of ileostomy could be beneficial, as recently shown in the Swedish EASY trial, where significantly fewer complications were observed when closing the ileostomy within 13 days of primary surgery\textsuperscript{134}. A recent meta-analysis also suggested the possibility of early closure for selected patients without signs of AL and an uneventful postoperative course\textsuperscript{135}.

**Adjuvant chemotherapy**

Adjuvant chemotherapy is given to eliminate potential micro-metastases after tumor resection. There is evidence of benefits with an increase in DFS in patients with stage II colon cancer with high-risk features, as well as in those with stage III colon cancer\textsuperscript{136-138}; however, evidence of the need for adjuvant chemotherapy in cases of rectal cancer is not convincing. In one meta-analysis, no benefits in overall survival or DFS were found; however in sub-group analyses, DFS was improved in patients with upper rectal cancers (hazard ratio [HR] 0.59; 95% confidence interval [CI] 0.40–0.85)\textsuperscript{138}. What factors are considered high risk for patients with stage II rectal cancer are not clearly defined, but, as in those with colon cancer, perforations, low tumor differentiation, serosal extension, venous, lymphatic, or perineural invasion, and a low number of examined lymph nodes have been associated with a poor prognosis\textsuperscript{12,139-141}. The advantages of receiving adjuvant chemotherapy might be seen in patients with positive pathological risk factors. In Sweden, adjuvant chemotherapy is mainly considered for patients with stage II rectal cancer with risk factors who have not received RT and for those with stage III rectal cancers, especially in the upper rectum\textsuperscript{25}. Adjuvant chemotherapy should be started no later than 8 weeks after surgery, since starting later decreases overall survival according to studies on patients with stage III colon cancers\textsuperscript{142,143}. The same limitations apply for those with rectal cancer in Sweden\textsuperscript{144}.

**Short-term postoperative complications**

Rectal cancer surgery puts the body under major stress and is associated with considerable morbidity. There are discrepancies in the definitions of different complications, which makes reporting difficult. The Clavien–Dindo classification of surgical complications in 2004 has been accepted in the surgical community\textsuperscript{145} and was introduced into the SCRCR in 2011.

Short-term complications include AL and its consequences, wound infection, intra-abdominal infection, ileus, and cardiopulmonary adverse events. One of the most severe complications is AL, described above. There is no consensus on the definition of AL in the literature. One way to define AL is clinically, with peritonitis caused by leakage from any staple line, rectovaginal
fistula, and pelvic abscess, even if leakage is not seen radiologically. The leakage should be verified by digital palpation and inspection of drain contents, endoscopically or radiologically (e.g., rectal contrast studies, CT scans). However, if leakage is seen on the radiological investigation without clinical symptoms, it is not defined as leakage\textsuperscript{93}. Another way to define AL after AR is “a communication between the intra- and extraluminal compartments at the site of anastomosis”, and this can be graded accordingly as follows: A, no active intervention; B, active intervention such as drainage without surgery; and C, active intervention requiring surgery\textsuperscript{146}. About 60% of patients with AL end up with a permanent stoma\textsuperscript{147}. About 10% of patients with a defunctioning stoma after AR develop AL\textsuperscript{93}. After APE, the most common complication is a perineal wound, seen in approximately 40% of cases\textsuperscript{101}.

Long-term complications and functional bowel disturbance

Rectal cancer surgery is associated with considerable long-term complications, so patients might suffer from sexual and urinary dysfunction due to the RT or TME surgery\textsuperscript{148-151}. Even though TME is nerve-sparing surgery, the hypogastric nerves might be damaged to some degree, depending on the size of the tumor and surgical technique used. Besides, rectal cancer surgery causes the highest patient readmission rates\textsuperscript{152-154} from SBO (see below).

In the case of stoma formation, there are long-term complications, such as prolapse, stenosis, and hernia\textsuperscript{126}, in patients undergoing APE or HP receiving a permanent colostomy or in patients undergoing AR and receiving a temporary ileostomy. As described above, having a stoma is associated with morbidity, hospital readmission for dehydration and renal failure, and peristomal skin problems or leakage\textsuperscript{126}.

Following AR, most patients have some degree of anorectal dysfunction and bowel disturbance. About 40%–80% of patients undergoing AR experience severe bowel disturbances\textsuperscript{155-158}. The symptoms can arise immediately after surgery or when the temporary ileostomy is closed. This dysfunction is also referred to as low anterior resection syndrome (LARS). To characterize the symptoms and each patient’s experience, a LARS score has been created by a Danish group\textsuperscript{159} based on a combination of the following five symptoms: flatulence and fecal incontinence, stool frequency, clustering, and urgency. The LARS score is classed as low, minor, or major depending on the total scores of 0–20, 21–29, and 30–42, respectively. Risk factors for developing LARS are pre-and postoperative RT, low anastomotic height when performing TME, temporary ileostomy, AL, age ≤ 64 years, and female sex\textsuperscript{92,156,158,160-162}. LARS is usually measured pre- and postoperatively, but comparisons between these are ineffective because patients have a rectal tumor that might
cause symptoms similar to LARS. Therefore, a recent study measured the prevalence of LARS in a normal population, with the results showing that 10%–15% of the general population have major LARS\textsuperscript{163}. Therefore, it is important to identify patients with LARS so that they can be treated appropriately.

**Small bowel obstruction**

The most common causes of SBO are abdominal adhesions, accounting for 60%–70% of cases\textsuperscript{164,165}. The formation of adhesions can start immediately after surgery. The symptoms of SBO include abdominal pain, vomiting, distention, and a lack of flatus and stool. SBO is classified according to completeness (partial vs. complete), etiology (adhesional vs. nonadhesional), or timing (early vs. late using a cutoff of 30 days after surgery).

The type of surgery has a major role in the development of SBO. Comparing open with laparoscopic approaches without previous open surgery, Reshef et al.\textsuperscript{166} evaluated the risk of SBO following colorectal surgery and found equal admission rates between groups. The rate of surgery for SBO was lower in the laparoscopic group, suggesting that this might be because of fewer adhesions. Other known risk factors include surgery to the colon, rectum, and gynecological organs, patient age <60 years, time from laparotomy <5 years, peritonitis, and multiple laparotomies\textsuperscript{153,164-170}.

The incidences of SBO after open AR and APE are 10% and 14%, respectively\textsuperscript{154}, with a hospital readmission rate of 30% during a 10-year period\textsuperscript{164}, most common in the first year after abdominal surgery\textsuperscript{152,171}. Rectal cancer surgery is associated with the highest readmission rates\textsuperscript{152,154}.

CT scans of the abdomen can be used to confirm the diagnosis, with signs of multiple air–fluid levels and distension of the small bowel. Such scans can also be used to identify the anatomical localization of the obstruction and the reason behind SBO: adhesional, non-adhesional, or strangulation (e.g., in hernias). Water-soluble contrast medium such as Gastrografin\textsuperscript{®} (diatrizoate) with follow-through is preferred over barium (especially in patients with signs of perforation), and can be of both diagnostic and therapeutic value\textsuperscript{172,173}; however, the results are contradictory.

Treatment for SBO is either operative or nonoperative management (NOM). NOM involves nasogastric intubation, intravenous fluid resuscitation, and clinical observation. The management of adhesion-related SBO is controversial because surgery can cause new adhesions, whereas NOM does not remove the cause\textsuperscript{169}. A retrospective review showed that a delay in operation for SBO places patients at a higher risk for bowel resection\textsuperscript{174}. Indications for NOM include the absence of signs of strangulation or peritonitis, no surgery within 6 weeks, and a combination of CT scan findings (e.g., lack of free fluid, mesenteric edema, small bowel feces signs, signs of devascularized.
bowel) and partial SBO. NOM can be prolonged for up to 72 hours in cases of adhesive SBO if no complications have been encountered or the drainage volume in the nasogastric tube on day 3 is <500 mL; thereafter, surgery is recommended\textsuperscript{175}. The reverse findings are indications for performing surgery; these include patients who had surgery within 6 weeks, signs of strangulation or peritonitis (e.g., fever, tachycardia, and leukocytosis, metabolic acidosis, continuous pain), irreducible hernias, complete SBO and/or CT signs (free intraperitoneal fluid, mesenteric edema, small bowel feces, signs of a devascularized bowel), a history of vomiting, severe abdominal pain reported by the patient (visual analog scale > 4), abdominal guarding, and leukocytosis.

The surgical approach is not without complications, and several studies have focused on adverse outcomes in adhesion-related SBO. Mortality rates in SBO surgery are 10%–15% when small bowel resection is performed\textsuperscript{176,177} and there is a 33% risk of inadvertent enterotomy during surgery for bowel obstruction\textsuperscript{178}.

Liver metastasis and prognostic scoring systems

The most common site of distant metastases from CRC is to the liver\textsuperscript{21}. Metastases can be either synchronous (SM; present at the time of diagnosis of the primary tumor) or metachronous (MM; occurring later in in the course of the disease). Unfortunately, there are discrepancies in the literature for the definitions of liver SM and MM that affect the results in different studies and make them difficult to compare. Approximately 15%–25% of patients with CRC present with SM disease, and 13%–29% later develop MM during follow-up\textsuperscript{21,179-181}. In a recent Danish study, patients with CRC without metastasis had a median survival of 86 months, but if SM were present, the median survival decreased to 11 months, and if MM were present, the median survival decreased to 36 months\textsuperscript{182}.

Most liver metastases are irresectable, with reported resection rates of 5%–15%\textsuperscript{183,184}. The prognosis for patients with stage IV rectal cancer and colon cancer is poor, with 5-year survival rates of 3% and 6.6%, respectively\textsuperscript{54,182}. However, with liver resection, 5-year survival rates of up to 58% have been reported\textsuperscript{185,186}. Liver surgeons are shifting toward a ‘liver-first’ approach, where liver metastases are resected after cycles of preoperative chemotherapy, followed by surgery for the rectal cancer\textsuperscript{187}.

Several scoring systems to predict survival after liver resection of CRC liver metastases have been suggested\textsuperscript{188-190}. Since being first reported in 1996 and 1999, more than 19 scoring systems concerning prognostic factors for survival after liver resection have been proposed for the optimal management of patients\textsuperscript{191}. There are contradictions in the literature, but some studies have shown that the maximum size\textsuperscript{185,189,190,192-196}, number\textsuperscript{185,189,190,192-195,197-204}, and
distribution of liver metastases\textsuperscript{192,193,205} are prognostic factors after metastasectomy for liver metastases from CRC. Positive resection margins are associated with worse survival\textsuperscript{185,206}. Preoperative carcinoembryonic antigen levels\textsuperscript{185,201} and different cutoff values are used randomly in different studies. Primary tumor stage\textsuperscript{190,194} and node status\textsuperscript{185,186,189,190,193-195,199,200,202-204} have also been proposed as prognostic factors.
Aims of this thesis

The overall aim of this thesis was to assess the risk factors and morbidity after surgery for rectal cancer and the factors affecting survival in patients with stage IV rectal cancer.

The specific aims of the studies were as listed below.

Paper I
The aim of the first study was to evaluate the safety and patient experiences of loop ileostomy closure in a 23-hour hospital stay setting.

Paper II
The aim of the second study was to investigate the risk factors for readmission and surgery for SBO following open surgery for rectal cancer, and the different causes of SBO.

Paper III
The aim of the third study was to evaluate whether patients with rectal cancer treated with anterior resection would have poorer bowel function depending on which part of the colon was used for the anastomosis (descending vs. sigmoid) and to identify possible risk factors for bowel dysfunction.

Paper IV
The aim of the fourth study was to identify patient-, tumor-, and treatment-related prognostic factors for 5-year survival in patients with rectal cancer and synchronous stage IV disease.
Materials and methods

Paper I
This was a prospective intervention study of 30 patients with rectal cancer with a diverting loop ileostomy between August 2015 and June 2019. Patients were examined for bowel integrity before inclusion. Loop ileostomy closure was performed in a standardized manner using a circumstomal technique. Within 23 hours of surgery, the patients were discharged from the post–anesthesia care unit if they met specific criteria and had daily telephone follow-ups with a colorectal research nurse. Outpatient appointments were planned on postoperative days 3, 7, and 30. A control group of 30 patients was selected (starting with the most recent and going backwards) from the local rectal cancer registry in Västmanland. These patients followed routine protocols and were hospitalized after stoma closure. Their medical records were scrutinized for any 30-day postoperative complications retrospectively.

Paper II
This retrospective study was based on a local population-based registry of all patients subjected to open rectal cancer surgery, diagnosed between January 1996 and January 2017. The data set includes follow-up data on admission for SBO with or without surgery. Patients were scheduled for follow-up at 1, 6, 12, 24, 36, 48, and 60 months after surgery. In total, 1136 patients were diagnosed with rectal cancer, 752 of whom underwent open rectal tumor resection. SBO was defined as radiographically verified small bowel obstruction requiring hospitalization or surgery after 30 postoperative days. Early postoperative bowel paralysis within 30 days of primary surgery was registered as a postoperative complication. Additional data were retrieved from the medical records of patients registered for SBO. The surgical platform was used to identify those who had been admitted and treated surgically for their SBO to identify the cause of the obstruction during surgery.
Paper III

This retrospective study was based on our local population-based registry of all patients with rectal cancer who underwent anterior resection for tumor stages I–III, as diagnosed between January 1996 and January 2019. Bowel function was registered prospectively at each follow-up at 1, 6, 12, 24, 36, 48, and 60 months after surgery. In total, 1062 patients had rectal cancer in 1996–2019, 470 of whom had stage I–III tumors and underwent AR. After excluding patients who died before follow-up, refused follow-up, had the ascending colon as an anastomosis or where the diverting stoma became permanent, 412 had available data on bowel function. Incontinence was defined as leakage more than once a week, urgency as a sudden need of defecation, evacuatory dysfunction as defecation lasting more than 15 min with or without an enema, and clustering/fragmentation as the need for going to the lavatory again within 30 minutes after defecation. Functional data used in the analysis were collected at a minimum of 12 months after primary surgery or loop ileostomy closure.

Paper IV

This case-control study was based on data from the SCRCR, and additional data were retrieved from medical records. On patients who underwent metastasectomy or ablative treatment of their metastases between 2000 and 2008, additional data were retrieved from the Swedish Inpatient Registry. All patients in Sweden diagnosed with rectal cancer with synchronous metastases who survived for more than 5 years were included as cases and designated long-term survivors (LTS). The control group, named short-term survivors (STS), lived less than 5 years and were matched (1:2) with the case group based on gender, age, resection of the rectal tumor, and study period. Synchronous and metachronous metastases were defined as metastases diagnosed within or after 3 months from diagnosis of the primary rectal tumor, respectively. A total of 405 patients were identified; however, after exclusions, the study population was composed of 99 cases and 182 controls. Data on patient characteristics and details of treatment of the primary tumor were retrieved from the SCRCR. Variables not registered in the SCRCR were retrieved from medical records, namely American Society of Anesthesiologists (ASA) classification, comorbidity, symptoms at the time of diagnosis, preoperative investigations, metastatic burden (number, size, and localization of the tumor) at the time of diagnosis, surgery for metastases, and pre- and postoperative oncological treatments.
Ethical considerations

All studies were approved by the Regional Ethics Review Board in Uppsala and complied with the Declaration of Helsinki.

**Paper I** (Dnr 2014/363 and 2020-04882) and (ClinicalTrials.gov No. NCT02774447)

**Paper II** (Dnr 2017/353)

**Paper III** (Dnr 2014/389 and 2020-05140)

**Paper IV** (Dnr 2011/079)
Statistical analysis

Paper I
Data presented as proportions and descriptive statistical analyses are described.

Paper II
Pearson’s chi-squared ($\chi^2$-test) was used for categorical variables. Binary logistic regression was performed in both univariable and multivariable analyses. The multivariable analyses used all possible factors associated with examined outcomes. Any association of SBO with incisional hernia was tested using Spearman correlation analysis. Data were analyzed using IBM SPSS Statistics (v. 24; IBM Corp., Armonk, NY, USA), and $P$ values < 0.05 were considered statistically significant.

Paper III
Univariable and multivariable analyses for factors affecting functional data were performed using logistic regression, with goodness of fit evaluated using the Hosmer–Lemeshow test. Collinearity of independent variables in the logistic regression was investigated using the variance inflation factor. $P$ values < 0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics as above.

Paper IV
Conditional Cox regression analysis with a dummy variable for time was performed because the links between the cases and controls were retained. Factors identified as significant in the univariable analysis were used in a multiple conditional Cox regression analysis. $P$ values < 0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics as above.
Results and discussion

Paper I

Study cohort
In total, 30 patients with loop ileostomy were included. Primary surgery was for rectal cancer in 28 patients and rectosigmoid cancer in two. The median time from primary surgery to loop ileostomy closure was 8 months (range 3–14 months). Twenty-nine patients were discharged within 23 hours of surgery. In total, seven patients (23%) were admitted, including one who did not meet the discharge criteria. The observed reasons for admission are described in detail in Table 2. Two patients underwent a re-operation with laparotomy for small bowel strangulation and AL. Their mean total LOS was 1.7 days. There was no 90-day mortality.

Table 2. Reason behind admission and the use of surgery for patients admitted after loop ileostomy closure in the study group

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Admission days after closure</th>
<th>LOS</th>
<th>Reason for admission</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>Male</td>
<td>3</td>
<td>1</td>
<td>Abdominal pain</td>
<td>No</td>
</tr>
<tr>
<td>69</td>
<td>Male</td>
<td>14</td>
<td>12</td>
<td>Small bowel obstruction with strangulation</td>
<td>Yes</td>
</tr>
<tr>
<td>56</td>
<td>Female</td>
<td>4</td>
<td>3</td>
<td>Abdominal pain caused by gallstones</td>
<td>No</td>
</tr>
<tr>
<td>72</td>
<td>Male</td>
<td>5 + 30*</td>
<td>2</td>
<td>Ileus + wound infections*</td>
<td>No</td>
</tr>
<tr>
<td>70</td>
<td>Female</td>
<td>3</td>
<td>4</td>
<td>Abdominal pain</td>
<td>No</td>
</tr>
<tr>
<td>52</td>
<td>Male</td>
<td>2</td>
<td>18</td>
<td>Anastomotic leakage</td>
<td>Yes</td>
</tr>
<tr>
<td>68</td>
<td>Male</td>
<td>0 + 5*</td>
<td>12</td>
<td>Anemia requiring blood transfusion + ileus*</td>
<td>No</td>
</tr>
</tbody>
</table>

*The “+” sign indicates different admissions.
LOS, length of hospital stay.
**Historical control group**

The control group had similar patient characteristics to the study cohort. The mean total LOS was 5 days (standard deviation 4.2), with a median of 4 days (range 1–19 days). The reasons for readmission are described in Table 3. Seven patients (23%) were readmitted, of whom, two underwent surgery for complications. Two patients underwent re-operation; for postoperative ileus and abscess at the stoma site. Most readmissions occurred after 10 days. There was no 90-day postoperative mortality.

Table 3. Reason behind readmissions and the use of surgery among patients admitted after loop ileostomy closure in the control group discharged from standard care in hospital

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Admission days after closure</th>
<th>LOS</th>
<th>Reason for admission</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>Male</td>
<td>11</td>
<td>9</td>
<td>Ileus</td>
<td>No</td>
</tr>
<tr>
<td>74</td>
<td>Male</td>
<td>11</td>
<td>11</td>
<td>Anastomotic leakage</td>
<td>No</td>
</tr>
<tr>
<td>81</td>
<td>Male</td>
<td>11+24*</td>
<td>15</td>
<td><em>Clostridium difficile + urinary tract infection</em></td>
<td>No</td>
</tr>
<tr>
<td>71</td>
<td>Female</td>
<td>11 + 17*</td>
<td>10</td>
<td>Abscess at the previous stoma site*</td>
<td>Yes</td>
</tr>
<tr>
<td>60</td>
<td>Female</td>
<td>10</td>
<td>4</td>
<td>Ileus</td>
<td>No</td>
</tr>
<tr>
<td>54</td>
<td>Female</td>
<td>3</td>
<td>9</td>
<td>Ileus</td>
<td>Yes</td>
</tr>
<tr>
<td>74</td>
<td>Female</td>
<td>6</td>
<td>6</td>
<td>Ileus</td>
<td>No</td>
</tr>
</tbody>
</table>

*The “+” sign indicates different admissions.

LOS, length of hospital stay.

**Patient experiences**

The experience of being an outpatient was registered, indicating that 26 (87%) of the patients felt no anxiety, 27 (90%) did not feel neglected, and 26 (87%) preferred staying home after surgery. Twenty-two (73%) had regular food on the first day after surgery and 26 (87%) by the third.

In this intervention study, loop ileostomy closure in a healthy selected group of patients with an intense follow-up in a 23-hour stay setting was feasible, safe, and had a high level of patient satisfaction. Compared with the historical study group, readmissions, complications, and reoperation rates were equal. Only one patient in the study cohort was not discharged. Most patients were satisfied with being outpatients. The most important issue in a
day-case or 23-hour stay setting is the early detection of complications. In both the study and historical cohorts, two patients (7%) with postoperative complications required reoperation and four admission. The mean total LOS was three times higher in the control group than in the study group.

Following loop ileostomy reversal, patients are usually hospitalized until spontaneous defecation occurs, even though no evidence supports this policy. To our knowledge, only four studies with a total of 72 patients have evaluated ambulatory ileostomy closure (in the USA and UK).\textsuperscript{129-131,133} Having a stoma is associated with morbidity with readmission for complications, as described above. Many patients have their stomas for a long time before reversal, probably because of a lack of hospital beds or low priority within the health-care system. Therefore, a day-case or 23-hour stay setting as an alternative to routine hospitalization would result in more patients having their stomas closed sooner, reduce stoma-related morbidity, prevent hospital-acquired conditions, and lead to substantial cost savings.

Paper II

In total, 752 patients who underwent open rectal cancer resection were included. The mean age was 68 ± 10 years, two thirds were men, and most were classified as ASA grade 1 or 2. Anterior resection was performed in 62% and the splenic flexure was mobilized in 60%. In total, 77% (N = 579) had RT. The incidence of SBO was 11% (N = 84), and in 57% of the patients (N = 48), it occurred within the first postoperative year. Surgery for SBO was performed in 4.3% (N = 32).

Postoperative surgical complications within 30 days of rectal cancer surgery were seen in 21% of the patients (N = 158); in 28, this resulted in relaparotomy. Re-laparotomy was an independent risk factor associated with an increased risk of admission for SBO in the multivariable analysis (odds ratio [OR] 2.824, 95% CI 1.129–7.065, P = 0.026). None of the other examined factors were associated with admission. Of the patients who underwent an AR, 74% received a loop ileostomy, with no increased risk of admission for SBO (P = 0.569). None of the analyzed factors were associated with an increased risk of surgical outcomes for SBO (data not shown). In the 32 patients who had surgery for SBO, the mechanism was determined and categorized accordingly as adhesion- and/or stoma-related and/or other reasons. Figure 5 shows the case distribution.
Figure 6. Causes of surgery for small bowel obstruction (SBO)

This study was based on a large prospectively collected cohort of patients with rectal cancer who had open surgery, and determined the risk of admission and surgery caused by SBO. Most admissions were within the first postoperative year, and a minority of patients had surgery for SBO (4.3%). The cause of SBO was adhesion-related in 75% and/or stoma-related in 28%. Postoperative complications within 30 days of primary surgery that resulted in re-laparotomy were an independent risk factor associated with a threefold higher risk of future admission for SBO. However, patient-, tumor-, and primary surgery-related factors were not associated with hospital admission rates or surgery for SBO.

We report high rates of loop ileostomy-related SBO and other negative ileostomy-related outcomes, such as poorer functional outcomes and costs, have been reported\textsuperscript{158,207}. Therefore, surgeons should consider these disadvantages when deciding whether to create a loop ileostomy during AR. The particular type of rectal cancer surgery with regard to resection with and without anastomosis, or the extent of dissection, were not risk factors for admission and surgery for SBO. We speculate that the descent of the small bowel into an empty pelvis would increase the risk of SBO and that more extensive dissection would result in more scar tissue and inflammation, accompanied by an increased risk of SBO. However, we did not find any significant association between these factors with admission and surgery for SBO. Surgical complications that resulted in re-laparotomy after rectal cancer surgery were an independent risk factor for admission for SBO. However, these results should be interpreted cautiously because of the low numbers of patients with SBO and patients who had surgery for this condition.

In conclusion, the risk of SBO was greatest among patients with complications after open rectal cancer resection resulting in re-laparotomy. The specific type of resection surgery was not associated with SBO.
In total, 470 patients with rectal cancer stage I–III underwent AR (Table 4). Most patients were male with ASA grade 1 or 2. Preoperative RT was given to 68% ($N = 320$) and total mesorectal excision was performed in 90% ($N = 422$). The descending colon was used in 68% ($N = 319$) when creating the anastomosis, and 75% ($N = 352$) received a diverting ileostomy.

Table 4. Demographic and surgical characteristics of patients with stage I–III rectal cancers undergoing AR after the exclusion of patients with synchronous metastases ($N = 470$)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total patients $N = 470$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>68 (32–86)</td>
</tr>
<tr>
<td>Gender (male:female) (%)</td>
<td>279:191 (60:40)</td>
</tr>
<tr>
<td>ASA grade</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>365 (78)</td>
</tr>
<tr>
<td>3</td>
<td>105 (22)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tumor distance from anal verge</td>
<td></td>
</tr>
<tr>
<td>Low (3–5 cm)</td>
<td>51 (11)</td>
</tr>
<tr>
<td>Middle (6–10 cm)</td>
<td>230 (49)</td>
</tr>
<tr>
<td>High (11–15 cm)</td>
<td>189 (40)</td>
</tr>
<tr>
<td>Radiotherap*y</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>320 (68)</td>
</tr>
<tr>
<td>No</td>
<td>150 (32)</td>
</tr>
<tr>
<td>Minimally invasive surgery</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37 (8)</td>
</tr>
<tr>
<td>No</td>
<td>433 (92)</td>
</tr>
<tr>
<td>Resection of other organs</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>75 (16)</td>
</tr>
<tr>
<td>No</td>
<td>395 (84)</td>
</tr>
<tr>
<td>Central ligature IMA</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>419 (89)</td>
</tr>
<tr>
<td>No</td>
<td>49 (10)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Type of anastomosis</td>
<td>77 (16)</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Colonic reservoir</td>
<td></td>
</tr>
<tr>
<td>End to side colo-anal</td>
<td></td>
</tr>
<tr>
<td>End-to-side colorectal</td>
<td></td>
</tr>
<tr>
<td>Part of colon used for anastomosis</td>
<td>139 (29)</td>
</tr>
<tr>
<td>Sigmoid</td>
<td></td>
</tr>
<tr>
<td>Descending</td>
<td></td>
</tr>
<tr>
<td>Transverse</td>
<td></td>
</tr>
<tr>
<td>Ascending</td>
<td></td>
</tr>
<tr>
<td>Anastomotic level (cm)*</td>
<td>4,5 (2–11)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>422 (90)</td>
</tr>
<tr>
<td>TME</td>
<td></td>
</tr>
<tr>
<td>PME</td>
<td></td>
</tr>
<tr>
<td>Diverting ileostomy</td>
<td>352 (75)</td>
</tr>
<tr>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>33 (7)</td>
</tr>
<tr>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>186 (40)</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td></td>
</tr>
</tbody>
</table>

# Continuous values are presented as the median and (range); other values in numbers and parentheses are percentages.

* Radiotherapy was defined as any radiotherapy given at any time prior to surgery for rectal cancer, including radiotherapy for cancers in other organs. Four patients had radiation treatment for other previous cancers.

AR, anterior resection; ASA, American Society of Anesthesiologists; BMI, body mass index; IMA, inferior mesenteric artery; TME, total mesorectal excision; PME, partial mesorectal excision.

Functional outcomes were registered for 412 patients. The most common defecatory outcomes were clustering (57%) and incontinence (29%), followed by urgency (22%) and evacuatory dysfunction (16%). In the multivariable analysis, neither the colon region used for anastomosis (sigmoid or descending) nor the level of the vascular ligature was associated with functional outcomes. However, a significant association was seen between the anastomotic level and defecatory outcomes. The higher anastomoses, in relation to the anal verge, the lower the risk of both incontinence (OR 0.75; 95% CI 0.63–0.90; $P$
< 0.001) and clustering (OR 0.78; 95% CI 0.67–0.90; P < 0.001). At a minimum of 1 year after closure of the diverting ileostomy, a significantly increased risk of clustering was seen (OR 1.89; 95% CI 1.08–3.31; P = 0.03), incontinence (OR 2.48; 95% CI 1.29–4.77; P < 0.01), and urgency (OR 4.61; 95% CI 2.02–10.60; P < 0.001). Gender, AL, and preoperative RT were not significant factors in the multivariable analysis.

This study was based on prospectively collected functional data from patients with stage I–III rectal cancers. The primary aim was to examine whether the part of colon used in anastomosis led to worse functional outcomes because the sigmoid colon is anatomically different and may be more prone to diverticula compared with the descending colon. To our knowledge, this issue has not been examined before. We did not find the level of intestinal transection to be associated with functional outcomes; however, the sigmoid colon was only used if it had normal bowel thickness and a lack of diverticula with acceptable distal arterial circulation.

When performing low AR, no consensus has been reached on the placement of the vascular ligation, but in theory, central ligation close to the aorta might cause bowel, urinary, and sexual disturbances. We did not find any significant associations between the level of ligation and bowel function, probably because the mean difference between a central and peripheral ligation is less than 1 cm in our department.

A low anastomotic level increased the risk of incontinence and clustering, in accordance with many studies examining anastomotic height in relation to LARS, probably caused by neorectal compliance.

A diverting ileostomy following LAR is used to reduce the adverse consequences of an AL; however, it has also been shown to impair bowel function, consistent with our findings. Surgeons should consider this disadvantage when creating one.

In a recent meta-analysis, AL was found to be associated with major LARS in several studies. However, as in the present study, some studies have not shown any increased risk. This discrepancy in the published results might arise from different definitions of AL or from type II statistical errors.

Preoperative RT has consistently been shown to be a risk factor for LARS. In the present study, we only found an association with continence and clustering in the univariable analysis, but not in the multivariable analysis after adjusting for anastomotic level, in accordance with a recent Scandinavian study.

In conclusion, the particular colon region used for anastomosis might not affect functional outcomes after AR. A low anastomotic level was associated with incontinence and clustering, and having had a diverting ileostomy was associated with functional difficulties at 1 year after stoma reversal.
Paper IV

Patient-related factors. Symptoms at diagnosis or comorbidity did not differ between the LTS and STS groups. Most patients (87%) were ASA class 1 or 2, and both groups were equally healthy.

Tumor-related factors. The T- and N-stages of the primary tumor did not differ between the LTS and STS groups. The LTS patients had fewer liver metastases (median of 2 vs. 4; \( P < 0.001 \)) and fewer multisite metastases (8% vs. 20%; \( P = 0.006 \)), and unilobar engagement was more common (65% vs. 36%; \( P = 0.002 \)). An increasing number of liver metastases was associated with an increased risk of becoming an STS \( (P < 0.001) \).

Treatment-related factors. The LTS group had preoperative RT more often (68% vs. 47.8%; \( P < 0.001 \)), local radical resection of the primary tumor (86% vs. 73%; \( P = 0.014 \)), and more metastasectomies (78% vs. 25%; \( P < 0.001 \)).

Table 4. Tumor- and treatment-related factors (primary tumor and metastatic burden) for survival beyond 5 years in patients with stage IV rectal cancers

<table>
<thead>
<tr>
<th></th>
<th>Long-term survivors N = 99</th>
<th>Short-term survivors N = 182</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor-related factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T-stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>11 (11)</td>
<td>10 (5.5)</td>
<td>0.293</td>
</tr>
<tr>
<td>3</td>
<td>62 (63)</td>
<td>127 (70)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15 (15)</td>
<td>24 (13)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>11 (11)</td>
<td>21 (11.5)</td>
<td></td>
</tr>
<tr>
<td><strong>N-stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>27 (27)</td>
<td>34 (19)</td>
<td>0.094</td>
</tr>
<tr>
<td>1 or 2</td>
<td>58 (58)</td>
<td>119 (65)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>14 (14)</td>
<td>29 (16)</td>
<td></td>
</tr>
<tr>
<td><strong>Metastasis localization</strong></td>
<td></td>
<td></td>
<td>0.007*</td>
</tr>
<tr>
<td>One site</td>
<td>91 (92)</td>
<td>144 (79)</td>
<td></td>
</tr>
<tr>
<td>Multiple sites</td>
<td>8 (8)</td>
<td>37 (20)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of liver metastases</strong></td>
<td>2 (1–10)</td>
<td>4 (1–10)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Missing data</td>
<td>9</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td><strong>Liver lobe localization of Metastases</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilobar</td>
<td>54 (65)</td>
<td>58 (36)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Bilobar</td>
<td>18 (21)</td>
<td>81 (50)</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>12 (14)</td>
<td>23 (14)</td>
<td></td>
</tr>
</tbody>
</table>
Treatment-related factors

<table>
<thead>
<tr>
<th>Treatment-related factors</th>
<th>67 (68)</th>
<th>87 (48)</th>
<th>0.001*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative radiotherapy(^b)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Radical primary resection (R0)</td>
<td>85 (86)</td>
<td>133 (73)</td>
<td>0.014*</td>
</tr>
<tr>
<td>Metastasectomy</td>
<td>77 (78)</td>
<td>46 (25)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Data are expressed as N and (%) or as median (range).
\(^a\)Data are based only on patients with liver metastases (long-term survival with liver metastases N = 84 and short-term survival with liver metastases N = 162).
\(^b\)Preoperative treatments are in relation to the primary tumor resection.

In the multivariable analysis, the single most important factor for LTS was metastasectomy (HR: 8.264, 95% CI: 3.984–16.949, \(P < 0.001\)). When excluding metastasectomy, preoperative RT (HR: 2.433, 95% CI: 1.345–4.404, \(P = 0.003\)) was an important factor for LTS.

Table 5. Multiple conditional Cox regression analysis of prognostic factors in patients with stage IV rectal cancers who survived beyond 5 years

Prognostic factors for long-term survival

<table>
<thead>
<tr>
<th>Prognostic factors for long-term survival</th>
<th>HR</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasectomy</td>
<td>8.264</td>
<td>3.984–16.949</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Preoperative radiotherapy</td>
<td>1.522</td>
<td>0.743–3.115</td>
<td>0.251</td>
</tr>
<tr>
<td>Radical primary resection</td>
<td>1.351</td>
<td>0.556–3.283</td>
<td>0.507</td>
</tr>
<tr>
<td>More than one site metastasis</td>
<td>0.422</td>
<td>0.131–1.361</td>
<td>0.149</td>
</tr>
</tbody>
</table>

The reference is the controls (short-term survivors). HR, hazard ratio; CI, confidence interval

In this study, all patients with rectal cancer with synchronous metastases in Sweden during 2000–2008 were included. The independent factor for 5-year survival was metastasectomy, followed by preoperative RT. Owing to the case-control study design, groups were comparable in regard to the following matched factors: gender, age, resection of the rectal tumor, and study period. Despite improvements in oncological and surgical treatments, few LTS were found in the SCRCR. We could not find any differences regarding symptom
onset between the LTS and STS groups. Despite this, whether the patients in the LTS group sought medical care earlier because of symptoms from the metastases or primary tumor remains an important question. No significant differences were found regarding comorbidity. This could be because the patients were a highly selected group of healthy individuals, as all of them had undergone surgery for a primary tumor.

Most previous studies have focused on prognostic factors for survival after liver surgery, including size\(^1\), number\(^2\), and distribution of liver metastases\(^3\), as well as primary tumor stage\(^4\) and node status\(^5\). However, the results show discrepancies, some of which are in line with our findings. These differences may have arisen from different study periods, study populations (including both colon and rectum cancer, as well as synchronous and metachronous metastases), end points, and long-term management, given that some studies are over 20 years old.

Metastasectomy was the most important factor associated with becoming LTS. Interestingly, a minority of the patients in the LTS group had not undergone surgery for metastases. The reason for this could be an incorrect radiological diagnosis of metastatic disease or metastases with good response to chemotherapy. A more thorough investigation of LTS who have not undergone metastasectomy would be of special interest.

In conclusion, metastasectomy—especially involving liver surgery—is important for becoming LTS. Thorough selection of patients with rectal cancers and synchronous metastasis for metastasectomy might result in more patients surviving for longer than 5 years.
General Discussion

Paper I

This study aimed to explore whether loop ileostomy closure in a 23-hour hospital stay setting was safe and feasible, and to explore patient experiences. We determined that this setup was safe and feasible in a selected group of patients with meticulous postoperative follow-up. Because a lack of hospital beds and/or operating rooms are obstacles for stoma reversal, especially in Sweden, a day-case or 23-hour stay setting is an alternative to routine hospitalization. This reduces the total LOS and thus can reduce costs, as shown in the study by Kalady et al.\textsuperscript{133}, even though this was not explored in the present study. It would be interesting to perform a cost analysis in a future study under Swedish conditions.

The inclusion and exclusion criteria led to a selected group of patients who were healthy and rated as only ASA grade 1 or 2. Therefore, the results cannot be generalized to all patients subjected to ileostomy. In a recent study\textsuperscript{220} and other previous studies\textsuperscript{221,222}, an ASA grade of $>2$, current smoker, chronic obstructive pulmonary disease, dyspnea, hypertension, steroid use, and bleeding disorders were shown to be associated with increased risks of morbidity and mortality following stoma closure. ASA class 3 includes a wide variation in health status, so it would be interesting to explore whether it might be possible to perform ambulatory ileostomy reversal in this group of patients.

After this study, we plan to implement ambulatory ileostomy closure on selected patients at our clinic. However, the intense follow-up program in our study setting might not be possible in everyday practice. Therefore, another follow-up setting needs to be designed. In a study on reconstructive surgery on patients with breast cancer\textsuperscript{223}, the effectiveness of a mobile phone app was compared with traditional in-clinic follow-up. The results indicated that the use of such apps as follow-up is suitable and cost-effective in selected low-risk patients undergoing ambulatory surgery. Other studies have shown that telephone or mobile phone apps can substitute conventional follow-up with high patient satisfaction when examining 30-day postoperative surgical site infection\textsuperscript{224-226}. In the present study, we used telephone follow-up by a specialist nurse. However, it is conceivable that a mobile phone app might become routine. The need for telephone follow-up with a nurse would be reduced and the need for synchronous communication bypassed: that is, fruitless attempts to call patients when they are unreachable would not be necessary.
In addition, patients would not need to travel for follow-up visits. In general, patients receiving ambulatory surgery are healthy and the risk of complications is low. In our study, 7% of the patients had complications requiring re-operation, and most complications in both cohorts were detected within the first 2 weeks. Hence, an alternative to the intense follow-up in this study might be to keep the follow-up at day 3 with laboratory samples and then use the follow-up protocol for other ambulatory surgeries, namely at 4 weeks after surgery. Patients can call the nurses at our outpatient clinic during office hours and go to the emergency department to consult a surgeon at other times.

**Paper II**

The independent factor associated with admission for SBO was re-laparotomy because of complications. No patient, treatment, and/or primary surgical factors were associated with admission or surgery for SBO. These results should be interpreted with caution because the numbers of patients with SBO and those who required surgery for this were small (seen in the 95% CIs of the results). Having a small sample size can lead to type II statistical errors; in other words, falsely conclusions that there are no associations between some of the factors and the measured outcomes (admission and surgery for SBO). If we had a larger population/sample size, some of the nonsignificant variables might have been associated with admission or surgery for SBO. However, it is reasonable to believe that re-laparotomy would lead to an increased risk of admission for SBO, since both the complications leading to re-laparotomy and re-laparotomy itself can lead to further inflammation and peritoneal injury, resulting in adhesions and ultimately, SBO. Almost all patients who undergo abdominal surgery develop adhesions; most are asymptomatic, but a large number suffer from SBO. The burden associated with adhesions is underestimated by surgeons, so this problem needs to be highlighted. Rectal cancer surgery is associated with the highest readmission rates\(^{152-154}\). Mortality rates following surgery for SBO are reported to be as high as 10%\(^{176}\), increasing to 15%\(^{177}\) if bowel resection is performed. During such surgery, there is a 33% risk of inadvertent enterotomy\(^{178}\), leading to an increased mortality rate from 20% to 50\(^{227}\). Hence, high morbidity as well as mortality is associated with SBO.

A temporary diverting ileostomy is usually created after an AR to minimize the consequences of AL. However, here, we report a high rate of loop ileostomy-related SBO and, as described earlier, having had an ileostomy can result in readmission for dehydration, renal failure, skin irritation, stomal prolapse, retraction, or hernia. Therefore, surgeons should acknowledge such stoma-related morbidity and take this into consideration before establishing a diverting ileostomy.
How should SBO be managed: with or without surgery? In NOM, the use of the hyperosmolar water-soluble contrast medium diatrizoate is a key approach that can have both diagnostic and therapeutic value; however, the results are contradictory. One of the largest randomized controlled trials did not find any difference regarding the risk of surgery or LOS between diatrizoate and placebo groups \(^{228}\). A large retrospective cohort study including 28,000 patients reported that the risk of recurrence for SBO increased with each SBO episode; after surgical intervention, the recurrence risk decreased by half \(^{229}\). However, one should always consider the mortality and risks involved with surgery for SBO.

How can SBO be prevented? Despite improved surgical techniques and the introduction of laparoscopic surgery, the literature is not convincing regarding the benefits of laparoscopic surgery with respect to the development of SBO \(^{230}\). There are increasing numbers of biomaterials used to prevent adhesions and different forms are available on the market. These materials function as barriers separating injured tissue surfaces for re-mesothelialization to occur. Hyaluronate carboxymethylcellulose (Seprafilm) and regenerated cellulose (Interceed) are used in clinics; however, there is shortage of evidence in this area, and no consensus for the use of anti-adhesion barriers has been reached \(^{231}\). In a Swedish randomized trial, icodextrin was used on patients undergoing colorectal surgery to investigate the effects on SBO; namely, the need for surgery or hospitalization for SBO, as well as complications and survival. That trial is ongoing and planned to be completed in 2022 \(^{232}\).

**Paper III**

When performing AR, an anastomosis is created between the colon and rectum. Which part of the colon is preferable to minimize the risk of bowel dysfunction: the sigmoid or descending colon? Information on the level of transection is not available in the SCRCR; however, fortunately, in our local rectal cancer registry in Västmanland, the level of large bowel transection has been registered prospectively since 1996. Hypothetically, the sigmoid colon is more narrow, rigid, and prone to diverticulosis compared with the descending colon. Hence, it could be preferable to use this region during surgery compared with the sigmoid colon. In this study, the descending colon was used in 68% of patients undergoing AR and the sigmoid colon in 29%. We did not find an association between bowel dysfunction and the level of transection; however, we did not measure the length from the anus to determine where the sigmoid or descending colon was transected. Instead, the definition depended on consensus among the few surgeons performing rectal cancer surgery. It would be preferable to perform a randomized clinical trial comparing the sigmoid with the descending colon and measuring the exact level of transection. However,
it would be unethical to perform such a study because there are factors to consider when choosing the region, such as the length of the colon, distal arterial circulation, quality of the bowel wall, or presence of multiple diverticula. Choosing a region with low bowel quality for the anastomosis with a high risk of failure would endanger the patient. However, in our study, we found that the functional outcomes were unassociated if the sigmoid or descending colon was chosen, provided the above-mentioned conditions were fulfilled.

Forming a diverting ileostomy following an LAR is typically used to protect the bowel. However, using this approach was shown to be associated with bowel dysfunction after an LAR for rectal cancer in several studies\textsuperscript{,160,216}. Results from the RECTODES clinical trial randomizing to stoma and no-stoma groups did not show any differences in bowel function between groups\textsuperscript{,158,233,234}. One should consider the known confounding factor, that patients with distal tumors usually receive RT and consequently have an increased risk of LARS. These patients also have a higher risk of AL and are at higher risk of receiving a temporary diverting ileostomy. In this study, having had a diverting ileostomy was an important independent risk factor associated with bowel dysfunction after adjusting for the abovementioned covariates (RT, anastomotic level, and AL). The effect of RT in itself was abolished in the multivariable analysis when adjusted for anastomotic level.

Having an AL was not significant in the univariable or the multivariable analysis, probably because of the low incidence in this cohort. It should be mentioned that the stoma in 35 patients became permanent (which is why they were excluded), some following AL. Therefore, because some of the worst ALs were excluded, this explains the low incidence in the analysis and may explain the results.

The median time for stoma closure was 8 months in our cohort and, as shown in several studies, the timing of such closure can affect bowel function\textsuperscript{,235-237}. Diversion of bowel contents can lead to changes in the gut biota, leading to inflammation\textsuperscript{,238,239}, and might lead to impaired bowel function. Theoretically, early closure of a diverting ileostomy would prevent this dysbiosis; however, there is lack of evidence regarding this, and large randomized studies are needed to assess the association between LARS and the timing of ileostomy closure.

Anastomotic level and tumor height from the anal verge are often used in studies on LARS, where tumor height is used as a surrogate measure for transection of the rectum and anastomotic level. In our study, we used anastomotic level, as noted in our local registry, because this provides more accurate information on the residual rectum. In our cohort, 10% of the patients underwent PME, but 40% of the tumors were in the upper rectum. Therefore, TME was performed on tumors in the upper rectum and these patients received a low anastomosis. In one study, postoperative MRI was used to assess rectum remnants; the results showed that the risk of major LARS was 46% in patients with a postoperative rectal remnant <4 cm, compared with 10% in patients
with a rectal remnant $>4$ cm ($P < 0.0001$)\textsuperscript{210}. Thus, it is important to preserve as much rectum as possible for anastomosis to reduce the risk of functional difficulties after surgery.

Finally, short and long course RT has been shown to affect bowel function in several studies\textsuperscript{162,217,218,240}. However, in the present study, the effect of RT was abolished when adjusted for anastomotic level, and in a recent Scandinavian study, the effect of RT was abolished when this was adjusted for tumor height. With the new indication for neoadjuvant RT in the recent Swedish national guidelines for patients with rectal cancer, the high rate of preoperative RT will probably decrease from the previous 60\%-65\% to an estimated 40\%\textsuperscript{144}. Considering these aspects, by performing PME in all patients with high rectal cancers and reducing the rate of preoperative RT, fewer patients with rectal cancers undergoing AR could be expected to experience bowel dysfunction.

**Paper IV**

In this study, metastasectomy (both liver and lung surgery) was the most important factor for becoming LTS if a patient had undergone surgical treatment for rectal cancer and had synchronous metastases. The majority of metastases were confined to the liver, which is why liver surgery was the most important factor for becoming LTS. Regarding lung metastases, in our study, metastasectomies including thoracic surgery to the lung were included. However, some advocate that pulmonary metastases do not necessarily require surgery for survival benefits\textsuperscript{241}.

When interpreting the results of our study, it should be noted that the cohort was from 2000–2008 and constituted a highly selected group of healthy patients because they had all undergone excision of their primary tumor. If such a cohort were to be chosen today, the demographics might be different. Patients with rectal cancer are getting older and have more comorbidities, resulting in fewer undergoing surgery. However, both oncological and surgical treatment are evolving and improving, enabling the removal of tumors that were previously untreatable. Therefore, if selecting a cohort today, metastasectomy would most likely be a significant survival factor.

In the present cohort, all patients underwent surgery for their primary tumor. However, there is still no consensus on whether the primary tumor should be resected to gain survival benefits in patients with stage IV rectal cancers. Many studies have been conducted on the effects of resection, but most have been retrospective, biased, and nonrandomized\textsuperscript{242}. Therefore, whether the primary tumor should be resected remains an area of interest for future studies.

Most studies on survival factors after liver surgery have been based on patients with colorectal disease. The advantages of the present study are its ho-
mogenous cohort involving only patients with rectal cancer, based on a validated registry (SCCRCR), complemented with medical charts to supply missing data. There are problems when mixing colorectal patients in studies, given that different parts of the colon have different biological, genetic, and prognostic factors\textsuperscript{243}, making the analysis of such patients as a single group misleading.

Liver surgery is the only curative treatment for resectable liver metastasis. Different strategies exist: the classical strategy (surgery of the primary tumor followed by liver surgery), liver-first strategy (reverse of the previous), and the simultaneous strategy (resection of both the primary tumor and metastasis in one session)\textsuperscript{187}. The preferred strategy in Sweden is now the liver-first strategy. However, a recent Swedish study did not show any difference in overall survival between the classic and liver-first approaches\textsuperscript{244}. Our results revealed that metastasectomy was important, and during that time, patients had either the classic strategy or simultaneous surgery. The most appropriate surgical approach is yet to be established.

Improvements in surgical techniques and adjuvant treatments make liver resection possible for more patients. Not all such patients benefit from the surgery – around 30% have tumor recurrence and 15% die within a year\textsuperscript{245}. Therefore, the selection of appropriate patients for surgery and personalized treatment are important. Several clinicopathological prognostic factors have been reported, but in the era of modern chemotherapy, tumor biology is gaining increased recognition as being important for prognosis\textsuperscript{246,247}. 
Conclusions

Paper I
Ileostomy closure during a 23-hour stay hospital setting in selected patients with meticulous follow-up is safe and feasible with high patient satisfaction.

Paper II
The risk of SBO is greatest in patients with complications after open rectal cancer resection resulting in a re-laparotomy. The type of resection surgery, with or without anastomosis, was not associated with SBO.

Paper III
Whether the descending or sigmoid colon is used for anastomosis to the rectum after AR might not be associated with functional outcomes. A low anastomotic level is associated with incontinence and clustering, and if patients receive a diverting ileostomy, this is associated with functional difficulties after stoma reversal.

Paper IV
The most important prognostic factor for long-term survival in patients with primary stage IV rectal cancer is metastasectomy, especially liver surgery. With thorough selection of patients for metastasectomy, more of them with metastasized rectal cancer could survive beyond 5 years.
Future perspectives

Paper I
The inclusion criteria could potentially be expanded to include selected patients of ASA class 3. Further, a cost-effectiveness analysis in a Swedish setting is needed. Instead of telephone and conventional follow-up, it would be interesting to compare follow-up using a mobile phone app with conventional follow-up.

Paper II
Larger studies are needed to identify risk factors for admission and surgery for SBO. Further research is also of interest regarding stoma-related SBO and laparoscopic vs. open surgery, as well as more specific research on patients with rectal cancer, because many studies are based on gynecological diseases or abdominal surgery in general. Research on preventive action with anti-adhesive barriers would also be of great interest.

Paper III
This study was based on functional data defined locally, so it would be interesting to examine LARS scores and quality of life in the cohort. Early ileostomy closure is an active theme in the world of colorectal surgery, and studies on whether the timing of ileostomy closure has any effect on LARS are lacking. Furthermore, it would be interesting to explore time trends of functional outcomes and possible factors affecting them over time. Finally, the lack of randomized trials for many of the treatment options for LARS indicates the need for well-designed studies.

Paper IV
In the era of modern chemotherapy and target therapies, it would be interesting to examine biological and genetic markers as prognostic factors. The im-
importance of primary tumor resection in palliative care for patients with metastases from rectal cancers needs to be elucidated with a powered randomized controlled trial, taking bias into consideration and investigating the best strategy for liver surgery. Furthermore, it remains uncertain whether the general resection of pulmonary metastases results in survival benefits, or whether only liver surgery is of importance.
Sammanfattning på svenska


Kirurgin för rektalcancer är förbunden med negativa effekter och komplikationer som att ha en tillfällig avlastande tunntarmsstomi (påse på magen), utveckla tunntarmsileus (tarmvred), samt långvariga funktionella tarmbesvär. I samband med så kallad främre resektion (där tumören opereras bort via buken) vid rektalcancer får många patienter en tillfällig tunntarmsstomi (loopileostomi) för att avlasta tarmanastomosen (ihopkopplingen). Att ha en tillfällig tunntarmsstomi kan dock medföra vätskeförluster som orsakar intorkning och i värsta fall njursvikt vilket kan leda till sjukhuskrävande vård. Dessa stomier opereras för att återskapa tarmkontinuiteten (stominedläggning) vid ett senare tillfälle, och då inneliggande med en vårdtid på ca 5-10 dagar. Tyvärr får många av dessa patienter vänta länge på en operation på grund av brist på vårdplatser. Det finns ett fåtal mindre studier som visar på att man kan lägga ner tunntarmsstomier dagkirurgiskt eller med hemgång inom 23 timmar. På så sätt vore det möjligt att operera flera patienter trots begränsade resurstillgångar och därmed skulle väntetiden för stominedläggning förkortas, vilket i sin tur skulle minska den stomirelaterade sjukligheten.

Efter bukkirurgi kan man utveckla tunntarmsileus, där vanligaste orsaken är sammanväxningar. Kända riskfaktorer för ileus är bland annat öppen bukkirurgi, inflammation i buken, tidigare operationer samt kirurgi i lilla bäckenet där operationer på rektum har högst risk. Att få tunntarmsileus kan medföra stort lidande för patienter med återkommande sjukhusvård, operationer och påverkan på livskvaliteten. ungefär hälften av patienterna med tunntarmsileus behöver genomgå en operation för detta, vilket i sig medför risker. Det är därför av intresse att identifiera ytterligare riskfaktorer för att minimera risken för ileus efter öppen bäckenkirurgi.

Efter främre resektion kan man också utveckla tarmdysfunktion (anorektal dysfunktion). Dessa besvär kan ge sig till känna på olika vis; inkontinens (läckage) för gas och avföring, frekventa tarmtömningar, trägningskänsliga och svårigheter att tömma tarmen. Upp mot hälften av patienterna har grava symtom som minskar livskvaliteten avsevärt. Symptomen uppstår antingen direkt efter den primära operationen eller efter att den avlastande stomin blivit

Patienter med rektalcancer kan få metastaser och cirka 20 % har redan spridd sjukdom vid diagnos. Prognosen för patienter med spridd sjukdom är mycket dålig och överlevnaden är cirka 1-2 år, men kan förbättras avsevärt hos patienter med spridning enbart till levern om leverkirurgi kan utföras i botande syfte. För att bättre kunna välja ut vilka patienter som ska erbjudas leverkirurgi har olika scoringsystem utvecklats. Det finns en liten grupp patienter med en initialt spridd sjukdom som överlever mer än 5 år och för att bättre selektera patienter till leverkirurgi behöver man identifiera prognostiskt gynnsamma faktorer som leder till långtidsöverlevnad.

Det övergripande syftet med avhandlingen var att studera riskfaktorer och morbiditet efter rektalcancerkirurgi och faktorer som påverkar överlevnad hos patienter med spridd rektalcancer. Målsättningen med detta avhandlingsarbete var att med utgångspunkt från kliniska studier belysa följande hos patienter opererade för rektalcancer:

- Att undersöka om det är möjligt och säkert att lägga ner loop-ileostomier med utskrivning av patienterna inom 23 timmar.
- Att identifiera riskfaktorer för inläggning och operation på grund av tunntarmsileus samt orsaker till tunntarmsileus hos de som är opererade för åkomman.
- Att undersöka om det finns någon skillnad i anorektal funktion berorande på om sigmoideum eller descendens används som anastomos till rektum samt om det finns andra potentiella riskfaktorer för att utveckla anorektal dysfunktion efter främre resektion.
- Att identifiera prognostiska faktorer hos patienter med rektalcancer med synkrona (samtidiga) metastaser som har överlevt mer än 5 år.

mar. I båda grupperna blev sju (23%) återinlagda, varav två genomgick laparotomi (reoperation) på grund av komplikationer. Vårdtiden var mer än dubbelt så långt hos den jämförande kohorten. Majoriteten av patienterna i studiekohorten (87%) var nöjda med upplägget att skrivas hem inom 23 timmar. Slutsatsen var att nedläggning av loop-ileostomi med utskrivning inom 23-timmar med ett noggrant uppföljningsprogram hos selekterade patienter är möjligt där majoriteten av patienterna var nöjda.

Delstudie II var en retrospektiv kohortstudie med prospektivt insamlade data på patienter med rektalcancer i Västmanland som genomgått öppen resektionskirurgi på grund av rektalcancer mellan 1996 och 2017 (N=752). Totalt utvecklade 84 patienter (11%) tunntarmsileus och majoriteten insjuknade under första året efter primäroperationen. Trettiofem (4.3%) genomgick operation för sitt tillstånd och orsaken var stomi-relaterade hos en fjärdedel av dessa. Reoperation i samband med den primära operationen var den starkaste riskfaktorn för inläggning för ileus (OR 2.824, CI 1.129–7.065, \( P = 0.026 \)) men inte för operation av tunntarmsileus. Slutsatsen var att risken för tunntarmsileus är störst för patienter som får komplikationer som resulterar i reoperation efter rektalcanceroperationen.

Delstudie III var en retrospektiv kohortstudie med prospektivt insamlade data på patienter med rektalcancer i Västmanland, vilka genomgått främre resektion på grund av rektalcancer mellan 1996 och 2019. Data om tarmfunktion registrerades prospektivt vid varje uppföljning. Totalt inkluderades 470 patienter och tarmfunktionen kunde utvärderas hos 412 av dessa. Eftertömning sågs hos 57%, inkontinens hos 29%, trängning hos 22% och evakueringssvårigheter hos 16% av patienterna. Kön, del av kolon som anastomoseras eller var mesenterica inferior-artären ligeras var inte associerad med tarmdysfunktion. Ju högre upp från analöppningen anastomosen gjordes, desto lägre var risken för både inkontinens (OR 0.75; CI 0.63-0.90; \( p<0.001 \)) och eftertömning (OR 0.78; CI 0.67-0.90; \( p<0.001 \)). Om man haft en avlastande loop-ileostomi som lagts ner, sågs en ökad risk för eftertömning (OR 1.89; 1.08-3.31; \( p=0.03 \)), inkontinens (OR 2.48; 1.29-4.77; \( p<0.01 \)), och trängning (OR 4.61; CI 2.02-10.60; \( p<0.001 \)). Slutsatsen var att vilken del av kolon som anastomoseras med ändtarmen inte är associerad med påverkan på tarmfunktionen och att låg anastomos och loop-ileostomi har negativ inverkan på tarmfunktionen.

Delstudie IV var en nationell fall-kontrollstudie baserad på det Svenska kolorektalcancerregistret och Patientregistret med kompletterande journalgranskning. Fallen utgjordes av patienter med synkrona metastaser i hela Sverige som opererats för sin rektalcancer mellan åren 2000 och 2008 och överlevt mer än 5 år (N=99). Kontrollerna utgjordes av en motsvarande matchad
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