Factors predicting recurrence in rectal cancer

Agger, Erik

2022

Document Version:
Publisher's PDF, also known as Version of record

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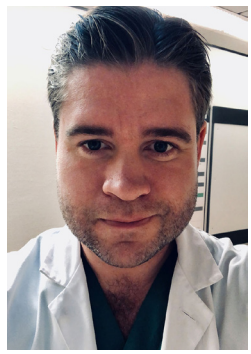
CLINICAL SCIENCES, MALMÖ | FACULTY OF MEDICINE | LUND UNIVERSITY

Printed by Media-Tryck, Lund 2022 NORDIC SWAN ECOLABEL 3041 0903



ERIK AGGER is a colorectal surgeon at Skåne University Hospital in Malmö.

His thesis examines factors associated with increased risk of local recurrence and distant metastasis after rectal cancer treatment.

LUND UNIVERSITY

FACULTY OF MEDICINE

Avdelning
Institution

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2022:65
ISBN 978-91-8021-226-7
ISSN 1652-8220

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Lilla Aulan lecture hall, Jan Waldenströms gata 1

Skåne University Hospital Malmö

May 25th, 2022 at 09:00

Faculty opponent
Professor of Surgery, Per Nilsson

Karolinska Institute, Stockholm

Organization LUND UNIVERSITY	**Document name** Doctoral dissertation
	Date of issue May 25th 2022
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Title and subtitle: Factors predicting recurrence in rectal cancer

Abstract

Background: Rectal cancer treatment has improved through important incremental surgical and oncological developments over the past decades. Localized disease is highly treatable with multimodal surgical and oncological therapy. Prognosis is dependent on several factors with tumour stage at diagnosis being the most important. Furthermore, curative treatment is highly dependent on radical surgical resection. Positive circumferential resection margin (CRM), lateral lymph node metastases and tumour deposits are examples of high-risk clinical situations associated with increased risk of recurrence and subsequently impaired long-term outcome and are investigated in this thesis.

Aims: Paper I & II, to investigate CRM-positive resections in rectal cancer and effect on local recurrence and distant metastasis risk. Paper III, to describe MRI-positive lateral lymph nodes – investigating therapy and outcome in high-risk rectal cancer. Paper IV, to investigate the prognostic significance of tumour deposits as a risk factor and in comparison with lymph node involvement in rectal cancer.

Method: Paper I-II & IV are retrospective national cohort studies. Paper III is a retrospective regional cohort study. Patient data was gathered from the Swedish ColoRectal Cancer Registry, medical records and the Swedish Cause of Death registry. Patients for paper I & II were between 2005 – 2013, for paper III between 2009 – 2014 and för paper IV between 2011 – 2014.

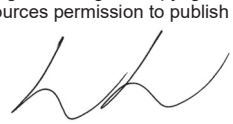
Main outcome measures: Paper I, local recurrence. Paper II, distant metastasis. Paper III, descriptive tumour characteristics, overall survival, local recurrence and distant metastasis. Paper IV, local recurrence, distant metastasis, overall and relative survival.

Results and conclusions: Exact CRM was associated with increased local recurrence risk. Neoadjuvant radiotherapy does not decrease risk of local recurrence in CRM-positive patients. Only a subset of patients with R1-resection (CRM 0.0 mm) suffered local recurrence during follow-up. Exact CRM equal to or less than 1.0 mm may be a risk factor for distant metastasis. However, several other factors likely contribute to increased risk of distant metastasis in CRM-positive patients. MRI-positive lateral lymph nodes were associated with synchrounous distant metastasis. Neoadjuvant (chemo)radiotherapy, abdominal rectal resection and selective lymph node dissection may be a useful approach in patients with MRI-positive lateral lymph nodes. Tumour deposits increased risk of both local recurrence and distant metastasis and decreased survival. The prognosis of patients with tumour deposits were comparable to pN1a-b stage mesorectal lymph node involvement.

Key words: Rectal cancer, Circumferential resection margin, Lateral lymph nodes, Tumour deposits, Prognosis

Lund University, Faculty of Medicine Doctoral Dissertation Series, 2022:65

Supplementary bibliographical information		**Language: English**
ISSN 1652-8220		**ISBN 978-91-8021-226-7**
Recipient's notes	**Number of pages 87**	Price
	Security classification	

Signature 

Date 2022-05-06

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ISBN 978-91-8021-226-7
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2022

To Alexander and Olivia

Table of Contents

Original papers

This thesis is based on the following papers, referred to in text as their Roman numerals (I-IV):

I. Risk of local recurrence of rectal cancer and circumferential resection margin: population-based cohort study.
Agger EA, Jörgren FH, Lydrup ML, Buchwald PL.
Br J Surg 2020; 5:580-85. doi: 10.1002/bjs.11478.

II. Circumferential resection margin is associated with distant metastasis after rectal cancer surgery; a nation-wide population-based study cohort.
Agger E, Jörgren F, Lydrup ML, Buchwald P.
Ann Surg 2021 Nov 18. doi: 10.1097/SLA.0000000000005302.

III. Management, treatment and prognostic significance of lateral lymph node metastases in rectal cancer - a regional cohort study.
Agger E, Åkerlund V, Ekberg O, Jörgren F, Lydrup ML, Buchwald P.
Int J Colorectal Dis 2021; 12:2707-14. doi: 10.1007/s00384-021-04018-1.

IV. Negative prognostic impact of tumor deposits in rectal cancer – a national study cohort.
Agger E, Jöud A, Jörgren F, Lydrup ML, Buchwald P.
Submitted

Abbreviations

APR	Abdominoperineal resection
AR	Anterior resection
BRAF	B-Raf mutation
CHT	Chemotherapy
CRM	Circumferential resection margin
CRT	Chemoradiotherapy
CT	Computed tomography
DM	Distant metastasis
DRM	Distal resection margin
EMVI	Extramural venous invasion
HR	Hazard ratio
IQR	Interquartile range
KRAS	K-Ras protein
LARC	Locally advanced rectal cancer
LLND	Lateral lymph node dissection
LLNM	Lateral lymph node metastasis
LN	Lymph node
LR	Local recurrence
MDT	Multidisciplinary therapy conference
MMR	Mismatch repair
MRF	Mesorectal fascia
MSI	Microsatellite instability
OS	Overall survival
FDG-PET/CT	Flourodeoxyglucose-Positron emission tomography-CT
RS	Relative survival
RT	Radiotherapy
SCRCR	Swedish ColoRectal Cancer Registry
SCRT	Short course radiotherapy
TD	Tumour deposit
TME	Total mesorectal excision

Thesis at a glance

Paper	Aim	Study design	Outcomes	Conclusion
I	To investigate CRM-positive resections in rectal cancer and effect of neoadjuvant therapy.	Retrospective national cohort study	Risk of local recurrence	Exact CRM is associated with increased local recurrence risk and neoadjuvant radiotherapy does not decrease risk of local recurrence in CRM-positive patients.
II	To investigate CRM-positive resections in rectal cancer and possible benefits of oncological therapy.	Retrospective national cohort study	Risk of distant metastasis	Exact CRM ≤1.0 mm may be a risk factor for distant metastasis. Most likely, several other factors contribute to increased risk of distant metastasis in these patients.
III	To describe MRI-positive lateral lymph nodes, therapy and outcomes in high-risk rectal cancer.	Retrospective regional cohort study	Prevalence of MRI-positive lateral lymph nodes. Tumour characteristics, recurrence and survival	MRI-positive lateral lymph nodes are associated with cM1-stage. Neoadjuvant therapy and selective lymph node dissection appear to be an applicable approach.
IV	To investigate the prognostic significance of tumour deposits, as a risk factor and in comparison, with lymph node involvement.	Retrospective national cohort study	Risk of local recurrence, distant metastasis, overall and relative survival	TDs increase risk of local recurrence, distant metastasis and decreased survival. TD-positive patients have prognosis comparable to that of pN1a-b stage patients.

Introduction

Rectal cancer

Epidemiology of rectal adenocarcinoma

Rectal cancer is the eight most common malignancy in the world accounting for approximately 3.8% (732'000) of cancer diagnoses annually[1]. Males are about twice as likely compared to females to suffer from rectal cancer and the disease is more common in Western countries compared to undeveloped countries[1]. This difference is likely explained by more sedentary lifestyle, increases in body weight, increased alcohol consumption and dietary habits with higher contents of red and processed meat[2,3].

The median age of diagnosis is approximately 63 years[2]. However, in recent decades an increase in early-onset colorectal cancer has been seen in adults 50 years or younger and it is expected that one-fourth of new cases will be diagnosed in this group within ten years[4,5]. The characteristics of tumour biology, genetics and molecular subtypes appears to be different in younger patients and warrants further investigation[6,7].

It is estimated that 90% of colorectal cancer cases are sporadic without any specific genetic predisposition and that the remaining cases can be characterized as part of a specific syndrome with known or unknown genetic causes[8].

In Sweden approximately two thousand individuals are diagnosed with rectal cancer annually, comprising 3.1% of all cancer cases and a slowly increasing incidence is observed[9]. After diagnosis, 66% of patients undergo abdominal surgical resection [10]. Relative 5-year survival is approximately 66% for all patients (stage I-IV) and relative 3-year survival among resected patients without distant metastasis (DM) 94% (stage I-III) [9,10].

Anatomy

The rectum and mesorectum

The rectum is the continuation of the large bowel in the small pelvis and ends with the anal canal. It can be divided in the upper, middle and lower rectum with some anatomical differences. The upper third of the rectum is completely intraabdominal and covered by the peritoneum on its anterior and lateral surfaces, it lies near other intraabdominal organs such as the sigmoid colon, ovaries and fallopian tubes in females. The middle third has an anterior peritoneal surface but is otherwise enclosed by the mesorectum, proximal organs are the bladder in men and the uterus in females. The posterior and lateral aspects of the lower third of the rectum is covered by the mesorectum. The anterior part of the lower rectum has a thin mesorectum which further distally ends and the rectoprostatic fascia (Denonvilliers' fascia) in men and the rectovaginal fascia in females forms a border to the prostate and posterior vaginal wall respectively.

The mesorectum contains adipose connective tissue, blood vessels, lymph nodes (LNs), lymphatic vessels and autonomic nerves. Surrounding the mesorectum is the mesorectal fascia (MRF) which defines the border of the "Holy plane" in total mesorectal excision (TME) surgery[11].

Venous drainage and arterial supply

The arterial and venous anatomy follows a similar anatomical pattern. The upper third of the rectum is mainly drained via the inferior mesenteric vein into the splenic vein and onto the portal vein whereas the middle and lower two-thirds of the rectum drain via the middle and inferior rectal veins which connect directly to the systemic circulation through the iliac veins. This difference in venous drainage means that tumour location affects hematogenous spread and likely DM locations[12]. The upper part of the rectum receives its major blood supply from the superior rectal artery, branched off from the inferior mesenteric artery. The lower part receives its principal arterial supply from the inferior rectal arteries which are branched from the internal iliac arteries. Several collateral arterial connections exist aiding vascularization. An overview of the vascular anatomy is provided in Figure 1.

Lymphatic drainage

The main paths of lymphatic drainage from the upper two-thirds of the rectum are LNs within the mesentery along the superior and middle rectal artery. From the lower third of the rectum lymphatic drainage may also take a path towards the internal iliac LNs and the inguinal nodes.

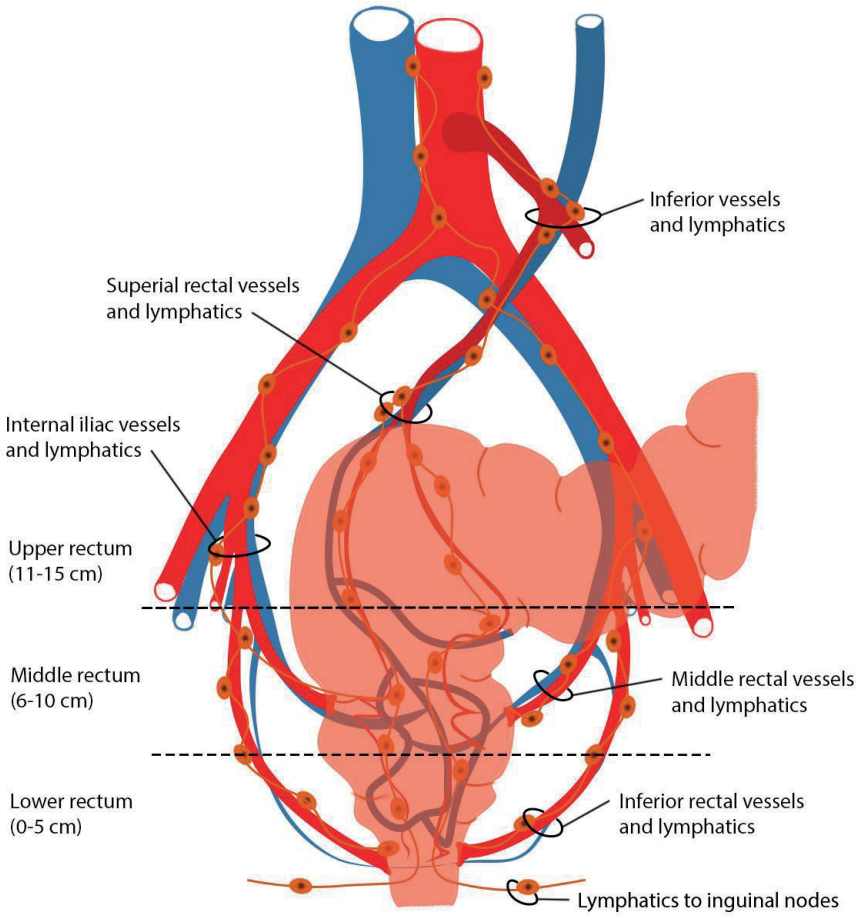

Figure 1 – Overview of the vascular and lymphatic anatomy of the rectum.

Lateral, inguinal and paraaortic lymph nodes

LNs located along the internal iliac and obturator vessels outside the MRF are classified as lateral lymph nodes (LLNs). These LNs are not resected during standard partial mesorectal excision or TME. If resected with lateral lymph node dissection (LLND) and found to contain malignant cells, they are added to the patients total N-stage[13].

Involved external iliac, common iliac, inguinal and paraaortic LNs are classified as M1-stage in current TNM-staging[14]. As described above, there is a feasible anatomic lymphatic drain path between tumours in the lower path of the rectum and inguinal LNs. Paraaortic LNs receive lymphatic drainage from the iliac LNs on its path back into systemic circulation. The paraaortic LNs are not connected to the mesorectal LNs.

Clinical presentation

Rectal cancer causes symptoms with varying characteristics and intensity. Common symptoms include changes in bowel habits with urgency to defecation, sensation of incomplete defecation, blood in stool or narrow stool. Obstruction caused by the tumour may cause abdominal pain, diarrhoea and constipation. Non-specific symptoms such as fatigue, weight loss and anaemia are also associated with rectal cancer. Inguinal LN enlargement might also be noticed in some patients.

Tumour staging

Endoscopy

Clinical symptoms from the lower gastrointestinal tract should serve as indication for a digital rectal exam and endoscopic examination with rigid sigmoidoscopy which could confirm the diagnosis[15]. Typically, patients undergo flexible sigmoidoscopy or colonoscopy during initial clinical work-up (Figure 2). The endoscopist should describe the characteristics of the lesion, its location and take biopsies for histopathological confirmation[15,16]. Tumour height from the anal verge is measured with rigid sigmoidoscopy.

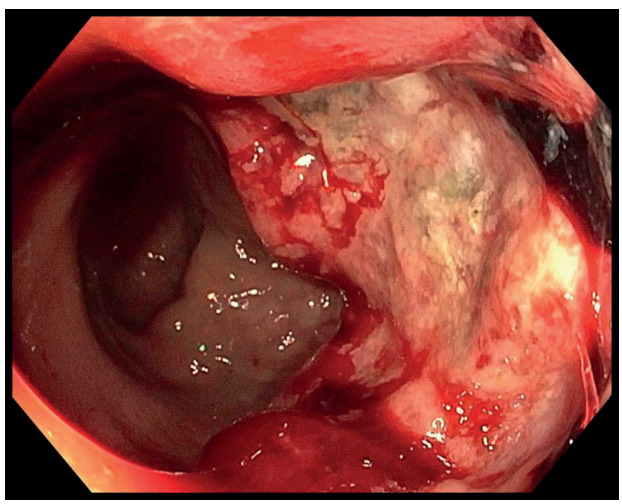

Figure 2 – Rectal tumour covering half of the rectal circumference with central necrosis. Image from the Department of Endoscopy and Radiology, Skåne University Hospital, Malmö, Sweden.

Biopsy

To verify diagnosis of adenocarcinoma, endoscopic biopsies are secured and sent for histological examination. The pathologist grade atypical lesions as low- or high-grade dysplasia or carcinoma[16]. Sometimes biopsies are not representative or deemed of inferior quality for diagnosis and repeated biopsies may be needed.

Radiology

Recommended radiology for metastatic screening is computed tomography (CT) of the thorax and abdomen while MRI of the pelvis provides detailed information about the local stage of the tumour, mesorectal LNs, tumour deposits (TDs), extramural venous invasion (EMVI), LLNs, MRF-involvement and tumour growth in relation to other pelvic organs[15–19]. Results of these exams are presented according to the TNM-staging system[19]. The TN-stage and information about MRF-involvement, suspected involvement of LLNs assessed by pelvic MRI provides high-resolution, essential information when discussing and planning neoadjuvant therapy[16,20]. In selected patients with locally advanced rectal cancer (LARC), suspected distant LN-involvement or suspected liver metastasis; FDG-PET/CT and/or MRI of the liver can be used to possibly enhance clinical staging[21,22].

Multidisciplinary therapy conference

Complete clinical staging and multidisciplinary therapy conference (MDT) improves outcome in rectal cancer treatment [23–25]. The tumour is staged according to the TNM-system based on information gathered from clinical examination, endoscopy, pathology and radiology (cTNM-stage). MDT should ideally consist of senior expertise in surgery, pathology, radiology, oncology and nursing. Treatment pathways are suggested in accordance with guidelines and patient performance and preference. MDT is a resource-intensive enterprise, could delay initiation of treatment and is more likely to affect treatment recommendations in patients with more advanced clinical tumour-stage[26].

Patients receiving neoadjuvant therapy may be radiologically and clinically re-evaluated before final decision regarding surgical intervention and approach during a second MDT (ycTNM-stage).

Postoperative MDT after surgery when histopathological examination of the specimen is complete (y/pTNM-stage) may recommend adjuvant therapy, routine follow-up or tailored follow-up.

Pathology of rectal adenocarcinoma

Histopathological examination

Rectal resection specimens are examined both macroscopically (before or after fixation) and microscopically after fixation[16]. Macroscopic grading according to Phil-Quirke score adds important information about surgical quality and recurrence risk[27,28]. The primary tumour is assessed regarding local infiltration depth, circumferential resection margin (CRM), distal resection margin (DRM), lympho-vascular invasion, presence of TDs, tumour grade, mucinous histology, tumour budding, EMVI and perineural infiltration[16,29]. Samples with high tumour cell concentration are secured for genetic testing. For adequate pN-staging a minimum of 12 mesorectal LNs should be dissected and examined[30,31].

Local tumour growth and mesorectal lymph node involvement

Rectal cancer is staged with the TNM-classification[13,14]. pT-stage describes tumour growth within the rectal wall, mesorectum and penetration to adjacent organs. Advanced pT-stage is associated with poor prognosis in rectal cancer[32].

pN-stage describes the number of LNs with metastases. LN-involvement is associated with impaired prognosis[32,33]. A summary of pTN-stages is provided in Table 1.

Table 1 – Summary of TN-stages in rectal cancer.

TN-classification of colorectal cancer	
Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Invades submucosa
T2	Invades muscularis propria
T3	Invades through the muscularis propria into perirectal tissues
T4a-b	Penetrates the visceral peritoneum (a) and/or invades other organs or structures (b)
Lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1a-b	Metastasis in 1 (a) or 2-3 (b) regional lymph nodes
N1c	TD in the subserosa, mesentery of nonperitonealized perirectal tissues without regional nodal metastasis
N2a-b	Metastasis in 4-6 (a) or ≥7 (b) regional lymph nodes

Histopathological risk factors beyond lymph node involvement

Beyond LN involvement there are other known factors associated with tumour recurrence and decreased survival. These are diagnosed during histopathological examination and considered additional risk factors which might motivate adjuvant

therapy[13,14]. TDs and EMVI may be detected with MRI during preoperative staging and may motivate neoadjuvant chemoradiotherapy (CRT) to improve prognosis[18].

Lympho-vascular invasion with tumour cells within the endothelial space of lymph or blood vessels are associated with decreased survival in stage I-III colorectal cancer and increases risk of LN metastasis[34–36]. Tumour infiltration in the perineural space is also associated with increased recurrence risk and decreased survival in colorectal cancer[37–39]. TDs and EMVI are two features of advanced local tumour growth within the mesorectum, the former as a solitary island of tumour growth separate from the primary tumour and the latter a significant invasion of larger veins. They are both associated with increased risk of recurrence and decreased survival in colorectal cancer patients[40–44].

Furthermore, histological grade, type and tumour budding have also been recognized as risk factors to different degrees in colorectal cancer[45]. Tumour differentiation grade is a recognized prognostic factor in colorectal cancer with higher grade and poor differentiation being associated with higher TN-stage and thereby worse overall prognosis[46]. Tumour budding is a histological growth pattern associated with invasive tumour characteristics, increased risk of LN involvement, increased recurrence risk and decreased survival[47]. Mucinous adenocarcinomas account for around one eighth of rectal cancers and are associated with mismatch repair (MMR) deficiency and microsatellite instability (MSI) which could affect tumour susceptibility to chemotherapy (CHT)[48,49]. Additionally, mucinous tumours seem to be less affected by neoadjuvant CRT with fewer instances of complete pathological response, less tumour down-staging, increased risk of CRM-positive resection margins and thereby decreasing survival and increasing local recurrence (LR) risk[50,51].

Genetic and molecular risk factors

It is generally established that most colorectal adenocarcinomas arise through a series of genetic changes during the adenoma-carcinoma sequence[52]. Progressive mutations with loss and gain of function in the adenoma cells eventually result in carcinoma[53]. Several genetic factors and epigenetic alterations are associated with colorectal carcinogenesis, influencing the total risk and time to develop malignant disease[54].

Mutations with current clinical implications for oncological treatment are KRAS, BRAF and MMR/MSI[16]. KRAS-mutation, causing unregulated cell-growth, have been shown in 30-50% of colorectal cancers and have been associated with poor prognosis and increased risk of DM. Additionally, tumours with KRAS-mutation has been difficult target with some CHT-regimes[55]. Evidence suggest however, that tumours with KRAS-mutation are susceptible to neoadjuvant CRT[56]. BRAF-mutation is often present in serrated adenomas and causes dysregulation in methylation, ultimately disrupting normal cell-proliferation, differentiation and

apoptosis. Although found in some rectal cancer patients, this mutation is more common in proximal colon cancers[57]. BRAF-mutation is associated with more pronounced increase of recurrence risk and decreased survival than isolated KRAS-mutation[58].

MMR is a repair system that detects DNA-replication error and has been found to be responsible for mutations in several genes involved in carcinogenesis for example in Lynch syndrome[59]. Defects in MMR (dMMR) have been found in 15-20% of colorectal cancers and causes MSI[54,59]. Presence of dMMR with MSI is associated with better prognosis overall and 5-FU based CHT have not been shown to improve outcome in stage I-II-patients[60]. In the neoadjuvant therapy setting, dMMR with MSI seems sensitive to CRT but might exhibit resistance to neoadjuvant CHT which would motivate testing for dMMR before a decision regarding neoadjuvant and adjuvant therapy is taken[60,61].

Chromosomal instability (CIN) is observed in approximately two thirds of sporadic colorectal cancers and represent an accelerated variability between chromosomes with loss and gain of function beginning in the adenoma and being most pronounced in the invasive carcinoma[62]. High degree of chromosomal instability has a negative prognostic impact and 5-FU based CHT could be ineffective in improving prognosis[62,63]. CpG island methylator phenotype (CIMP) is an epigenetic alteration which deactivates tumour suppressor genes and high grade of this alteration seems to have a negative impact on prognosis, particularly in early stage colon cancer[64,65]. Early mutations in the tumour suppressor gene adenomatous polyposis coli (APC), affecting the adenoma-carcinoma sequence, are common in sporadic colorectal cancers and might be a target for therapeutic inhibitors[66].

Distant metastasis in rectal cancer

A synchronous metastasis is present at time of diagnosis and the disease is classified as stage IV regardless of TN-stage. A metachronous metastasis is diagnosed after curative treatment of the primary lesion and known synchronous DM. A widely accepted definition of the interval between primary disease and metachronous disease does not exist but intervals between zero to twelve months after curative surgery has been suggested[67]. Patients with stage IV-disease have the poorest prognosis. In some patients, however, metastasis surgery with curative intent is possible[68,69].

Metastasis pattern in rectal cancer differs to some extent from colon cancer with patients being more likely to suffer from metastases to the lungs and nervous system and less likely to the peritoneum[70]. Patients with tumours in the upper third of the rectum are more susceptible to hematogenous spread to the liver while patients with tumour in the middle and lower part of the rectum are more likely to suffer

hematogenous spread to the lungs and other organs[12]. Certain histopathological features of the primary tumour, for example mucinous adenocarcinoma and signet cell carcinoma may also influence risk of metastasis and localization[71]. A summary of M-stages is provided in Table 2.

Table 2 – Summary of M-stages in rectal cancer.

M-classification of colorectal cancer	
Metastases	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1a-c	Distant metastasis in one site (a) or multiple sites (b) or peritoneum (c)

Swedish ColoRectal Cancer Registry (SCRCR)

The Swedish Rectal Cancer registry was founded in 1995 and merged with the Swedish Colon Cancer Registry in 2007 forming the SCRCR. Clinically diagnosed rectal cancers are registered prospectively by surgeons, radiologists, pathologists and oncologists forming a registry with a coverage of more than 97%[10]. The set of variables has evolved over time. Recorded data include basic patient characteristics, preoperative staging, neoadjuvant therapy, surgery, pathology, postoperative complications and adjuvant therapy. Follow-up data is available for LR and DM. The follow-up data is registered at one, three and five years after surgery including date of recurrence diagnosis. Data on survival is linked to the Swedish Cause of Death registry. The SCRCR has been validated several times showing high degree of completeness and validity [72–76]

Rectal cancer treatment

Surgical resection

Early surgical techniques

When Miles published his article on abdominoperineal resection (APR) in the Lancet 1908, he laid the foundation of principles in the surgical treatment of rectal cancer still relevant more than a hundred years later[77]. Up until this point, rectal cancer was treated with perineal resection of the tumorous mass without proper surgical exposure, almost always resulting in non-radical resections and LR. Miles considered, based on anatomical studies, that local tumour dissemination through

lymphatic vessels and LNs could be the source of LR and suggested including local LNs in the resected specimen *en bloc*[77]. Advances in anaesthesia, aseptic surgical technique and utilizing earlier knowledge on abdominal stoma creation made the combined APR possible and thereby changing the course of rectal cancer surgery forever[78]. In 1923 Miles reported a recurrence rate of 29.5% and a mortality rate a 31% after rectal cancer treated with APR[79]. APR became the gold standard of rectal resection, regardless of tumour height.

Anterior resection (AR) with anastomosis was first described by Balfour in 1910 but was not initially popularised due to mortality caused by anastomotic leaks and belief that tumour dissemination toward the anus caused recurrence irrespective of tumour height[80]. Dukes and Gabriel could show that distal tumour dissemination was unusual and Dixon demonstrated results in 1948 of AR with a five-year survival rate of 64% and mortality at 2.6%; thereby introducing a feasible sphincter-preserving surgical option for tumours in the middle and upper rectum[81,82].

These somewhat promising results unfortunately fell short in the middle of the twentieth century with the introduction of blunt dissection techniques for tumour mobilisation in the pelvis. Survival rates of 45-50% in stage I-III patients and 25-35% in stage III was reported and equally dismal LR-rates between 30 and 40%. Blunt dissection outside anatomical planes, damaging the mesorectum and autonomic nerves rendered patients with high risk of recurrence and poor functional outcomes often with colostomy and impotence[83].

Developed surgical techniques

In Quirke's article from 1986 the probable cause of the poor outcomes were described as resulting from inadequate resection and CRM-involvement[84]. Heald had proposed the TME already in 1982, thereby both re-introducing known anatomical concepts of the MRF and changing the course of surgical rectal cancer treatment[85]. MacFarlane could demonstrate the superior performance of the TME in high-risk tumours compared to blunt dissection combined with oncological therapy in 1993 and the following decades the TME was established as a gold standard surgical approach[86]. Successful TME-training programs confirmed declining LR-rates with Heald's technique[87]. Recognising the functional importance of autonomic nerves, Enker described in 1992 how nerve-preserving dissection could preserve autonomic function without jeopardizing radicality[88].

Over the past decades, introduction of laparoscopic surgery has added a new layer to the application of the TME-technique. Although not improving cancer-specific outcomes further, these technical innovations have contributed to improved short-term surgical outcome and better patient experience[89,90]. Endoscopic techniques offering local excision of adenomas and early-stage cancer tumours offers new prevention and treatment options in some patients[91].

Lateral lymph node dissection

Stearns suggested that LLND might be necessary to prevent LR since some rectal cancers could metastasize to LLNs along the pelvic wall[92]. It is recognized that LLND leads to increased frequency of urogenital dysfunction[93,94]. LLND has demonstrated lower LR-rates compared to TME without neoadjuvant therapy[95,96]. In patients treated with neoadjuvant radiotherapy (RT) or CRT however, the recurrence and survival benefits are limited[97,98]. Treatment traditions differ regarding the use of LLND, especially between eastern Asia which primarily relies on LLND while Western countries utilize treatment strategies involving oncological therapy and selective LLND to treat lateral lymph node metastases (LLNMs)[99].

Oncological therapy

Neoadjuvant therapy

Binkley introduced the concept of multimodal treatment of rectal cancer in 1938 and published results showing promising potential of RT on rectal cancer regression[100]. Furthermore, work by Morson suggested that tumours with high-risk factors such as stage III rectal cancer, distal tumours and locally advanced tumours might benefit the most from neoadjuvant RT[101].

The MERCURY-study demonstrated the high accuracy of pelvic MRI in imaging invasion depth of rectal tumours and thereby improving the basis for neoadjuvant therapy[20]. Blomqvist and Glimelius suggested classifying rectal cancers in three categories based on their location and radiologic features; 'good' (low risk), 'bad'(intermediate risk) or 'ugly'(high risk)[102]. Patients with a low-risk tumour could be treated with TME-surgery alone, whereas intermediate and high-risk tumours were ideally treated with short course radiotherapy (SCRT, 5x5Gy) and CRT respectively before TME-surgery.

Studies on neoadjuvant RT and TME-surgery demonstrated reduced LR risk, possibly increased survival and potentiation of the improvements already shown for TME-surgery alone[103–106]. Additionally, the effects of neoadjuvant RT remained over time regarding LR reduction and possibly survival improvement in the Swedish rectal cancer trial[107]. The Dutch TME-trial could confirm the lasting effects in reducing LR, however, survival benefits were shown only in stage III-patients[106].

In patients with more advanced tumour-stage, CRT seems to improve local control compared to SCRT. CRT may however, induce more radiation-related complications without improving survival outcomes[108,109]. In patients with LARC and non-resectable tumours CRT, SCRT with delayed surgery or SCRT+CHT may lead to tumour regression and improved local control[109–113]. In patients with CRM-positive resection, neoadjuvant RT seems beneficial compared to adjuvant CHT in reducing LR[114].

Neoadjuvant CHT has not shown results comparable to regimes incorporating RT in rectal cancer, neither have strategies with local tumour excision in good clinical responders[115,116]. Total neoadjuvant therapy with organ preservation is an emerging field of research that has yet to prove feasibility in terms of long-term oncological outcomes[117,118].

The introduction of neoadjuvant RT has undoubtedly improved oncological prognosis in rectal cancer patients significantly. The side-effects of RT can, as with surgical resection, affect functional outcome and induce short and long-term complications[119–121].

Adjuvant therapy

The additional benefit of adjuvant CHT in rectal cancer is debated. Especially in patients treated with neoadjuvant RT or CRT, there is currently no strong evidence advocating adjuvant CHT[122,123]. However, there might be patients with high-risk tumours who could be considered for adjuvant CHT[15,123,124]. In a small subset of patients, postoperative RT/CRT might be regarded, for example if no neoadjuvant therapy was given and tumour characteristics or surgical conditions motivate further local therapy[15]. CHT-regimes are mainly based on 5-FU with addition of Oxaliplatin to further reduce recurrence risk[125]. Both 5-FU and Oxaliplatin are associated with short and long-term side-effects and could affect long-term quality of life in some patients suffering motor or postural weakness, numbness, pain and other neuropathic symptoms[126].

Immunotherapy targeting specific cancer-associated antigens and tumour progression pathways are available and several are under development undergoing preclinical and clinical trials[127]. Immunotherapy might offer a new therapeutic horizon and can be used in the treatment of DM or possible in neoadjuvant or adjuvant regimes.

Follow-up

Swedish guidelines recommend a follow-up protocol after radically resected rectal cancer with CT and CEA blood sample one and three years after surgery[16]. Patients should undergo regular colonoscopies up until 75 years of age to detect new adenomas and metachronous cancer[15]. Different intensity of follow-up have been evaluated in randomized and retrospective cohorts without improvements in survival or recurrence favouring more frequent follow-up[128,129]. However, follow-up may be individualized in certain high-risk clinical scenarios, for example after CRM-positive resection, to improve recurrence detection and treatment options[15,130].

Treatment of local recurrence

As noted above, LR in rectal cancer used to be a common occurrence until the introduction of TME and neoadjuvant therapy[83]. The treatment of recurrent disease are even more challenging with even worse outcome for patients; high operative mortality and morbidity, often with an equally discouraging prognosis after surgery[131]. Some authors have suggested abandoning recurrent resection surgery entirely due to the poor results[132].

The alternative, to not pursue radical re-resection, inevitably results in disease progression and death[133]. Treatment of LR have shown improved results over time, both in terms of local control and survival[134]. Furthermore, radical resection of LR may improve patient outcome and prognosis but continues to be associated with significant operative risks[135,136]. RT and CHT for LR may offer symptom-relief, however, rarely the chance of cure[134,137,138]. Neoadjuvant reirradiation is an option for locally recurrent disease and radical resection margins is associated with improved prognosis[139,140].

Prognosis

Prognosis in patients with rectal cancer is dependent on several factors. Some of these factors are accounted for by the TNM-staging system, however, as described above there are a number of histopathological, molecular and (epi)genetic factors not accounted for by TNM-staging. Furthermore, there are several ways to measure prognosis in rectal cancer. It could be argued that TNM-staging may serve as an acceptable proxy for the general aggressiveness of the rectal cancer with the sum of other risk factors translating into a specific stage.

Available treatment options for the patient and the patient's response to such treatment further affects long term outcome. In multimodal rectal cancer therapy, with the ultimate goal of radical tumour resection, some patients may not be eligible for curative treatment related to comorbidity or due to complications related to the treatment efforts.

Relative five-year survival has improved for patients with rectal cancer over the last decades and is estimated at 66-67% for all stages with no difference between genders[10,141]. Survival is dependent on TNM-stage at diagnosis with five-year relative survival (RS) approximately 95% in stage I, 84% in stage II, 68% in stage III and 17% in stage IV-patients[10,142]. LR-rates have been decreasing steadily and might currently be as low as 2.1% in patients three years after curative resection of tumours with T1-3-stage compared to around 6% a decade ago[10]. DM-rates after curative resection remains a significant issue with DM-rates close to 20% in patients stage I-III three years after curative resection[143].

Aims of the thesis

This thesis investigates three high-risk conditions in rectal cancer treatment; patients with small and no-margin resection, patients with suspected lateral lymph node involvement and patients with tumour deposits. These situations are clinically challenging due to the complexity of rectal cancer therapy. Re-resection is typically technically very challenging and, in some patients, oncological treatment options are limited. The presented work in this thesis may offer some guidance in the care of these patients.

Specific aims

Paper I	To investigate whether there was a difference between microscopic margins regarding LR risk between subgroups with CRM ≤1.0 mm and between resection margins of 1.1 - 1.9 mm and ≥2 mm.
Paper II	To investigate whether there was a difference in risk of DM between subgroups with CRM ≤1.0 mm and between resection margins of 1.1 - 1.9 mm and ≥2 mm.
Paper III	To describe results and practises in a regional high-risk rectal cancer cohort with MRI-positive LLNs treated with neoadjuvant therapy and TME-surgery according to current Swedish guidelines.
Paper IV	To investigate TDs in rectal cancer and the impact on LR, DM and survival.

Methods

Study design

Paper I and II

Both studies were of retrospective design and based on a national cohort of prospectively registered patients between January 1, 2005 and December 31, 2013. The SCRCR was used to identify patients eligible for inclusion. Patients with rectal adenocarcinoma (C20.9) treated with abdominal surgery (AR, Hartmann's procedure, APR) were evaluated for inclusion.

Paper III

This study was of retrospective design and based on a regional cohort of patients with rectal adenocarcinoma (C20.9) and high-risk factors; tumour ≤10 cm from the anal verge, cT3-4 and cN1-2 stage. Patients diagnosed and treated in southern Sweden (Skåne) between January 1, 2009 and December 31, 2014 were identified with the SCRCR and medical records were reviewed.

All patients with suspected LN outside or in the vicinity of MRF on primary pelvic MRI were subjected to secondary review of the original MRI according to predefined criteria. In addition, the surgical and histopathological records of patients with MRI-positive LLN were analysed to determine outcome of LLND. Survival during follow-up was obtained from the Swedish Cause of Death Registry until September 1, 2020.

Paper IV

This study was a retrospective study based on national data from the SCRCR. Patients prospectively registered and treated for rectal adenocarcinoma (C20.9) between January 1, 2011 and December 31, 2014 were eligible for inclusion. Only patients treated with abdominal surgery (AR, Hartmann's procedure, APR) were included. Survival data was obtained at the end of data collection from the Swedish Cause of death Registry September 2, 2020.

Sources of error

Validity of SCRCR

The SCRCR has been validated several times[72–76]. In the most recent validation, agreement between medical charts and the registry was on average 90%. However, some variables such as preoperative staging contained large amounts of missing data. The least valid group of parameters was reports on the post-operative course. DRM and CRM showed agreement in approximately 80% of the reviewed patients [72].

Missing data

This is a common problem in retrospective cohort studies. The papers in this thesis all have missing data some extent. Missing data from the SCRCR may exist for different reasons; incomplete registration, variables not available for registration during the specific time period or registration faults. To a limited extent, obvious registration faults were identified and handled as missing data if no other variable entry could provide corrected information. Missing data was disclosed in each paper respectively.

Missing data can be of different types, missing completely at random, missing at random or missing not at random. In the papers making up this thesis, missing data has been considered as missing completely at random due to some variables not being available for registration during the study period. This reduced the sample size and statistical power of multivariable analysis but should not, in principle, introduce bias. Missing data has been handled this way throughout the thesis.

Data management

The handling of large datasets may pose a risk of human error during the different stages of data management. To avoid such errors, inclusion and exclusion criteria has been established during the design of each study in this thesis. Excluded patients' data has been compared regarding basic characteristics after each step of exclusion. Included patients' data has been reviewed for accuracy and completeness within the data-set throughout. Data files containing individual health-data was stored and managed out of one file location.

Secondary review of medical records

In paper III secondary review of medical records and radiology was performed. Data in medical journals may have been entered incorrectly and may have been interpreted incorrectly during data collection. The secondary radiological review was performed by one experienced radiologist according to a predetermined review protocol. Although experienced and following strict review criteria, in some cases it is likely that another reviewer would have made different judgements in some cases. Furthermore, quality of MRI-exams varied slightly during the study period.

Outcome measures

The exposures in this thesis (CRM-positive resection, LLNs and TDs) were all hypothesized to contribute to a high risk of recurrence and decreased survival. Subsequently, the main outcome measures in this thesis were LR, DM, overall survival (OS) and RS.

In paper I the primary outcome was LR, diagnosed >90 days, after primary surgical resection. Secondary outcome measures included the association between neoadjuvant therapy and LR risk in CRM-positive patients and data on when LR occurred among CRM-positive and CRM-negative patients after surgery.

In paper II the primary outcome was DM, diagnosed >90 days, after primary surgical resection. Secondary outcome measures included the association between neoadjuvant and adjuvant therapy with DM risk in CRM-positive patients.

In paper III the primary outcomes were tumour characteristics (clinical stage and histopathology) and distribution of MRI-positive LLNs. Secondary outcomes included results of LLND, LR, DM and OS.

In paper IV the primary outcomes were LR and DM, diagnosed >90 days, after primary surgical resection. Secondary outcomes included OS and RS. TD-positivity was examined as a prognostic factor both against TD-negative patients and in relation to different pN-stages.

In paper I, II and IV data on LR and DM was obtained from the SCRCR. In paper III data on LR and DM was mainly obtained from the SCRCR. In cases with uncertainty regarding whether the DM registered in the SCRCR represented synchronous or metachronous disease, medical records were reviewed. Furthermore, in cases of LLND, data was obtained from medical records since this is not registered in the SCRCR.

Patients with early recurrences, within 90 days of primary surgery, were excluded from analysis in paper I, II and IV. Even though complete clinical staging was performed in most patients, the aim of the study design was to analyse patients without synchronous metastatic disease or incomplete resections. In some patients, repeated CT or MRI of suspected lesions found during primary staging unveiled synchronous metastasis. Similarly, patients with tumour spread below the detection capabilities of the staging method used, such as very small lesions to the liver or limited carcinomatosis were hereby excluded. Regarding early LR, this was considered as cases of incomplete tumour resection not recognised during surgery. Although rare, this sometimes occurs during complex rectal resections. Early anastomotic recurrences would also typically have been diagnosed within this 90-day time frame.

Limitations

Every study design has its benefits and limitations. The studies in this thesis were all of retrospective design and take advantage of a national population-based registry. This could reduce selection bias and give an opportunity to study the effect of the exposures on outcomes in patients treated in a clinical setting with its patient-specific challenges. Uneven distribution of risk factors with effect on both exposure and outcome (confounders) have been identified by causal diagrams and univariable analysis and adjusted for in multivariable analysis.

Missing data is a challenge in cohort studies and requires addressing in a uniform way. Missing data in exposures was handled with exclusion since these patients could not be grouped for comparative analysis. Patients with missing data in confounding variables were included in univariable analysis but censored in multivariable analysis. Even though missing data was similarly distributed across groups this needs to be considered when interpreting results. Rate of missing data after exclusion has clearly been stated in each of the papers and are similar to reported rates of missing data in the SCRCR.

Missing data might also occur in outcome variables. This is more difficult to address beyond external validations of the SCRCR. Registration of colon cancer recurrence has been validated with overall high completeness and accuracy[75]. No similar validation of rectal cancer recurrence has been published, however, follow-up rates after five years is above 90%[76].

The data registration in the SCRCR is dynamic with addition of more variables over time. Some variables of potential interest were not available during the study periods and could not be analyzed or assessed for potential confounding effect.

Study I, II and IV were designed with regards to sample size to comparatively study rare clinical circumstances in the treatment of rectal cancer. Performing these studies in a randomized fashion to achieve higher level of scientific evidence would not be feasible for ethical and practical reasons. Study III is descriptive and investigates the management of MRI-positive LLNs in a regional cohort. With available high-accuracy national data this might be repeated in a larger cohort to reduce the risk of type II-error. Treatment strategies of patients with MRI-positive LLNs could potentially be evaluated in randomized study design.

Ethical considerations

Ethical approval was granted prior to each study in this thesis. Paper I and II were approved by the Regional Ethical Review Board in Lund (Dnr 2017/157).

Paper III and IV were approved by the Swedish Ethical Review Authority (Dnr 2019-02175 and 2020-01769).

Data extraction from the SCRCR (paper I-IV) and review of medical records (paper III) were conducted in accordance with these approvals. Owing to the retrospective design of the studies, no treatment intervention was made. Information and general consent with an opt-out alternative was given all patients prior to registration of data in the SCRCR.

Statistical analysis

Study design, statistical methods and analyses have been discussed and planned with statisticians to ensure correct reporting of results. In all studies, missing data was excluded when calculating differences between groups. Multivariable analysis was performed adjusting for confounders in paper I, II and IV. Adjustment variables were chosen after univariable and causal analysis and limited by the number of outcome-events.

Statistical analyses were conducted using IBM® SPSS® Statistics version 25.00/27.00 for Windows® (IBM Corp, Armonk, NY, USA). In paper IV, R version 4.0.1 (R Core Team 2020, Vienna, Austria; http://www.R-project.org) was used for survival analysis.

Differences with a p-value <0.05 was considered statistically significant throughout.

Paper I and II

Categorical variables were presented as numbers and proportions in percentages. Pearson's chi-square test, Fisher's exact test was used for intergroup comparisons of categorical data, as appropriate. Numerical data was reported as mean with IQR and two-tailed t-test was used for intergroup comparisons.

In paper I, Cox regression analysis was used to calculate outcome differences between CRM-groups. Multivariable analysis was adjusted for sex, age, tumour height, tumour stage, neoadjuvant CRT and RT, surgical procedure, rectal washout and intraoperative perforation. As there were few patients in each group who had RT and developed LR, the multivariable analysis for CRM and RT was adjusted for

tumour height and stage only. Results were presented as hazard ratio (HR) with confidence intervals.

In paper II, Cox regression analysis was used to calculate outcome differences between CRM-groups. Multivariable analysis was performed adjusting for age, sex, tumour height, neoadjuvant RT and CRT, T3/4-stage, N-stage, V/L-infiltration, perineural growth, and adjuvant CHT. Results were presented as HR with confidence intervals.

Paper III

Categorical variables were presented as numbers and proportions in percentages. Pearson's chi-square test or Fisher's exact test was used when calculating differences in categorical data between groups. Numerical data was reported as means with IQR and two-tailed t-test was used for intergroup comparisons of means.

Survival analysis was performed with Mantel-Cox regression and presented with a Kaplan–Meier survival plot of the follow-up period. OS was reported with confidence intervals of each group respectively.

Paper IV

Categorical variables were presented as numbers and proportions in percentages and Pearson's chi-square test was used when estimating differences in categorical data between groups. Numerical, normally distributed data was reported as means with standard deviation whereas unevenly distributed numerical data was reported as median with IQR. Two-tailed t-test was used for intergroup comparisons of numerical data.

Modified Poisson regression analysis was used to estimate risk of recurrence at 1, 3 and 5 years and presented as relative risk (RR) with confidence intervals. Cox regression analysis was used for outcome comparisons between groups for LR, DM, OS and RS and presented as HR with confidence intervals. RS was calculated against a national cohort derived from Statistics Sweden[144].

Multivariable analysis was adjusted for age, sex, neoadjuvant RT, neoadjuvant CRT, lympho-vascular infiltration, perineural growth and adjuvant CHT. In some analyses, limited number of outcome-events prohibited multivariable analysis and results were subsequently presented only with univariable estimates.

Definitions

Rectal cancer

Rectal cancer is defined as an adenocarcinoma with the lower border located ≤15 cm from the anal verge measured with rigid sigmoidoscopy.

CRM-positive, R1 and R2-resection

Description of the resection margin in rectal cancer surgery might be done in several ways. The basic purpose is to answer whether the tumour has been removed with surgical resection. This might be evaluated in two principal ways; macroscopically during surgery where no residual tumour may be left behind and microscopically during histopathological examination of the resection specimen after resection.

Macroscopically radical resection is frequently used to describe a complete resection of the tumour locally. If residual tumour or known distant metastases are left behind, for whatever reason, some argue the resection should be classified as R2-resection[145]. In the SCRCR, R2-resection is typically used in case of macroscopically non-radical local resection although some inconsistency may exist.

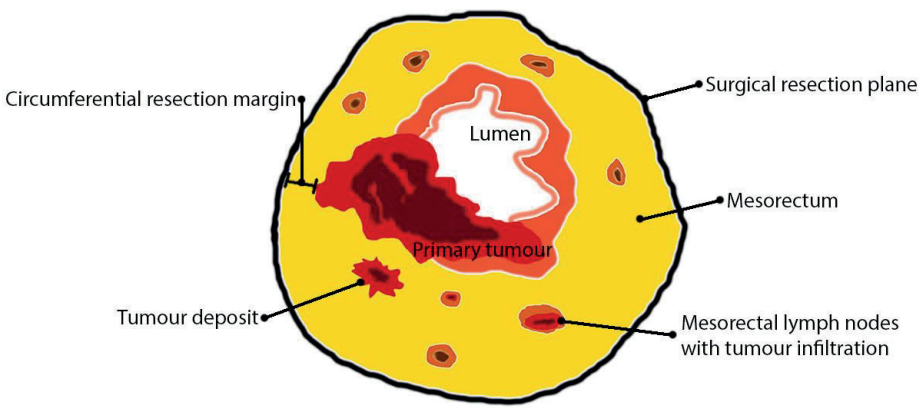

Figure 3 – Schematic illustration of CRM between tumour tissue and resection plane.

During microscopic examination the specimen may be closely studied and margins between tumour tissue and resection plane measured. However, both the definition of what constitutes microscopically radical resection and what terminology to use have been debated[27,84,145–147]. In the current thesis, R1-resection was used when no margin between tumour tissue or resection plane could be identified microscopically and corresponds to CRM = 0.0 mm. CRM-positive resection was used, defining a resection margin of 1.0 mm or less between tumour tissue and resection plane (Figure 3).

Lateral lymph nodes

In paper III, LNs located outside the MRF along the common iliac, internal iliac, external iliac and obturator vessels were classified as LLNs (Figure 4). Inguinal and paraaortic LNs constituted M1-disease by this definition. This differ from the classification proposed in the UICC TNM classification 8th ed. and AJCC staging manual 8th ed. where only LNs along the internal iliac and obturator vessels are considered LLNs whereas LNs along the common iliac, external iliac together with inguinal and paraaortic LNs are classified as M-stage disease[13,14].

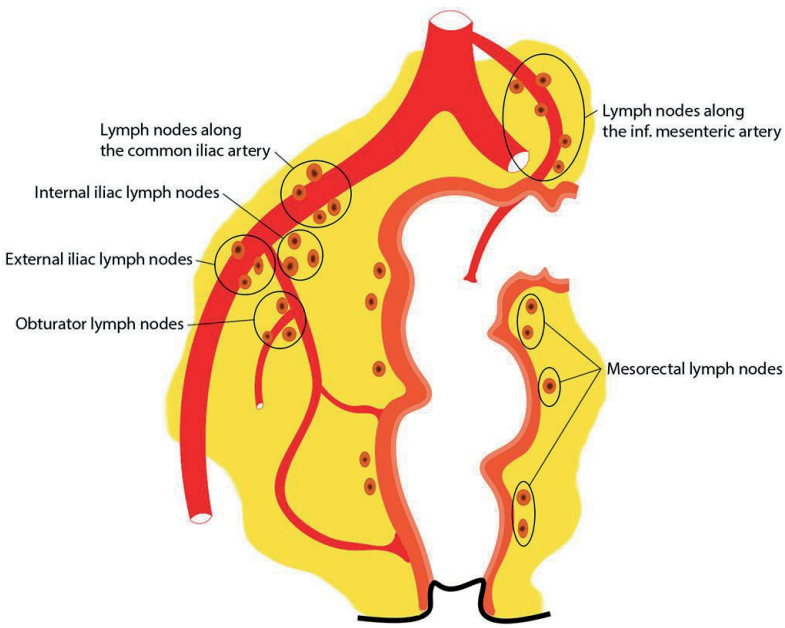

Figure 4 – Schematic illustration of perirectal, mesorectal and lateral lymph node stations along the major pelvic vessels.

Tumour deposit

TDs in rectal adenocarcinoma are irregular tumour nodules with infiltrative borders in the perirectal adipose tissue, discontinuous from the primary tumour (at least one centimetre from the advancing edge), and lacking a thick fibrous capsule (Figure 5)[13,14].

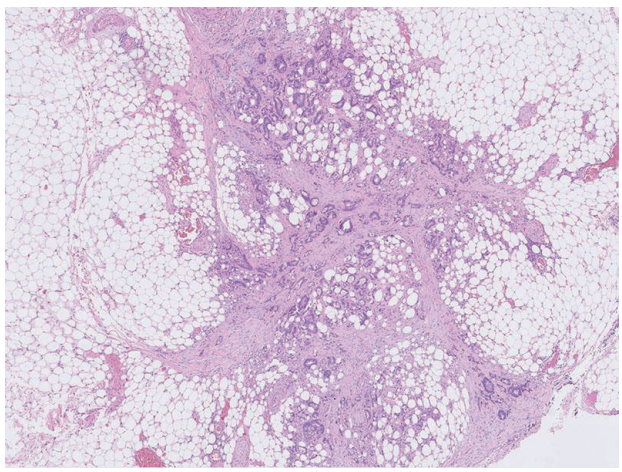

Figure 5 – Tumour deposit infiltrating mesorectal adipose tissue without signs of vessels or lymphoid structures. Image from the Department of Pathology, Skåne University Hospital, Malmö, Sweden.

Recurrence

Local recurrence

LR was defined as local extraperitoneal tumour recurrence, tumour growth in local LNs, intraluminal tumour recurrence or peritoneal tumour growth below the promontory >90 days after primary surgery.

Distant metastasis

DM was defined as tumour recurrence in an organ outside the small pelvis such as lungs, liver, LNs, peritoneum and/or any other distant organ >90 days after primary surgery.

Results

Paper I

Data on 12,146 patients treated with abdominal resection for rectal cancer between January 1st 2005 and December 31st 2013 was retrieved from the SCRCR. Patients with incomplete histopathology regarding resection margins, non-curative resection or stage IV-disease were excluded. Patients with early LR within 90 days of primary surgery were also excluded. Two hundred seventy-four patients were lost to follow-up or died within 30 days of surgery and were not analysed.

The analysed cohort consisted of 8,392 patients. CRM-positive resection occurred in 8.8% (n=739/8392) of patients. Among CRM-negative patients 3.3% (n=256/7653) LR was diagnosed compared to 8.9% (n=66/739) in the CRM-positive patients (Figure 6).

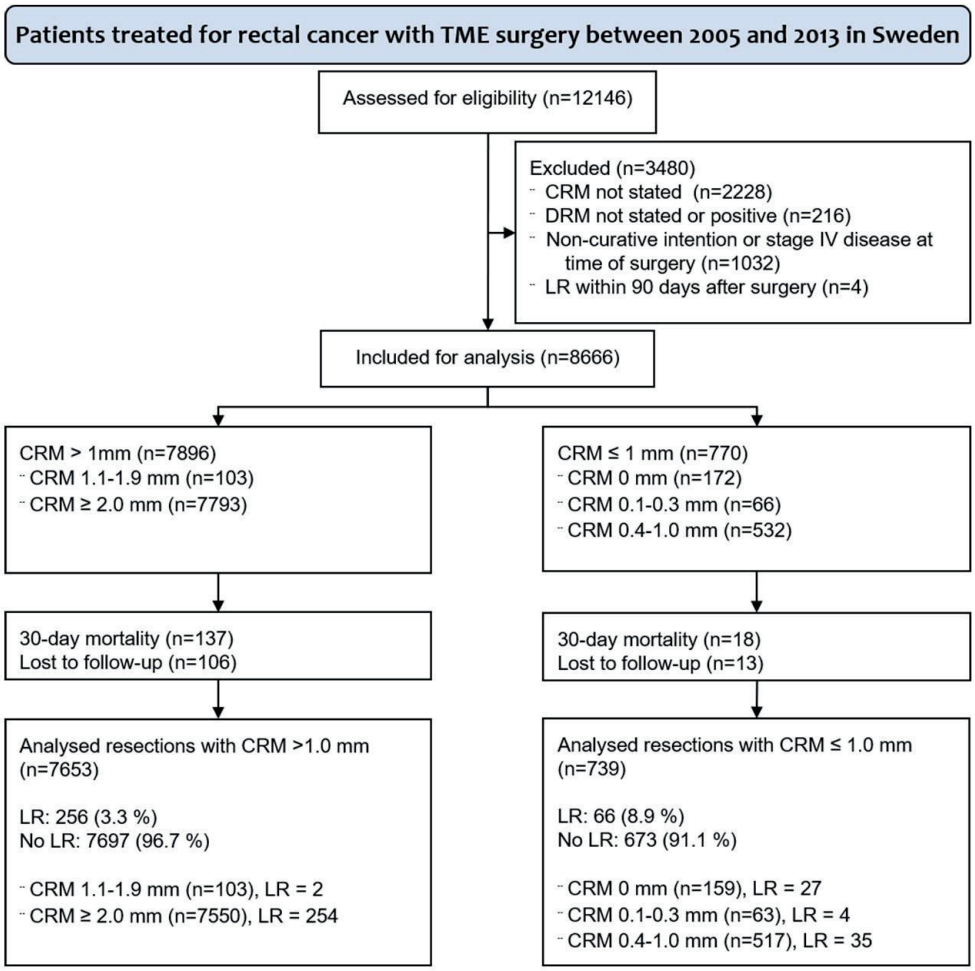

Figure 6 – Study flow diagram. TME, total mesorectal excision; CRM, circumferential resection margin; DRM, distal resection margin; DM, distant metastasis; LR, local recurrence.

The rate of LR decreased with increasing CRM (Figure 7). In multivariable cox regression analysis, smaller CRM was associated with increasing LR risk. The highest LR risk was seen in patients with CRM 0.0 mm, i.e. R1-resection compared to all other groups except CRM 0.1-0.3 mm (Table 3 and 4). No difference was detected in LR risk between patients with a CRM >1.0 mm (Table 4).

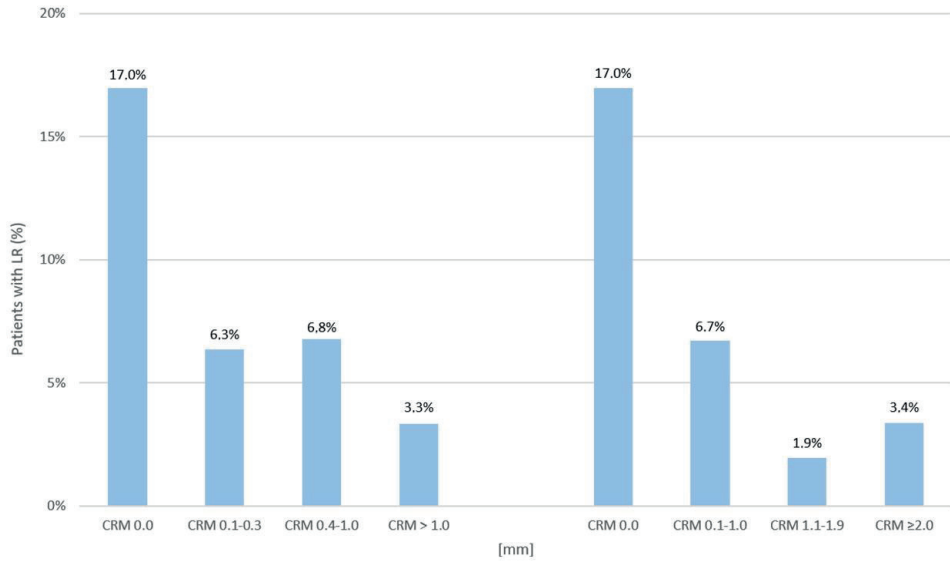

Figure 7 – LR-rate based on exact CRM within the analysed subgroups. CRM, circumferential resection margin; LR, local recurrence

Table 3 – Multivariable cox regression analysis of LR risk in relation to specified CRM

Circumferential resection margin	Hazard Ratio (95% CI)	p-value
0.0 mm vs 0.1-0.3 mm	2.45 (0.85 ; 7.09)	0.098
0.0 mm vs 0.4-1.0 mm	2.44 (1.45 ; 4.10)	<0.001
0.0 mm vs > 1.0 mm	3.79 (2.48 ; 5.80)	<0.001
0.1-0.3 mm vs 0.4-1.0 mm	0.99 (0.35 ; 2.81)	0.990
0.1-0.3 mm vs > 1.0 mm	1.55 (0.57 ; 4.17)	0.387
0.4-1.0 mm vs > 1.0 mm	1.56 (1.08 ; 2.24)	0.017

Adjusted for sex, age, tumour height, tumour stage, neoadjuvant chemotherapy and radiotherapy, surgical procedure, rectal washout and intraoperative tumour perforation. Patients with complete data in all adjustment variables were analysed (n=8061).

Table 4 – Multivariable cox regression analysis of LR risk in relation to specified CRM

Circumferential resection margin	Hazard Ratio (95% CI)	p-value
0.0 mm vs 0.1-1.0 mm	2.43 (1.46 ; 4.05)	<0.001
0.0 mm vs 1.1-1.9 mm	15.88 (2.15 ; 117.5)	0.007
0.0 mm vs ≥ 2.0 mm	3.73 (2.44 ; 5.71)	<0.001
0.1-1.0 mm vs 1.1-1.9 mm	6.53 (0.89 ; 47.62)	0.064
0.1-1.0 mm vs ≥ 2.0 mm	1.53 (1.09 ; 2.17)	0.015
1.1-1.9 mm vs ≥ 2.0 mm	0.24 (0.03 ; 1.68)	0.149

Adjusted for sex, age, tumour height, tumour stage, neoadjuvant chemotherapy and radiotherapy, surgical procedure, rectal washout and intraoperative tumour perforation. Patients with complete data in all adjustment variables were analysed (n=8061).

LR was on average diagnosed earlier (mean 17.6 months vs 27.3 months) in patients with CRM-positive resection compared to CRM-negative patients. Approximately 80% of LR was diagnosed within two years in CRM-positive patients (Figure 8). Only fourteen LR was detected more than five years after surgery, all in the CRM-negative group.

CRM-negative and positive patients were treated with neoadjuvant RT to a similar extent. CRT was given to 12.6% in the CRM-negative group and to 17.2% of patients in the CRM-positive group, likely due to more advanced stage among those patients. The possible effect of RT was estimated with univariable and multivariable Cox regression analysis. No reduction in LR risk could be seen in relation to CRM (Paper I, Table 3).

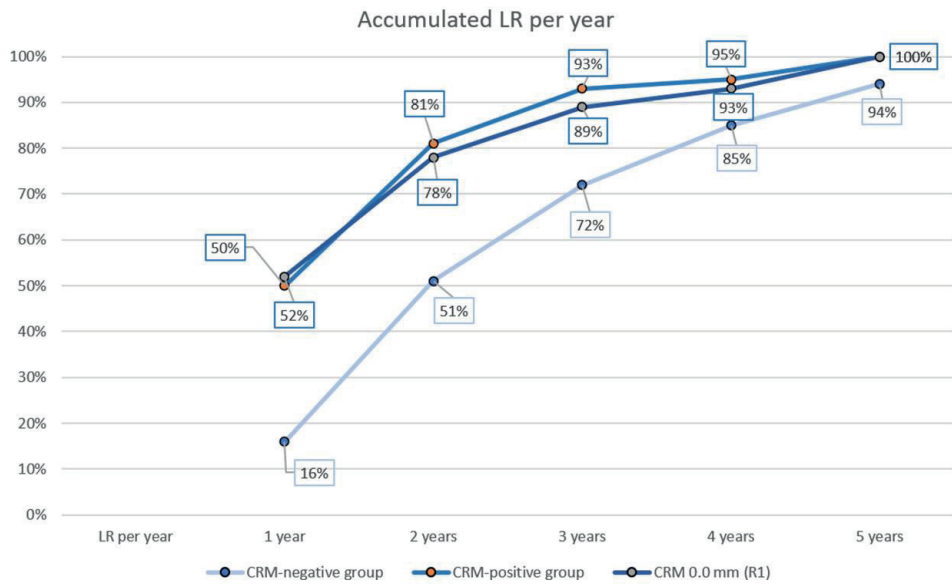

Figure 8 – Accumulated number of LR diagnosed per year after primary surgery; CRM, circumferential resection margin; LR, local recurrence

Paper II

Data on 12,146 patients treated with abdominal resection for rectal cancer between January 1st 2005 and December 31st 2013 was retrieved from the SCRCR. Patients with incomplete histopathology regarding resection margins, non-curative resection or stage IV-disease was excluded. Patients with early LR or DM within 90 days of primary surgery were also excluded. Two hundred ninety-nine patients were lost to follow-up or died within 30 days of surgery and were not analysed.

The analysed cohort consisted of 8,294 patients. CRM-positive resection occurred in 8.5% (n=717/8294) of patients. Among CRM-negative patients 18.3% (n=1387/7577) DM was diagnosed compared to 30.7% (n=220/717) of the CRM-positive patients (Figure 9).

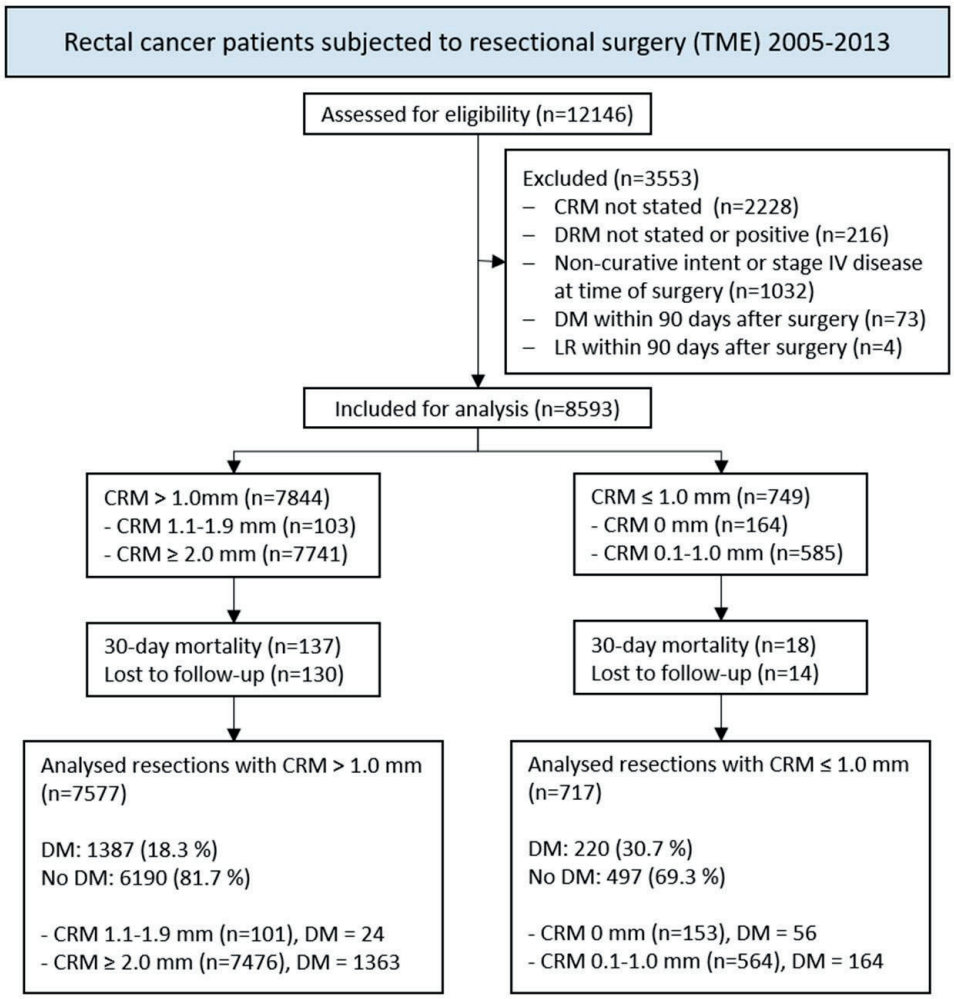

Figure 9 – Study flow diagram. DM, distant metastasis; CRM, circumferential resection margin; DRM, distal resection margin; LR, local recurrence.

In univariable analysis, DM risk was significantly increased in CRM-positive patients. Compared to CRM ≥2.0 mm HR of DM was 2.50 (95% CI 1.92 – 3.27, P=<0.001) and 1.77 (95% CI 1.51 – 2.09, P=<0.001) among patients with CRM 0.0 mm and CRM 0.1-1.0 mm respectively. No significant difference was detected when comparing DM risk CRM ≥2.0 mm vs CRM 1.1-1.9 mm HR 1.40 (95% CI 0.94 – 2.10, P=0.101). Kaplan-Meier plot of DM-free survival comparing these groups is provided in Figure 10.

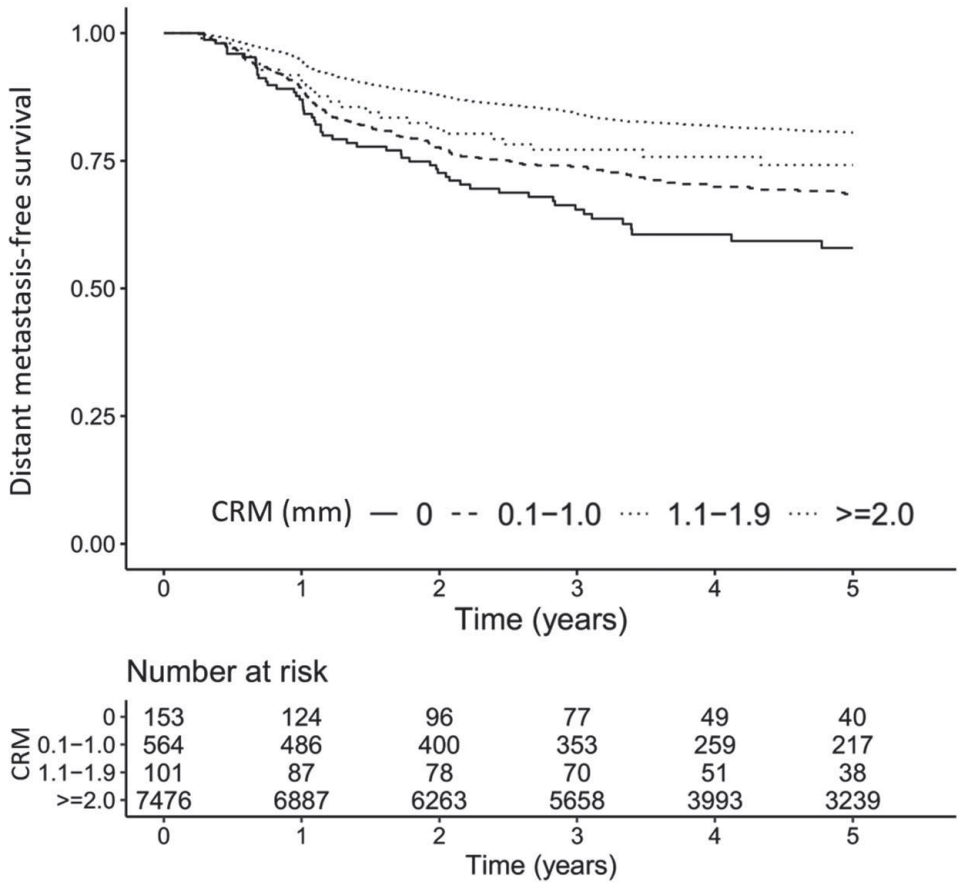

Figure 10 – Freedom (survival) from distant metastasis after surgery according to circumferential resection margin (CRM).

When comparing CRM >1.0 mm with CRM-positive patients in univariable analysis, CRM 0.0 mm had HR 2.49 (95% CI 1.91 – 3.25, P=<0.001) and CRM 0.1-1.0 mm HR 1.76 (95% CI 1.50 – 2.08, P=<0.001) of DM.

The cumulative DM-rate was also associated with CRM in this cohort. Patients with CRM-positive resection had an increased DM recurrence rate during follow-up (Table 5).

Table 5 – Cumulative DM recurrence rate for each year and each CRM-group

	CRM ≥2.0 mm	CRM 1.1-1.9 mm	CRM 0.1-1.0 mm	CRM 0.0 mm
Cumulative %	DM recurrence rate (95% CI)			
1 year	5.5% (5.0-6.0)	9.3% (3.3-14.8)	11.4% (8.7-14.0)	13.0% (7.4-18.3)
2 years	12.2% (11.4-12.9)	18.6% (10.5-26.1)	22.4% (18.8-25.8)	27.4% (19.6-34.4)
3 years	15.8% (15.0-16.6)	22.8% (14.0-30.8)	26.1% (22.3-29.8)	34.5% (26.1-42.1)
4 years	18.2% (17.3-18.2)	24.2% (15.0-32.4)	30.1% (26.0-34.0)	39.4% (30.3-47.3)
5 years	19.5% (18.5-19.5)	25.8% (16.2-34.4)	31.5% (27.3-35.5)	42.1% (32.5-50.3)

DM, distant metastasis

In multivariable analysis, adjusted for tumour specific risk factors and oncological therapy, the association between CRM and DM risk was less pronounced (Table 6). However, CRM >1.0 mm or ≥2.0 mm was associated with lower DM risk compared to CRM 0.1-1.0.

Table 6 – Multivariable Cox regression analysis with HR of DM after surgery according to CRM

Circumferential resection margin	n	Hazard Ratio (95% CI)	p-value
0.0 mm	86	1.23 (0.83−1.80)	0.303
0.1-1.0 mm	303	1.29 (1.04−1.59)	0.018
1.1-1.9 mm	52	0.66 (0.34−1.28)	0.224
≥2.0 mm	4894	Ref	
Circumferential resection margin	n	Hazard Ratio (95% CI)	p-value
0.0 mm	86	1.23 (0.84-1.81)	0.283
0.1-1.0 mm	303	1.30 (1.05−1.60)	0.015
>1.0 mm	4946	Ref	

Adjusted for age, sex, tumor height, neoadjuvant radiotherapy and chemotherapy, T3/4-stage, N-stage, V/L-infiltration, perineural growth and adjuvant chemotherapy. Two thousand nine hundred fifty-nine patients were excluded in the multivariable analysis due to missing data in any of the adjustment variables.

Multivisceral pelvic resections (coccyx, bladder, prostate, vesicles, ureters, ovaries, uterus), involvement of pelvic floor and large or small bowel resections were more common in CRM-positive patients.

Especially in patients with CRM 0.0 mm where 30.7% (n=47/153) underwent multivisceral resection compared to 16.7% (n=94/564), 16.8% (n=17/101) and 10.7% (n=797/7476) among CRM 0.1-1.0 mm, CRM 1.1-1.9 mm and CRM ≥2.0 mm respectively.

Patients may suffer from both LR and metachronous DM following rectal cancer resection. DM was the most prevalent type of recurrence irrespective of CRM,

however, in CRM-positive patients LR and DM were diagnosed in a greater proportion of patients (Table 7).

Table 7 – Recurrence pattern in relation to circumferential resection margin (CRM)

Recurrence	n	CRM ≥2.0 mm	CRM 1.1-1.9 mm	CRM 0.1-1.0 mm	CRM 0.0 mm
DM	1433	1231 (90.3%)	22 (91.7%)	138 (84.1%)	42 (75.0%)
DM and LR	174	132 (9.7%)	2 (8.3%)	26 (15.9%)	14 (25.0%)

DM, distant metastasis; LR, local recurrence.

As noted above, CRM should be measured between any type of tumour growth and the resection margin. Local tumour growth occurs in a number of different histopathological manifestations. Detailed analysis of the available histopathological data in relation to CRM-groups showed a tendency towards more advanced risk factor composition associated with smaller CRM (Table 8).

Table 8 –Detailed histopathological data for each examined group

		All patients	CRM ≥2.0 mm	CRM 1.1-1.9 mm	CRM 0.1-1.0 mm	CRM 0.0 mm
Patients		8294	7476	101	564	153
pT-stage	T0	58 (0.7)	53 (0.7)	1 (1.0)	4 (0.7)	0 (0.0)
	T1	533 (6.4)	524 (7.0)	1 (1.0)	7 (1.2)	1 (0.7)
	T2	2406 (29.0)	2337 (31.3)	16 (15.8)	46 (8.2)	7 (4.6)
	T3	4784 (57.7)	4194 (56.1)	75 (74.3)	447 (79.3)	68 (44.4)
	T4	497 (6.0)	353 (4.7)	8 (7.9)	60 (10.6)	76 (49.7)
	Missing	*2 (0.0)*	*2 (0.0)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*
pN-stage	N0	5081 (61.3)	4735 (63.3)	50 (49.5)	230 (40.8)	66 (43.1)
	N1	1989 (24.0)	1759 (23.5)	30 (29.7)	157 (27.8)	43 (28.1)
	N2	1154 (13.9)	922 (12.3)	20 (19.8)	171 (30.3)	41 (26.8)
	NX	70 (0.8)	60 (0.8)	1 (1.1)	6 (1.1)	3 (2.0)
	Missing	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*
L/V-infiltration	Yes	1309 (15.8)	1089 (14.6)	28 (27.7)	145 (25.7)	47 (30.7)
	No	4942 (59.6)	4572 (61.2)	58 (57.4)	245 (43.4)	67 (43.8)
	Missing	*2043 (24.6)*	*1815 (24.3)*	*15 (14.9)*	*174 (30.9)*	*39 (25.5)*
Perineural growth	Yes	804 (9.7)	639 (8.5)	14 (13.9)	110 (19.5)	41 (26.8)
	No	4791 (57.8)	4465 (59.7)	51 (50.5)	220 (39.0)	55 (35.9)
	Missing	*2699 (32.5)*	*2372 (31.7)*	*36 (35.6)*	*234 (41.5)*	*57 (37.3)*
Tumour deposits	Yes	298 (3.6)	241 (3.2)	6 (5.9)	36 (6.4)	15 (9.8)
	No	2236 (27.0)	2082 (27.8)	22 (21.8)	101 (17.9)	31 (20.3)
	Missing	*5760 (69.4)*	*5153 (69.0)*	*73 (72.3)*	*427 (75.8)*	*107 (69.9)*
Tumor grade	High	6351 (76.6)	5815 (77.8)	83 (82.2)	360 (63.8)	93 (60.8)
	Low	965 (11.6)	811 (10.8)	14 (13.9)	109 (19.3)	31 (20.3)
	Missing	*978 (11.8)*	*850 (11.4)*	*4 (4.0)*	*95 (16.8)*	*29 (19.0)*

V/L, vascular/lymphatic. Values in parentheses are percentages unless indicated otherwise.

Paper III

One-thousand one-hundred and nineteen patients treated with abdominal resection surgery for rectal adenocarcinoma between 1 January 1st 2009 and December 31st 2014 were assessed for eligibility. Patients were identified and data retrieved from SCRCR. Patients with tumour above 10 cm from the anal verge, cT1-2N0-stage, positive CRM or DRM and no MRI of the pelvis available for analysis were excluded. In total, 344 patients met inclusion criteria and formed the study cohort. After primary MRI analysis, 106 patients underwent secondary MRI-evaluation with review of the primary exam.

MRI-positive LLNs were identified in 8.7% (n=30/344) of patients (Figure 11).

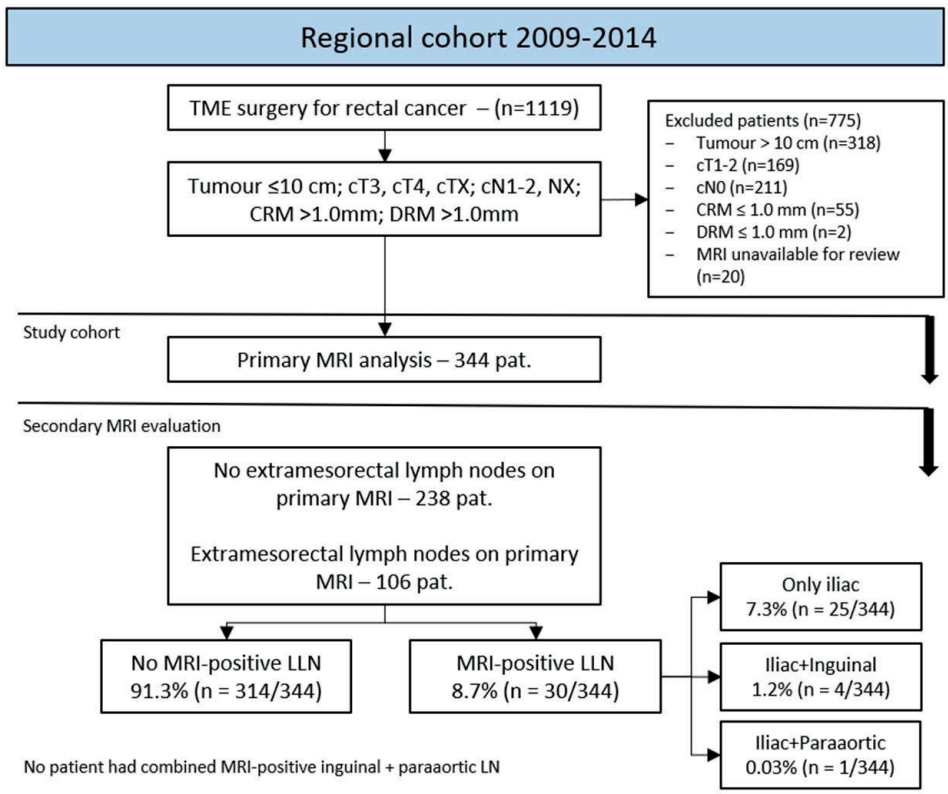

Figure 11 – Study flow diagram. DM, distant metastasis; CRM, circumferential resection margin; DRM, distal resection margin; LR, local recurrence.

The high-risk features of the entire cohort were evident when comparing the group with MRI-negative with MRI-positive LLNs (Table 9). Synchronous DM was the only statistically significant difference between groups.

Table 9 – Descriptive patient characteristics and outcome

		All patients	MRI-negative LLN	MRI-positive LLN	p-value
Patients		344	314	30	
Sex	Male	206 (59.9)	185 (58.9)	21 (70.0)	0.237
	Female	138 (40.1)	129 (41.1)	9 (30.0)	
Age	Mean	66.4	66.4	66.2	0.238
Neoadjuvant therapy	None	26 (7.6)	25 (8.0)	1 (3.3)	0.128
	SCRT	170 (49.4)	160 (51.0)	10 (33.3)	
	LCRT	139 (40.4)	121 (38.5)	18 (60.0)	
	Other	9 (2.6)	8 (2.5)	1 (3.3)	
Surgical procedure	APR	188 (54.7)	167 (53.2)	21 (70.0)	0.209
	Hartmann	33 (9.6)	31 (9.9)	2 (6.7)	
	AR	123 (35.8)	116 (36.9)	7 (23.3)	
Tumour height (cm)	Low (0-5)	139 (40.4)	125 (39.8)	14 (46.7)	0.465
	Medium (6-10)	205 (59.6)	189 (60.2)	16 (53.3)	
cT-stage	cT3	227 (66.0)	209 (66.6)	18 (60.0)	0.250
	cT4	88 (25.6)	77 (24.5)	11 (36.7)	
	cTX	29 (8.4)	28 (8.9)	1 (3.3)	
cN-stage	cN1-2	235 (68.3)	210 (66.9)	25 (83.3)	0.064
	cNX	109 (31.7)	105 (33.4)	5 (16.7)	
cM-stage (Synchronous)	cM0	292 (84.9)	274 (87.3)	18 (60.0)	<0.001
	cM1	52 (15.1)	40 (12.7)	12 (40.0)	
pT-stage	pT0-2	108 (31.4)	98 (31.2)	10 (33.3)	0.744
	pT3-4	233 (67.7)	213 (67.8)	20 (66.7)	
	pTX	3 (0.9)	3 (1.0)	0 (0.0)	
pN-stage	pN0	193 (56.1)	173 (55.1)	20 (66.7)	0.407
	pN1-2	149 (43.3)	139 (44.3)	10 (33.3)	
	pNX	2 (0.6)	2 (0.6)	0 (0.0)	
Perineural growth	Yes	70 (20.3)	67 (21.3)	3 (10.0)	0.135
	No	271 (78.8)	244 (77.7)	27 (90.0)	
	Missing	3 (0.9)	3 (1.0)	0 (0.0)	
Lympho-Vascular infiltration	Yes	59 (17.2)	55 (17.5)	4 (13.3)	0.547
	No	282 (82.0)	256 (81.5)	26 (86.7)	
	Missing	3 (0.9)	3 (1.0)	0 (0.0)	
Adjuvant therapy	None	235 (68.3)	213 (67.8)	22 (73.3)	0.536
	CHT	109 (31.7)	101 (32.2)	8 (26.7)	
Local recurrence	Yes	16 (4.7%)	13 (4.1)	3 (10.0)	0.154
	No	328 (95.3)	301 (95.9)	27 (90.0)	
Distant metastasis (Metachronous)	Yes	111 (32.3)	99 (31.5)	12 (40.0)	0.343
	No	233 (67.7)	215 (68.5)	18 (60.0)	
Follow-up	Mean (m)	75 (IQR 55-99	76 (IQR 60-100)	65 (IQR 34-97)	<0.001

SCRT, short course radiotherapy; LCRT, long course chemoradiotherapy; CHT, chemotherapy; AR, anterior resection; APR, abdominoperineal resection. Values in parentheses are percentages unless indicated otherwise.

The anatomic location of MRI-positive LLNs were registered. The most common location was at the internal iliac artery (Table 10). Two patients had LLNs in multiple locations along the iliac arteries.

Table 10 - Locations of MRI-positive LLNs

Right internal iliac	Right external iliac	Right obturator	Right common iliac
12 (48.0%)	2 (8.0%)	0 (0.0%)	4 (16%)
Left internal iliac	Left external iliac	Left obturator	Left common iliac
9 (36.0%)	2 (8.0%)	3 (12.0%)	2 (8.0%)

LR-rate was 4.1% (n=13/314) and 10.0% (n=3/30) among MRI-negative and MRI positive patients, respectively. No difference was detected in LR-rate (P=0.154). DM-rate was 31.5% (n=99/314) in MRI-negative patients and 40.0% (n=12/30) in MRI-positive patients without significant difference between groups (P=0.343). There was no difference in OS between groups (P=0.142) (Figure 12).

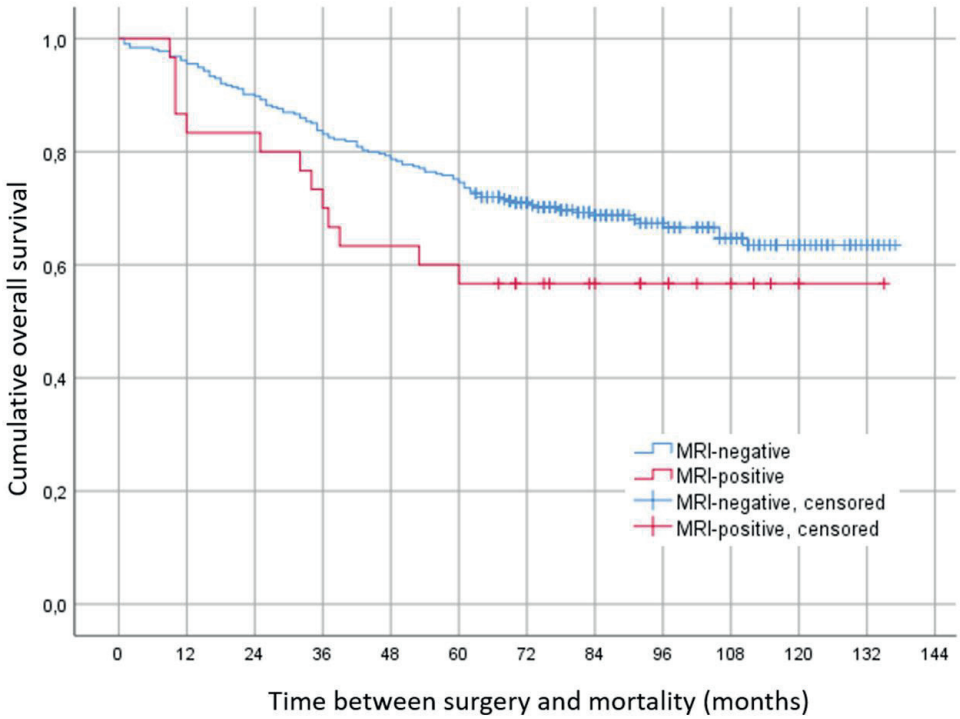

Figure 12 – Kaplan-Meier survival plot between MRI-negative (n=314) and MRI-positive (n=30) patients.

As described above, there was a difference in synchronous DM between groups. In MRI-negative patients 12.7% (n=40/314) had DM at time of diagnosis compared to 40.0% (n=12/30) among patients with MRI-positive LLN (Table 9). Patients with MRI-positive LLNs were more often diagnosed with synchronous DM in inguinal LNs (Figure 13).

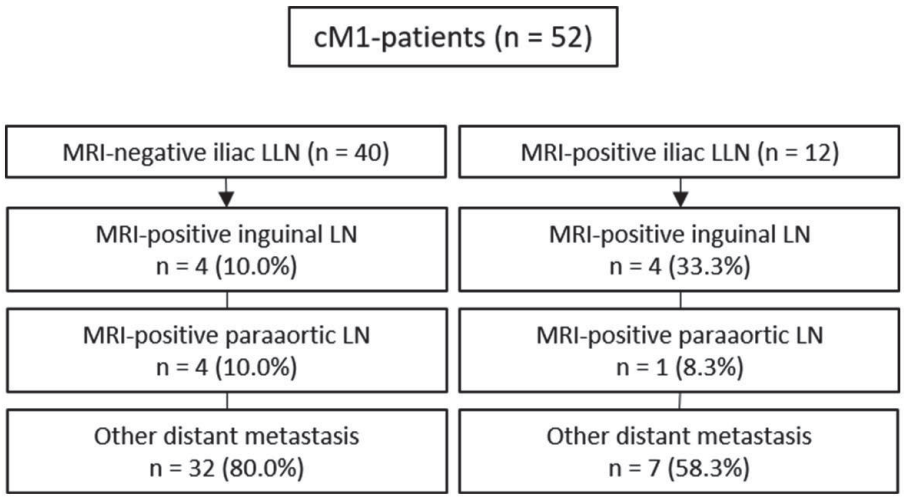

Figure 13 - cM1-distribution in patients with MRI negative and positive lateral lymph nodes (LLN). LN, Lymph node.

Paper IV

Data on 5,455 patients treated with abdominal resection for rectal cancer between January 1st 2011 and December 31st 2014 was retrieved from the SCRCR. Patients without histopathological TD-status, stage IV-disease and non-radical resection margins were excluded. Patients with early LR, DM or death within 90 days of primary surgery were not analysed. Eighty-two patients were lost to follow-up. The analysed cohort consisted of 3,750 patients. Out of these patients, 10.7% (n=400/3750) were TD-positive and 89.3% (n=3350/3750) TD-negative. Among TD-positive patients 6.0% (n=24/400) LR and 37.8% (n=151/400) DM were diagnosed. In TD-negative patients 2.6% (n=86/3350) LR and 14.1% (n=473/3350) DM were diagnosed during follow-up (Figure 14).

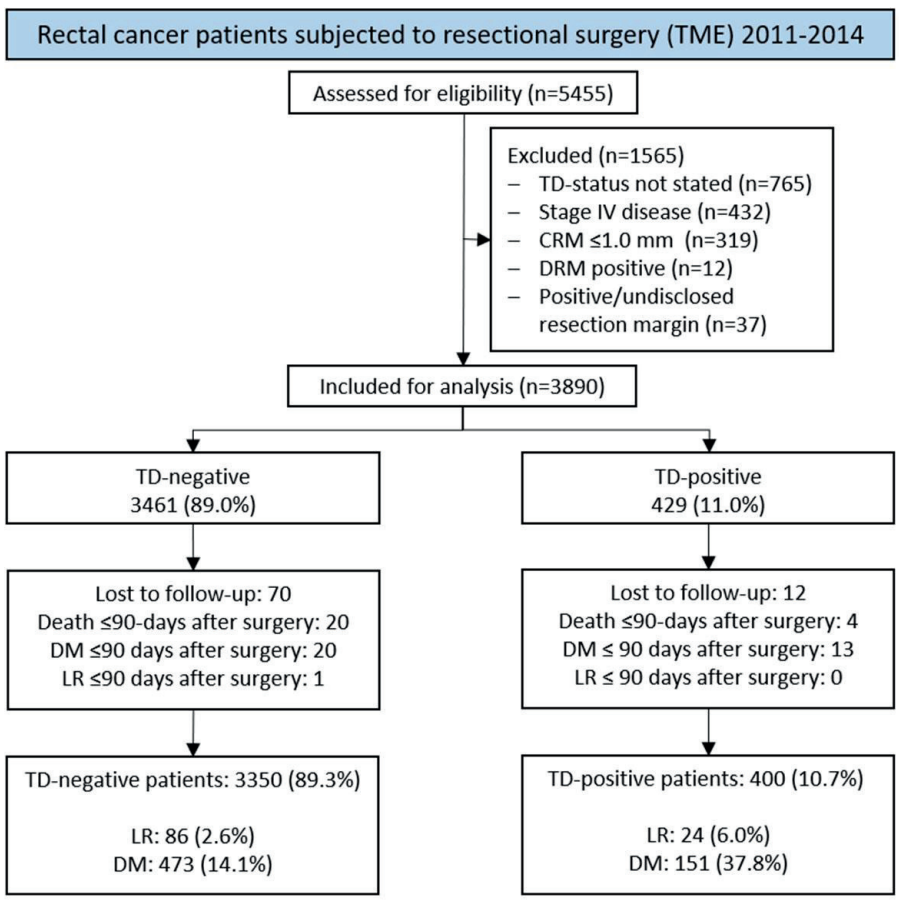

Figure 14 – Study flow diagram. TD, tumor deposit; CRM, circumferential resection margin; DRM, distal resection margin; DM, distant metastasis; LR, local recurrence.

Data on analysed patients clinical, oncological treatment and histopathological characteristics are presented in Table 11. Median TD-count was 1 and mean 2.3. Mortality during follow-up was 27.8% (n=931/3350) in TD-negative patients and 43.0% (n=172/400) in TD-positive patients. Median follow-up were comparable between groups at 60 (IQR 57-63) and 59 (IQR 48-63) months in TD-negative and TD-positive patients respectively.

Table 11 – Tumour characteristics and oncological therapy

		All patients	TD-negative	TD-positive
Patients	(n)	3750	3350	400
Tumor height (cm)	Low (0-5)	1024 (27.3)	945 (28.2)	79 (19.8)
	Medium (6-10)	1555 (41.5)	1370 (40.9)	185 (46.3)
	High (11-15)	1132 (30.2)	1001 (29.9)	131 (32.8)
	Missing	39 (1.0)	34 (1.0)	5 (1.3)
Clinical stage	I	710 (18.9)	678 (20.2)	32 (8.0)
	II	800 (21.3)	746 (22.2)	57 (14.2)
	III	1903 (50.7)	1628 (48.6)	275 (68.8)
	Missing	337 (9.0)	301 (9.0)	36 (9.0)
Neoadjuvant therapy	RT	1781 (47.5)	1557 (46.5)	224 (56.0)
	CRT	726 (19.4)	632 (18.9)	94 (23.5)
	CHT	9 (0.2)	9 (0.3)	0 (0.0)
	None	1233 (32.9)	1151 (34.4)	82 (20.5)
	Missing	1 (0.0)	1 (0.0)	0 (0.0)
Histopathological stage	0	121 (3.2)	121 (3.6)	0 (0.0)
	I	1199 (32.0)	1199 (35.8)	0 (0.0)
	II	1119 (29.8)	1118 (33.4)	1 (0.3)
	III	1277 (34.1)	879 (26.2)	398 (99.5)
pT-stage	pT1	323 (8.6)	317 (9.5)	6 (1.5)
	pT2	1169 (31.2)	1120 (33.4)	49 (12.3)
	pT3	1936 (51.6)	1647 (49.2)	289 (72.3)
	pT4	167 (4.5)	119 (3.6)	48 (12.0)
	Missing	8 (0.2)	8 (0.2)	0 (0.0)
pN-stage	pN0	2445 (65.2)	2444 (73.0)	1 (0.3)
	pN1	911 (24.3)	630 (18.8)	281 (70.3)
	pN2	368 (9.8)	251 (7.5)	117 (29.3)
	Missing	26 (0.7)	25 (0.7)	1 (0.3)
L/V-infiltration	Yes	698 (18.6)	508 (15.2)	190 (47.5)
	No	3025 (80.7)	2818 (84.1)	207 (51.7)
	Missing	27 (0.7)	24 (0.7)	3 (0.8)
Perineural growth	Yes	471 (12.6)	342 (10.2)	129 (32.3)
	No	3163 (84.3)	2903 (86.7)	260 (65.0)
	Missing	116 (3.1)	105 (3.1)	11 (2.8)
Adjuvant CHT	Yes	884 (23.6)	1264 (37.7)	213 (53.3)
	No	2852 (76.1)	2085 (62.2)	182 (45.5)
	Missing	14 (0.4)	1 (0.0)	5 (1.3)
	Alive at follow-up	2632 (70.2)	2406 (71.8)	226 (56.5)
	Missing	15 (0.4)	13 (0.4)	2 (0.5)

DM, distant metastasis; RT, radiotherapy; CRT, chemo-radiotherapy; CHT, chemotherapy; L/V, lympho-vascular. Values in parentheses are percentages.

Recurrence risk differed significantly between groups when comparing the cumulative recurrence rate and calculated recurrence risk both in univariable and multivariable analysis except regarding adjusted LR risk one year after surgery (Table 12).

Table 12 – Diagnosed recurrence at follow-up at one, three and five years

	Local recurrence				Distant metastasis			
	Univariable				Univariable			
Follow-up	TD-neg (ref.)	TD-pos	RR (CI 95%)	p-value	TD-neg (ref.)	TD-pos	RR (CI 95%)	p-value
RR year 1	3284	390	3.24 (1.16-9.04)	0.025	3281	395	4.15 (3.10-5.56)	<0.001
RR year 3	3029	347	2.66 (1.59-4.46)	<0.001	3126	377	2.94 (2.49-3.47)	<0.001
RR year 5	2749	291	2.59 (1.66-4.04)	<0.001	2946	364	2.64 (2.27-3.06)	<0.001
	Multivariable				Multivariable			
Follow-up	TD-neg (ref.)	TD-pos	RR (CI 95%)	p-value	TD-neg (ref.)	TD-pos	RR (CI 95%)	p-value
RR year 1	3127	372	2.68 (0.54-13.3)	0.230	3169	377	2.36 (1.61-3.46)	<0.001
RR year 3	2926	330	1.98 (1.03-3.81)	0.041	3017	359	1.76 (1.45-2.14)	<0.001
RR year 5	2656	277	2.01 (1.71-3.46)	0.012	2844	346	1.67 (1.40-1.98)	<0.001

Relative risk (RR) estimated by modified Poisson regression analysis. Multivariable analysis adjusted for age, sex, neoadjuvant radiotherapy, neoadjuvant chemoradiotherapy, lympho-vascular infiltration, perineural growth and adjuvant chemotherapy.

Both OS and RS were worse in patients with TDs. Relative HR of death was 1.98 (95% CI 1.64 – 2.40, P=<0.001) in univariable analysis and 1.52 (95% CI 1.23 – 1.89, P=<0.001) in multivariable analysis (Figure 15 and Table 13).

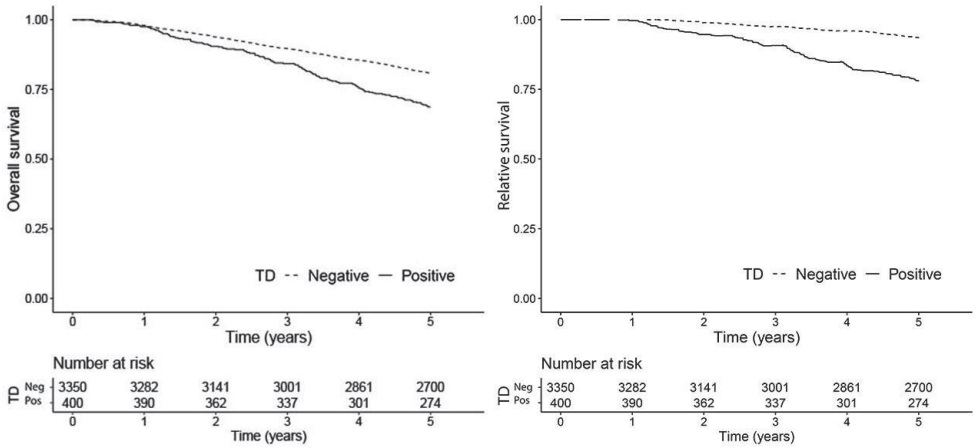

Figure 15 – Kaplan-Meier plots of overall and relative survival between TD-groups.

Table 13 – Cox regression analysis of overall survival and relative survival at five years

		Overall survival		Relative survival	
		Univariable			
TD-status	n	HR (CI 95%)	p-value	HR (CI 95%)	p-value
Negative	3350	1.00	ref.	1.00	ref.
Positive	400	1.75 (1.44-2.11)	<0.001	1.98 (1.64-2.40)	<0.001
		Multivariable			
TD-status	n	HR (CI 95%)	p-value	HR (CI 95%)	p-value
Negative	3234	1.00	ref.	1.00	ref.
Positive	382	1.53 (1.24-1.90)	<0.001	1.52 (1.23-1.89)	<0.001

Multivariable analysis adjusted for age, sex, neoadjuvant radiotherapy, neoadjuvant chemoradiotherapy, lympho-vascular infiltration, perineural growth and adjuvant chemotherapy. HR shows mortality ratio.

TD-status appeared to affect DM outcome more than LR when comparing pN1-stage patients with patients without positive mesorectal LNs (pN0). Patients with pN1c-stage had increased HR of DM compared with patients without positive LNs. Distant metastasis-free survival was similar between patients with pN1a-b and pN1c (Figure 16 and Table 14).

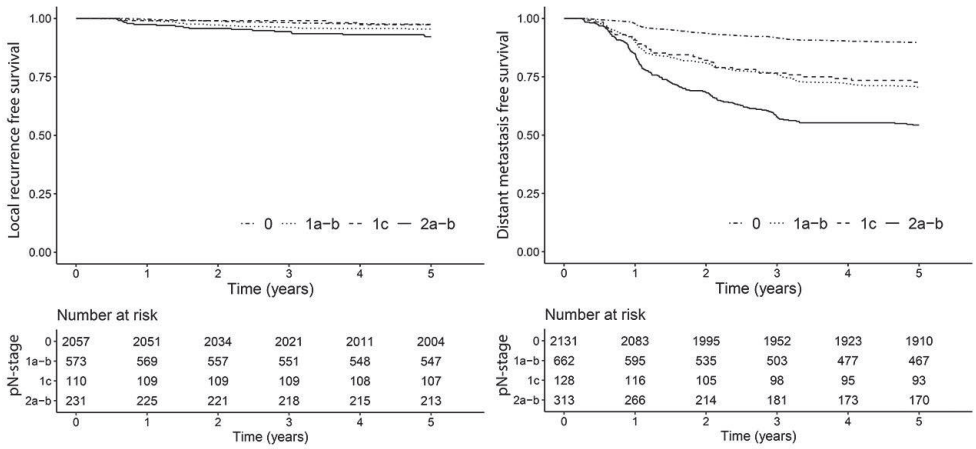

Figure 16 – Kaplan-Meier plots of LR and DM free survival between different pN-stages.

Table 14 – Cox regression analysis of LR and DM at five years according to pN-stage

	Local recurrence			Distant metastasis		
	Univariable					
pN-status	n	HR (CI 95%)	p-value	n	HR (CI 95%)	p-value
pN0	2057	1.00	ref.	2131	1.00	ref.
pN1a-b	573	1.79 (1.12-2.86)	0.015	662	3.12 (2.65-3.89)	<0.001
pN1c	110	1.06 (0.33-3.38)	0.925	128	2.94 (2.06-4.21)	<0.001
pN2a-b	231	3.12 (1.83-5.33)	<0.001	313	5.66 (4.58-6.99)	<0.001

When examining TD as a risk factor within pN-stages, presence of TD was associated with higher HR of LR (univariable) and DM (univariable and multivariable) among patients with pN1a-b stage but not if patients had more advanced pN-stage (Table 15).

Furthermore, RS was negatively impacted by TD-presence in patients with pN1a-b stage, both in univariable and multivariable analysis. Although not significant but noteworthy, is the relative HR of death in pN2a-b stage patients at 1.40 (95% CI 0.98 – 2.00, P=0.064) and 1.37 (95% CI 0.93 – 2.01, P=0.107); univariable and multivariable analysis respectively (Table 15).

Table 15 - Cox regression analysis of LR, DM and survival at five years

	Local recurrence			**Distant metastasis**		
	Univariable					
pN & TD-status	n	HR (CI 95%)	p-value	n	HR (CI 95%)	p-value
pN1a-b, no TD	612	1.00	ref.	610	1.00	ref.
pN1a-b, with TD	138	4.54 (2.10-9.79)	<0.001	139	2.36 (1.75-3.19)	<0.001
pN2a-b, no TD	239	1.00	ref.	238	1.00	ref.
pN2a-b, with TD	114	1.04 (0.40-2.87)	<0.879	114	1.18 (0.84-1.67)	0.345
	Multivariable					
pN & TD-status	n	HR (CI 95%)	p-value	n	HR (CI 95%)	p-value
pN1a-b, no TD		n/a	ref.	594	1.00	ref.
pN1a-b, with TD		n/a		129	1.88 (1.35-2.61)	<0.001
pN2a-b, no TD		n/a	ref.	225	1.00	ref.
pN2a-b, with TD		n/a		112	1.06 (0.74-1.53)	0.738
	Overall survival			**Relative survival**		
	Univariable					
pN & TD-status	n	HR (CI 95%)	p-value	n	HR (CI 95%)	p-value
pN1a-b, no TD	612	1.00	ref.	612	1.00	ref.
pN1a-b, with TD	139	1.38 (0.99-1.92)	0.061	139	1.67 (1.20-2.33)	0.003
pN2a-b, no TD	240	1.00	ref.	240	1.00	ref.
pN2a-b, with TD	114	1.17 (0.82-1.67)	0.383	114	1.40 (0.98-2.00)	0.064
	Multivariable					
pN & TD-status	n	HR (CI 95%)	p-value	N	HR (CI 95%)	p-value
pN1a-b, no TD	596	1.00	ref.	596	1.00	ref.
pN1a-b, with TD	129	1.47 (1.02-2.11)	0.037	129	1.48 (1.03-2.12)	0.035
pN2a-b, no TD	227	1.00	ref.	227	1.00	ref.
pN2a-b, with TD	112	1.35 (0.92-1.99)	0.122	112	1.37 (0.93-2.01)	0.107

Multivariable analysis adjusted for age, sex, neoadjuvant radiotherapy, neoadjuvant chemoradiotherapy, lympho-vascular infiltration, perineural growth and adjuvant chemotherapy. Multivariable analysis was not feasible for local recurrence due to limited number of events. In survival analysis, HR shows mortality ratio.

Discussion

Methodological discussion

The study design of the papers included in this thesis were observational and made it possible to investigate the prognostic outcome associated with comparatively rare clinical conditions. Thanks to the SCRCR, we have been able to access and examine population-based detailed patient data on both national and regional level. Cohort-based observational studies come with some inherent weaknesses but also strengths and possibilities.

The research questions we aimed to investigate can be readily answered by the methods used and they would have been ethically and methodologically difficult to address with for example a randomized design. Patient selection bias may be limited by using prospectively collected data and retrospective analysis based on a predefined hypothesis with corresponding research questions. This could increase generalizability of results. Inclusion and exclusion criteria have been defined as part of initial study design to avoid bias during the analysis phase.

Results are never better than the available original data being analysed. As described above, the SCRCR was used for data collection throughout the research process. In paper III, additional data was gathered from medical records. Although the SCRCR has high overall validity and completeness, the possibility of inaccurate and incomplete reporting must be taken into account when discussing and interpreting results. Furthermore, such reporting inaccuracies and incompleteness may also exist in reviewed medical records. As outlined above, extreme values or inconsistent variable data may have had to be interpreted or deemed inaccurate and not suitable for analysis.

Missing data has been present with varying abundance in the different cohorts and may be addressed in different ways. Missing data completely at random should in principle not introduce bias and we have chosen not to use data imputation techniques to reduce missing data and bolster data available for analysis. We considered this to be the most honest way to analyse data and discuss subsequent results.

Propensity score matching was not used as it would not have accounted for unknown variables that might have an effect on outcome. This could for example include, but

not limited to, histopathological variables that were unknown but could impact outcome and increase bias when using propensity score matching.

Uneven distribution of risk factors associated with recurrence and survival were addressed with multivariable analysis. Possible confounders, affecting both the exposure and outcome, were identified and included as adjustment variables. There are some considerations in multivariable analysis that have been addressed. First, the theoretic and empiric relevance of possible confounders was investigated. Directed acyclic graph diagrams were used to map out possible relations between exposure, confounders and outcome measures. Second, univariable analysis was performed to examine whether the factor was in-fact unevenly distributed across groups. Third, the number of possible adjustment variables was limited by the number of outcome-events.

Sample size and confidence level might affect the ability of a study to produce reliable results and rejecting or confirming the null-hypothesis. A significance level of 0.05 was used throughout the thesis. We have aimed to investigate adequately sized cohorts to avoid type II-errors. However, as shown by the presented results, in some groups and subgroups the number of patients and events were small. This affected confidence intervals and thereby statistical certainty in these analyses.

Follow-up might also affect results when measuring recurrence and survival. The aim has been to present a follow-up of at least five years. This corresponds with the follow-up registration of the SCRCR. We have deemed this follow-up time sufficient in respect to outcome measures. In paper III where medical records were reviewed mortality and recurrence could be identified beyond five years.

R1 and CRM-positive resection

Paper I and II investigate the association between CRM and recurrence risk in rectal cancer. As described above, CRM-negative resection was associated with decreased risk of both LR and DM. This has been shown by other studies and authors[147–151]. In the papers presented in this thesis we have further explored the prognosis in patients with CRM-positive resection. The findings may be useful in clinical decision making and in discussions with patients about adjuvant therapy and follow-up.

CRM-positive resection may occur for a number of reasons: incorrect clinical staging, poor surgery, intraoperative misjudgement of tumour borders or anatomy, obscure tumour growth in tissues or vessels and undetected LLNM. Furthermore, tumour susceptibility to neoadjuvant therapy may vary which could affect recurrence risk[152,153]. Incorrect staging could underestimate the need for neoadjuvant therapy and thereby increasing the risk of insufficient resection margins[154].

Regardless of underlying cause of CRM-positive resection, it seems to increase the risk of LR and DM, especially in patients with R1 resection (CRM 0.0 mm). However, not all patients with histopathological R1-resection suffer LR. The reasons for this might be associated with preoperative neoadjuvant therapy or the specific surgical technique used at the resection margin where electrocautery might offer some additional resection margin not measurable when determining the CRM postoperatively.

Paper I examined whether neoadjuvant therapy could be associated with reduction in LR risk in the different CRM-groups and no such effect could be confirmed. This might be attributed to some interlinked factors in these patients. Patients with more advanced tumour stage are more likely to receive neoadjuvant therapy which could induce tumour downstaging and possibility of radical surgical resection. Tumour biology and resistance to RT or CRT may increase the probability of CRM-positive resection and LR risk after neoadjuvant therapy[151].

An association between CRM-positive resection and DM was shown in paper II of this thesis however, this association was not as obvious as for LR, especially when adjusting for other known risk factors of DM in multivariable analysis. Localized malignant rectal tumours have the capability to set metastasis at any time, either by transmural growth into the abdominal cavity, through hematogenous pathways or via the lymphatic drainage[155]. The results presented in this thesis may offer some guidance in the treatment of patients with CRM-positive resection recognizing the increase in DM risk. The possible effect of adjuvant therapy was not investigated in the current study and results were somewhat conflicting. Univariable analysis showed a reduction in HR of DM in patients receiving adjuvant CHT but also that DM was common among patients receiving both neoadjuvant and adjuvant therapy. This indicates that development of DM is a complex process, beginning after malignant transformation in the primary lesion, and is affected by anatomical, morphological, molecular and genetic factors in relation to oncological and surgical success. In the presented paper only a limited number of potential variables of this process could be investigated. Further research is needed and the shifting treatment paradigm in high-risk rectal cancer towards SCRT combined with neoadjuvant CHT might show reductions in DM and survival benefits beyond clinical trials[111,112].

Radical surgical resection remains an essential cornerstone in the cure for rectal cancer. Beyond this however, implementation of improved diagnostics and oncological therapeutic strategies probably holds the key to further improve prognosis[60,127,156,157].

Lateral lymph node management

Dissemination of malignant tumour cells via lymphatic vessels and LNs is a significant risk factor and marker of more advanced stage in rectal cancer. The importance of mesorectal resection, including the mesorectal LNs, has reduced the risk of LR even before the advent of RT[86,146]. However, as described above there are several lymphatic pathways emanating from the rectum, in part dependent on the anatomic tumour location. Tumours in the middle and lower part of the rectum are associated with an increased risk of lymphatic spread to LNs outside the mesorectal envelope and involvement of LNs along the iliac vessels in particular[158]. The management of LLNs is still a subject for debate and management differs to some extent based on treatment traditions[99,159]. Western countries mainly rely on a strategy based on RT combined with TME-resection where LLNs are included in the field of RT but no LLND is performed. A strategy mainly dependent on TME and LLND without neoadjuvant RT is more common in eastern (Asian) countries[99,159,160]. The aim of both strategies is essentially the same, to reduce the risk of viable residual tumour cells within lymphatic vessels and LNs causing LR and potentially DM after resection of the primary tumour.

Pelvic MRI is the most accurate radiological modality to identify LLNM before and after neoadjuvant therapy[17]. Persistent MRI-positive LLNs after CRT are associated with increased LR risk and LLND is recommended in such cases[99]. However, some studies indicate that patients with MRI-positive LLNs prior to CRT could have an increased LR risk despite radiological LLN regression after CRT[161,162]. This might serve as indication for LLND based on the primary MRI results rather than results of re-evaluation MRI-examination.

The efficacy of LLND to reduce the LR risk in patients with or without MRI-positive LLNs show somewhat conflicting results. In the randomized trial by Fujita *et. al.* LR risk was reduced after LLND in patients not receiving neoadjuvant therapy[96]. However, in a meta-analysis by Fahy *et. al.* no such reduction was observed although LLND demonstrated potential of achieving local control without use of neoadjuvant therapy[98]. CRT has been shown to decrease LR risk and increase survival in patients with MRI-positive LLNs regardless of the addition of LLND to TME-resection[97,163].

In paper III we studied a cohort of patients with rectal cancers typically associated with increased risk of LLNM. In patients with MRI-positive LLNs, synchronous DM was more common. Both patients with MRI-negative and MRI-positive LLNs were treated with neoadjuvant therapy to a high extent with only a few patients being subjected to LLND. No differences in LR-rate, DM-rate or survival were observed in this study-cohort.

Despite advancements in diagnostics and neoadjuvant therapy, LLNM likely remains an important contributor to LR risk and reduced survival in rectal cancer.

Although highly accurate, MRI might still underestimate the true prevalence of LLNMs[164]. The high rate of neoadjuvant RT and CRT might mitigate a lack of preoperative detection and contribute to reducing LR emanating from LLNs involved by tumour cells not detectable with current diagnostic modalities. Development of radiological techniques and protocols resulting in improved diagnostics is needed[165]. Diffusion-weighted MRI and FDG-PET/CT might offer future clinical guidance. However, the utilization and efficacy of these techniques needs further examination[17,165–168].

The potential of LLND to improve radicality and reducing LR demonstrated by for example Fujita *et. al.* may be humbly considered when planning treatment for patients with suspected LLNMs within current western treatment traditions[96,162].

Significance of tumour deposits

TDs are recognised as a negative prognostic factor in colon cancer and may motivate adjuvant therapy after resection[40,169]. The prognostic significance in rectal cancer is, however, less well investigated. In single centre studies, TDs in rectal cancer have shown to be related to worse OS and DFS[41,170]. In paper IV we aimed to further explore TDs prognostic impact in a national cohort of rectal cancer patients.

Results show a significant negative prognostic effect of TDs on especially DM risk and survival. Although similar significant effects could be seen regarding LR, this was less pronounced. Previous studies in mixed cohorts of colorectal cancer patients have yielded comparable results[171,172].

In the current study, pN1c stage was associated with DM risk and reduced survival identical to what has been reported in pN1a-b stage patients. Previous studies have shown pN1c to represent a significant risk factor of shorter DFS and negative impact on survival[41,42,170].

Neoadjuvant CRT might reduce risk of LR in TD-positive patients. However, the risk of DM and reduced survival seems to be increased despite neoadjuvant CRT[173,174]. Higher tumour grade and less tumour regression after CRT among TD-positive patients could contribute to negative impact on prognosis[175]. However, patients with TDs responding well to CRT might have improved prognosis similar to that of TD-negative patients[18].

In the presented study adjuvant CHT was associated with a two-fold increase in DM risk, it is however not possible to determine the impact of adjuvant CHT on TD-positive disease based on this study. Furthermore, TDs are related to other negatively prognostic histopathological factors such as EMVI, lymph node metastases, lympho-vascular infiltration and perineural growth[41,42,172,176]. There might be a benefit of adjuvant CHT in TD-positive patients but pending further

studies this effect remains largely unclear[177,178]. However, the significant impact on DM risk and survival could be arguments in favour of adjuvant CHT in TD-positive patients.

TDs appear to evolve due to several possible adverse invasive mechanisms acquired by the primary tumour[179]. The implantation pattern and aggressive local growth might contribute to the increase in DM risk and subsequent decreased survival.

Evolving therapeutic options and challenges

The clinical scenarios investigated in this thesis will continue to pose relevant oncological and surgical challenges. Increased knowledge about the prognostic impact of CRM-positive resection, LLNs and TDs could possibly translate into adjusted indications for CHT therapy and follow-up routines. The advent of total neoadjuvant therapy and technological improvements facilitating local endoscopic excisions with possible organ preservation could change the treatment paradigm of rectal cancer but also introduce new challenges[118,157,180–183].

Accurate clinical staging and risk factor assessment is a field of vital importance in patient selection and evaluation. Some studies indicate that accurate radiological staging needs further precision to guide personalized surgery[154,184–186]. Molecular diagnostics could potentially help improve tumour classification and patient selection for oncological therapy[8,60]. Specific tumour phenotypes may be more susceptible to immunotherapy than 5-FU based CHT for example demonstrated by the Keynote-study with improved treatment response of pembrolizumab in dMMR tumours[187]. Furthermore, with potentially more patients being considered for neoadjuvant and adjuvant oncological therapy, improved understanding of pharmacokinetics could improve drug effects and reduce side-effects[188,189].

The risk of DM in rectal cancer continues to be a concern with 20-30% of patients suffering DM despite successful local control. Changes in neoadjuvant treatment protocols according to the principles introduced by the RAPIDO and PRODIGE23-trials might reduce DM risk in patients with advanced rectal cancer[111,112].

Implementation of screening programs might increase early-detection of colorectal lesions in eligible cohorts and could potentially increase survival. Epidemiological evidence of increasing incidence in younger individuals should raise awareness among general practitioners[5]. Basic clinical examination and expedient rigid sigmoidoscopy in patients with anorectal symptoms should always be performed.

Conclusions

This thesis explores three clinically high-risk circumstances in rectal cancer and their impact on recurrence and outcome. The major conclusions are:

- CRM-positive resection greatly increases the risk of LR although most patients with CRM-positive and R1-resection do not suffer LR. LR occurs earlier in patients with CRM-positive resection and intensified follow-up during the first two years postoperatively might be beneficial to patients.

- CRM-positive resection is associated with increased risk of DM. The process of metastatic spread is multifactorial and CRM should be one factor to take into account when discussing adjuvant therapy with patients postoperatively.

- LLNM is a risk factor for synchronous DM. Neoadjuvant therapy with RT or CRT combined with standard TME-resection could be an applicable clinical strategy when treating patients with MRI-positive LLN.

- TDs are a risk factor of both LR, DM and decreased survival in rectal cancer. Patients with TDs should be considered having at least the same risk of recurrence and decreased survival as patients with pN1a-b stage. Patients with TDs might be candidates for adjuvant CHT therapy.

Future perspectives

The successful treatment of rectal cancer is multimodal and is likely to remain so in the foreseeable future. The results we see today are results of incremental improvements in all parts of this multimodal offering to patients; surgery, oncology, pathology, molecular analysis, radiology and perioperative care. This thesis offers some further knowledge that could be taken into account when managing patients with advanced disease and unfavourable surgical outcome.

The studied cohorts in this thesis were treated for their rectal cancer almost a decade ago and some elements of disease understanding as well as therapeutical options have evolved during this time. Furter histopathological variables such as EMVI and to some extent TDs have been recognized as potential prognostic factors. The connections between genetic, molecular and epigenetic components of tumour biology have been further investigated and linked to outcomes of oncological therapy. Future studies should aim to incorporate these factors in their analytic platforms. Furthermore, comprehensive registration of these factors in large population registries could aid such research.

Treatment guidelines have changed recently with stricter indications for RT and expanded utilization of the potential in early CHT-therapy, especially in patients with LARC. It remains to be seen how these protocol changes affect patient's outcome in general clinical practice. Complete tumour regression after neoadjuvant therapy and organ preservation strategies are under scientific scrutiny and might offer more options in the care for rectal cancer patients. Long-term results on oncological outcome after organ preservation strategies have yet to be published.

Radical, curative, surgery for LR and DM are further examples of evolving fields that also might change the prognosis of patients with recurrent disease. Improvements in perioperative care, novel non-surgical interventions to tackle DMs in the lung and liver could offer treatment options to more patients. Aggressive neoadjuvant therapy could push the borders of curative possibilities in patients with advanced disease including oligometastatic situations or multivisceral tumour growth. Oncological medical treatment with CHT and immunotherapy could potentially further improve the chance of extended survival in some patients.

A wide range of treatment options are encouraging and offer future promise. Let's not forget however, the patients sacrifice and impact on quality of life in the strive towards the definitive cure of cancer.

Populärvetenskaplig sammanfattning

Ändtarmscancer drabbar cirka 2000 personer årligen i Sverige och är en dödlig sjukdom om tumören inte upptäcks i tid och hinner sprida sig till andra organ. Historiskt var behandlingsmöjligheterna begränsade och risken för återfall var stor trots omfattande kirurgi. Tack vare viktiga behandlingsinnovationer under senare delen av 1900-talet förändrades prognosen för patienter med ändtarmscancer betydligt. Idag överlever de flesta patienter sjukdomen fastän tumören hunnit växa djupt in i tarmväggen. Ibland förekommer överväxt på andra organ eller till och med spridning till lokala lymfkörtlar innan tumören upptäcks. Diagnos ställs med rektoskopi och vävnadsprovtagning. Patienten utreds med skiktröntgen och magnetkamera för att noggrant kartlägga tumören inför behandling. Behandlingsmöjligheterna är flera men grunden för botande behandling är kirurgi, ofta i kombination med strålbehandling som ges innan patienten blir opererad. Förbehandlingen används för att öka chansen till radikal kirurgi, det vill säga att hela tumören kan opereras bort lokalt i det trånga bäckenet och för att minska risken för lokalt tumöråterfall. Ibland ges cellgiftsbehandling i kombination med strålbehandlingen före eller efter operationen. Patienterna kan opereras med olika tekniska metoder som antingen innebär att tarmen kan kopplas ihop eller att patienten får en stomi.

Flera faktorer hos tumören, dess biologi, anatomiska placering och hur omfattande den hunnit bli påverkar hur det går för patienten på lång sikt. Tumöråterfall kan uppstå lokalt, i anslutning till operationsområdet, eller genom fjärrmetastaser till exempelvis levern, lungorna eller lymfkörtlar runt om i kroppen. Hos patienter med fjärrmetastaser är prognosen dålig oavsett om metastaserna finns redan vid diagnostillfället eller om de uppkommer efter att tumören opereras bort.

I denna avhandling undersöks tre högrisksituationer för tumöråterfall efter behandling för ändtarmscancer; icke-radikalt opererade patienter, avancerad lymfkörtelspridning lokalt i lilla bäckenet och lokal tumörspridning i form av fria tumörhärdar.

Arbete **I** och **II** undersökte hur det går för patienter där avståndet mellan tumör och frisk vävnad blivit undermåligt vid operationen. Patienter från hela Sverige inkluderas för uppföljning. Kirurgi för ändtarmscancer är tekniskt begränsad av bäckenanatomin och vitala omkringliggande strukturer men tack vare förbehandling kan avancerade större tumörer krympas för att göra det möjligt att överhuvudtaget

operera bort dem. Trots standardiserad kirurgisk teknik och förbehandling så blev knappt nio procent av patienterna opererade med undermåliga kirurgiska marginaler. I studierna följdes patienterna upp avseende lokalt återfall och fjärrmetastaser. Resultaten visade att risken för lokalt tumöråterfall och fjärrmetastaser var störst hos patienter där det inte fanns någon synlig marginal i mikroskop mellan tumör och där vävnaden delats vid operationen. Det var emellertid bara en begränsad andel av patienterna med dålig resektionsmarginal som fick tumöråterfall. Detta är viktig information när efterbehandling med cellgifter och uppföljning planeras tillsammans med patienterna. Med ökande resektionsmarginal minskade risken för tumöråterfall. Vid marginal på en millimeter eller mer sågs en betydlig minskning av risken för återfall.

I arbete **III** undersöktes en grupp patienter från Skåne som hade cancer i ändtarmen med egenskaper som är förknippade med hög risk för spridning till lymfkörtlar i lilla bäckenet. Vi studerade patienternas magnetkameraundersökningar avseende misstänkta lymfkörtelmetastaser, granskade vilken behandling de fått; kirurgisk med och utan strålbehandling eller cellgifter. Resultaten visade att spridning till lymfkörtlar längs de stora kärlen i lilla bäckenet hängde samman med fjärrmetastaser redan när ändtarmscancern upptäcktes. De flesta patienter hade fått kombinationsbehandling med strålning och cellgifter tillsammans med kirurgi. Hos några patienter opererades lymfkörtlarna bort men det var sällsynt att tumörceller från ändtarmscancern hittades i dessa vid mikroskopisk undersökning. I den undersökta gruppen patienter var det ingen skillnad i återfallsrisk mellan de patienter som hade misstänkt lymfkörtelspridning jämfört med dem som inte hade det.

I arbete **IV** undersöktes fria tumörhärdar vid ändtarmscancer. En fri tumörhärd eller satellithärd hänger inte samman med huvudtumören eller någon annan vävnadsstruktur via vilken tumörceller kan förväntas sprida sig som kärl, lymfbanor eller nervbanor. Fria tumörhärdar är ett tecken på aggressiv lokal tumörväxt. Resultaten visade att fria tumörhärdar ökade risken för lokalt tumöråterfall men framförallt fjärrmetastaser. Patienter som hade fria tumörhärdar vid mikroskopisk undersökning av operationspreparatet hade dessutom betydligt sämre överlevnad även om man tog hänsyn till vilken behandling patienterna fått och tumörbiologin. Riskökningen för återfall och försämrad överlevnad var jämförbar med spridning till lymfkörtlar omkring ändtarmen. Denna riskökning bör tas i beaktande efter operationen och skulle kunna vara ett argument för ytterligare cellgiftsbehandling för att möjligen förbättra prognosen hos dessa patienter.

Acknowledgements

Pamela Buchwald, my main supervisor who has skilfully guided me through the work of this thesis and continues to inspire me every day with her enthusiasm for research. Her feeling for the scientific process and never-ending flow of ideas is something very special.

Marie-Louise Lydrup, my co-supervisor and one of the most inspiring surgical clinicians I have had the opportunity to learn the complex art of surgery from.

Fredrik Jörgren, my co-supervisor with an eminent eye for details during the research process which has increased the quality of the studies presented in this thesis.

Julia, Alexander, Olivia, my family who have always been there with love, patience and understanding when deadlines call and surgery runs long. You fill every moment with meaning.

Inger, Fritz and Karin, my parents and sister, who gave me the possibilities, endurance and motivation to pursue a career in medicine.

Morgan Nordén and **Dragan Divkovic**, my surgical mentors who taught me the virtues of surgery, techniques and the responsibility in care for your patients.

Dan Sevonius, who originally inspired me to become a surgeon and pursue research to become a better clinician.

Annika Malmquist and **Jenny Brändstedt**, my former and current chief, both of whom have supported and made it possible to combine research with clinical work.

Johan Abrahamsson and **Robert Jablonowski**, my ever-inspirational peers in pursuing this doctoral thesis beyond the medical degree.

I would also like to thank my **colleagues** at the Colorectal Department and all of my loving **friends** who share their horizon with me; supporting and challenging me when the books have been closed and the last stitch is sewn.

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