Colorectal cancer

Aspects of staging, treatment, recurrence and survival

ÄSA COLLIN
Abstract

Colorectal cancer is the third most common malignancy in the world, and major breakthroughs have been made regarding both surgical and oncological treatment. Still, postoperative complications, such as perineal infections after abdominoperineal resection (APR), are a major cause of morbidity, and distant recurrence rate is nearly 20%. In this thesis, means to improve postoperative infection rates, nodal staging in rectal cancer (and resulting overtreatment through (chemo)radiotherapy), cancer recurrence rates and survival, were investigated. In Paper I, the effects on complication rates, recurrence rates and survival of antibiotics applied locally after an APR, by means of a gentamicin-collagen sponge in the perineal wound, were analysed in a randomized setting. No difference was seen regarding any of the endpoints. The results suggest that local antibiotics can safely be omitted in APRs. Paper II investigated the effects of mechanical bowel preparation (MBP) on cancer recurrence and survival, among colon cancer patients undergoing a colon resection. Data from the Swedish randomized MBP trial were used. After follow-up, no improvement in recurrence rates or overall survival was seen, but cancer-specific survival was improved in the MBP group. In conclusion, MBP might be a prognostic favourable factor for outcome in colon cancer patients. In Paper III, the effect of new national guideline criteria for MRI nodal staging in rectal cancer was assessed, regarding the proportion of clinically positive nodes and staging accuracy, and resulting effects on preoperative (chemo)radiotherapy use. Comparing the two years prior to guideline implementation with the two years after implementation revealed a significant decrease in the proportion clinically positive nodes, but staging accuracy remained low, and (chemo)radiotherapy rates decreased with seemingly no correlation to guidelines. Thus, new guidelines decreased the rate of clinically positive nodes, but nodal accuracy remained poor and nodal staging should perhaps not be a criterion in preoperative treatment decisions. Paper IV investigated the impact of the total mesorectal excision quality, by means of the three Quirke grades, mesorectal (best quality), intramesorectal and muscularis propria (worst quality), on recurrence and survival, and assessed risk factors for intramesorectal or muscularis propria resection. Muscularis propria grade was associated with a higher local recurrence rate, but not with distant recurrence or survival. Several factors were associated with intramesorectal and muscularis propria grade, and more caution is warranted in these patients. In conclusion, this thesis provides insight into treatment choice, and the association of day-to-day treatment details with postoperative complications, recurrence and survival rates, as well as the challenges of nodal staging.

Keywords: colorectal cancer, recurrence, survival, staging, postoperative complications

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All carcinomas of the lower sigmoid and upper rectum are tabooed by all practical surgeons [...] on account of their anatomical inaccessibility. All [...] are abandoned without hope to linger on for a few months until death relieves them of their loathsome condition.
- H.W. Maunsell, The Lancet, 1892

To Clara-Lykke and Elliot
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

5-FU  5-fluorouracil
AJCC  American Joint Committee on Cancer
APC   Adenomatous polyposis coli
APR   Abdominoperineal resection
AR    Anterior resection
ASA   American Society of Anesthesiologists
BMI   Body mass index
BRAF  V-raf murine sarcoma viral oncogene homolog B
CI    Confidence interval
CIN   Chromosomal instability
CMS   Consensus molecular subtypes
cN    Clinically staged nodes
CRC   Colorectal cancer
CTL-4 Cytotoxic T-lymphocyte-associated antigen 4
dMMR  Deficient mismatch repair
EGFR  Epidermal growth factor receptor
Gy    Grey
HIPEC Hyperthermic intraperitoneal chemotherapy
HR    Hazard ratio
IQR   Interquartile range
KRAS  Kirsten rat sarcoma viral oncogene homolog
MBP   Mechanical bowel preparation
MLH1  MutL homolog 1
MMR   Mismatch repair
MRI   Magnetic resonance imaging
MSI   Microsatellite instability
MSS   Microsatellite stability
<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>NRAS</td>
<td>Neuroblastoma RAS viral oncogene homolog</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PD-1</td>
<td>Cell death protein 1</td>
</tr>
<tr>
<td>pMMR</td>
<td>Proficient mismatch repair</td>
</tr>
<tr>
<td>pN</td>
<td>Pathologically staged nodes</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>SCRCR</td>
<td>Swedish colorectal cancer registry</td>
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<td>TME</td>
<td>Total mesorectal excision</td>
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<td>TNM</td>
<td>Tumour, node, metastasis</td>
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<tr>
<td>TP53</td>
<td>Tumour protein 53</td>
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<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<tr>
<td>Wnt</td>
<td>Wingless-related integration site</td>
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Introduction

Whereas interest in colorectal cancer and surgery came quickly and in an all-in manner, joining the PhD path was a decision made more hesitantly, and pursued at a somewhat different pace, as my late former supervisor, and professor Lars Pålhlman, had to experience. His energy and enthusiasm still made me embark on this journey, far too many years ago than I want to acknowledge.

There was not so much a main thread in this thesis, but rather a main highway of colorectal cancer, from potential effects of locally applied antibiotics, mechanical bowel preparation and surgical quality on recurrence and survival, as well as aspects of clinical staging.

Several projects were started and some were almost finished, before life or other unforeseen events created detours and sank them to the ground. However, new doors have opened, and a new and more determined energy has developed over the years, as this student has matured and learned to appreciate and acknowledge the fruits of perseverance.

Colorectal cancer is extensively studied, as it is the third most common cancer worldwide, and many ground-breaking findings regarding oncological and surgical treatment have been made over the years – and are still being made, with exciting results. The exploration of the microbiota and its role in the development of colorectal cancer and in modifying the therapeutic responses to chemotherapy and immunotherapy, remains in its bud. Our increasing knowledge and understanding of the human genome and main cancer drivers have opened up new treatment possibilities with immunotherapy for this heterogenous disease, and are – together with increasing interest in organ-preserving treatments, such as watch-and-wait – challenging the surgeon’s role as the ‘primary healer’. We await these developments with excitement. Meanwhile, the humble hope and aim of this thesis was to shed further light on colorectal cancer. The thesis focuses on the impact of pre- and perioperative factors on recurrence and survival, as well as the challenges of magnetic resonance imaging-based nodal staging.
Background

Epidemiology

Colorectal cancer (CRC) is the third most common malignancy in the world, and the second leading cause of cancer mortality worldwide. It accounts for 10% of all cancers, and the estimated worldwide incidence is 1.9 million per year. The incidence is highest in Western Europe, Australia, New Zealand, and North America, whereas South-Central Asia and African countries have the lowest incidence (1). CRC is closely linked to a ‘Western lifestyle’ and is increasing in many low- and middle-income countries, whereas rates in high-income countries are stabilizing or decreasing, probably as an effect of screening and better therapeutical possibilities (2, 3).

In Sweden, the lifetime risk to be diagnosed with CRC is around 5%, and increases with increasing age. About 5,000 patients each year are diagnosed with colon cancer, and 2,000 with rectal cancer (4). At diagnosis, approximately 20% of CRC patients have stage I disease, 20% stage II, 35–40% stage III, and 20–25% stage IV (5, 6). Relative survival in colon and rectal cancer, stage by stage, as reported by the Swedish colorectal cancer registry (SCCR), is seen in Figure 1.

Colon cancer is slightly more common in women, whereas rectal cancer is more common in men (7). Mortality is higher in male CRC patients (8, 9). The median age at diagnosis is about 73 years for both colon and rectal cancer (5, 6). In Sweden, the number of patients with CRC has increased over the years, mainly due to an aging population, but for colon cancer, there is also a slight increase in age-standardized incidence (8, 9).

Only 5–7% of CRC patients in Sweden are younger than 50 years (5, 6). An increase in CRC in younger adults, under the age of 50 years, has been seen in some countries. It is believed to be explained by increasing obesity, a sedentary lifestyle and other unfavourable health behaviours, which are not counterbalanced by screening for the younger population (10). The American Cancer Society update from 2023 reported a rapid shift of CRC toward diagnosis at younger age, at a more advanced stage, and in the left colon and rectum (11).
Figure 1a (left) and 1b (right). Relative survival in colon (a) and rectal (b) cancer diagnosed in 2016–2022, stage by stage, as reported by the Swedish colorectal cancer registry (SCRCR) (8, 9).

Anatomy

The colon consists of the cecum, the ascending colon, the right/hepatic flexure, the transverse colon, the left/splenic flexure, the descending colon and the s-shaped sigmoid colon, deriving its name from the Greek letter sigma. The right colon stretches from the cecum to the distal 1/3 of the transverse colon and originates from the midgut, whereas the left colon stretches from the distal 1/3 of the transverse colon to the rectum and derives from the hindgut. The neurovascular supply of the colon is closely linked to its embryological origin. The ascending and transverse colon has its lymphatic drainage into the superior mesenteric nodes, and the descending and sigmoid colon into the inferior mesenteric nodes (12). There is increasing evidence that the genetics and clinical outcomes of left- and right-sided colon cancers differ (13).

The definition of the rectum varies internationally. In Sweden, the rectum is defined as extending from the anal verge and for 15 cm, measured with rigid sigmoidoscopy, in accordance with the European Society for Medical Oncology guidelines (14). The rectum is divided into 3 sections: low (≤ 5 cm from anal verge), middle (>5–10 cm from anal verge) and high (>10–15 cm from the anal verge). The international expert-based Delphi consensus suggests defining the upper limit of the rectum as the point of the sigmoid take-off, as visualized through magnetic resonance imaging (MRI) (15).

Histology

Adenocarcinomas make up 95% of all CRCs, and are the type of cancer addressed in this thesis and here referred to as CRC. They originate from the glandular epithelial cells lining the colon and rectum. There are several
histological subtypes of adenocarcinoma, of which conventional (non-mucinous, non-signet ring) adenocarcinoma is the most common, followed by mucinous adenocarcinoma (16). Mucinous carcinomas consist of more than 50% extracellular mucin and account for approximately 10% of all CRCs (16, 17). They are most often present in the right colon, and more common in women (18). When found in the rectum, they have been associated with advanced disease stage and poor prognosis (19). Another histopathological subtype is signet ring cell carcinoma, which is uncommon (1%), but associated with especially poor prognosis, younger age, later stage at presentation, and right-sided tumours, and seems to be equally common in males and females (19-21). Rectal signet ring cell carcinoma is less common, but seems to be increasing, is nearly twice as common in men, and has a worse prognosis than signet ring cell carcinoma of the colon (19, 22, 23). Signet ring cell carcinomas consist of more than 50% signet ring cells, a type of cell with intracellular mucin production (16, 20, 24). Signet ring cell carcinomas can be extracellular mucin-rich or mucin-poor, with mucin-poor carcinomas having the poorest prognosis among all CRC adenocarcinomas (25). Both mucinous and signet ring cell carcinomas tend to metastasize to multiple sites, including the liver, lungs and peritoneum (26), and signet ring cell carcinomas have been found to have a high rate of distant lymph node metastasis and may involve rare metastatic sites, such as bone, skin, pancreas and heart (22). A signet ring cell component (< 50%) in conventional adenocarcinomas is also associated with lower survival rates (27).

Aetiology
Molecular pathogenesis
CRC is a heterogenous disease that arises by stepwise accumulation of genetic and epigenetic alterations that activate oncogenes or inactivate tumour suppressor genes, transforming normal colorectal epithelial cells of the colorectal mucosa to adenocarcinoma (16). CRC has a high mutational burden, with dozens of somatic mutations identified, and can be categorized as hypermutated or non-hypermutated (28). Still, all CRCs appear to develop through one of several distinct pathways. The three main pathways are the chromosomal instability pathway (CIN), the microsatellite instability (MSI) pathway and the serrated pathway (29), see Figure 2.

The CIN pathway accounts for 60–70% of all sporadic CRC (30, 31) and is associated with a high frequency of genomic copy number alterations, resulting in karyotypic instability, which in turn results in mutations in the tumour suppressor genes for adenomatous polyposis coli (APC) and tumour protein 53 (TP53) and in the proto-oncogene for the Kirsten rat sarcoma viral oncogene homolog (KRAS). Loss of APC activity results in activation of the
wingless-related integration site (Wnt)/β-catenin signalling pathway, which is activated in almost all CIN tumours. A majority of microsatellite stable (MSS)/proficient (p) mismatch repair (MMR) tumours are developed through the CIN pathway. CRCs that develop through the CIN pathway are considered non-hypermutated and tumours develop slowly, often over decades and are usually observed in the left colon. Familial adenomatous polyposis also develops through the CIN pathway, due to a germline mutation in the APC gene.

The MSI pathway is a hypermutated pathway, where CRC develops within a few years (29). Defects within the MMR system cause cells not to detect and repair mismatched DNA, but to maintain and replicate their mutations. MSI/deficient (d)MMR tumours account for about 15% of all sporadic CRC and 95% of CRC in patients with Lynch syndrome. Approximately 80% of sporadic MSI tumours develop by epigenetic hypermethylation that causes silencing of MutL homologue 1 (MLH1), while the rest seem to be caused by APC mutations. Lynch is caused by a germline mutation in DNA MMR genes. Sporadic tumours have a high V-raf murine sarcoma viral oncogene homolog B (BRAF) mutation compared with MSS tumours and Lynch tumours (32). MSI tumours are often situated in the right colon and have increased mucin production (33).

Approximately 15–30% of CRC develop from serrated lesions, including hyperplastic polyps, sessile serrated lesions, sessile serrated lesions with dysplasia and traditional serrated adenoma, through the serrated pathway (34, 35). The majority of CRCs from serrated polyps are initiated by BRAF mutation and then develop either via mutations in an MMR gene, or MLH1 methylation, resulting in an MSI-high tumour, with hypermutation. They may also develop via TP53 mutations and activate several oncogenic pathways, leading to a non-hypermutated MSS tumour (36).

Figure 2. Pathways of colorectal carcinogenesis. Activation of the Wnt pathway (primarily via APC mutation) or a mutation in BRAF can initiate colorectal tumorigenesis. BRAF mutations promote tumorigenesis via the serrated neoplasia pathway, leading to MSI with hypermutation or MSS without hypermutation (indicated in the figure). Colorectal tumour classifications include CIN, MSI, and the serrated pathway (see CMS). EMT, epithelial to mesenchymal transition; H, high; L, low; neg, negative. Printed with permission (29).
Molecular subtyping

While stage based on the Tumour Node Metastasis (TNM) system is still the strongest prognostic factor for CRC (37), there are significant differences in prognosis within any single TNM stage (38). Molecular classification of tumours and information regarding KRAS and BRAF mutations and MSI/MMR status are important factors in treatment decisions, as KRAS-, neuroblastoma RAS viral oncogene homolog (NRAS)- and BRAF-mutated tumours do not respond well to anti-epidermal growth factor receptor (EGFR) therapies (39, 40) and MSI tumours could be potential targets for immunotherapies (41–43). A great effort in subtyping CRC, based on tumour biological characteristics, resulted in the consensus molecular subtype (CMS), dividing CRC into 4 groups (CMS1–4) (44) that have both prognostic and therapeutical relevance (45, 46).

CMS1 (immune) are more common in females with right-sided tumours and include the majority of MSI tumours. They are hypermutated, and BRAF-mutated, and have strong immune activation and low prevalence of somatic copy number alterations (47). Serrated MSI lesions are often classified as CMS1 (44). CMS2 (canonical) are CIN tumours, predominantly found in the distal colon and rectum, with more frequent somatic copy number alterations than CMS3 (metabolic) and 4 (mesenchymal) (47, 48). CMS3 is a heterogeneous type with both MSI and MSS tumours, without any predominate site, and has an overrepresentation of KRAS mutations (47). CMS4 have mutations in fibrogenesis pathways and the mesenchymal-epithelial transition, are more common in the distal colon and rectum and have the worst overall survival rates of all CRCs (44). They include serrated MSS lesions (44). CMS1 and CMS3 are more common in stage II–III tumours, whereas the frequency of CMS4 is increased in stage IV (49). In the metastatic setting, CMS2 has the best prognosis, with superior survival after relapse. CMS1 has a poor survival rate after relapse, a higher risk of progression and death after chemotherapy, and responds to immunotherapy (44).

Risk factors

The majority of CRCs are sporadic. That means they are caused by nonhereditary, spontaneous mutations, and a variety of risk factors exist. The World Cancer Research Fund reviewed current evidence on diet, weight and physical activity, and found strong evidence that red and processed meat, alcohol, obesity and being tall increased the risk of CRC. They found some evidence that low consumption of non-starchy vegetables and fruit, and consumption of food containing haem iron might be risk factors for CRC (50). Furthermore, smoking (51, 52), inflammatory bowel disease (53, 54) and diabetes mellitus types I and II increase the risk (55, 56). Recently, the effect of microbiota on the risk of developing CRC has been explored, identifying *Streptococcus*
bovis, enterotoxigenic Bacteroides fragilis, Fusobacterium nucleatum, Enterococcus faecalis, Escherichia coli and Peptostreptococcus anaerobius as being among the CRC candidate pathogens (57-62).

Protective factors

There is strong evidence that physical activity, wholegrains, foods containing dietary fibre, dairy products and calcium supplements decrease the risk or CRC. In addition, there is some evidence that foods with vitamin C, fish, vitamin D and multivitamin supplements might decrease the risk (50), as well as long-term use of acetylsalicylic acid (63, 64).

Hereditary factors

According to estimates, more than 20% of CRCs have a familial component, and approximately 5% are due to a known hereditary syndrome (65-67). Hereditary CRCs have identifiable germline mutations and phenotypes, whereas familial CRCs have no identifiable germline mutation or specific pattern of inheritance, but a higher incidence of CRC within a family compared with the rest of the population (68). A family history of CRC in one or more first-degree relatives can increase the risk of CRC up to fourfold, especially if a relative was diagnosed before the age of 60 years (69). The most well-known hereditary syndromes are Lynch syndrome, also called hereditary non-polyposis colon cancer, and familial adenomatous polyposis. Both are autosomal dominant syndromes. Lynch syndrome is caused by germline mutations in DNA MMR genes, and familial adenomatous polyposis by mutation in the APC gene (70, 71). People with Lynch syndrome have a 30–70% lifetime risk of developing CRC and an increased risk of developing several other tumours, such as endometrial, ovarian, urothelial, gastric, small bowel, breast, prostate and brain tumours (72-75). In familial adenomatous polyposis, polyps develop from an early age in both colon, stomach and duodenum, and nearly 100% will have developed CRC by the age of 40 years, unless the colon and rectum are surgically removed (76, 77).

The gut microbiota

The human gut microbiota consists of bacteria, fungi, viruses, Archaea and parasites, and there is a wide variation in its composition between individuals. Dysbiosis, or disruption of the microbiota, can result from factors such as infections, drug intake, age, diet and smoking. It is associated with several
diseases, including CRC (78-80), and is estimated to be associated with 20% of all cancers (81, 82). Large-scale meta-analyses have detected a ‘core microbiome’ with pro-tumorigenic functions in CRC patients (57-62), as well as in adenoma patients (83, 84), suggesting that microbiota plays an early role in CRC development. The absence of beneficial gut bacteria in CRC patients could be equally important (85). Gut microbiota also has the ability to modulate the response to chemotherapy (86) and immunotherapy (87-89). Mouse studies indicate that faecal transplantation inhibits CRC development by reversing dysbiosis, decreasing excessive intestinal inflammation and cooperating with anti-cancer immune responses (90) and is also studied with the aim of improving the efficacy of anti-programmed cell death protein 1 (PD-1) therapy (91).

Screening
CRC meets the World Health Organization criteria for meaningful screening, as it is a common, serious disease, with effective treatment, that often presents with limited symptoms, and where prognosis is stage-dependent (92). Screening with faecal immunological test has been introduced in Sweden, and will, when fully implemented, be offered to all citizens between 60 and 74 years of age. It is considered simple, safe and cost-effective. Randomized controlled trials suggest a decrease of CRC mortality rates by 16–31% in countries with CRC screening, and a shift toward earlier stages (93-98). In the United States, CRC screening is considered the single most important factor for the decrease of CRC incidence and mortality (99, 100). In Sweden, screening is estimated to save 300 lives yearly, and cause a shift toward earlier stages, with a 40–45% increase in stage I diagnoses (101).

Tumour staging
CRC TNM stage is described in accordance with the American Joint Committee on Cancer (AJCC) 8th edition, where T is based on the depth of tumour invasion into the bowel wall, N on the number of metastatic lymph nodes and M on the metastatic sites (102). Stages I–IV are described in Table 1.
Table 1. TNM stage of CRC as described by the American Joint Committee on Cancer (AJCC) 8th edition (102).

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1–2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II A</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II B</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>II C</td>
<td>T4b</td>
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<td>III A</td>
<td>T1–2</td>
<td>N1/N1c</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td>III B</td>
<td>T3–4a</td>
<td>N1/N1c</td>
<td>M0</td>
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<td></td>
<td>T2–3</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1–2</td>
<td>N2b</td>
<td>M0</td>
</tr>
<tr>
<td>III C</td>
<td>T4a</td>
<td>N2a</td>
<td>M0</td>
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<tr>
<td></td>
<td>T3–4a</td>
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<td>M0</td>
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<tr>
<td>IV C</td>
<td>Any T</td>
<td>Any N</td>
<td>M1c</td>
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Radiology-based preoperative staging should, apart from TNM staging, include information regarding extramural vascular invasion and mesorectal fascia involvement. Preoperatively, genetic analysis of MMR/MSI status, KRAS, NRAS and BRAF should be performed. The postoperative pathology report should, in addition to TNM staging, include information on vascular invasion, extramural vascular invasion, lymphatic and perineural invasion, presence of mucin, tumour grade and circumferential resection margin. Many of these factors add prognostic information and some are taken into account in the decision on oncological treatment (103).

MRI

MRI uses a magnetic field and computer-generated radio waves to create 3D images of the body. Nuclear magnetic resonance was first described in 1938, by Isidor Isaac Rabi, who was awarded the Nobel Prize in Physics for his work. Since its first clinical use in the 1980s, substantial improvements have been made to MRI technology, pulse sequence acquisition strategies and hardware components (104).

In rectal cancer, locoregional staging is routinely performed with high-resolution MRI (105). MRI has high accuracy in predicting mesorectal fascia
involvement, clinical T-staging, involvement of the surgical resection margin (≤ 1 mm) and extra mural vascular invasion (106, 107). However, distinguishing a malignant lymph node from a benign one is challenging, and the sensitivity and specificity for clinical node staging have ranged from 60–95% and 50–95%, respectively, in past studies (107-110). In a revision of the Swedish national guidelines for CRC in 2016, stricter MRI criteria for nodal staging were instated, where at least two of three criteria – diameter over 5 mm, irregular shape and heterogeneous signal – had to be met to stage a lymph node as malignant. Figure 3 illustrates the challenges of clinical lymph node staging.

Figure 3. Patient staged as mrT3a/b mrN2b due to multiple bulky lymph nodes in the mesorectum of which one is depicted, measuring 13 mm in the long axis and 10 mm in the short axis. The patient underwent surgery and was a pT3N0. While carefully reviewing the lymph node appearance on T2-WI, we notice they all presented with well-defined borders, homogeneous signal intensity and a preserved chemical shift effect. Figure and byline reprinted with permission (111).

Treatment

Surgical treatment

Surgery remains the most important step to cure CRC. It may be performed as open surgery or minimally invasive – laparoscopically or robotically. Minimally invasive surgery has increased in the last decade, and national guidelines stipulate that minimally invasive surgery should be the first choice in all patients suited for it, as it leads to less postoperative pain, shorter recovery and shorter postoperative hospital stay, as well as a decreased risk of hernia, and is considered to have an equal oncological outcome to open surgery (103). In colon cancer, the choice of resection (right hemicolecotomy, extended right hemicolecotomy, left hemicolecotomy, sigmoid resection or high anterior resection (AR) with partial mesorectal excision) depends on the location of the tumour. Transverse tumours should undergo an extended right hemicolecotomy, as the lymph drainage in the transverse colon is toward the medial colic artery. The most common procedures in rectal cancer surgery are AR for tumours in the upper or middle part of the rectum, abdominoperineal resection (APR) for low rectal cancers, and Hartmann’s procedure, a choice in patients too fragile
or with too poor sphincter function to manage an AR or APR (112). For some early tumours, endoscopic resections such as transanal endoscopic microsurgery, endoscopic submucosal dissection or endoscopic mucosal dissection can be performed (103, 113, 114).

**Total mesorectal excision (TME)**

In the 19th century, some attempts to resect rectal tumours were made, but morbidity and mortality were high and rectal tumours were long considered ‘tabooed by all practical surgeons’ (115). In 1908, Ernest Miles introduced APR, presenting mortality rates of 42%. Over time, as the procedure was improved, mortality decreased, and Miles managed to decrease local recurrence rates from nearly 100% to 30% (116).

In the 1980s, Heald introduced total mesorectal excision (TME), a surgical method for rectal cancer with dissection in the mesorectal plane, located immediately outside the layer of mesorectal fascia. This was in total contrast to the blunt dissection previously applied, and local recurrence has since its implementation dropped from 40% to 4–5%, making it one of the most revolutionary improvements of CRC surgery in modern times (117-119). The quality of the mesorectal surgical specimen is graded by a pathologist as mesorectal, intramesorectal or muscularis propria, depending on the TME quality, in accordance with Quirke et al. (120, 121). The three different TME grades can be seen in Figure 4.

![Figure 4. The definitions used to judge mesorectum in sphincter-saving procedure specimens are illustrated. (A) A complete mesorectum shows good bulk of mesorectum with smooth surface and no defects on mesorectum. (B) A nearly complete mesorectum shows good bulk of mesorectum, but some defects or irregularities in the surface (arrows) are present. (C) An incomplete mesorectum shows a deep defect on the mesorectum under the peritoneal reflection that allows visualization of the muscularis propria (arrow). Printed with permission [91].](image)

**Treatment of local recurrence in rectal cancer**

In patients who undergo resection surgery, the 5-year local recurrence rate is approximately 3% and 4% for colon and rectal cancer, respectively (5, 6). Local recurrences in rectal cancer usually arise within 2 years (122, 123). They
often present with severe local symptoms and result in increased mortality (124, 125). Surgery is challenging, as the recurrent tumour often invades adjacent tissue, beyond the mesorectal plane. In addition, fibrosis caused by radiotherapy further complicates surgery. Overall 5-year survival after a local recurrence was 9% in 2007, according to the SCRCR (112). However, there has been a significant improvement in surgical management (126), including the development of specialized units and multimodal treatment, and 5-year survival in local recurrence among those who have undergone a radical pelvic exenteration is now reported to be 28–50% (127-129).

**Treatment of stage IV disease**

Approximately 25% of CRC patients present with a stage IV disease at diagnosis, and 5-year distant recurrence rate is 17% for colon cancer and 20% for rectal cancer (5, 6). The liver is the most common organ for metastatic disease in CRC, and approximately 50% of CRC patients present with liver metastases at some point during their disease (130). In 1/3 of patients with stage IV disease, the liver is the only organ of spreading (131). Approximately 10–15% of patients will develop metastases to the lung (132). Lung metastases are more common in rectal cancer than colon cancer, due to the systemic venous drainage of rectal tumours through the hemorrhoidal veins (133). Metastases to the peritoneum are seen in 4–13% of CRC patients (134, 135). Among the less common sites for metastases are bone and brain (136-138).

Treatment of metastatic disease has developed rapidly in recent decades, in both the surgical and medical field (42, 139-147). Surgical treatment of liver metastasis has developed remarkably since it was first tried in the 1970–1980s, and was more widely introduced in the 1990–2000s. Resection was often proposed to be limited to 1–3 unilobar tumours with no extrahepatic disease (148). New technical developments with a parenchymal-sparing approach and the use of additional thermal ablation or stereotactic body radiotherapy, together with developments in preoperative treatment in more advanced disease, have increased the group of patients available for surgical treatment (149, 150), as have methods to improve future liver remnants (151-153). The current criteria for resection include any tumour number with any liver distribution, stable or resectable extrahepatic disease, appropriate future liver remnant, venous involvement with the ability to resect or reconstruct and the ability to achieve a tumour-free margin (151, 154). Total hepatectomy liver transplant is being investigated in the Swedish soulmate trial (155) and has shown possibility of long-term survival and even cure in selected patients (156). A meta-analysis published in 2022, encompassing 58 studies (45 published and 13 ongoing), concluded that while a benefit from liver transplant was suggested in some patients, prospective data were scarce, and further evidence was needed, especially considering the limited availability of donor organs (157).

Recurrence after liver metastasis resection most often occurs within two years (158). Such metastases usually occur in the liver (159) and new resection
surgery has shown survival benefits (160). Approximately 15–20% of patients with liver metastases are suitable for upfront surgery at diagnosis, and more after conversion chemotherapy (161, 162). In patients with stage IV colon cancer undergoing elective liver resection, the 5-year relative survival is now over 40% (8).

Surgical treatment of lung metastases has also improved and several therapeutic options apart from pneumectomy exist – the most common being wedge resections, followed by lobectomy and segmental resections. In the majority of cases, minimally invasive surgery is performed, allowing safe resections with low morbidity and fast recovery (163). In addition, stereotactic radiotherapy and radiological ablation by radiofrequency have evolved. There is no standard management and evidence of the best surgical treatment strategy of lung metastases is scarce (103). Studies have reported 5-year overall survival of 68% and up to 94% in select patients (164), but long-term disease-free survival has been considered exceptional (165).

Pulmonary recurrence have been reported to occur in approximately 40–50% of patients undergoing metastasectomy (166, 167), with a median time to pulmonary recurrence of approximately 10–20 months (168, 169), and 5-year overall survival rates equivalent to those for primary resections (169). Data regarding prognosis for patients not undergoing resection are scarce (170) and lung metastases left unremoved have long been considered associated with very poor survival, <5% (171). A trial from 2010–2018 of 93 patients with resectable lung metastases randomized to surgical resection or no resection found median survival in the no surgery group to be surprisingly high (3.5 years vs. 3.8 years in the surgery group) (172). In the PulMiCC cohort trial, 5-year survival was 58.5% in the metastasectomy group and 24% in the no resection group, far better than what is presumed. Baseline factors favoured the metastasectomy group and were proposed to be the main reason for survival differences (173).

Indications for treatment of peritoneal metastases with cyto-reductive surgery and Hypertherm Intraperitoneal Chemotherapy (HIPEC) have also moved its boundaries since it was first introduced by Sugarbaker in the 1980s (174). Synchonous lung or liver metastases are no longer a contraindication (175-177). The need to reach consensus on various treatment details have been emphasized (178). The effect of HIPEC, as opposed to cyto-reductive surgery alone, was questioned in the Prodigie 7 trial, which showed no improvement in overall survival in the HIPEC group (179). Criticisms regarding choice of endpoint and overestimation of effect size, as well as the intraoperative chemotherapy regime and duration chosen (180), have been presented and a new phase IV randomized trial addressing these issues is ongoing (181).

Though the technical improvements increase treatment possibilities, pushing the boundaries of what can be done, there is sometimes little evidence on what perhaps should be done in term of patient benefits. Having a joint multidisciplinary team for patients with multiple metastatic sites, with participation
of specialized surgeons, is of great importance, and has been implemented at many Swedish university hospitals.

**Complications from surgery**

Factors such as age, sex, body mass index (BMI), preoperative (chemo)radiotherapy, patient comorbidities, medications such as steroids, smoking and malnutrition affect the risk of postoperative complications (182), and should be taken in account when deciding on treatment strategy.

Complications are often classified using the Clavien-Dindo grading system (183). Early complications include wound infection, intra-abdominal abscesses, anastomotic leakage, haemorrhage, wound rupture, urinary tract complications and stoma-related complications. Late complications include bowel obstructions, intra-abdominal abscesses, anastomotic complications (late insufficiency or stricture), stoma-related complications and hernias. After rectal cancer surgery, many patients struggle with low anterior resection syndrome, which can take the form of incontinence, urgency, frequent bowel movements and sexual and urinal dysfunction (184-186).

**Surgical site infection and perineal wound infection**

In the early 1900s, operative mortality after colorectal surgery, as reported by the more prominent surgeons, was 20%, due mainly to sepsis (187). Modern surgical techniques and improved perioperative care with the introduction of antimicrobial therapy, improved anaesthesia and blood replacements has significantly lowered the mortality rate. Care bundles, addressing preoperative, intraoperative and postoperative components, have been developed and implemented in order to decrease surgical site infection rates (188-190). However, infectious complications remain a cause of morbidity and mortality. Surgical site infection occurs in over 10% of all surgical operations (191), and colorectal surgery has one of the highest incidences of surgical site infections, with rates up to 30% (188, 192). Infection in the perineal wound after an APR is particularly challenging, probably due to impaired blood supply to the sacral cavity and the large size of the wound, which means that oral or parenteral antibiotics provide insufficient concentration at the site (193). Preoperative radiotherapy often makes the tissue fibrotic and poorly perfused, and increases the risk of infection from 10–15% to 20–30% (194-198). When preoperative radiotherapy is combined with chemotherapy, infection rates are as high as 50% (198).

As systemic antibiotics might not have adequate penetration at a local site, local treatment with a variety of agents has been studied, including using a gentamicin sponge, beads or local injection, chlorhexidine impregnated suture, antibiotic powder, lavage/irrigation or local injection, silver ionized dressing, vitamin E oil, ointments or hyperoxia to reduce surgical site infection (199-202).
**Gentamicin-collagen sponge**

Gentamicin-collagen sponges have been found effective in lowering surgical site infection in both thoracic and orthopaedic surgery (203, 204). They are fully absorbable and have both rapid and prolonged release of gentamicin, ensuring sufficient antibiotic concentration in the surgical site for an adequate time. Application of a gentamicin-collagen sponge in the wound has in some studies been reported to reduce the rates of wound infection, including perineal wound sepsis, after colorectal surgery (193, 199, 205, 206), whereas other studies have found no effect (202, 207, 208).

**Mechanical bowel preparation (MBP)**

MBP refers to cleansing the large bowel from its contents. MBP can be achieved with different methods; oral agents used in the MBP trial were polyethylene glycol (Laxabon®; Astra Zeneca, Oslo, Norway) and sodium phosphate (Phosphoral®; Ferring Pharmaceuticals, Limhamn, Sweden). After the Rosenberg trial in 1971, MBP was considered crucial to reduce surgical site infection, by decreasing the faecal mass and the bacteria load, to prevent anastomotic leakage due to passing of hard faeces, and to facilitate handling of the bowel during surgery (209). In recent decades, MBP has been questioned in several studies, and in 2018, the Rollin study, a large meta-analysis, showed no effect of MBP on the incidence of postoperative complications, and concluded it ought not to be used routinely in colorectal surgery (210).

The use of MBP is still debated, as well as whether, if given, it should be used in combination with oral antibiotic decontamination, usually given 18–24 hours before surgery. This addition has been shown to reduce the risk of surgical site infection (211, 212), but is not widely implemented, partly due to fear of disturbing the gastrointestinal microbiota, leading to enteritis (213). The World Health Organization guidelines recommend routine use of oral antibiotics combined with MBP in elective colorectal surgery (214), whereas the National Institute of Clinical Excellence recommends against routine use of MBP (215). The enhanced recovery after surgery guidelines do not recommend MBP in patients undergoing elective colon cancer resection, and in many countries where this concept is implemented, MBP is not routinely performed. However, MBP is still used in many parts of the world, such as the United States and Japan (216, 217). There are no studies on oral antibiotic decontamination alone and hence no comparison between the combinations – oral antibiotics, intravenous antibiotics and MBP versus only oral antibiotics, with no MBP – has been made.
Oncological treatment

Chemotherapy

The cornerstone of chemotherapy in CRC is 5-fluorouracil (5-FU), a pyrimidine antagonist, which was the only effective chemotherapy for CRC until the mid-1990s. In the 1990s, a meta-analysis reported a benefit on tumour response when adding leucovorin, a folic acid, to 5-FU (139). In 2000, studies showed prolonged recurrence-free survival in advanced CRC when combining 5-FU and leucovorin with either a platinum analogue, oxaliplatin, (FOLFOX) (140) or a topoisomerase inhibitor, irinotecan (FOLFIRI) (141). In the 2000s, treatments specific for genetic mutations of the tumour were developed, such as bevacizumab, targeting vascular endothelial growth factor (VEGF), and cetuximab and panitumumab, targeting the EGFR, both showing survival benefit (142-144). In recent years, a remarkable effect of immunotherapy with pembrolizumab and nivolumab (PD-1 inhibitors) and ipilimumab cytotoxic T-lymphocyte-associated antigen 4 (CTL-4 inhibitor) has been shown when used for MSI-H/dMMR tumours (42, 145-147). Anti-EGFR and VEGF antibody therapy and immunotherapy are so far only recommended in the metastatic or conversion setting. Double chemotherapy should be offered to patients with unresectable stage IV CRC, and triple chemotherapy may be offered. Chemotherapy with anti-EGFR-based treatment is recommended for MSS/pMMR left-sided RAS wild-type tumours and chemotherapy and VEGF antibody therapy is recommended for MSS/pMMR right-sided RAS wild-type tumours. Immunotherapy is recommended for MSI-H/dMMR, with pembrolizumab as first-line treatment (218).

Preoperative treatment

Preoperative oncological treatment aims to promote tumour regression, to gain higher rates of local control, as well as to eradicate microscopic disease (219-222).

In rectal cancer, (chemo)radiotherapy significantly decreases local recurrence rate (223-225), but is afflicted with short- and long-term adverse effects, such as delayed wound healing, diarrhoea, faecal incontinence and sexual dysfunction, which have to be taken into consideration when deciding on treatment strategy (226) (227). In Sweden, treatment recommendations for rectal cancer are based on the division of tumours into low-risk, intermediate-risk and high-risk (good-bad-ugly concept) (103, 228) (Table 2). Preoperative treatment in rectal cancer has been studied extensively. During the 1990s and early 2000s, several trials showed the benefits of preoperative treatment, primarily in regard to local recurrence (224, 229, 230). In 2017, the Sthlm III trial highlighted the benefits of delayed surgery after short-course radiotherapy (231). The RAPIDO trial compared standard chemoradiotherapy treatment (1.8 Grey (Gy) x 25 or 2 Gy x 25 with preoperative capecitabine and optional adjuvant chemotherapy) for locally advanced rectal cancer, to short-
course radiotherapy (5 Gy x 5) and full-dose chemotherapy (CAPOX (capecitabine + oxaliplatin) for 18 weeks, a total neoadjuvant therapy concept, with radiotherapy and all chemotherapy given preoperatively. The results were published in 2021 and showed superior results with the total neoadjuvant treatment regime, with 24% pathologic complete response and 20% distant recurrence rate after 3 years in the experimental group, compared with 12% complete response and 27% distant recurrence rate at 3 years in the standard care group (232, 233). Similar results have been seen in other randomized studies (234-236), and there is an ongoing follow-up study LARCT-US (237), further evaluating short-course radiotherapy + chemotherapy in locally advanced rectal cancer, comparing the RAPIDO experimental arm of 5 Gy x 5 and 18 weeks CAPOX with 5 Gy x 5 and 12 weeks CAPOX.

Table 2. Treatment strategies for rectal cancer according to national guidelines (103).

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Surgery alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate risk</td>
<td>Short-course radiotherapy (5 Gy for 5 days) followed by immediate (within 4 days) or delayed (after 4–8 weeks) surgery</td>
</tr>
<tr>
<td>High risk</td>
<td>Short-course radiotherapy (5x5 Gy) and chemotherapy (CAPOX x 4–6 or FOLFOX x 6–9)</td>
</tr>
</tbody>
</table>

Oncological treatment for colon cancer is still mainly given in an adjuvant setting. Based on results from the FOxTROT study, national guidelines state that neoadjuvant treatment can be considered in MSS/pMMR patients, with T4 or N2 tumours, especially in left-sided tumours (103, 238). Further studies have shown neoadjuvant treatment to be feasible and safe (239, 240).

Conversion treatment
In a primarily unresectable locally advanced or metastasized CRC, (chemo)radiotherapy can be given with the aim to downsize the extent of the disease, making surgery with curable intent possible in a later stage.

Adjuvant treatment
Adjuvant chemotherapy is given after radical surgery, normally with 5FU/capecitabine, with or without the addition of oxaliplatin, with the aim to eradicate any micro-metastatic disease left after surgery. It is recommended to colon cancer patients with at least 20–30% risk of recurrence, that is, stage III cancers and stage II cancers with risk factors (103). There is not the same evidence for adjuvant treatment in rectal cancer, but it can be considered in the same groups as colon cancer, especially if they have not received preoperative treatment (103).
**Palliative treatment**

Palliative treatment is given in case of non-curable CRC with the intent of improving quality of life, reducing symptoms and prolonging life. Treatment is often given with a lower intensity, and fewer side effects are accepted. Radiotherapy can also be used in palliative patients with rectal cancer, to reduce local symptoms of stricture, bleeding or pain (241).

**Other oncological treatments**

Very promising results with immunotherapy in MSI-H/dMMR stage IV CRC has been seen, with long-term anti-tumour response with PD-1 inhibitors in both the KEYNOTE-164 trial and the CheckMate-142 trial (41, 43). The Keynote 177 trial compared immunotherapy with conventional chemotherapy in stage IV MSI-H/dMMR colon cancer patients, and reported a 13% complete response in the pembrolizumab (immunotherapy) group, and 75% ongoing response after 36 months, vs. 4% complete response and 24% ongoing response in the chemotherapy group. No difference in overall survival was seen, probably due to a 60% crossover from the chemotherapy group to the pembroluzimab group (42). These results have led to further trials investigating the possibility to extend immunotherapy treatment to non-metastatic CRC. The NICHE trial studied the effect of preoperative immunotherapy in MSI-H/dMMR, non-metastatic colon cancer patients and found a remarkable major response in 95% of patients, with 67% complete response (242). Attempts are being made to find pMMR tumours that respond to immunotherapy (243).

In elderly or severely comorbid patients with rectal cancer, who are not fit for surgery, brachytherapy or contact therapy (Papillon) might be an option. In the last decade, organ-preserving strategies that achieve a complete clinical response after preoperative (chemo)radiotherapy, such as watch-and-wait in patients with rectal cancer, have gained increased attention, after being introduced by Habr-Gama (244). Complete response can be reached in up to 50% of early tumours and 10–20% of locally advanced tumours (245). A large meta-analysis, published in 2017, found no significant difference between patients managed with watch-and-wait and patients with clinical complete response treated with surgery, in terms of non-regrowth recurrence, cancer-specific mortality, disease-free survival or overall survival. Local regrowth rate was 15.7% (246). An analysis of all patients (n = 1,009) included in the International Watch & Wait Database between 2015–2017 showed a local regrowth rate of 25.3%, with regrowth usually occurring within the first two years and in the bowl wall. Local unsalvageable disease after watch-and-wait was rare. Five-year overall survival was 84.6% and 5-year disease specific survival was 93.8% (245). In Sweden, patients with a radiological and clinical complete response after neoadjuvant treatment, may be included in a watch-and-wait study protocol (247). Early tumours are recommended treatment in accordance with the guidelines, and are not recommended chemoradiotherapy.

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or short-course radiotherapy and chemotherapy with the aim to obtain a complete response and avoid surgery (103). However, there are several ongoing or still unpublished studies on early tumour and organ-preserving treatment, such as STAR-TREC (248).

Registers

SCCR

SCCR is a national register with prospectively registered data, run by the regional cancer centres in Sweden (249). Rectal cancer registration started in 1995 and colon cancer was included in 2007. The SCCR is one of the largest Swedish cancer registers, and contains over 800 variables, including patient characteristics such as sex, age, BMI and American Society of Anesthesiologists (ASA) score, tumour characteristics, treatment data, data on early and late complications, histopathological data and recurrence data. The SCCR has been validated and has a patient coverage of > 99%, a coverage in terms of correctly registered variables of > 90%, and high validity (112, 250). Information regarding death is available through linkage to the National Cause of Death register. Linkage to other national registers such as the Patient Register and the National Cancer Register, all run by the National Board of Health and Welfare, is possible using Swedish personal identification numbers.

The National Cause of Death Register

The National Cause of Death register goes back to 1749, and is one of the oldest death registers in the world. From 1831, mandatory reports were limited to deaths caused by smallpox or other plagues, childbirth, accidents, crime or suicide. To obtain an international standardization, the sixth revision of the International Classification of Cause of Diseases, Injuries and Causes of Death, was adopted in 1948. The current register contains data from 1961 onward and is updated on a yearly basis. The register includes all deaths that occur in Sweden (251).

The National Patient Register

The National Patient Register was implemented throughout Sweden in 1987 and at that time only contained data from in-patient care. In 2001, the register expanded to contain information from outpatient visits, with the exception of primary care. It provides information on diseases and treatment, as well as injuries, cases of poisoning, involuntary psychiatric care and timepoints for emergency visits, and aims to follow the development of public health,
improve treatment and prevention and indicate the quality of Swedish health care (252).

The National Cancer Register
The National Cancer Register has existed since 1958 and is the basis for official cancer statistics in Sweden. It is compulsory to report newly detected cancers to the register. The purpose is to identify the incidence/prevalence and changes over time of different types of cancer. It contains a variety of data, such as personal identification number, sex, age, place of residence, date of diagnosis, medical data and follow-up data (253).
Aims of the thesis

The overall aim of the thesis was to investigate aspects of preoperative staging and CRC treatment, and their impact on preoperative treatment and long-term oncological results.

Specific aims:

I. To assess the potential benefit of locally applied gentamicin-collagen to the perineal wound after an APR, as regards perineal wound complications, cancer recurrence and cancer-specific death.

II. To investigate the association between MBP before colon cancer resection and cancer recurrence, cancer-specific survival and overall survival.

III. To assess the impact of stricter MRI criteria for nodal staging in rectal cancer on the proportion of clinically positive nodes, the use of (chemo)radiotherapy and clinical nodal staging accuracy.

IV. To determine the prognostic value of TME grade on rectal cancer recurrence and survival in a population-based setting, and to identify risk factors for intramesorectal and muscularis propria resection.
Materials and methods

Patients and follow-up

Paper I

Patients from seven hospitals in Sweden, undergoing APR for benign or malignant disease between February 2000 and April 2003, were randomized to surgery with or without local application of a gentamicin-collagen sponge in the perineal wound.

The perineal wound was followed up at 7–10 days, 30 days, 90 days and 1 year after surgery, and graded in terms of infectious or non-infectious complications. Wound healing was categorized into one of six groups on each occasion, as follows: 1, healing without complication (healed at 30 days); 2, redness, swelling; 3, purulent discharge; 4, open clean wound; 5, open infected wound; 6, persistent sinus or fistula. Perineal wounds categorized as 2, 3 or 5 were recorded as infected.

Preoperative or postoperative radiotherapy or chemotherapy, hospital length of stay and any complications within 30 days of surgery were recorded. Any perineal reoperation during the follow-up period was also registered. Patients who underwent surgery due to rectal or anal cancer were followed for 5 years regarding cancer recurrence and cancer-specific death, through hospital medical records, the SCRCR and the National Cause of Death Registry.

Paper II

In the randomized multi-centre MBP trial by B. Jung et al. (254) between 1999 and 2005, 1,343 patients aged 18–85 years, with an ASA score of I–III, scheduled for elective colonic resection of benign or malignant disease at any of 20 Swedish hospitals and one German hospital, were randomized to MBP or no MBP.

In Paper II, Swedish colon cancer patients from this randomized MBP study (254) were followed up regarding cancer recurrence, cancer-specific survival and overall survival up to 2011 (6–12 years after surgery). Data were collected from the National Patient Register, the National Cause of Death Register and the National Cancer Register. Patients operated for other reasons than colon cancer, patients with stage IV cancer and patients who died within the first 30 days of surgery were excluded from analyses, as were those registered
with an incorrect patient identification number or whose data could not be retrieved from the registers. Register data were then validated against medical records. For medical record validation, diagnosis was based on the postoperative pathology report, instead of preoperative diagnosis, and inclusion and exclusion were adjusted accordingly. Patients for whom no medical record could be retrieved, patients who did not have radical surgery and patients who underwent surgery for local recurrence of a colon cancer were excluded from the analyses.

Paper III

Data for all patients in Sweden diagnosed with an adenocarcinoma of the rectum between January 2009 and December 2017, were retrieved from the SCRCR. Data included information regarding sex, age, tumour localization, modality of preoperative staging, clinical and pathological TNM stage, neoadjuvant treatment, type and date of surgery and health care region. Patients with stage I–III rectal cancer, undergoing either an APR, AR or Hartmann’s operation and staged through preoperative MRI were included in the analyses of clinically positive nodes and (chemo)radiotherapy. Exclusion criteria were stage IV disease, missing data regarding distant metastasis, no surgery or missing data regarding type of surgery and no date of surgery.

Changes over time in clinical node staging and use of preoperative treatment were analysed, both nationally and regionally. Patients who had surgery alone or short-course radiotherapy with immediate surgery – defined as a maximum of 15 days from the radiotherapy start to surgery – were included in the accuracy analyses, as radiotherapy has not been shown to cause nodal downstaging in this time interval (255). Nodal staging and preoperative treatment rates were compared using the two years before and after implementation of new MRI guidelines regarding nodal staging.

Paper IV

Data from patients diagnosed with rectal cancer between January 2015 and December 2019, who had undergone a surgical procedure, were extracted from the SCRCR. Data comprised information on sex, age, BMI, ASA score, tumour level, clinical and pathological stage, perioperative and histopathological data and local and distant recurrence.

To ensure that all included patients had undergone TME, only standard radical procedures for rectal cancer – AR, APR, or Hartmann’s resection – with a tumour level ≤ 10 cm from the anal verge, were included. Patients with clinical stage IV disease, non-radical resection or missing data regarding type of surgical procedure, tumour level, clinical stage or TME grade, were excluded. Patients were divided into three groups based on TME grade (mesorectal, intramesorectal and muscularis propria), and included in risk factor analyses for
intramesorectal or muscularis propria resection. Patients who died within 30 days of surgery or had cancer recurrence within 90 days of surgery, were excluded from recurrence and survival analyses. Recurrence-free patients with less than three years’ follow-up, and patients lacking data regarding recurrence, were also excluded from recurrence analyses. Date of death was obtained from the National Cause of Death Register at the end of data collection (29 May 2021).

Methodological considerations

Paper I

Randomization
Patients were randomized one by one from numbered, sealed envelopes in blocks of four. The envelopes were prepared by a research secretary and the size of the blocks was unknown to both patients and surgeons. The patients were stratified in each participating centre, with a separate set of envelopes for each centre. After being enrolled by their treatment surgeon and being given verbal and written information about the study, patients gave informed consent. Patients and surgeons performing the surgery and/or follow-up were not blinded to the randomization result.

The gentamicin-collagen sponge
The gentamicin-collagen sponge (Collatamp®G, Schering-Plough AB, Stockholm, Sweden) consists of a matrix of purified bovine collagen type I (2.8 mg/cm²) impregnated with 2.0 mg/cm² of gentamicin sulphate. The drug is released by a combination of diffusion and enzymatic breakdown of the collagen matrix, resulting in a high local concentration for at least 48 hours [18]. Thus, resistance to antibiotics caused by a low drug dosage is avoided, while antibiotic blood concentrations remain low and reduce the risk of adverse effects (e.g., nephrotoxicity and ototoxicity) [18,19]. According to the manufacturer, the collagen matrix is fully absorbed within 1–7 weeks depending on its location (vascularized tissues or bone cavities).

Application of the gentamicin-collagen sponge
All patients had MBP and preoperative antibiotic prophylaxis in accordance with the local routines at each centre. Perirectal dissection was performed based on diagnosis, with extra-sphincteric or inter-sphincteric dissection, depending on diagnosis and the surgeon’s judgment. In patients randomized to a gentamicin sponge, a 10 x 10 cm sponge was placed immediately distal to the levator ani muscle (if present), or in the space corresponding to the excised anal canal if an inter-sphincteric excision had been performed. The remaining
levator muscle, perineal fat and skin were sutured in layers. If a perineal drain was used, this was not placed in contact with the gentamicin-collagen sponge and was separated from the sponge by sutures. Perioperative faecal contamination, primary suture of the perineum and any use of a perineal drain were recorded.

Paper II

MBP
MBP was performed in each unit in accordance with local standards and consisted of oral agents, polyethylene glycol (Laxabon®; AstraZeneca, Oslo, Norway; 47.2% of patients) and sodium phosphate (Phosphoral®; Ferring Pharmaceuticals, Limhamn, Sweden; 48.5% of patients). The remaining patients in the MBP group received an enema. Patients not receiving MBP had no dietary restrictions.

Paper III

MRI guidelines for nodal staging
In a revision of the Swedish national guidelines for colorectal cancer in 2016, stricter MRI criteria for clinical node staging was created. The three criteria – diameter over 5 mm, irregular shape and heterogenous signal – were based on the available literature, and at least two had to be met for a lymph node to be considered positive.

Paper IV

TME grading
The three-tier TME grading constructed by Quirke et al. (121), used by pathologists when examining the rectal specimen, and registered in the SCRCR, is shown in Table 3.
Table 3. Definition of TME grades.

<table>
<thead>
<tr>
<th>Mesorectal plane</th>
<th>Intact mesorectum with only minor irregularities of a smooth mesorectal surface. No defect deeper than 5 mm. No coning toward the distal margin of the specimen. Smooth circumferential resection margin on slicing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-mesorectal Plane</td>
<td>Moderate bulk to the mesorectum, but irregularity of the mesorectal surface. Moderate coning of the specimen is allowed. At no site is the muscularis propria visible, with the exception of the insertion of the levator muscles.</td>
</tr>
<tr>
<td>Muscularis propria</td>
<td>Little bulk to the mesorectum with defects down onto the muscularis propria and/or a very irregular circumferential resection margin.</td>
</tr>
</tbody>
</table>

Statistical analysis

General statistics

Continuous variables were presented as median with range or interquartile range (IQR). The chi-squared test or Fisher’s exact test was used to compare proportions and the Wilcoxon rank sum test was used to compare continuous data from two groups.

Survival rates and cumulative incidence were visually illustrated using Kaplan-Meier curves, and compared using the log-rank test. Follow-up time was measured from date of surgery to date of recurrence, death, censoring or data extraction. Cancer-specific survival was measured from the date of surgery to death in CRC. Overall survival was calculated as time from surgery to death from any cause. Relative survival was defined as the ratio of the observed survival to the expected survival in a general population, matched regarding age, sex and year of surgery. The Ederer II method was used for calculations. Mortality data were retrieved from the Human Mortality Database (256).

Univariable and multivariable Cox proportional hazard regression models were used to identify predictors of cancer-specific survival (Paper II) and for relating the TME grades to local recurrence, distant recurrence, overall survival and relative survival (Paper IV), presented as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). A directed acyclic graph was made to choose relevant variables and potential confounders for the Cox proportional hazard regression models in Paper IV.
Logistic multiple regression models were used to test for risk factors for intramesorectal or muscularis propria TME grade (Paper IV) and presented as odds ratios (ORs) with 95% CIs. A p-value of < 0.05 was considered statistically significant in all statistical tests.

Statistical analyses were performed with STATISTICA (data analysis software system) (Stat Soft Inc. 2011, Tulsa, OK, USA) version 10 (Paper I), R (http://www.R-project.org) (Paper II), IBM SPSS® Statistics for Macintosh, version 28 (Paper III) and IBM SPSS® Statistics for Windows, version 28 and Stata 16.1 (StataCorp, College Station, TX, USA) (Paper IV).

Sample size calculation
A power analysis was performed in Paper I with the test of equality of two proportions to detect a reduction in perineal infection by 50% from a 40% perineal complication rate. A significance level of 95% and a power of 80% was used for all analyses.

Ethical considerations

Paper I
The study was approved by the Regional Ethics Committees in Uppsala (dnr 99 195), Örebro (dnr 369 / 00) and Umeå (dnr 03-028) and was conducted before registration in an online registration system, e.g., ClinicalTrials.gov, was compulsory.

Papers II–III
Both studies were approved by the Regional Ethics Committee in Uppsala (dnr 2009/220, dnr 2018/126).

Paper IV
The study was approved by the Swedish Ethical Review Authority (2020-00981) and complies with the guidelines of the Declaration of Helsinki.
Results

Paper I

In all, 102 patients were randomized (52 to a gentamicin sponge and 50 to no gentamicin sponge). The median (range) number of days was 8 (4–18) for the first assessment, and 34 (14–73), 97 (48–276) and 375 (197–701) for the 30- and 90-day and 1-year assessments, respectively.

There were no differences in infectious or non-infectious perineal wound complications between the group that received a gentamicin sponge and the group that did not. There were no differences in other infectious complications or other non-infectious complications between the two groups (Table 4).

Table 4. Postoperative complications.

<table>
<thead>
<tr>
<th></th>
<th>gentamicin n = 52</th>
<th>no gentamicin n = 50</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perineal wound infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week</td>
<td>6 (52)</td>
<td>6 (49)</td>
<td>1.000</td>
</tr>
<tr>
<td>30 days</td>
<td>10 (52)</td>
<td>14 (49)</td>
<td>0.351</td>
</tr>
<tr>
<td>90 days</td>
<td>3 (51)</td>
<td>1 (48)</td>
<td>0.618</td>
</tr>
<tr>
<td>1 year</td>
<td>0 (48)</td>
<td>0 (43)</td>
<td></td>
</tr>
<tr>
<td>Perineal non-infectious complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week</td>
<td>2 (52)</td>
<td>3 (49)</td>
<td>0.672</td>
</tr>
<tr>
<td>30 days</td>
<td>14 (52)</td>
<td>12 (49)</td>
<td>0.823</td>
</tr>
<tr>
<td>90 days</td>
<td>12 (51)</td>
<td>17 (48)</td>
<td>0.269</td>
</tr>
<tr>
<td>1 year</td>
<td>5 (48)</td>
<td>5 (43)</td>
<td>1.000</td>
</tr>
<tr>
<td>Other infectious complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week</td>
<td>5 (52)</td>
<td>4 (49)</td>
<td>1.000</td>
</tr>
<tr>
<td>30 days</td>
<td>8 (52)</td>
<td>7 (49)</td>
<td>1.000</td>
</tr>
<tr>
<td>Other non-infectious complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 week</td>
<td>4 (52)</td>
<td>7 (50)</td>
<td>0.353</td>
</tr>
<tr>
<td>30 days</td>
<td>8 (52)</td>
<td>12 (50)</td>
<td>0.324</td>
</tr>
</tbody>
</table>

Numbers in parentheses are patients at risk. Surgery with a gentamicin-collagen sponge vs. surgery without a gentamicin-collagen sponge. Other infectious complications were urinary, abdominal abscess, abdominal wound infection, pneumonia and cholecystitis. Other non-infectious complications were ileus, hypotonia, arrhythmia, bleeding and death.
After exclusion, 28 patients in the group without gentamicin and 26 patients with gentamicin were operated for a rectal cancer and were available for recurrence and survival analysis. The tumour stages are presented in Table 5. There was no difference in the incidence of local recurrence (2/26 in gentamicin and 4/28 in no gentamicin, \( p = 0.670 \)) or distant metastases (9/26 patients in the gentamicin group and 14/28 in the no gentamicin group, \( p = 0.284 \)). Cancer-specific death at 5 years was 8/26 in the gentamicin group and 11/28 in the no gentamicin group (\( p = 0.577 \), Table 6).

Table 5. Staging of rectal cancer.

<table>
<thead>
<tr>
<th></th>
<th>gentamicin</th>
<th>no gentamicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>8 (31)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Stage II</td>
<td>6 (23)</td>
<td>10 (36)</td>
</tr>
<tr>
<td>Stage III</td>
<td>8 (31)</td>
<td>10 (36)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>2 (8)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are n (%). Stage according to TNM. Surgery with a gentamicin-collagen sponge vs. surgery without a gentamicin-collagen sponge.

Table 6. Cancer-specific outcome at 5-year follow-up.

<table>
<thead>
<tr>
<th></th>
<th>gentamicin</th>
<th>no gentamicin</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer recurrence</td>
<td>9 (35)</td>
<td>14 (50)</td>
<td>0.284</td>
</tr>
<tr>
<td>Local recurrence</td>
<td>2 (8)</td>
<td>4 (14)</td>
<td>0.670</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>9 (35)</td>
<td>14 (50)</td>
<td>0.284</td>
</tr>
<tr>
<td>Cancer-specific death</td>
<td>8 (31)</td>
<td>11 (39)</td>
<td>0.577</td>
</tr>
</tbody>
</table>

Values are n (%). Surgery with a gentamicin-collagen sponge vs. surgery without a gentamicin-collagen sponge.

**Paper II**

In all, 947/1,343 (499 MBP and 448 no MBP) patients fulfilled inclusion criteria. Register analyses showed fewer cancer recurrences, improved cancer-specific survival and overall survival in the MBP group compared with the no MBP group.

After validation by means of medical records, a total of 238 patients in the MBP group and 266 in the no MBP group were excluded or lost to follow-up, leaving 839 of the original 1,343 patients for analysis (448 MBP and 391 no MBP, Figure 5).
A total of 80/448 patients (18%) in the MBP group and 88/391 (23%) in the no MBP group developed cancer recurrence ($p = 0.093$, Figure 6). Cancer-specific survival was higher in the MBP group (84% in MBP group versus 78% in the no MBP group, $p = 0.019$, Figure 7). There was no difference in overall survival (59% and 56% respectively, $p = 0.186$, Figure 8).
Figure 6. Validation analysis: comparison of recurrence after resection for colonic cancer in patients randomized to mechanical bowel preparation (MBP) or no MBP, \( p = 0.093 \).

Figure 7. Validation analysis: comparison of cancer-specific survival after resection for colon cancer in patients randomized to mechanical bowel preparation (MBP) or no MBP \( p = 0.019 \).
Figure 8. Validation analysis: comparison of overall survival after resection for colonic cancer in patients randomized to mechanical bowel preparation (MBP) or no MBP $p = 0.186$.

In the multivariable analysis, tumour stage III, randomization to MBP or no MBP, and age had significant impact on cancer-specific survival (Table 7).
Table 7. Results of Cox proportional hazard analysis of cancer-specific survival.

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>Univariable analysis†</th>
<th>Multivariable analysis‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>p</td>
</tr>
<tr>
<td>No MBP</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>MBP</td>
<td>0.68 (0.49, 0.94)</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>0.66 (0.47, 0.92)</td>
<td>0.016</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Female</td>
<td>0.91 (0.65, 1.25)</td>
<td>0.550</td>
</tr>
<tr>
<td></td>
<td>0.92 (0.65, 1.30)</td>
<td>0.639</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (1.00, 1.04)</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>1.03 (1.01, 1.05)</td>
<td>0.006</td>
</tr>
<tr>
<td>Type of resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileoecal resection</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Right hemicolecotomy</td>
<td>1.66 (0.53, 5.27)</td>
<td>0.386</td>
</tr>
<tr>
<td>Transverse resection</td>
<td>1.78 (0.40, 7.96)</td>
<td>0.449</td>
</tr>
<tr>
<td>Left hemicolecotomy</td>
<td>1.36 (0.39, 4.76)</td>
<td>0.635</td>
</tr>
<tr>
<td>Sigmoid resection</td>
<td>1.73 (0.53, 5.64)</td>
<td>0.360</td>
</tr>
<tr>
<td>Other</td>
<td>2.43 (0.61, 9.73)</td>
<td>0.209</td>
</tr>
<tr>
<td></td>
<td>2.93 (0.53, 16.20)</td>
<td>0.218</td>
</tr>
<tr>
<td>Anastomosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handsewn</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Stapled</td>
<td>1.16 (0.83, 1.62)</td>
<td>0.391</td>
</tr>
<tr>
<td></td>
<td>1.23 (0.86, 1.76)</td>
<td>0.249</td>
</tr>
<tr>
<td>TNM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>II</td>
<td>2.62 (1.03, 6.63)</td>
<td>0.043</td>
</tr>
<tr>
<td>III</td>
<td>10.73 (4.37, 26.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>11.14 (4.49, 27.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Amount of bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.00 (1.00, 1.00)</td>
<td>0.674</td>
</tr>
<tr>
<td></td>
<td>1.00 (1.00, 1.00)</td>
<td>0.717</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>1.00 (1.00, 1.00)</td>
<td>0.992</td>
</tr>
<tr>
<td></td>
<td>1.00 (1.00, 1.00)</td>
<td>0.425</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>1.02 (1.00, 1.04)</td>
<td>0.058</td>
</tr>
<tr>
<td></td>
<td>1.02 (1.00, 1.04)</td>
<td>0.113</td>
</tr>
<tr>
<td>Complication - cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>0.66 (0.24, 1.78)</td>
<td>0.410</td>
</tr>
<tr>
<td></td>
<td>0.52 (0.19, 1.46)</td>
<td>0.213</td>
</tr>
<tr>
<td>Complication - infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>1.14 (0.62, 2.11)</td>
<td>0.678</td>
</tr>
<tr>
<td></td>
<td>1.08 (0.57, 2.05)</td>
<td>0.815</td>
</tr>
<tr>
<td>Complication - local</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>1.01 (0.63, 1.62)</td>
<td>0.966</td>
</tr>
<tr>
<td></td>
<td>1.09 (0.63, 1.90)</td>
<td>0.750</td>
</tr>
<tr>
<td>Reoperation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Yes</td>
<td>1.05 (0.46, 2.38)</td>
<td>0.907</td>
</tr>
<tr>
<td></td>
<td>0.92 (0.35, 2.43)</td>
<td>0.870</td>
</tr>
</tbody>
</table>

Values in parentheses are 95 percent CI. *Included 807 (96.2%) of 839 patients. †Included only patients with information on the variable of interest in each separate model. ‡Included only patients with information on all the variables in the model.

MBP, mechanical bowel preparation; TNM, tumour, node, metastasis.
Paper III

In all, 10,352 patients were included for analyses of clinical node positivity and preoperative treatment. Clinical node accuracy was analysed in 6,616 patients with no downstaging treatment.

A continuous increase in the proportion of clinically positive nodes was seen from 36% in 2009 to 62% in 2015, followed by a decrease after the introduction of the new guidelines in 2016, to 56% in 2017 (Figure 9, \( p = 0.008 \) comparing 2014–2015 and 2016–2017).

![Figure 9](image-url)

Figure 9. Clinically staged positive nodes in percent over the years, in stage I–III patients undergoing an anterior resection, abdominoperineal resection, or Hartmann’s procedure, with a preoperative magnetic resonance imaging. All patients (\( n = 10,352 \)) and patients with no downstaging therapy (\( n = 6,616 \)) are shown separately.

The use of (chemo)radiotherapy decreased from 71% in 2009 to 63% in 2017 (Figure 10). No difference was seen when comparing 2014–2015 and 2016–2017 (\( p = 0.285 \)).
Clinical node accuracy was 68% in 2009, then decreased to a median of 62% (61-66). No difference was seen when comparing 2014–2015 with 2016–2017 ($p = 0.46$).

The proportion of false positive nodes was 10% in 2009 and increased to 25% in 2015, then decreased to 19% in 2017. No difference was seen when comparing 2014–2015 and 2016–2017 ($p = 0.15$). Correlations between clinical and pathological node stage are shown in Figure 11. A comparison in specificity, sensitivity, negative predictive value (NPV) and positive predictive value (PPV) between the years 2014–2015 and 2016–2017 showed an increase in specificity from 60% to 66%, and a decrease in sensitivity from 68% to 54%. The NPV decreased from 74% to 72% and the PPV decreased from 52% to 47%.
Figure 11. Correlation between clinical and pathological locoregional lymph node staging in percent, 2009–2017 in 6,186 patients, stages I–III, undergoing an anterior resection, abdominoperineal resection or Hartmann’s surgery, with a preoperative magnetic resonance imaging, without downstaging therapy. cNx and pNx excluded. cN+pN- = false positive, cN-pN+ = false negative, cN+pN+ = true positive, cN-pN- = true negative, cN=pN = accurate

Paper IV

In all, 2,476 patients were included in risk factor analyses, of whom 1,856 (75%) were graded as mesorectal, 426 (17%) as intramesorectal and 194 (8%) as muscularis propria. After exclusions, 2,441 patients were included in survival analysis and 1,499 patients were included in recurrence analysis (Figure 12). Median follow-up for survival was 44 (range 1–77) months in the mesorectal group, 39 (range 1–77) months in the intramesorectal group, and 36 (range 4–75) months in the muscularis propria group.
Patients in SCRCR diagnosed 2015-2019, with rectal cancer and surgical intervention n = 7,979

Surgery other than AR, APR or Hartmann’s n = 450
Type of surgery missing n = 588
Emergency resection n = 30
Stage IV or stage missing n = 594 and n = 25 respectively
Tumor level ≥ 11cm or level missing n = 1,775 and n = 50 respectively
R1 resection n = 158
Uncertain R resection or data missing n = 31 and n = 318 respectively
TME grade uncertain or missing n = 118 and n = 1,366 respectively

Included risk factor analysis n = 2,476
Mesorectal n = 1,856
Intramesorectal n = 426
Muscularis propria n = 194

Dead ≤ 30 days postop n = 24
Recurrence ≤ 90 days postoperative n = 11

Eligible survival analyses n = 2,441

Less than 3 years since surgery and recurrence free/data missing n = 878
More than 3 years since surgery, recurrence data missing n = 64

Eligible recurrence analysis n = 1,499

Mesorectal n = 1,162
Intramesorectal n = 236
Muscularis propria n = 101

Figure 12. Study flowchart. SCRCR, Swedish colorectal cancer registry, AR, anterior resection; APR, abdominoperineal resection; R1, non-radical resection; TME, total mesorectal excision.

Local recurrence occurred in 27/1,160 (2.3%), 8/236 (3.4%) and 7/101 (6.9%) in the mesorectal, intramesorectal and muscularis propria group, respectively. In the adjusted Cox regression analyses, muscularis propria resection was independently associated with higher local recurrence rate (HR 2.73 (95% CI 1.07–7.0, p = 0.036, Table 10)). Distant recurrence occurred in 226/1,160 (19.5%) and 46/236 (19.5%) of the patients in the mesorectal and intramesorectal group, respectively, and 27/101 (26.7%) in the muscularis propria group. There was no difference in distant recurrence rate between the three TME grades (Table 8). There was no difference in overall survival or relative survival between the three TME groups (Table 8).
Table 8. Unadjusted and adjusted Cox regression relating TME grading in accordance with Quirke to local recurrence, distant recurrence, overall survival and relative survival.

<table>
<thead>
<tr>
<th>TME grade</th>
<th>Local recurrence</th>
<th>Distant recurrence</th>
<th>Overall survival</th>
<th>Relative survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
<td>HR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Mesorectal</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Intramesorectal</td>
<td>1.67 (0.74–3.78)</td>
<td>0.215</td>
<td>0.79 (0.54–1.15)</td>
<td>0.217</td>
</tr>
<tr>
<td>Muscle propria</td>
<td>2.82 (1.14–6.99)</td>
<td>0.025</td>
<td>0.96 (0.58–1.58)</td>
<td>0.874</td>
</tr>
<tr>
<td>Unadjusted, n = 2,441</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesorectal</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Intramesorectal</td>
<td>1.67 (0.73–3.80)</td>
<td>0.223</td>
<td>0.75 (0.51–1.09)</td>
<td>0.130</td>
</tr>
<tr>
<td>Muscle propria</td>
<td>2.73 (1.07–7.00)</td>
<td>0.036</td>
<td>0.85 (0.51–1.41)</td>
<td>0.529</td>
</tr>
<tr>
<td>Adjusted*, n = 2,421</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesorectal</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Intramesorectal</td>
<td>1.67 (0.69–3.93)</td>
<td>0.071</td>
<td>0.87 (0.56–1.36)</td>
<td>0.395</td>
</tr>
<tr>
<td>Muscle propria</td>
<td>2.34 (0.87–6.32)</td>
<td>0.004</td>
<td>0.97 (0.65–1.46)</td>
<td>0.894</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, body mass index, clinical tumour stage, surgical approach, tumour level and preoperative treatment. TME, total mesorectal excision; HR, hazard ratio; CI, confidence interval.
In multivariable analyses, APR and minimally invasive surgery were risk factors for both intramesorectal and muscularis propria resection. Female sex, tumour level < 5 cm, blood loss > 800 ml, and intraoperative perforation were risk factors for muscularis propria resection, but not for intramesorectal resection. Duration of surgery > 9 hours was a risk factor for intramesorectal resection, but not for muscularis propria resection (Table 9).

Table 9. Risk factors for intramesorectal or muscularis propria grade.

<table>
<thead>
<tr>
<th></th>
<th>Intramesorectal</th>
<th></th>
<th>Muscularis propria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 75</td>
<td>1.00 (Ref.)</td>
<td>0.539</td>
<td>1.00 (Ref.)</td>
<td>0.568</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>1.09 (0.83–1.42)</td>
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<td>1.11 (0.77–1.61)</td>
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<tr>
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<td>&lt; 18.5</td>
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<td>0.402</td>
<td>1.07 (0.36–3.17)</td>
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<td>≥ 30.0</td>
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<td>0.488</td>
<td>2.02 (1.32–3.09)</td>
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<td>1.00 (Ref.)</td>
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<tr>
<td>1 and 2</td>
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<td>1.00 (Ref.)</td>
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<td>3</td>
<td>0.83 (0.64–1.09)</td>
<td>0.189</td>
<td>0.89 (0.61–1.32)</td>
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<td>4</td>
<td>0.86 (0.58–1.28)</td>
<td>0.456</td>
<td>0.78 (0.45–1.38)</td>
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<tr>
<td>x</td>
<td>0.40 (0.12–1.37)</td>
<td>0.146</td>
<td>1.78 (0.71–4.48)</td>
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<td></td>
<td>1.00 (Ref.)</td>
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<td>Radiotherapy</td>
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<td>0.84 (0.56–1.28)</td>
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<td>Chemotherapy + radiotherapy</td>
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<td>0.690</td>
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<td><strong>Type of surgery</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Anterior resection</td>
<td>1.00 (Ref.)</td>
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<td>1.00 (Ref.)</td>
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</tr>
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<td>Abdominoperineal resection</td>
<td>1.66 (1.21–2.26)</td>
<td>0.002</td>
<td>2.37 (1.42–3.96)</td>
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<td>Hartmann's procedure</td>
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<td>0.365</td>
<td>1.47 (0.75–2.85)</td>
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<tr>
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<td>5–9</td>
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<td>1.18 (0.80–1.73)</td>
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<td>&gt; 9</td>
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<td>0.024</td>
<td>1.37 (0.70–2.68)</td>
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<td><strong>Perioperative blood loss, ml</strong></td>
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<td>&lt; 200</td>
<td>1.00 (Ref.)</td>
<td></td>
<td>1.00 (Ref.)</td>
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</tr>
<tr>
<td>200–800</td>
<td>1.33 (1.04–1.71)</td>
<td>0.025</td>
<td>1.24 (0.86–1.81)</td>
<td>0.249</td>
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<tr>
<td>&gt; 800</td>
<td>1.42 (0.96–2.11)</td>
<td>0.081</td>
<td>1.98 (1.17–3.33)</td>
<td>0.010</td>
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<tr>
<td><strong>Intraoperative perforation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>1.00 (Ref.)</td>
<td></td>
<td>1.00 (Ref.)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.22 (0.72–2.05)</td>
<td>0.457</td>
<td>3.92 (2.37–6.48)</td>
<td>&lt;0.001</td>
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</table>

BMI, body mass index; OR, odds ratio; CI, confidence interval.

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Discussion

The treatment possibilities and outcome for CRC have improved substantially in recent decades, and continue doing so. This is illustrated in this thesis, where 5-year local recurrence rate was 11% in Paper I, which is in line with what is reported in the SCRCR during the same years (10% in 2000–2003, APR, T1–3, T4 (6)), as opposed to the current 4% local recurrence rate for rectal cancer undergoing Hartmann’s, AR or APR. A continuous evaluation of the treatment given is a vital part of this improvement.

Papers I, II and IV highlight different aspects of surgical treatment and their impact on long-term results (recurrence and survival), whereas Paper III focuses on rectal cancer nodal staging challenges and their impact on preoperative treatment. In Papers I and II, the aim was to assess recurrence rate after an evaluated treatment, hypothesized to decrease postoperative infection.

Paper I assessed the effect on perineal wound complications, cancer recurrence and cancer-specific death of a gentamicin-collagen sponge locally applied to the perineal wound after an APR, in a prospective randomized multicentre setting. It was hypothesized that gentamicin-collagen would lead to less postoperative perineal infection, and that a decrease in infection rates would have a positive prognostic impact on oncologic outcome, but no effect on perineal wound complications, other complications, cancer recurrence or survival was seen.

Perineal wound sepsis is a common problem after APR, with a reported incidence of 10–15% in previously non-irradiated patients (257, 258), 20–30% in patients with preoperative radiation (219, 230, 258, 259) and up to 50% among patients subjected to preoperative radiation combined with chemotherapy (260). Other risk factors observed for impaired perineal healing are hypoalbuminemia and smoking (261), BMI > 30 kg/m² (262) and lithotomy position (263). A gentamicin-collagen sponge was used as it is considered safe and can be applied in exactly the desired position (198). Furthermore, gentamicin has proven efficacy against the organisms causing most infections in bone and soft tissue (193). The collagen matrix is biocompatible and can be remodelled, has haemostatic activity and provides rapid and prolonged gentamicin release (193, 197).

The trial aimed to detect a reduction in perineal infection by 50%, from a 40% complication rate, but the overall perineal infection rate and the difference between the two groups was lower than anticipated, indicating a type II
error. Also, the number of patients estimated to be required was 182, but due to slow recruitment, the trial was terminated after three years and 102 patients. Still, other studies of similar or smaller size (193, 206) have identified a lower rate of postoperative perineal wound complication or infection rates with gentamicin-collagen application. A meta-analysis of 15 randomised control trials concluded that gentamicin-collagen implants decrease the rate of surgical site infections (204). However, a variety of surgical wound sites were included, and the conditions for perineal wound healing are in many aspects different from those for other surgical wounds. Perineal healing may be compromised by impaired blood supply to the sacral cavity and the large size of the wound, which has rigid boundaries, owing to the bony margins of the lateral pelvic wall and the sacrum. Fluid may accumulate in the sacral cavity and become secondarily infected. Radiotherapy is frequently used in rectal cancer, which increases perineal wound complications (258). A review of 8 studies (including ours) in 2015, focusing on gentamicin-collagen in perineal wounds and perineal wound healing, found no evidence to support application of gentamicin after an APR (202).

There was no difference in cancer recurrence after adding a gentamicin-collagen sponge. Data from several studies indicate that patients with perineal wound sepsis have an increased risk of local recurrence (194, 195, 264). Although this might be a result of local infection per se, it could also be due to suboptimal surgery with some tumour cells being left. In a randomized trial by Nowacki et al. (196), patients in the group receiving a gentamicin-sponge in the pelvic cavity after rectal cancer surgery had lower rates of postoperative complications and distant metastasis, and improved overall survival. Rutkowski et al. also found that a gentamicin-collagen implant in the pelvic cavity reduced the distant metastasis rate in one randomized and one confirmative study (265, 266). In the present study, no difference in local recurrence rate or overall cancer recurrence was shown. However, the trial was clearly underpowered for detecting any effect on recurrence or survival. Other weaknesses of the study were the heterogeneity in diagnosis among the study patients, with different risks of perineal complication, and the wide range of timing in follow-up.

In Paper II, the long-term effects of MBP on cancer recurrence and survival after colon cancer resection were evaluated. Register analysis showed surprising results, with lower cancer recurrence rates and improved cancer-specific and overall survival in patients receiving MBP. However, there were several sources of error in the register analysis, and after validation through patient charts, no difference in recurrence or overall survival could be detected. Still, cancer-specific survival was improved in the MBP group, indicating that patients with colon cancer might benefit from MBP in the longer perspective. Though stage III cancer was more common in the MBP group, both tumour stage and MBP independently affected survival in a multivariable analysis.
Adjuvant therapy was not recorded, and possible differences between the two groups in this regard could not be analysed.

The hypothesis preceding this study was that there would be no effect of MBP on recurrence or survival, since the MBP trial had shown no effect on infectious or other complications (254). However, there are various theories to explain the effect: MBP might cleanse the colon of any circulating cancer cells and thereby reduce the risk of spread. A reduced risk of local recurrence in patients who had a rectal washout during rectal cancer surgery has been reported (267-270), and MBP might have a similar effect in patients with colon cancer. On the same note, some studies have found more exfoliated colon cancer cells in the staple line in patients without MBP or other types of irrigation (271-273). It could also be that MBP eradicates bacteria promoting carcinogenesis. A recent study showed combined mechanical and oral antibiotic bowel preparation to be independently associated with improved recurrence-free survival in patients undergoing surgery for colorectal cancer (274). The study was based on the finding that a combined MBP and oral antibiotic reduced the colonization of collagenase-producing bacteria found to drive cancer recurrence in mice (275).

The effect on recurrence and survival has not been widely studied, neither before nor after the current study. As this study is a secondary analysis of the Swedish MBP trial (254), firm conclusions cannot be drawn, owing mainly to lack of power. To evaluate the effect on cancer recurrence and survival, and determine whether MBP should be used in colorectal surgery for cancer, a prospective randomized trial with a correct sample size calculation is necessary.

In Paper III, the impacts of new stricter criteria for MRI nodal staging on the proportion of clinically positive nodes, the use of (chemo)radiotherapy and clinical node staging accuracy were investigated. An increasing rate of clinically positive nodes and clinically over-staged nodes had been observed, prior to the development of the new guidelines. This study confirmed a continuous increase in the proportion of clinically positive nodes from the beginning of the study period (2009) up to the year prior to the release of the new guidelines. This increase was seen in all regions, without any change in the official recommendations, perhaps due to the technical developments of MRI, with increased spatial resolution. In addition, during the same time period, the number of clinically non-assessed/missing nodes decreased to very low levels, which could partly explain the increase in clinically positive nodes.

After the release of the new guidelines, the proportion of clinically positive nodes started to decrease. However, staging accuracy did not improve. The proportion of accurately staged nodes was actually at its highest in 2009. However, the proportion of clinically non-assessed/missing nodes was also at its highest in 2009, and when these were excluded from calculations, accuracy decreased by almost 10%, implying that the ambition to always determine a
clinical node as positive or negative has had a negative effect on staging accuracy.

The challenges of node staging are well-known. In the Netherlands, a study aimed at evaluating the use of neoadjuvant radiotherapy and the diagnostic accuracy of preoperative MRI for nodal staging after new guidelines showed increased specificity in clinical node staging, and a reduction in neoadjuvant radiotherapy, the year after guideline implementation, suggesting an improvement toward more correct nodal staging with stricter nodal staging criteria (276). In the study described in Paper III, (chemo)radiotherapy decreased continuously, seemingly unaffected by the new MRI guidelines. This probably reflects a general desire to decrease preoperative treatment, underlined in the national guidelines.

In Paper IV, the prognostic value of TME grade on rectal cancer recurrence and survival was analysed, and risk factors for intramesorectal and muscularis propria resection were identified. TME surgery was revolutionizing when introduced, decreasing the rate of the dreaded local recurrences from 25–40% to 5–10% (118, 277, 278). When a rectal specimen is examined by a pathologist, the surgical quality of the mesorectal excision is registered as mesorectal, intramesorectal or muscularis propria. Here, a higher local recurrence rate in the worst grade, that is, muscularis propria, was detected. Several earlier studies have shown an association between TME grade and local recurrence (121, 279-283), but this was, to our knowledge, the first population-based study to highlight this.

In the present study, there was no impact of TME grade on distant recurrence or survival. The lack of correlation between distant recurrence or overall survival and TME grade is consistent with two recent studies (282, 283). However, one of them found mesorectal resections to correlate with increased 5-year disease-free survival (283). Muscularis propria grade has also been shown to predict distant recurrence, disease-free survival and overall survival with a two-tier grading, combining mesorectal and intramesorectal vs. muscularis propria grade (284). This study may have had too short a follow-up time to detect any differences in distant recurrence and survival between the three groups.

Several risk factors for intramesorectal or muscularis propria grade were found: Low tumour height (< 5 cm) was associated with muscularis propria resection. APR, the procedure of choice in low tumours, was related to both intramesorectal and muscularis propria grade, which is in line with several earlier studies (120, 121, 280, 282, 285, 286). This is probably due to the challenges of the perineal part of the operation, where no well-defined dissection plane is offered.

Minimally invasive surgery was associated with intramesorectal and muscularis propria grade. This association was found in two earlier meta-analyses and two randomized controlled trials (287-290). However, there are studies where no association between TME quality and surgical approach has been
seen (286, 291, 292). A recent study comparing robotic and open mesorectal excision reported similar oncologic outcomes (293). In 2015, robotic surgery was under introduction in many parts of Sweden, and the finding of more intramesorectal or muscularis propria resections could be due to the learning curve.

Surprisingly, female sex was a risk factor for muscularis propria resection. This is reported in one previous study (285). The finding may reflect higher attentiveness in the mesorectal dissection in male patients, in whom TME is generally considered more challenging.

A long duration of surgery, intraoperative perforation and high blood loss were all associated with intramesorectal and/or muscularis propria grade. All these risk factors probably indicate an advanced tumour or strenuous surgery, with a resulting increased risk of not achieving mesorectal resection.
Conclusions

I. Local administration of gentamicin-collagen in the perineal wound after an APR did not decrease perineal wound complications. No association was seen regarding local administration of gentamicin-collagen and cancer recurrence rate or cancer-specific survival.

II. MBP did not decrease cancer recurrence or improve overall survival, but improved cancer-specific survival was seen in the MBP group, suggesting a benefit from MBP in the longer perspective.

III. The rate of clinically positive nodes decreased after implementation of new MRI guidelines, but staging accuracy did not improve. The use of radiotherapy decreased continuously, unaffected by the new MRI guidelines.

IV. Muscularis propria resection in TME surgery was associated with a higher local recurrence rate, but not with distant recurrence or survival. Several risk factors were identified for intramesorectal and muscularis propria resection and extra caution is warranted in such patients.
Future perspectives

While this thesis found no effect on infectious complication of the application of a gentamicin-collagen sponge in the perineal wound, and the MBP trial (254) preceding Paper II found no effect of MBP prior to colorectal surgery on infectious complication, the role of both gentamicin-collagen and MBP in preventing cancer recurrence have not been sufficiently studied. Further investigation in a randomized controlled setting, with a more homogenic study group than that presented in Papers I and II, is needed.

The reason for a potential effect on cancer recurrence with local antibiotics or MBP is unclear, but is perhaps associated with the microbiota. Studies are warranted of its role in colorectal cancer development and progression and regarding the potential effect of MBP and local antibiotics on the gut microbiota.

Further, the role of preoperative MBP, and whether it, combined with the proper antibiotic and the proper administration (orally, intravenously, or both), has an effect on postoperative infection rates is still debated. MBP is extensively studied, with various antibiotic regimes. A combination of intravenous antibiotics, oral antibiotics and MBP has been shown to decrease surgical site infection, but it has not been compared with oral antibiotics without MBP. Further studies in this area, with the aim to reach an international consensus, are also warranted.

A correct clinical node staging is of great importance in both rectal and colon cancer, in order to present the patient with the best treatment option. Though the MRI technology has evolved, the enhanced visual capacity has perhaps made radiologists inclined to over-stage nodes. A search for criteria that can lead to more accurate staging should continue, and further advancements in the development of MRI are important, together with the development of other emerging technologies, such as artificial intelligence and deep learning.
Bakgrund

Tjock- och ändtarmscancer utgör tillsammans den tredje vanligaste cancerformen, och är en av de cancerformer som leder till flest dödsfall per år. Återfallsrisk och överlevnad är starkt kopplade till vilket stadium tumörsjukdomen har vid diagnos, med nästan 100 % överlevnad för stadium I och 10–15 % överlevnad för stadium IV.

Avhandlingen belyser olika aspekter av tjock- och ändtarmscancer, kirurgiska aspekter och deras inverkan på cancerrecidiv och överlevnad, samt klinisk lymfkörteldiagnostik och dess koppling till radio(kemo)terapi.

En av studierna var en randomiserad kontrollerad multicenterstudie, en baserades på en tidigare randomiserad kontrollerad studie, med uppföljning via register och journalgranskning, och de två återstående var nationella kohortstudier som baserades på data från svenska kolorektalcancerregistret och dödsorsaksregistret.

Delarbete I

Delarbete II

Tarmrengöring ansågs länge obligat inför tjocktarmskirurgi, för att minska risken för infektioSA komplikationer och defekt läckning av tarmssammankoppelingen. Många studier har analyserat tarmrengöring och dess påverkan på komplikationer efter operation, men effekten av tarmrengöring på långtidsöverlevnad och återfall i cancer är mindre väl studerad. Patientkohorten för denna studie kom från B. Jungs multicenterstudie, där 20 svenska sjukhus och ett tyskt sjukhus randomiserade ca 1 300 patienter, vilka genomgick en tjocktarmsresektion mellan 1999 och 2005, till tarmrengöring eller inte. Vi följde upp de patienter som hade opererats för tjocktarmscancer avseende återfall i cancer, cancerspeciflik överlevnad och total överlevnad, med hjälp av patientregistret, dödsorsaksregistret och nationella cancerregistret, 6–12 år efter kirurgi. Registerdata validerades sedan med hjälp av sjukhusjournaler. Efter journalgranskning kvarstod 839 patienter, där 448 var randomiserade till operation med föregående tarmrengöring och 391 till operation utan tarmrengöring. Totalt 80/448 (18 %) med och 88/391 (23 %) utan tarmrengöring återföll i cancer (p = 0.093). Cancerspeciflik överlevnad var högre i gruppen med tarmrengöring än i gruppen utan (84 % mot 78 %; p = 0.019). Det var ingen skillnad i total överlevnad mellan grupperna (59 % mot 56 %; p = 0.186). I multivariatanalysen hade tumörstadium III, randomiserings till tarmrengöring och ålder signifikant påverkan på cancerspeciflik överlevnad.

Delarbete III

Preoperativ strålning ensamt, eller i kombination med cellgiftsbehandling, så kallad radiokemoterapi, minskar risken för lokalt canceråterfall i ändtarmscancer efter en ändtarmsoperation. Behandlingen ger dock svåra biverkningar för patienten, varför det är viktigt att inte överbehandla. Ett av kriterierna för att ge preoperativ strålning har varit om den kliniska utredningen påvisat spridning till närliggande lymfkörtlar. Denna utredning sker med magnetresonanstomografi (MR) och flera studier har rapporterat dålig träffsäkerhet, med framför allt tendens till överdiagnostik. Denna studie utvärderade effekten av de striktare MR-kriterier för lymfkörtelbedömning, som publicerades i Nationella vårdprogrammet 2016, på andelen positivt bedömda körtlar. Den studerade också påverkan på träffsäkerheten i lymfkörtelbedömning, samt om en eventuell minskning av andelen positivt bedömda körtlar i sin tur ledde till en minskning av andelen patienter som erhöll radio(ke)mo)terapi.

Data från alla patienter diagnostiserade med ändtarmscancer mellan 2009 och 2017 hämtades från svenska kolorektalcancerregistret. Totalt inkluderades 10 352 patienter i analyser angående positivet bedömda körtlar och radio(ke)mo)terapi. De 6 616 patienter som inte hade erhållit

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behandling vilken ansågs kunna påverka ursprungliga lymfkörtelbedömnin-ningen inkluderades i analyser avseende träffsäkerhet.


### Delarbete IV

Total mesorektal excision (TME) introducerades på 80-talet som kirurgisk teknik vid ändtarmcancer och resulterade i att andelen lokala canceråterfallet minskade från ca 40 % till 5–10 %. TME-preparatets kvalitet graderas av patolog enligt en tregradig skala: mesorektal (bäst kvalitet), intramesorektal (mellan) och muskularis propria (sämst kvalitet). Denna studie utvärderade TME-gradens påverkan på återfallsfrekvensen i cancer och överlevnad, samt identifierade riskfaktorer för de båda sämre graderingarna.


Av 2 476 patienter hade 1 856 (75 %) mesorektal gradering, 426 (17 %) intramesorektal gradering och 194 (8 %) muskularis propria gradering. Bland de patienter som kunde inkluderas i canceråterfallsanalyserna (n = 1 497) hade 27 (av 1 160; 2 %) lokalrecidiv i mesorektalgruppen, 8 (av 236; 3 %) i intramesorektalgruppen och 7 (av 101; 7 %) i muskularis propria-gruppen. Multivariataanalysen visade att muskularis propria-resektion var associerad med högre frekvens av lokala canceråterfall (HR 2.73 (1.07–7.0) \( p = 0.036 \)), men ingen association syntes mellan TME-grad och fjärråterfall eller överlevnad. Låg tumörnivå (0–5 cm ovan ändtarmsöppningen), rektumamputation, minimalinvasiv
kirurgi, lång operationstid, tarmperforation under operationen och positiv cirkumferentiell resektionsmarginal var alla riskfaktorer för intramesorektal och/eller muskularis propria-resektion.

Slutsatser

I. Lokal applicering av en gentamicin-kollagenplatta i det perineala såret efter en rektumamputation hade ingen effekt på komplikationsfrekvensen efter kirurgi. Studien visade inte heller någon effekt på risken för canceråterfall eller cancerspecifik död.

II. Patienter med tjocktarmscancer som fick tarmrengöring innan operation hade en bättre cancerspecifik överlevnad, men ingen skillnad i canceråterfall eller total överlevnad syntes.

III. Nya, striktare MR-riktlinjer minskade andelen kliniskt positivt bedömda lymfkörtlar, men förbättrade inte träffsäkerheten. Andelen patienter som erhöll radio(kemo)terapi innan operation minskade över tid och verkade inte påverkas av de nya riktlinjerna.

IV. Muskularis propria-resektion vid TME-kirurgi var associerad med högre andel lokala canceråterfall, men inte med fjärråterfall eller överlevnad. Flera riskfaktorer för intramesorektal och muskularis propria-resektion identifierades och extra uppmärksamhet och försiktighet krävs i dessa fall.
Acknowledgments

I wish to express my sincere gratitude to all those who have contributed to make this thesis possible. A special thanks to:

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The cover picture is drawn by Malin Enblad.
References

5. Samverkan RCi. Interaktiva rapporten SCRCR (Tjocktarm) 2023 [Available from: https://statistik.icanet.se/kolorektal/kolon/].


92. WHO. A short guide to cancer screening


218. Van K. Morris MEBK, MHSc2; Nancy N. Baxter, MD, PhD3; Al B. Benson III, MD4; Andrea Cercek, MD5; May Cho, MD6; Kristen K. Ciombor, MD, MSC17; Chiara Cremolini, MD, PhD8; Anjee Davis, MPPA9; Dustin A. Deming, MD10; Marwan G. Fakih, MD11; Sepideh Gholami, MD12; Theodore S. Hong, MD13; Ishmael Jaiesimi, DO14; Kelsey Klute, MD15; Christopher Lieu, MD16;; Hanna Sanoff M, MPH17; John H. Strickler, MD18; Sarah White, MD19; Jason A. Willis MD, PhD1; and Cathy Eng, MD7.


233. Bahadoer RR, Dijkstra EA, van Etten B, Marijn CAM, Putter H, Kranenbarg EM, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and


249. samverkan RCi. Kvalitetsregister Tjock- och ändtarm 2023 [Available from: https://cancercentrum.se/samverkan/cancerdiagnoser/tjocketarm-och-antarm-och-
-


256. HMD. Human Mortality Database. Max Planck Institute for Demographic Research (Germany) UoC, Berkeley (USA), and French Institute for Demographic Studies (France). [Available from: https://www.mortality.org.


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