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ON PREOPERATIVE TREATMENT SELECTION AND MAGNETIC RESONANCE IMAGING IN RECTAL CANCER

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On preoperative treatment selection and magnetic resonance imaging in rectal cancer

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To my mother

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ABSTRACT

In Sweden, 2000 patients are diagnosed with rectal cancer annually. Developments in surgery have improved survival and the addition of preoperative radiotherapy (RT) or chemoradiotherapy (CRT) has reduced local recurrence rates to 5 %. However, (C)RT is associated with side effects. In order to achieve balance between improved outcomes and risk of treatment-associated morbidity, optimized treatment selection is crucial. Guidelines for rectal cancer management are mainly based on tumour characteristics from magnetic resonance imaging (MRI). Thus, correct interpretation of MRI is essential for optimal selection. In addition, all pre-therapeutic information available, e.g. on age and comorbidity, should ideally be taken into consideration in treatment-decisions. The aim of this thesis was to increase the knowledge regarding preoperative treatment selection in rectal cancer.

Paper I aimed at evaluating the influence of pretherapeutic parameters on preoperative treatment selection. Patients undergoing elective abdominal rectal cancer surgery 2000-2010 in the Stockholm-Gotland region were included (n = 2619). Patients with comorbidity or old age (≥ 80 years) received less preoperative (C)RT. Deviations from guideline recommendations regarding preoperative (C)RT were revealed.

From the study cohort of paper I, patients with stage I-III tumours were included in **Paper II** (n = 2300). The influence of age and comorbidity on long-term outcome after preoperative (C)RT, was evaluated. Overall, preoperative (C)RT did not influence long-term outcome but in patients with comorbidity overall survival was improved following preoperative (C)RT whereas no significant differences were seen among the elderly (≥ 80 years).

The objective of **Paper III** was to investigate the performance and reporting of rectal cancer MRI and the influence on preoperative treatment selection. MRI investigations and reports on 94 patients were re-evaluated. Predefined standards for rectal cancer MRI were not universally applied. Because of incomplete original reports, clinical tumour staging was possible in only 70 % of the patients. The agreement was unsatisfactory both regarding tumour staging between the re-evaluation and the original reports and regarding treatment selected compared to recommended after re-evaluation.

Paper IV assessed the MRI characteristics of the primary tumour regarding prediction of outcomes after surgery for local recurrence. Treatment selection for the primary tumour was also evaluated. Patients undergoing surgery for local recurrence 2003-2013 at Karolinska University Hospital were included (n = 54). No factors on primary tumour MRI were found to predict long-term outcomes after surgery for local recurrence. However, a MRI-detected primary tumour response to preoperative (C)RT correlated to fewer R0 resections of the local recurrence. Only 11 of 30 patients with locally advanced primary tumour received preoperative CRT.

LIST OF SCIENTIFIC PAPERS

- I. Preoperative treatment selection in rectal cancer: A population-based cohort study**
A.H. Elliot, A. Martling, B. Glimelius, C. Nordenvall, H. Johansson, P.J. Nilsson
European Journal of Surgical Oncology
2014; 40: 1782-1788
- II. Impact of pre-treatment patient-related selection parameters on outcome in rectal cancer**
A.H. Elliot, A. Martling, B. Glimelius, H. Johansson, P.J. Nilsson
European Journal of Surgical Oncology
2016; 42:1667-1673
- III. Performance, interpretation and influence of pretherapeutic MRI in rectal cancer: room for improvement?**
A.H. Elliot, L. Blomqvist, A. Sigurdsson, A. Martling, H. Johansson, B. Glimelius, P.J. Nilsson
Submitted for publication
- IV. Pretherapeutic MRI of the primary tumour as a predictor for oncological outcomes after surgery for locally recurrent rectal cancer**
A.H. Elliot, B. Othman, C. Suzuki, L. Blomqvist, A. Martling, H. Johansson, B. Glimelius, P.J. Nilsson, H. Iversen
Manuscript

ABBREVIATIONS

APE	Abdominoperineal excision
AR	Anterior resection
ASA	American Society of Anesthesiologists
BMI	Body mass index
CCI	Charlson comorbidity index
CI	Confidence interval
CT	Computed tomography
CRM	Circumferential resection margin
CRT	Chemoradiotherapy
DFS	Disease-free survival
ELAPE	Extralevator abdominoperineal resection
EMVI	Extramural vascular invasion
Gy	Gray
HAR	High anterior resection
HR	Hazard ratio
LAR	Low anterior resection
LLND	Lateral lymph node dissection
MDT	Multidisciplinary team conference
MRF	Mesorectal fascia
MRI	Magnetic resonance imaging
OR	Odds ratio
OS	Overall survival
PME	Partial mesorectal excision
PNI	Perineural invasion
RT	Radiotherapy
SCRCR	Swedish colorectal cancer registry
TEM	Transanal endoscopic microsurgery
TNM	Tumour Node Metastasis
TME	Total mesorectal excision
TRG	Tumour regression grade

BACKGROUND

Epidemiology

More than 1.3 million patients worldwide are diagnosed with colorectal cancer annually and it is the third most common form of cancer. The colorectal cancer incidence shows a strong variation throughout the world with the highest incidence rates in Europe, Northern America, Australia and New Zealand and the lowest in Africa, Middle East and Asia. In Australia and New Zealand the age-standardised incidence rate is 44.8 for men and 32.2 for women per 100,000 and in Western Africa 4.5 and 3.8, respectively. Worldwide, there are almost 700,000 deaths from colorectal cancer every year, equivalent to 8.5 % of the total mortality. The difference in mortality rates is less pronounced than that of incidence rates between the developed and the less developed regions¹.

Rectal cancer is responsible for one third of all colorectal cancer. In Sweden some 2000 patients are diagnosed with rectal cancer every year and about 40 % of them are women². The rectal cancer incidence increases by age and in Sweden almost one fourth of all rectal cancer patients are at least 80 years old at diagnosis (Figure 1a)³. The incidence of rectal cancer increases slowly but the age-standardised rectal cancer incidence has not substantially changed the last decades (Figure 1b). In 2015 the age-standardised rectal cancer incidence was 25 per 100,000 among men and 15 per 100,000 among women, respectively. The age-standardised mortality in rectal cancer decreased from the 1970s through the 1990s in Sweden but has been relatively stable the last 15 years. For men, the age-standardised mortality rate was 10 per 100,000 and for women 7 per 100,000 in 2015 (Figure 1b)⁴. For patients who were diagnosed with rectal cancer in 2005-2009 the relative 5-year survival for men and women was 61 % and 64 %, respectively³.

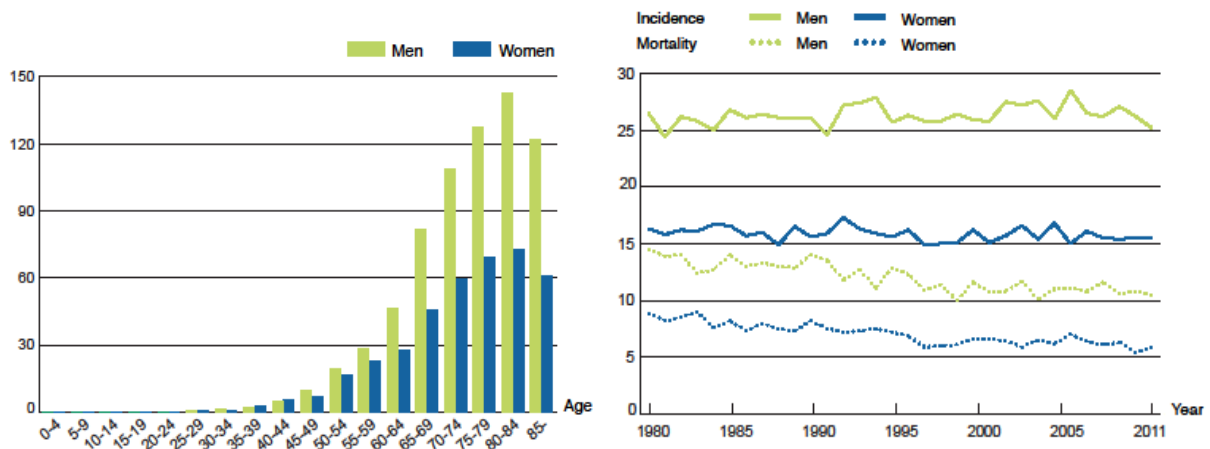


Figure 1. a. Rectal cancer incidence in Sweden according to age group. **b.** Age-standardised rectal cancer incidence and mortality 1980 – 2011⁵.

Aetiology

According to the model described by Vogelstein *et al.*, colorectal adenocarcinoma develops from adenomas through sequential mutations of oncogenes and genes that suppress tumorigenesis, a process that takes many years⁶. In a second pathway, mutations in the DNA mismatch repair system leads to inactivation of tumour suppressor genes⁷. Sporadic tumours account for about 80 % of all colorectal cancers whereas the remaining 20 % are found in patients with a family history of colorectal cancer⁸. As the incidence of colorectal cancer varies throughout the world, it is believed that sporadic colorectal cancers are associated with life style factors. A high intake of red meat and fat, a diet with a low proportion of fibre, smoking, high alcohol consumption, obesity and diabetes mellitus are related to increased risk of colorectal cancer. Other known risk factors for sporadic colorectal cancer are advanced age, male sex, a history of colorectal polyps or cancer and inflammatory bowel disease (Crohn's disease and ulcerative colitis), especially with severe grade of inflammation⁸. Patients with a family history of colorectal cancer have a 2 to 4 fold increased risk of having colorectal cancer⁹. Among the 2-5 % of all colorectal cancer patients with defined hereditary syndromes such as Lynch syndrome, familial adenomatous polyposis and MUTYH-associated polyposis, the lifetime risk of developing colorectal cancer are 50-100 %¹⁰.

Anatomy

Rectum is the most distal part of the gastrointestinal tract before the anal canal. Several definitions regarding proximal and distal limits of the rectum exist. Surgeons usually consider the muscular anorectal ring as the lower border whereas the upper border is considered to be the promontory on radiological examination or by surgery. In the European Society for Medical Oncology (ESMO) guidelines, rectal tumours are defined as lesions ≤ 15 cm from the anal verge with a rigid rectoscope¹¹. The dentate line in the anal canal represents the border of the columnar epithelium of the rectum and the stratified squamous epithelium of the lower anal canal. The mesorectum within the mesorectal fascia (MRF) is fatty tissue that contains arterial blood supply and venous and lymphatic drainage of the rectum. In the upper rectum the mesorectum is located dorsally while more distally it is circumferential, enclosing the rectum down to the pelvic floor.

The arterial blood supply of the upper rectum derives from the inferior mesenteric artery that continuous into the superior rectal artery. The inferior rectal artery, a branch of the internal iliac artery, supplies the lower rectum. Some individuals also have a middle rectal artery originating from the internal iliac artery. The venous drainage from rectum runs through rectal veins to the internal iliac vein. The lymphatic drains mainly along the superior rectal artery to the inferior mesenteric nodes but especially for the lower third of rectum, also along the middle rectal artery to the internal iliac artery. Clinically the nodes along the internal iliac artery and in the obturator spaces are often referred to as lateral pelvic nodes. From the anal

canal below the dentate line lymphatic drainage also occurs to superficial inguinal nodes¹².

Besides the rectum the pelvis contains several other organs and vital structures such as the iliac vessels, autonomous nerves innervating anorectal and urogenital tract, somatic nerves, urinary bladder, uterus, ovaries, vagina, prostate and seminal vesicles. This, together with the narrow space of the pelvis, requires considerable consideration in rectal cancer treatment, both regarding planning of surgery and radiation therapy.

Histopathological staging

After rectal cancer surgery a pathologist should assess the resected specimen macroscopically, before the microscopic analysis is undertaken. An examination of the tumour and resection surfaces and optimally also a mesorectal grading is performed to evaluate the quality of the total mesorectal excision (TME). According to this three-graded classification, the resected mesorectum should be judged as complete, nearly complete or incomplete and it has been shown to correlate to outcome after rectal cancer surgery¹³.

TNM

In order to describe cancer tumours by stage, the Tumour Node Metastasis (TNM) classification of malignant tumours was created. The TNM classification enables prognosis assessment, treatment selection and evaluation of treatment effect for cancer tumours. The TNM classification is developed and revised by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC). The 7th edition, recommended in the Swedish national guidelines for colorectal cancer, was published in 2009^{3, 14}.

T stage

In colorectal cancer, the T describes the primary tumour regarding the depth of invasion and if there is growth into adjacent organs (Figure 2). The prognosis deteriorates with each stage and substage of T^{15, 16}.

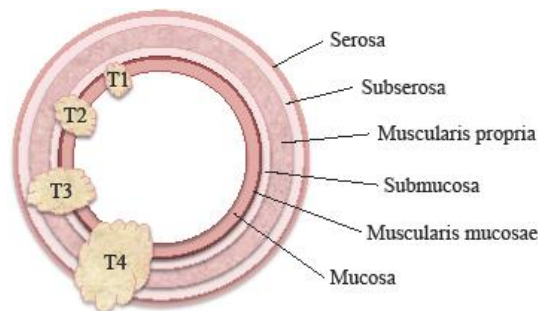


Figure 2. *T stage colorectal cancer.*

N stage

N refers to metastatic involvement of regional lymph nodes. Presence of tumour deposits, i.e. mesenteric metastatic nodules near the primary tumour without signs of lymphatic tissue, is also included in the N-stage. A higher level of T stage is associated with a increased risk of regional lymph node metastases¹⁷.

M stage

M describes whether metastases in distant organs, non-regional lymph nodes or peritoneal carcinomatosis are present or not.

Table 1. TNM classification of colorectal cancer, 7th edition¹⁴.

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into the pericorectal tissues
T3a	Minimal invasion: <1 mm beyond the borders of the muscularis propria
T3b	Slight invasion: 1-5 mm beyond the borders of the muscularis propria
T3c	Moderate invasion: >5-15 mm beyond the borders of the muscularis propria
T3d	Extensive invasion: >15 mm beyond the borders of the muscularis propria
T4	Tumour penetrates the visceral peritoneum and/or directly invades other organs or structures
T4a	Tumour penetrates to the surface of the visceral peritoneum
T4b	Tumour directly invades or is adherent to other organs or structures
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumour deposit(s) in the subserosa, mesentery or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in ≥ 4 regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in ≥ 7 regional lymph nodes
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site
M1b	Metastases in more than organ/site or peritoneum

The histopathological TNM staging (pTNM) for colorectal cancer is the result of the analysis of the resected specimen whereas the clinical TNM staging (cTNM) is based on preoperative radiological examination. The prefix y is used for staging after neoadjuvant therapy. Table 1 shows the colon and rectum cancer staging according to the TNM classification.

Table 2. *Colorectal cancer stage according to TNM and Dukes' classification.*

T N M	TNM Stage	Dukes
Tis N0 M0	0	-
T1-2 N0 M0	I	A
T3 N0 M0	IIA	
T4a N0 M0	IIB	B
T4b N0 M0	IIC	
T1-2 N1 M0 / T1 N2a M0	IIIA	
T3-4a N1 M0 / T2-3 N2a M0 / T1-2 N2b M0	IIIB	C
T4a N2a M0 / T3-4a N2b M0 / T4b N1-2 M0	IIIC	
Any T Any N M1a	IVA	
Any T Any N M1b	IVB	D

Dukes classified tumours according to primary tumour invasion and regional lymph node status already in the thirties and later presence of distant metastasis was added¹⁸. However, the Dukes' classification has largely been replaced by the TNM classification in the staging of colorectal cancers. In Table 2 colorectal cancer classifications according to TNM and Dukes are shown. Figure 3 displays the TNM stage dependent prognosis as reported by the Swedish colorectal cancer registry.

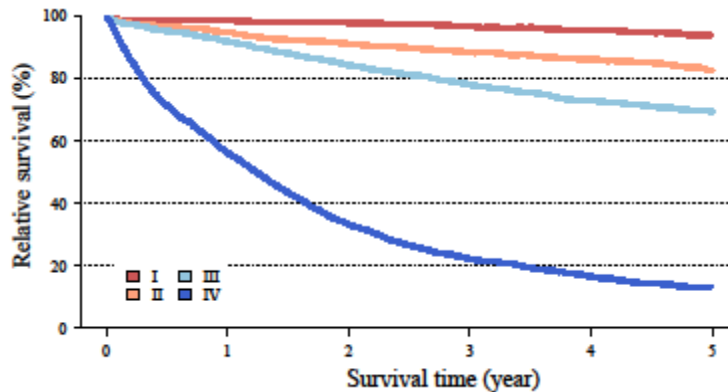


Figure 3. Relative rectal cancer survival according to TNM stage in Sweden 2008-2015².

Circumferential resection margin (CRM)

The shortest distance between the lateral border of the rectal tumour or tumour deposit and the resection margin is defined as the circumferential resection margin (CRM). Quirke *et al.* established the CRM as a major predictor for local recurrence in rectal cancer in 1986¹⁹. Since then several studies have confirmed the strong association between CRM involvement and inferior long-term outcomes, both regarding local and systemic control and survival²⁰. A positive CRM (CRM+) is usually defined as a CRM \leq 1 mm and a negative CRM (CRM-) as a CRM $>$ 1 mm. Other limits such as 2 mm have been proposed, although without changing practise as the 1 mm limit remains as the gold standard²¹.

Distal resection margin (DRM)

Rectal cancer spread occurs not only laterally but also proximally and distally. Traditionally a distal resection margin (DRM) of at least 5 cm and later 2 cm has been considered necessary to include distal tumour deposits and to optimise local control²². According to a review examining the sufficient DRM, distal intramural spread is seen in 25 % of the patients but only in 10 % $>$ 1 cm distally of the primary tumour²². The authors concluded that a DRM of 1-2 cm is sufficient since tumour spread beyond 1 cm is associated with systemic disease and in these relatively few patients a wider DRM will not influence long-term outcome. In the Swedish national guidelines for colorectal cancer a DRM of at least 1-2 cm is accepted in low and middle rectal cancer, given that TME is performed. A 5 cm DRM is motivated in upper rectal cancer in patients undergoing partial mesorectal excision (PME)³.

Residual tumour

Residual tumour (R) describes the microscopic or macroscopic tumour involvement directly at the distal or circumferential resection margin and has been incorporated in the TNM

classification (Table 3)¹⁴. Hence, a CRM positive specimen (≤ 1 mm) could still be defined as R0. There have been attempts to unify these two histopathological variables using the minimal distance in the CRM definition into a renewed R classification, although so far without great impact in reports published²³. The presence of residual tumour in the resected specimen (R1 or R2) is clearly correlated to inferior survival and increased rates of local recurrence and distant metastasis²⁴.

Table 3. *Classification of Residual Tumour*¹⁴.

<i>RX</i>	<i>Residual tumour cannot be assessed</i>
<i>R0</i>	<i>No residual tumour</i>
<i>R1</i>	<i>Microscopic residual tumour</i>
<i>R2</i>	<i>Macroscopic residual tumour</i>

Vascular invasion

According to the Swedish national colorectal cancer guidelines, type of vascular tumour invasion should be specified so that lymphatic invasion is reported as L (0/1), intramural venous invasion as V (0/1) and extramural venous invasion as EMVI³. The histopathological detection of venous invasion in rectal cancer is associated with a higher risk of distant metastasis and worse survival outcomes whereas lymphatic vessel invasion predicts for lymph node metastasis²⁵⁻²⁷. Inconsistencies regarding terminology and variability in recognition and diagnosis make results from investigations in this field difficult to compare and in a recent review the reported prevalence of EMVI varied between 9 to 61 %^{28, 29}.

Perineural invasion

Controversies exist concerning the definition of perineural invasion (PNI) in rectal carcinoma. PNI was defined by Batsakis in 1985 as tumour growth in, around and through peripheral nerves while some other authors have proposed a subdivision in PNI surrounding the nerve sheath and PNI invading through the nerve sheath^{30, 31}. Although the definition and thereby the diagnosis of PNI is afflicted by discrepancies, it remains as an independent prognostic factor^{32, 33}.

Histopathological grading

The vast majority of colorectal cancers are adenocarcinomas, which originate from the epithelial cells of the mucosa of colon and rectum. Mucinous adenocarcinomas (greater than 50 % mucinous) represent the second most common form of colorectal cancer while signet ring cell carcinomas, neuroendocrine carcinomas, adenosquamous carcinomas and medullary

carcinomas are more uncommon³⁴. Adenocarcinomas can be graded based on the proportion of normal glandular formation into well, moderately and poorly differentiated and the less differentiated tumours have poorer survival outcomes³⁵. However, to reduce the interobserver variability and increase the prognostic significance, a stratification into two grades has been proposed so that well and moderately differentiated tumours are defined as low grade and poorly differentiated as high grade³⁶. This two-tier categorisation is recommended in the Swedish national guidelines for colorectal cancer³.

Tumour regression

Tumour regression refers to the effect of neoadjuvant radio- or chemoradiotherapy on the tumour. The tumour regression grade (TRG) is determined by the amount of residual tumour cells and the extent of fibrosis induced by the neoadjuvant therapy³⁷. A high degree of tumour regression is correlated to better survival and lower rates of local recurrence³⁸. Several TRG scales have been developed, for example by Mandard and Dworak but there is no consensus on which one is the preferable^{39,40}. Hence, comparison of prognosis and treatment selection in different reports is somewhat difficult. In the Swedish national guidelines for colorectal cancer treatment the TRG scale as defined by AJCC is recommended (Table 4)⁴¹.

Table 4. TRG scale according to AJCC⁴¹.

0	Complete regression, no viable cancer cells
1	Moderate regression, single cells or small groups of cancer cells
2	Minimal regression, residual cancer outgrown by fibrosis
3	Poor regression, extensive residual cancer

Clinical investigation and staging

Clinical presentation

Common symptoms of rectal cancer include anaemia, rectal bleeding, rectal pain, change of bowel habits, anal incontinence, abdominal pain, weight loss and fatigue. Presentation of rectal cancer can also be related to locally advanced tumour growth with urogenital symptoms or pain from the pelvis or limbs as a result of the tumour compressing pelvic structures. Furthermore, synchronous distant metastasis can give rise to the presenting symptoms and under the investigation for other diseases a small number of patients will be diagnosed with rectal cancer *en passant* by radiological examination. Finally, a proportion of patients are diagnosed with rectal cancer through screening programs for colorectal cancer including faecal tests and/or endoscopy¹².

Clinical examination

The symptoms in rectal cancer vary and may commonly also be present for other both benign and malign diseases. Therefore there is a certain risk of delay in the diagnosis and the threshold for clinical examination should be low. In patients presenting with anaemia and rectal bleeding further investigation is mandatory to rule out neoplasms in the colon or rectum, especially in patients > 40 years since colorectal cancer incidence increases with age. A digital rectal exam should be performed including description of mobility and surface in the case of a rectal tumour. The size and the distance of the lower border from the anal verge are examined with a rigid rectoscope and biopsies are taken to establish the diagnosis. The categorisation of tumour level depending on the distance from anal verge differs between guidelines. According to the ESMO guidelines rectal cancers should be classified into low (0-5 cm), mid (> 5- 10cm) and high (> 10–15 cm)¹¹. To rule out synchronous colon tumours or polyps a colonoscopy or a computed tomographic colonography should be undertaken.

Imaging to detect distant metastasis

About one fifth of patients with colorectal cancer will have synchronous metastases at diagnosis, sometimes at multiple locations⁴². The most common location for synchronous distant metastases in colorectal cancer is the liver followed by the lungs, peritoneum and non-regional lymph nodes while other metastatic locations such as are bones, brain and ovaries and more uncommon⁴².

Computed Tomography (CT)

To detect systemic disease a CT of the thorax, abdomen and pelvis is included in the work-up of rectal cancer. The sensitivity and specificity of CT for hepatic metastasis is relatively good while regarding imaging of the lungs, a number of unspecified nodules are found and only in about one fourth of these lesions metastases are established⁴³. Historically the sensitivity offered by CT in detecting peritoneal metastases has been low. With emerging techniques such as the multidetector CT (MDCT) the performance of CT has improved even though small lesions and certain anatomical locations remains to be a challenge and the results reported regarding sensitivity and specificity vary⁴⁴.

Magnetic resonance imaging (MRI)

The specificity of (MRI) is comparable to CT for hepatic metastases of colorectal cancer but MRI has a higher sensitivity, especially for smaller lesions⁴⁵. In Sweden MRI of the liver is mainly used for re-evaluation of lesions difficult to categorize with CT and for surgical and oncological planning after a CT has confirmed liver metastasis.

Abdominal ultrasonography (AUS)

Contrast-enhanced AUS of the liver is fairly inexpensive and can be performed with relatively good accuracy regarding liver metastases but is not generally recommended because of its low sensitivity in patients with fibrosis or steatosis and for the detection of small lesions (< 5 mm)⁴⁶. Furthermore some lesions are difficult to assess with AUS because of their position in the liver (i.e. subdiaphragmatic), and US examination is also highly operator dependent. Finally, AUS does not enable planning of the liver surgery in the same way as MRI⁴⁷. Thus, contrast-enhanced AUS is above all an alternative when MRI cannot be performed.

FDG-PET/CT

In FDG-PET (Fluorodeoxyglucose-Positron Emission Tomography) investigations a radioactive tracer (i.e. Fluorine 18) is incorporated into a glucose analogue (FDG) and after injection into the patient, the positron emission decay of the short-lived radioisotope can be detected using the PET scanner⁴⁸. Because of the increased metabolism in tumour cells, glucose (FDG) uptake is higher and therefore tumours can be revealed⁴⁹. Combining FDG-PET with contrast enhanced CT allows for the detection of smaller lesions and a more precise determination of the tumour location⁴⁷. FDG-PET/CT can also adequately evaluate tumour response to chemotherapy and thereby be of importance in the selection of treatment strategy⁴⁹. On the other hand, the sensitivity of FDG-PET/CT in detecting tumours is reduced in patients that have received chemotherapy⁵⁰. Also, whereas FDG-PET/CT is sensitive in the detection of areas with increased metabolic activity it cannot sufficiently differ tumour from inflammation or postoperative findings and the sensitivity of the detection of mucinous tumours is low⁴⁹. Furthermore FDG-PET/CT is expensive and does not enhance the diagnostic accuracy of hepatic colorectal metastases compared to MRI⁴⁹. In the Swedish national guidelines for colorectal cancer FDG-PET/CT is therefore not recommended as a routine investigation in primary rectal cancer but it is considered a valuable tool to rule out extra-hepatic distant metastases and to assess the curative options in patients with locally advanced or recurrent rectal cancer³.

Imaging for local tumour growth

Endorectal Ultrasonography (EUS)

EUS is a relatively inexpensive procedure but also operator-dependent and associated with a learning curve⁵¹. Furthermore, EUS is not possible in patients with stenosing tumours. The accuracy of EUS to assess tumour invasion into the rectal wall is relatively good (69-94 %), especially for early (T1) and advanced (T3-4) tumours⁵². However, restaging after neoadjuvant treatment is more accurate with MRI and the diagnostic value of EUS in detecting lymph node involvement is rather low^{52, 53}. In many centres EUS is therefore used

merely as a complement to MRI, especially for early tumours.

Magnetic resonance Imaging (MRI)

The development of MRI for the pretherapeutic staging of the local tumour growth has had a profound effect in rectal cancer management. Correctly performed high resolution T2-weighted MRI can adequately stage primary rectal cancer and thereby optimize treatment selection. Also, MRI enables restaging after neoadjuvant treatment and predicts resectability and oncological outcomes⁵⁴⁻⁵⁶.

T stage

According to a systematic review and meta-analysis including rectal cancer patients who did not receive neoadjuvant therapy and where histopathology was used as the reference standard, the sensitivity and specificity for preoperative MRI-based T stage was 87 % (95 % CI 81-92) and 75 % (95 % CI 68-80) respectively⁵⁷. MRI can adequately measure extramural tumour growth and differ between substages of T3 tumours thereby predicting the risk of local recurrence after surgery^{16, 58}. For the staging of early tumours and distinction between T1/T2 tumours, MRI accuracy is relatively low and instead EUS is recommended^{52, 59}.



Figure 4. T2 weighted magnetic resonance images of the pelvis in a male patient with rectal cancer. **a.** Sagittal view where the semi annular rectal tumour is clearly depicted in its dorsal aspect (white arrows). **b.** Transaxial view showing a mesorectal lymph node (ML), the mesorectal fascia (MRF) and a lateral lymph node (LL) in the left obturator fossa.

N stage

Brown *et al.* showed that MRI can predict mesorectal lymph node involvement based on irregular contour and mixed signal intensity with a sensitivity of 85 % (95 % CI 74-92) and a specificity of 97 % (95 % CI 95-99)⁶⁰. In this study the lymph node size, measured as the short-axis diameter, was an inaccurate predictor of metastatic growth. Although it appears as if there is an association between nodal size and the risk of metastatic growth the optimal cut off seems to be difficult to find whereas a low cut off will render a high sensitivity but a low specificity while a high cut off will lead to low sensitivity and a high specificity⁶¹. Despite the promising results from Brown *et al.* the morphological criteria have not been universally adopted, possibly because small nodes are difficult to evaluate. In a meta-analysis MRI performance was more disappointing regarding sensitivity (range 54-76 %) and specificity (range 59-87 %) for lymph node involvement⁶². Restaging of suspected mesorectal nodes after neoadjuvant chemotherapy however appears to be more adequate with accuracy ranging between 64 - 88 %⁶³. Historically the presence of mesorectal lymph node metastases has been associated with increased rates of local recurrence but with TME surgery, N status appears to be of less importance as a predictor of local control⁶⁴.

Lateral lymph nodes

The data on incidence and relevance of lateral lymph node metastases in rectal cancer is relatively sparse. According to a Japanese multicentre trial that randomised 701 patients with stage II-III low rectal cancer to TME surgery alone or TME and lateral lymph node dissection (LLND), the proportion of patients with lateral lymph node metastases in the latter group was 7 %⁶⁵. Another retrospective Japanese study including patients with low (< 8 cm) T3/T4 rectal cancer, reported metastatic lateral lymph nodes in 17 % of the patients⁶⁶. In a study by Kim *et al.* the presence of positive lateral lymph nodes based on lymph node short-axis diameter of \geq 5 mm on pre-treatment MRI, predicted for a lateral local recurrence (26.6 % vs. 2.3 %, $p < 0.001$) in patients with primary rectal cancer who underwent preoperative radiochemotherapy but not LLND⁶⁷. The MERCURY study group showed that the disease-free survival (DFS) was inferior in primary rectal cancer patients with positive lateral lymph nodes on pretherapeutic MRI compared to in patients without suspicious lateral lymph node involvement (42 % vs. 70.7 %, $p < 0.001$)⁶⁸. However, in this retrospective investigation lateral lymph node involvement were defined by the presence of irregular capsular border or mixed signal intensity and not by size.

Mesorectal fascia (MRF)

CRM is a strong prognostic indicator in rectal cancer surgery^{19, 20}. MRI can accurately identify the MRF that represents the surgical circumferential resection plane when TME surgery is performed and thereby foresee the surgeon's possibility to accomplish a clear CRM⁶⁹. The MERCURY study group reported an accuracy of 87 % of MRI-based CRM compared to histopathology⁷⁰. In multivariate analyses an involved CRM according to MRI was statistically significantly associated with inferior rates of overall survival (OS), DFS and

local recurrence. In another recently reported German prospective multicentre study with T4 rectal cancer, MRI accurately predicted a negative histopathological CRM in 98.3 % of the patients⁷¹.

Extramural venous invasion (EMVI)

MRI before and after neoadjuvant therapy can adequately identify the presence of EMVI (mrEMVI) in rectal cancer^{72,73}. Several investigations have reported mrEMVI to be highly specific (88-96 %) when correlated to histopathology while the sensitivity (28-62 %) appears to be lower^{72,74,75}. Nevertheless, mrEMVI is a strong predictor for survival and distant spread, both before and after preoperative chemoradiotherapy (CRT)^{72-74,76}.

Preoperative treatment response

The evaluation of preoperative treatment response with MRI in rectal cancer is an area of increasing attention, both regarding prediction of outcomes and complete response, but conclusive data and clinical implications so far is limited⁷⁷. The MERCURY study showed that TRG can be assessed with MRI (mrTRG) after preoperative (chemo-)radiotherapy ((C)RT) by using differences in signal intensity between tumourous and fibrous tissue in the rectal tumour⁷⁸. In this investigation, the 5-year OS was 27 % vs. 72 % (p = 0.001) and the 5-year DFS 31 % vs. 64 % (p = 0.007) for a good compared to a poor mrTRG. The predictive role of a good mrTRG has also been shown for low rectal cancers⁷⁹. Also, Nougaret *et al.* reported that volumetric assessment with MRI in patients receiving preoperative CRT is of prognostic significance⁸⁰. In this study a tumour volume reduction of at least 70 % was correlated to a better DFS (HR 13.7; 95 % CI 3.98-31.93).

Locally advanced and locally recurrent tumours

Imaging of locally advanced primary rectal cancer and locally recurrent rectal cancer is demanding regarding diagnosis, staging, prediction of resectability and outcomes⁸¹. MRI for local recurrence lacks specificity in the differentiation between tumour regrowth and fibrotic scar tissue but the use of diffusion-weighted MRI appears to be promising in this respect^{82,83}. While locally advanced primary rectal cancer is staged by the same criteria as non-advanced primary rectal cancer, several classifications of local recurrence based on anatomical localisation in the pelvis exist that give predictive information regarding resectability and prognosis⁸¹. In the widely adopted classification from the Memorial Sloan Kettering group the pelvis is separated in 4 compartments: Axial, anterior, posterior and lateral⁸⁴. Several investigations using preoperative MRI for locally recurrent rectal cancer have shown that an axial recurrence compared to a posterior or lateral recurrence has superior outcomes regarding R0 resection rate and OS, after curatively intended surgery⁸⁵⁻⁸⁷.

Multidisciplinary team (MDT) conference

When all information from the pretherapeutic investigation is collected, a decision on treatment selection should be made. Since there are many therapeutic options and strategies including radiation, chemotherapy and surgery for primary tumour and metastases, several competences must be gathered for the optimal decision-making. Improved staging and increased knowledge of predictive indicators enables more individualised rectal cancer management but also makes treatment selection more complex. In the last decades MDT conferences have been introduced as a routine in cancer care, but also in the management of other diseases.

In rectal cancer the MDT usually includes colorectal surgeons, oncologists, radiologists, pathologists and a specialised nurse but the composition varies depending on specific needs and local routines. Each patient can be discussed at several MDT conferences: after staging but before preoperative treatment, after preoperative treatment and after surgery but also throughout the care of metastases or local recurrence. Treatment recommendations are made based on pre- or postoperative stage but must also be made with individual patient factors such as age and comorbidity in mind. The final treatment decisions, however, should always be made together with the patient. The use of MDT conference has increased continuously and in Sweden 97 % of all rectal cancer patients are now discussed at an MDT conference before undergoing surgery².

The use of MDTs as a routine practise in rectal cancer care has evolved without the support of strong evidence. There is a lack of randomised studies in this area and this will probably not change since it is believed that MDT conferences is beneficiary for the patients and the omittance of MDT discussions in a randomised trial would be unethical. However, there are reports supporting the benefit of MDT conferences in rectal cancer management such as increased usage of pretherapeutic MRI, more complete staging, increased use of neoadjuvant treatment, increased proportion of CRM negative and R0 resections, decreased postoperative mortality and improved local control⁸⁸⁻⁹¹. It appears that MDT conferences, although resource demanding, are not associated with any other disadvantages.

Staging and treatment decisions at the MDT-conferences are aided by national and international guidelines. However, the organisations issuing these guidelines such as the European Society of Medical Oncology (ESMO), the European Rectal Cancer Consensus Conference (EURECCA-CC2) and the National Comprehensive Cancer Network (NCCN) differ in their recommendations regarding some of the aspects of rectal cancer management^{11, 92-94}. Furthermore, guidelines usually do not take patient characteristics such as age and comorbidity into account.

Swedish Colorectal Cancer Registry (SCRCR)

The Swedish Rectal Cancer Registry was initiated in 1995 and the Swedish Colon Cancer Registry in 2007 and the two separate registries have since then merged into the SCRCR administered by the regional cancer centres (RCC) in Sweden. Reporting from surgeons, oncologists and pathologists to the register include information on pre- and postoperative staging, surgery performed, postoperative course, neoadjuvant and adjuvant therapy, palliative treatment, treatment of metastases, recurrence and follow-up. All data are registered prospectively. Information on death is also available through linkage to the Swedish Cause of Death Register administered by the Swedish National Board of Health and Welfare. Data on comorbidity is not included in the SCRCR.

The SCRCR is continuously revised and annual reports from the registry allows for the comparison of rectal cancer management between hospitals and regions in Sweden. The high coverage (> 99 %) and data validity in the SCRCR make it a valuable source of information for population-based investigations^{95, 96}.

The Swedish National Patient Register

This register is maintained by the National Board of Health and Welfare, a Swedish government agency. Registration started in the 1960s and became mandatory in 1984. Since 1987 it includes information regarding in-patient care from all hospitals in Sweden and from 2001 outpatient visits are included. Validation of the register has shown positive predictive values of 85-95 % for diagnoses in inpatient care according to the International Classification of Diseases (ICD)⁹⁷. The presence of personal identification numbers in Sweden allows for linkage between registries in populations-based studies.

Surgical treatment

Except for a small number of rectal cancer patients with a complete tumour regression following (C)RT, a radical resection of the tumour in rectal cancer is a prerequisite for cure. In the last hundred years dramatic improvements have been made in rectal cancer surgery. In 1908, the British surgeon Miles presented a novel surgical method combining abdominal and perineal surgery into abdominoperineal excision (APE)⁹⁸. Before this new surgical technique the local recurrence rates were almost 100 %. Although improved, Miles still reported local recurrence rates of 29.5 % and the rates of complication and mortality were substantial⁹⁹.

Because of improved perioperative conditions mortality decreased but local recurrence rates remained high throughout the major part of the 20th century.

The understanding of lymphatic tumour spread along the superior rectal artery in Miles' method, was followed by the subsequent removal of mesorectal lymph nodes *en bloc* with the rectosigmoideum. However, it was not until the 1980s that the importance of lateral tumour margins was fully understood¹⁹. In 1982 Heald described the concept of total mesorectal excision (TME), where the dissection line runs along the MRF and all of the mesorectum is removed together with the rectal specimen to decrease tumour involvement of the lateral resection margins¹⁰⁰. As a result, Heald could show a dramatic decrease in local recurrence rates down to 4 %¹⁰¹. Several investigations have confirmed that TME-surgery of good quality results in local recurrence rates below 10 %, but also in improved long-term survival¹⁰²⁻¹⁰⁴.

Pelvic surgery is associated with a high risk of urogenital dysfunction. However, in the last decades of the 20th century, Japanese surgeons showed that identification and sparing of autonomic nerves (hypogastric nerves, inferior hypogastric plexus, pelvic splanchnic nerves) during rectal cancer surgery resulted in better outcomes regarding sexual function and urinary voiding^{105, 106}. TME-surgery with autonomic nerve preservation has been shown to decrease postoperative urogenital dysfunction without jeopardising long-term oncological outcome¹⁰⁷.

The TME-technique is today the gold standard of rectal cancer surgery in the low and mid rectum and is used regardless of what kind of rectal resection that is performed: with anastomosis (anterior resection) or without (APE, Hartmann's operation) and in open as well as minimally invasive surgery. However, controversies exist regarding the surgical management of tumours in the upper rectum. Since the lymph of the upper rectum drains upwards along the superior rectal artery it is reasonable to argue that harvesting the lymph node of the lower mesorectum is unnecessary in upper rectal cancer. Furthermore, although vast improvements in rectal cancer surgery have been accomplished, complications after TME-surgery still constitute a considerable problem and a low anastomosis appears to be related to worse quality of life scores¹⁰⁸. A partial mesorectal excision (PME) transecting the rectum 5 cm below the tumour has been suggested and several reports have shown a better functional outcome compared to after TME without compromising local control¹⁰⁹⁻¹¹¹. In contrast, other authors have reported increased local recurrence rates after PME and it appears as if the benefit regarding functional outcome in patients undergoing PME is abolished following preoperative radiotherapy (RT)^{112, 113}.

Improvements in perioperative care during the last century have led to better outcomes in abdominal surgery. To further reduce the adverse effects of major surgery an Enhanced Recovery After Surgery (ERAS) program or "Fast track" surgery was developed in the last decades^{114, 115}. The ERAS protocol includes several perioperative interventions that aim to

reduce the surgical strain and have been shown to reduce complications and the length of stay compared to traditional care^{116, 117}.

Anterior resection (AR)

Following the introduction of TME the proportion of patients with a permanent stoma after rectal cancer surgery was substantially reduced¹¹⁸. In addition, circular stapling devices facilitated this development. In faecal continent patients with a rectal tumour without sphincter involvement in the low or mid rectum, a low anterior resection (LAR) is preferred. A LAR includes the division of the proximal sigmoid colon, TME-dissection and transection of the rectum at or immediately above the pelvic floor. A coloanal anastomosis is created, usually with the aid of a circular stapling device. The term high anterior resection (HAR) originally was used to describe an anterior resection above the peritoneal reflection but has more recently been used as an equivalent to PME. In about half of the patients undergoing rectal cancer surgery in Sweden an AR is performed².

The use of a temporary defunctioning stoma in patients undergoing LAR, has been shown to decrease the risk of symptomatic anastomotic leakage and also the need for re-operation among patients with anastomotic leakage¹¹⁹. Defunctioning stomas are standard practise in many centres and usually stoma closure is undertaken within 3 month after the LAR.

Hartmann's procedure

The Hartmann procedure was originally described for obstructive cancer of the left colon¹²⁰. In rectal cancer surgery the Hartmann procedure includes TME or PME but unlike with AR, no restoration of bowel continuity. After division of the rectum, the distal colon end is used to create a stoma that most often is permanent. The Hartmann operation is mainly considered in palliative surgery, in patients with anal incontinence or in situations with impaired healing. It is also performed for tumours in the sigmoid colon and for benign diseases such as diverticulitis.

Abdominoperineal excision (APE)

In principal, an APE consists of the removal of the entire rectum and anal canal with the construction of a permanent end-colostomy. APE can be sub-divided into four different types: intersphincteric APE, conventional APE, extralevator APE (ELAPE) and ischioanal APE¹²¹. In the intersphincteric APE, the external sphincter and the pelvic floor is left intact and the operation is an alternative to the Hartmann procedure in patients with a tumour well above the sphincter complex in whom an anastomosis is contraindicated or if the patient suffers from

anal incontinence. The advantage of an intersphincteric APE compared to the Hartmann procedure is the absence of a rectal stump that can cause postoperative pelvic abscesses¹²². On the other hand, following APE problems with impaired perineal wound healing are common, especially after preoperative RT¹²³.

In a conventional APE the abdominal part ends at the pelvic floor and the perineal part includes resection of the anal canal, the sphincter complex and the lower part of the levator muscle. The resected specimen shows a waist at the distal border of the mesorectum, above the levator muscle¹²⁴. From this waist and distally where the external sphincter is forming the outer border of the excision, the CRM is naturally shorter. Several investigations have showed that a conventional APE for low rectal cancers is associated with high rates of CRM positivity, local recurrence and poor survival¹²⁵⁻¹²⁷. In 2007 Holm *et al.* proposed ELAPE as a method to decrease the risk of inadvertent bowel perforation and involved lateral margins¹²⁴. In ELAPE the abdominal part ends at the level of the upper border of the coccyx thereby keeping the distal mesorectal attachment to the levator muscle. The perineal dissection line runs along the outer border of the external sphincter and continues below and along the levator muscles until the insertion onto the pelvic sidewall where it is divided. The cylindrical specimen resected with ELAPE results in the theoretical benefit of an increased lateral margin. In APE the perineal wound usually can be closed primarily whereas an ELAPE usually requires a pelvic floor reconstruction with a musculocutaneous flap or a biological mesh. Several publications including a review, a meta-analysis and a randomised trial have shown favourable outcomes with ELAPE compared to APE with regards to rates of bowel perforation, CRM positivity and local recurrence¹²⁸⁻¹³¹. Other reports however, could not show difference regarding these outcomes but a higher rate of wound problems with ELAPE¹³²⁻¹³⁴.

In the ischioanal APE, the abdominal part is similar to the ELAPE but instead of following the external sphincter, the perineal dissection runs along the fascia of the internal obturator muscle. This method is mainly considered for patients with locally advanced tumours involving the ischioanal compartment or the perianal skin¹²¹.

Lateral lymph node dissection (LLND)

Controversies regarding whether to define lateral lymph node metastases as localised or systemic disease have led to different treatment strategies throughout the world. In Japan LLND is recommended for rectal cancer growing below the perineal reflection whereas in the western world instead preoperative (chemo-)radiation is recommended^{11, 135}.

According to a multicentre trial by Fujita *et al.* where patients with stage II-III rectal cancer without lateral lymph node enlargement (> 10 mm) on MRI or CT were randomised to TME surgery with or without LLND, patients in the LLND arm had significantly longer operation

time (360 vs. 254 min, $p < 0.0001$), greater blood loss (576 vs. 337 ml, $p < 0.001$) and a tendency of more complications but there were no significant differences regarding male postoperative sexual or urinary dysfunction^{65, 136}. The recently published 5-year data from this trial showed no significant differences in OS but the local recurrence rates were significantly lower in the LLND arm (7.4 % vs. 12.6 %; $p = 0.024$)¹³⁷. Furthermore, the proportion of lateral recurrences out of all local recurrences were significantly lower in the LLND arm compared to in the TME alone arm (15 % vs. 52 %; $p = 0.02$). In this trial, none of the patients received preoperative treatment. An investigation based on data from a Japanese nationwide registry reported improved OS (HR 0.85; 95 % CI 0.78-0.93) in rectal cancer patients who underwent LLND¹³⁸. However, in a meta-analysis by Georgiou *et al.*, LLND did not significantly improve survival or local recurrence rates but was correlated with higher rates of urinary and sexual dysfunction in males¹³⁹. Although the presence of lateral lymph nodes metastases in rectal cancer is associated with inferior prognosis, more data are needed to fully understand the role of LLND, especially following preoperative (C)RT^{67, 68, 140}.

Minimal invasive surgery

Two large randomised multicentre trials (COREAN, COLOR II) have proven superior short-term outcomes in terms of blood loss, time to recovery, return to bowel function and length of stay with laparoscopic vs. open TME with similar rates of CRM positivity and equivalent specimen quality^{141, 142}. The 3-year follow up from these trials also showed similar rates of OS, DFS and local recurrence^{143, 144}. However, the operation time was significantly longer in the laparoscopic group and T4 tumours were not included. Two other randomised trials (ACOSOG, ALaCaRT) failed to show non-inferiority with laparoscopic compared to open rectal cancer surgery when results regarding CRM, DRM and completeness of TME were combined^{145, 146}. Laparoscopic rectal cancer surgery may be justified in experienced centres and with good quality outcome data, but otherwise as well as for locally advanced rectal cancers, open surgery is preferable.

Robotic surgery has the same minimal invasive gains as laparoscopic surgery but has features that may improve the possibility to perform advanced nerve-sparing surgery in the narrow pelvis. There are some studies showing benefit of robotic over laparoscopic rectal cancer surgery regarding outcomes and conversion rates but no published data from randomised multicentre trials are available¹⁴⁷. Furthermore, the robotic technique is associated with high costs and therefore more solid data is warranted before it can be widely adopted.

Transanal TME (ta-TME) is a relatively new technique, which combines laparoscopic abdominal surgery and transanal TME-dissection¹⁴⁸. It appears to have advantages over laparoscopic surgery in male patients with distal tumours, narrow pelvis and high BMI but more evidence is required to determine its short-term and long-term benefits¹⁴⁹.

Local excision

Transanal endoscopic microsurgery (TEM), endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are local excision techniques for polyps or early rectal tumours where the risk of lymph node metastases is low according to MRI and/or EUS. The advantage with these types of surgery is the shorter operation time, low grade of morbidity imposed and that they usually can be performed without general anaesthesia, which makes local excision attractive in fragile patients. However, using these techniques implies a risk of positive resection margins and also, engaged lymph nodes are not sufficiently yielded.

In the Japanese guidelines for colorectal cancer EMR and EMD are recommended for Tis and T1 tumours with only slight submucosal invasion since only part of the rectal wall is removed with these techniques¹³⁵. ESD is more demanding for the endoscopist and associated with higher complication rates and longer operation time but also with lower rates of local recurrence and more *en bloc* resections, especially for larger lesions (≥ 2 cm)¹⁵⁰.

TEM includes a full-thickness excision of the rectal wall and suturing of the defect but without resection of the mesorectum. TEM compared to TME for T1 tumours results in significantly less morbidity and mortality and shorter length of stay but also higher local recurrence rates¹⁵¹. The higher rates of local recurrence after TEM may also increase the proportion of patients who need to undergo more advanced surgery with APE after TEM surgery compared to if TME with LAR had been performed for the primary tumour¹⁵².

Surgery for locally advanced and locally recurrent rectal cancer

The surgical principles guiding surgery for primary rectal cancer also apply to locally advanced and locally recurrent rectal tumours. However, surgery for advanced rectal tumours also imposes the need for dissection outside the TME planes and resection of other involved organs. Consequently, a need for reconstructive surgery is common, complication rates reported are high (48-68 %) and mortality is not negligible¹⁵³⁻¹⁵⁸. Surgery is the only curative option for locally advanced or locally recurrent rectal cancer and oncological outcomes are largely dependent on the ability to perform radical resections¹⁵⁹. Although improvements appear to have been made, the rate of R1 or R2 resection still ranges between 23-46 % and according to a meta-analysis the range of median survival for R0, R1 and R2 resection is 28-90 month, 12-50 month and 6-17 months, respectively^{86, 153, 154, 156, 157, 159}.

What is defined as locally advanced tumours differs between investigations, making comparison of results difficult. Also, the management of patients with locally advanced or locally recurrent rectal cancer displays a wide variation between centres throughout the world and there are no guidelines that fully cover the care of these patients. The need for complex treatment decisions and arduous surgery for this patient group demands a multidisciplinary approach in devoted centres to improve outcome and patient selection. Indeed, in a recent

publication from the Royal Marsden Hospital, R0 resection was achieved in 93 % of patients with locally advanced or recurrent colorectal cancer after a structured multidisciplinary approach in a highly specialised centre¹⁶⁰.

Complications after rectal cancer surgery

Except for the local excision techniques, rectal cancer surgery is a major procedure rendering considerable morbidity. In addition, a substantial proportion of rectal cancer patients are treated with (C)RT that further increases complication rates. Morbidity after rectal cancer surgery can be divided into postoperative short-term complications and long-term functional outcome. Since the management of rectal cancer surgery as well as the definition and registration of morbidity vary, there is diversity in complication rates reported.

Short-term complications

Short-term complications include anastomotic leakage after AR, wound problems, intraabdominal infection, ileus, medical adverse events such as cardiac and respiratory complications and death. According to a review by Paun *et al.*, including studies with patients who had undergone open or laparoscopic AR or APE, the rates of anastomotic leakage were 11 % (AR), pelvic sepsis 12 %, wound infection 7 % and mortality 2 %¹⁶¹. In the COLOR II trial there were no significant difference between the laparoscopic and open group concerning overall morbidity, anastomotic leakage, wound infection, postoperative ileus or mortality but the COREAN trial reported a lower frequency of wound discharge in the laparoscopic group (1.2 vs. 6.5 %, $p = 0.020$)^{141, 142}. Perineal wound complications after APE constitutes a major problem and has been reported in 20-38 % after conventional APE and in 38-46 % after ELAPE^{129, 132, 162}.

Male sex, malnutrition, advanced age, comorbidity, smoking, high BMI, preoperative (C)RT and advanced tumour stage have been identified as risk factors for adverse short-term outcomes after rectal cancer surgery¹⁶³⁻¹⁶⁶. Beside prolonged hospital stay, increased suffering and mortality caused by postoperative complications there are also indications of inferior oncological outcome following anastomotic leakage¹⁶⁷.

Long-term complications

Low anterior resection syndrome (LARS) refers to anorectal dysfunction following anterior resection. The symptoms include faecal incontinence and urgency but also fragmentation of stool and difficulty to defecate. According to a review by Bryant *et al.*, the reported prevalence of incontinence is between 0-71 % and of evacuatory disorder 12-74 % after anterior resections¹⁶⁸. Because of the diversified terminology and difficulties in result comparison, a LARS-score composed of 5 questions was developed and validated in Denmark¹⁶⁹. Preoperative (C)RT, TME vs. PME, anastomotic leakage, age ≤ 64 years and

female sex have been shown to correlate to inferior anorectal function in terms of a high LARS-score¹¹¹.

Although improved by TME surgery and nerve sparing dissection, the prevalence of erectile dysfunction (14-80 %), and retrograde ejaculation (20-40 %) in men and decreased lubrication (15-57 %) and dyspareunia (25-59 %) in women after rectal cancer surgery remains considerable^{107, 136, 170-173}. Moreover, even when nerve damage clearly can be avoided other factors than the surgery itself, such as preoperative RT, advanced age, comorbidity, the presence of a stoma and faecal incontinence increases the risk of postoperative sexual dysfunction^{136, 172, 173}. Also, the overgrowth of locally advanced tumours can make nerve sparing surgery impossible. Damage to the autonomic nerves during pelvic surgery also increases the risk for urinary dysfunction. From the Dutch TME trial postoperative incontinence and difficulties in emptying the bladder was reported in 38 % and 31 % of the patients¹⁷⁴.

Patients undergoing APE or Hartmann's procedure will receive a permanent colostomy and a large proportion of patients will have a temporary diverting ileostomy after an AR. Stoma formation is associated with many complications. Stoma necrosis, retraction, prolapse, stenosis and hernia is relatively common for both ileostomies and colostomies while fluid and electrolyte imbalances, leakage and peristomal skin problems is associated chiefly with ileostomies due to their more frequent and watery stools¹⁷⁵. Beside the risk of morbidity imposed by an ileostomy, the time to stoma closure can be prolonged for several reasons and in up to one fourth of the patients the ileostomy will be permanent^{176, 177}. Also, the morbidity after stoma closure is not negligible¹⁷⁸.

Preoperative radiotherapy (RT)

RT induces cell death through damage to the DNA and has the greatest effect on proliferative cells in the mitotic phase. Since cancer tumours have proportionally more cells undergoing mitosis and also because DNA-repair is impaired, tumour cells are more sensitive to RT than cells in normal tissue. In most tumour forms, including adenocarcinoma of the rectum, cell death continuous long after administration of radiation. The purpose of RT in rectal cancer is twofold: to kill tumour cells near the primary tumour that may not be resected by standard rectal cancer surgery (TME) and to induce downsizing and downstaging of the tumour, thereby increasing the rates of R0 resection, sphincter preservation and local control. The effect of RT on rectal tumours and the risk of damage to normal tissue depends on the total dose in Gray (Gy), the dose per fraction, the number of fractions, irradiated volume and time interval between RT and surgery¹⁷⁹.

There has been a long-lasting controversy on whether pre- or postoperative RT should be used, optimal dose and fractionation of RT, timing of surgery, and the gain of chemotherapy added to RT for rectal cancer, to achieve the best oncological outcomes and minimise RT-induced morbidity. In recent years, it has also been debated if it is reasonable to try to accomplish complete tumour response and thereby organ preservation with intense CRT alone.

Pre- vs. postoperative (C)RT

Several large randomised European trials have demonstrated the benefit of preoperative RT. These trials have demonstrated a reduction in local recurrence rates of 41-56 % with preoperative RT and surgery compared to surgery alone¹⁸⁰⁻¹⁸⁶. This risk reduction persisted also in the trials where TME surgery was performed with local recurrence rates of about 5 % after preoperative RT^{180, 186}. Other trials comparing preoperative (C)RT and postoperative (C)RT showed local recurrence rates of 4-13 % and 11-22 %, respectively and with less radiation induced toxicity if (C)RT were given preoperatively^{184, 186, 187}. Based on these investigations the preoperative (C)RT regime has become the gold standard in Europe as in many other parts of the world¹¹. In Northern America (C)RT for many years was delivered postoperatively based on histopathological staging. Nowadays however, with enhanced pretherapeutic staging (i.e. MRI), preoperative CRT is recommended for stage II-III disease according to the National Comprehensive Cancer Network (NCCN) Guidelines in the U.S.⁹³.

In the early Swedish Rectal Cancer Trial, patients randomised to preoperative RT had better OS than patients randomised to direct surgery (58 % vs. 48 %; $p = 0.004$)¹⁸¹. However, other trials, especially since the introduction of TME surgery, have not been able to reproduce this result and RT is now considered to be of importance mainly regarding achieving better local control^{186, 188}.

Dose and fractionation of RT

Numerous regimens of preoperative RT for rectal cancer have been proposed but it is usually administered as short course hypofractionated RT or long course conventionally fractionated RT. In short course RT 5 Gy is given daily during 5 days (5 x 5 Gy). In long course RT 1.8-2 Gy is given in 23-28 fractions during 4-5 weeks and often combined with chemotherapy (CRT)¹⁸⁹. The late side effects of 5 x 5 Gy have been explored and seem to have decreased over time due to improvements in radiation technique, but is less investigated concerning preoperative long course RT¹⁹⁰. Two trials (TTROG Trial, Polish Colorectal Study Group trial) randomising patients with T3 and T3/4 rectal cancers to preoperative short course RT or preoperative long course (C)RT, were unable to demonstrate any significant differences

regarding late toxicity, local recurrence rates or survival^{191, 192}. However, in the Polish trial the rate of CRM positive resection was significantly higher in patients who received short course RT (12.9 % vs. 4.4 %; $p = 0.017$).

Since there is no clear evidence regarding the superiority on outcome of either RT regime, there is a variation in practise throughout the world. Due to the short duration and because it is less resource demanding, 5 x 5 Gy is preferred in the north-western Europe. In other countries, because of the known risks of late toxicity with 5 x 5 Gy and, possibly, also due to economic gains in privately financed health care with more treatment given during several days, long course (C)RT is mainly used¹⁸⁹.

Timing of surgery

Traditionally preoperative long course (C)RT has been followed by a delay of 6-8 weeks before surgery is performed to reduce the effect of acute radiation toxicity, to increase tumour regression and achieve downstaging¹⁹³. According to a meta-analysis by Martin *et al.*, patients with a pathological complete response (pCR) compared to patients with incomplete response after preoperative CRT, had lower local recurrence rates (OR 0.25; $p = 0.002$) and improved OS (OR 3.28; $p = 0.001$)¹⁹⁴. In another recently published meta-analysis by Petrelli *et al.* investigating the effect of prolonged delay after preoperative CRT, the proportion of patients with pCR increased from 13.7 % to 19.5 % if the delay was more than the usual 6-8 weeks¹⁹⁵. In this meta-analysis, there were no significant associations between length of delay and rates of anastomotic leakage, wound complications, R0 resections, sphincter preservation or survival outcomes. A report from the Dutch TME trial, randomising rectal cancer patients to TME surgery with or without preoperative RT 5 x 5 Gy, showed a downsizing effect in the RT group but there were no significant differences regarding T or N stage¹⁹⁶. However, all patients receiving RT in this trial had direct surgery (within 10 days from the start of RT) and it is reasonable to believe that the downstaging effect of RT continuous also after the first week. The Swedish Rectal Cancer Trial demonstrated evidence of tumour regression after preoperative short course RT if surgery was delayed more than 10 days after the start of RT and this finding was confirmed also in other investigations^{186, 197, 198}.

The three-armed Stockholm III trial randomised patients with resectable rectal cancer to short course RT with immediate surgery, short course RT with delayed surgery after 4-8 weeks and long course RT with delayed surgery after 4-8 weeks¹⁹⁹. An interim analysis of this trial including only patients receiving short course RT, showed a significantly higher rate of pCR (11.8 % vs. 1.7 %; $p = 0.001$) and Dworak grade 4 tumour regression (10.1 % vs. 1.7 %; $p < 0.001$) in the delay group compared to the immediate surgery group²⁰⁰. In another recent publication from this trial, no significant differences regarding rates of local recurrence, distant metastasis and OS were reported¹⁹⁹. In a pooled comparison of the two short course

arms, delayed surgery was associated with higher rate of acute radiation toxicity (OR 24.67; 95 % CI 3.31-138.72) but lower rate of postoperative complication (OR 0.61; 95 % CI 0.45-0.83) compared to direct surgery.

RT vs. CRT

In the TTROG and Polish trials the use of concomitant chemotherapy with preoperative long course RT did not influence oncological outcome or late toxicity in the comparison with preoperative short course RT^{191, 192}. In two other trials (EORTC trial, FFCD trial) where patients with resectable T3/4 rectal cancer were randomised to preoperative long course RT with or without chemotherapy, the rate of local recurrence was significantly reduced if chemotherapy was added to RT whereas no effect was seen on OS^{201, 202}. In the FFCD trial where chemotherapy was delivered concurrent with preoperative RT, the 5-year local recurrence rates were 16.5 % vs. 8.1 % (p = 0.004), the rate of pCR 11.4 % vs. 3.6 % (p < 0.001) and acute grade 3-4 toxicity 14.6 % vs. 2.7 % (p < 0.001) in the CRT arm compared to the RT arm. In the 4-armed EORTC trial randomising patients to preoperative RT alone or with chemotherapy concomitant to RT and/or postoperatively, the local recurrence rates were similar irrespective of timing of chemotherapy but patients who received chemotherapy had lower local recurrence rates than patients in the RT alone arm (7.6-9.6 vs. 17.1 %; p = 0.002).

The LARCS trial, randomising 184 patients with non-resectable T4 rectal cancer and 25 patients with locally recurrent rectal cancer to long course preoperative RT with or without concurrent chemotherapy, showed a benefit of adding chemotherapy regarding R0 resections (84 % vs. 68 %; p = 0.02), pCR (16 % vs. 7 %; p = 0.04), local control (82 % vs. 67 %; p = 0.03), distant metastasis (26 % vs. 39 %; p = 0.04) and cancer-specific survival (72 % vs. 55 %; p = 0.02) although acute grade 3-4 toxicity was more common than after RT alone (29 % vs. 6 %; p = 0.001)²⁰³. Thus, CRT appears to increase local and systemic control in patients with locally advanced tumours, albeit with increased acute toxicity whereas for patients with intermediate rectal cancer the evidence is more incongruent. The recommendations for these tumours vary accordingly^{11, 92, 93, 135, 204}.

Recently published data from a randomised trial comparing conventionally fractionated CRT with preoperative 5 x 5 Gy and upfront chemotherapy before surgery for fixed T3/4 rectal cancer, showed no significant differences in pCR, postoperative complications, R0 resection rates, local recurrence rates or DFS but less acute toxicity (75 % vs. 83 %; p = 0.006) and better 3-year OS (73 % vs. 65 %; p = 0.046) in the 5 x 5 Gy arm²⁰⁵. The multicentre RAPIDO trial, recently closed for inclusion, with a similar design but with longer preoperative chemotherapy in the 5 x 5 Gy arm, aims to further investigate the effectiveness and safety of combined preoperative short course RT and full-dose chemotherapy for locally advanced rectal cancer²⁰⁶.

The most commonly used chemotherapeutic agent in CRT for rectal cancer is 5-fluorouracil (5-FU) administered intravenously, but the oral drug Capecitabine may also be used having the same radiation sensitisation properties. CRT with combinations of chemotherapeutic agents has been investigated in several trials although without demonstrating any clear benefit over single-agent chemotherapy regimens¹⁸⁹.

Organ preservation

The knowledge regarding tumour response and the downsizing and downstaging effect of preoperative treatment has rendered an increasing interest in exploring treatment regimens aiming at achieving organ preservation. A pCR is known to occur in approximately 20 % of rectal cancer patients following preoperative CRT and is associated with improved local and distant control and survival^{194, 207}. Tumour factors correlated to pCR include low grade of differentiation, small tumour size, low cT or cN stage, high radiation dose and longer delay of surgery (> 6-8 weeks)²⁰⁸.

From a series of 265 patients with resectable distal rectal cancer treated with preoperative CRT, Habr-Gama *et al.* reported that 8 weeks after completion of CRT, 71 (26.8 %) patients had a clinical CR (cCR), assessed by a combination of digital rectal exam (DRE), endoscopy, EUS, biopsy and CT²⁰⁹. The patients with a cCR were followed by frequent clinical investigations and patients with incomplete response underwent surgery. In the cCR group two patients developed local tumour re-growth that was treated locally and three patients developed distant metastasis. The 5-year OS in this group was 100 % although this was based only on the 28 (39 %) patients that remained in follow-up. Some other groups have shown similar promising survival outcomes and a relatively low proportion of patients with an initial cCR who later develop a need for salvage surgery, but the results reported overall are heterogeneous and based chiefly on small retrospective series^{210, 211}. There is a growing interest in using TEM as a part of organ preservation programmes for rectal cancer. In a phase II trial including 79 patients with T2N0 cancer in the distal rectum that received CRT followed by TEM, the 3-year DFS was 86.9 % according to the per-protocol analysis and 8 patients had a local recurrence²¹².

Numerous non-operative strategy programs have been proposed (“Watchful waiting”, “Wait and watch”, “Watch and wait”, “Wait and see”) with differences regarding patient inclusion (T stage), choice and timing of preoperative CRT, definition of cCR, timing and modality of clinical response assessment and follow-up programme, but there is little evidence on the optimal setting²¹³. CRT is associated with both acute toxicity and late adverse effects and there is a risk of overtreatment of patients with early tumours who would be recommended primary surgery outside the organ preservation programmes. Moreover, there is concern regarding outcomes in those patients needing salvage surgery because of local regrowth in

such a programme²¹¹. Furthermore, although there are obvious advantages with the omittance of major surgery, the follow-up programme for patients with a cCR is resource demanding. Since there is a lack of evidence based on randomised trials on all aspects of organ preservation programmes, patients eligible for such programmes should be treated within clinical trials²¹³.

Adverse events after radiotherapy

Acute toxicity

The acute adverse effects after preoperative (C)RT depends on the target volume of radiation, adjacent organ included in the radiation field and regime of RT and chemotherapy. The frequency of acute adverse effects has likely decreased with improved radiation technique. Symptoms of acute toxicity related to (C)RT include fatigue, nausea, diarrhoea, proctitis, perineal dermatitis, pelvic and perineal pain and urinary problems^{201, 214, 215}. Chemotherapy in rectal cancer patients is associated with fever, infections, stomatitis, skin reactions and cytopenia^{201, 214}. Contrary to the late adverse effects due to (C)RT, acute toxicity is usually transient. The Common Terminology Criteria for Adverse Events (CTCAE) developed by the National Cancer Institute (NCI), is used to grade the severity of adverse events after oncologic treatment (Table 5)²¹⁶.

Table 5. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0²¹⁶.

Grade 1	<i>Mild</i> ; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	<i>Moderate</i> ; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	<i>Severe or medically significant but not immediately life-threatening</i> ; hospitalization or prolongation of hospitalization indicated; disabling limiting self care ADL
Grade 4	<i>Life-threatening consequences</i> ; urgent intervention indicated
Grade 5	<i>Death</i> related to adverse events

In a Cochrane review from 2013 including 5 trials with rectal cancer patients randomised to preoperative RT or CRT, there was a significantly lower proportion of grade 3-4 toxicity in patients treated with RT than CRT (5.1 % vs. 14.9 %; OR 4.1; 95 % CI 1.68-10)²¹⁷. Although, the included trials were heterogeneous regarding the RT regime, data from a more recently published randomised trial confirmed the lower rate of grade 3-4 toxicity with 5 x 5 Gy vs. CRT (1.9 % vs. 27.1 %; p < 0.001)²¹⁴. Even in trials comparing conventional CRT and 5 x 5 Gy with preoperative consolidation chemotherapy, CRT is correlated to significantly more

acute toxicity²⁰⁵.

Late adverse effects

Several of the late adverse effects associated with RT are common also after rectal cancer surgery alone because of pelvic nerve injury and bowel reconstruction, but it appears that RT has an additive effect on these symptoms. According to a review by Birgisson *et al.*, bowel dysfunction after AR is more common after preoperative RT than after surgery alone with symptoms including faecal incontinence (14-72 % vs. 3-38 %), increased stool frequency (20-83 % vs. 8-23 %), urgency (53 % vs. 0 %) and evacuation difficulties (52 % vs. 36 %)¹⁹⁰. RT is also associated with a higher frequency of small bowel obstruction and symptoms of urinary dysfunction including incontinence, increased frequency and chronic cystitis²¹⁸. Furthermore, increased rates of erectile, ejaculatory and overall sexual dysfunction among male rectal cancer patients after RT have been reported^{173, 190, 219, 220}. According to recently published data, RT also results in testicular failure increasing the risk of hypogonadism²²¹. In females, RT for rectal cancer has been associated with dyspareunia, vaginal dryness and overall sexual dysfunction^{173, 222}.

From an investigation including patients from the Uppsala trial and the Swedish Rectal Cancer Trial, Birgisson *et al.* reported an increased risk of secondary cancers located not only in the pelvis, after RT for rectal cancer²²³. However, a Canadian report from the Surveillance, Epidemiology, and End Results (SEER) registry including 20,910 patients previously treated for rectal cancer did not demonstrate any significant difference in the risk of secondary cancer overall, but the risk of cancers in the uterine corpus and cervix was increased (HR 2.5; 95 % CI 0.48-0.84) and the risk of prostate cancer was decreased (HR 0.63; 0.48-0.84) in irradiated compared to non-irradiated patients²²⁴. Also in a study analysing 13,457 rectal cancer patients from the SCRCR and from five randomised trials, there were no overall impact of irradiation on the risk of secondary cancer but a decreased risk of prostate cancer (HR 0.68; 95 % CI 0.51-0.91)²²⁵.

Although the knowledge regarding late adverse effects after short course RT is profound, less is known about CRT in this matter. In two trials randomising patients to preoperative short course RT or CRT, there were no significant differences regarding late adverse effects^{191, 192}. In a retrospective analysis of patients receiving preoperative 5 x 5 Gy or CRT, the health-related quality of life (HRQL) was similar apart from more nausea/vomiting ($p < 0.01$) and less satisfaction with urinary function in patients who received CRT ($p < 0.01$)²²⁶.

Preoperative treatment according to clinical tumour stage

To facilitate preoperative treatment selection at the MDT conferences, guidelines have recommendations based on the extent of local tumour growth. In the guidelines issued by the

NCCN, recommendations are based merely on T and N stage where patients with T1-2 N0 tumours should undergo surgery alone and patients with T3-4 and/or N1-2, preoperative treatment (CRT) before surgery⁹³. The Japanese guidelines reserve preoperative CRT for patients with tumours growing below the peritoneal reflection and/or judged primarily unresectable¹³⁵. In several European guidelines, other known predictors of recurrence readily assessed by MRI, such as tumour height, MRF involvement and EMVI status, are used for the guidance of preoperative treatment and the categorisation of tumours into very early, early, intermediate and locally advanced are commonly adopted^{11, 92, 204}.

In a publication from 2008, Blomqvist and Glimelius classified rectal cancer into “good”, “bad” or “ugly”, based on pretherapeutic investigation with MRI²²⁷. According to this paper, the proportion of rectal cancer judged to be “good” is 20-40 %, “bad” 40-60 % and “ugly” 10-20 % and the local recurrence risk is < 10 %, 10-20 % and 20-100 %, respectively^{3, 227}. The recommendation regarding preoperative treatment for each tumour category in that article is consistent with the Swedish guidelines for colorectal cancer, although the recommendation of preoperative 5 x 5 Gy is added in patients with EMVI positive tumours³.

Table 6. “Good”, “bad” and “ugly” rectal cancer and recommended preoperative treatment according to Blomqvist and Glimelius²²⁷.

Tumour stage category		
Good	Bad	Ugly
Mid/upper rectum (> 5 cm) T1-3b	Mid/upper rectum (> 5 cm) T3c/d	T4 with overgrowth to prostate, seminal vesicles, base of urinary bladder, pelvic sidewalls or floor, sacrum
Low rectum (≤ 5 cm) T1-2, T3a	Low rectum (≤ 5 cm) T3b	
N0	T4 with peritoneal or vaginal involvement only	Positive lateral lymph nodes
MRF clear	N1-2 MRF clear	MRF positive
↓	↓	↓
Primary surgery	Preoperative 5 x 5 Gy with immediated surgery	Preoperative CRT or 5 x 5 Gy with delayed surgery

Adjuvant chemotherapy

Adjuvant (postoperative) chemotherapy for stage II colon cancer with risk factors and stage III colon cancer has been shown to increase DFS and is routinely used in colon cancer management^{228, 229}. In contrast, there is little evidence regarding adjuvant chemotherapy in rectal cancer. Exploring the benefit of adjuvant treatment in rectal cancer is difficult since many rectal cancer patients receive preoperative (C)RT and this may alter postoperative tumour stage and indications for adjuvant chemotherapy. In a meta-analysis, Breugom *et al.* included 4 trials with rectal cancer patients receiving preoperative (C)RT that were randomly assigned to adjuvant chemotherapy or not²³⁰. No significant differences were shown regarding survival or distant recurrence, although patients with upper rectal cancers that received adjuvant chemotherapy had better DFS (HR 0.59; 95 % CI 0.40-0.85) and fewer distant recurrences (HR 0.61; 95 % CI 0.40-0.94). In the Swedish national colorectal cancer guidelines, adjuvant chemotherapy for rectal cancer is mainly recommended for un-irradiated stage II tumours with risk factors and stage III tumours, especially in the upper rectum³.

Age and comorbidity

The knowledge on how to best treat rectal cancer patients with advanced age or comorbidity is scarce since the inclusion of these patients in clinical trials is limited²³¹. As a result of this, preoperative treatment recommendations in guidelines taking patients frailty into consideration are meagre. Since performance status is less often reported than age, the evidence is even sparser concerning comorbidity. As life expectancy increases and comorbidity as well as rectal cancer incidence increases with age, more frail patients will be considered for rectal cancer therapy.

Treatment selection regarding patients with high age or comorbid conditions is complex. Omission of rectal cancer treatment will lead to inevitable death and is associated with substantial suffering and less extensive treatment increases the risk for recurrence. On the other hand, treatment related morbidity and mortality is increased in the elderly and in patients with comorbidity. It has been reported that advanced age in patients that undergo rectal cancer surgery correlates to a lower proportion of abdominal surgery (i.e. more local excisions) and R0 resections, more postoperative complications, more permanent ostomies and a higher frequency of postoperative mortality²³²⁻²³⁵. Other authors failed to demonstrate any significant difference concerning postoperative morbidity between young and old patients²³⁶. Numerous population-based investigations have demonstrated that being old or having comorbidity is associated with significantly lower probability of receiving RT for rectal cancer^{232, 233, 237-240}. Although improvements have been reported over time, rectal cancer patients with advanced age or comorbidity have worse survival outcomes^{164, 235, 241}. However,

several investigations have shown that elderly rectal cancer patients who receive RT have significantly lower local recurrence rates and in some reports also improved survival compared to patients in whom RT is omitted^{234, 242, 243}.

There is little knowledge regarding tolerability of CRT in frail patients. In a study by Margalit *et al.* 36 rectal cancer patients aged 75 years or older and in whom comorbidity was judged as moderate or severe in 17 of the patients, were investigated regarding treatment deviation during CRT²⁴⁴. Some 33 patients completed the RT but in 9 of the patients a temporary break in RT was required and only 14 patients completed ≥ 4 months of chemotherapy. In another investigation where patients ≥ 70 years received preoperative RT or CRT, 37 % of the patients treated with chemotherapy required dose modification or discontinuation²⁴⁵. There were no differences in 3-year OS after RT or CRT but advanced comorbidity was associated with worse OS (71.1 % vs. 26.4 %, $p = 0.0003$). Likely, RT is preferable to CRT in frail patients with rectal cancer when preoperative treatment is indicated although there are reports showing relatively low rates of dose reduction or discontinuation of CRT in elderly rectal cancer patients²⁴⁶. Short course RT with delayed surgery may be a useful alternative in aged or comorbid patients with locally advanced rectal cancers¹⁹⁸.

The assessment of comorbidity in cancer care is important in the guidance of optimal treatment for the individual patient. Ideally, a comorbidity measure should be simple to perform, not time-consuming and valid in predicting outcomes. Traditionally oncologists have used the Karnofsky or the Eastern Cooperative Oncology Group (ECOG) performance status scores to assess disease progression and determine appropriate treatment^{247, 248}. More recently the Comprehensive Geriatric Assessment (CGA) has gained popularity in guiding cancer management among the elderly²⁴⁹. However, these assessment tools presume a clinical evaluation and especially CGA is rather extensive and resource demanding.

Several comorbidity measures have been developed allowing for administrative data to be used, the most cited being the Charlson Comorbidity Index (CCI)^{250, 251}. Originally, Charlson *et al.* used the information from a cohort of 559 patients admitted to the medical service at a New York Hospital, to predict the 1-year relative risk (RR) of death depending on each medical condition. Using the number and the seriousness of the comorbid disease as measured by the RR, a weighted index was created where the risk of death increased with each score. The CCI has been validated in several investigations, also using the ICD diagnosis codes from medical records²⁵⁰. Despite the fact that it was developed 30 years ago and the prognosis for different medical conditions likely has improved, the CCI is widely used also in rectal cancer research due to its simplicity regarding information retrieval^{237, 239, 241, 250}.

In the SCRCR there has previously been no recording of CCI or other comorbidity measures. Since 2007 the American Society of Anesthesiologists (ASA) physical status classification is registered but the knowledge regarding the reporting of this variable in the SCRCR and its validity in evaluating comorbidity in rectal cancer patients is limited²⁵².

AIMS OF THE THESIS

Overall aim

To optimise preoperative treatment selection in rectal cancer, thereby improving long-term oncological outcome and minimising treatment-associated morbidity.

Specific aims

Paper I

To investigate patient characteristics affecting the selection to preoperative radiotherapy and whether non-relevant treatment selection occurs.

Paper II

To assess the impact on long-term outcomes in patients with advanced age and comorbidity when selected to preoperative radiotherapy.

Paper III

To evaluate adherence to pretherapeutic MRI protocol standards and the relation between MRI interpretation of images and preoperative treatment selection.

Paper IV

To explore if MRI characteristics in primary rectal cancer can predict oncological outcome after curatively intended surgery for local recurrence and also the localisation of the local recurrence.

To investigate selection to preoperative treatment for the primary tumour in relation to MRI and the effect on oncological outcome after curatively intended treatment for local recurrence.

PATIENTS AND METHODS

Table 7. Study cohorts in the thesis.

Paper	Study cohort	Inclusion period	Number of patients
I	All rectal cancer patients undergoing abdominal surgery in the Stockholm-Gotland region (SCRCR)	2000-2010	2619
II	Stage I-III rectal cancer patients undergoing abdominal surgery in the Stockholm-Gotland region (SCRCR)	2000-2010	2300
III	Consecutive rectal cancer patients undergoing abdominal surgery in the Stockholm-Gotland region (SCRCR)	2010	94
IV	Patients undergoing curatively intended surgery because of locally recurrent rectal cancer at Karolinska University Hospital	2003-2013	54

Paper I

In this population-based cohort study all rectal cancer patients undergoing elective abdominal resection from January 2000 to December 2010 in the Stockholm-Gotland area of Sweden were included. Data was retrieved from the SCRCR regarding patient and tumour characteristics, treating unit, surgery and preoperative treatment. Before 2007 reporting to SCRCR concerning preoperative treatment was limited to delivered RT or not. From 2007 the SCRCR was expanded allowing for more data to be analysed including discussion at a MDT conference, BMI, ASA, pretherapeutic clinical tumour stage and dose and fractionation of preoperative RT. Patients were divided by time period into three groups: 2000-2002, 2003-2006 and 2007-2010. Age was categorised into < 65 years, 65-79 years and \geq 80 years.

In a subgroup analysis of patients operated 2007-2010 a simplified three-tier tumour stage description was composed. This was an adaption of previous classifications with early, intermediate and locally advanced tumours and based on tumour level, cT and cN stage

(Table 8)^{11, 227}. The clinical tumour stage was then related to selected treatment regime: surgery alone, preoperative short course RT or preoperative CRT. During this study period two trials were ongoing. The Stockholm III trial randomised patients with resectable rectal cancer to short course RT with immediate or delayed surgery or to long course RT¹⁹⁹. Since all patients participating in the Stockholm III were eligible to short course RT they were considered as selected for short course RT in this study. Patients included in the Expert C trial, randomising patients to preoperative CRT with or without cetuximab were considered to have received preoperative CRT²⁵³. Patients with missing data, distant metastases or preoperative treatment regimens not listed above were excluded from this subgroup analysis.

Table 8. Tumour staging based on tumour level, T and N stage 2007-2010.

Tumour stage category		
Early	Intermediate	Locally advanced
cT1-2 cN0 any Tumour level	cT1-2 cN1-2 any Tumour level	cT4 cN0 Tumour level ≤5 cm
cT3 cN0 Tumour level >5 cm	cT3 cN0 Tumour level ≤5 cm	cT4 cN1-2 any Tumour level
	cT3 cN1-2 any Tumour level	
	cT4 cN0 Tumour level >5 cm	

Data on in-patient care for all patients five years prior to the rectal cancer diagnosis were retrieved from the Swedish National Patient Register. Main and secondary diagnoses according to ICD-9 and ICD-10 were collected to classify comorbidity into three groups using the CCI: CCI score 0, 1 or ≥ 2 ²⁵¹. The rectal cancer diagnosis was not included in the CCI score. Data from the two registries were merged for the analyses.

Statistical analysis

To determine differences between the three periods of time the Anova F-test and the Chi-square test were used for continuous and categorical variables, respectively. To detect factors associated with delivery of preoperative treatment, univariable logistic regression analyses were performed whereby odds ratios (OR) were calculated. A multivariable model included age, gender and variables based on a significance level of $p < 0.1$: tumour level, CCI score, hospital volume, year of surgery and in the subgroup analysis of the 2007-2010 cohort also cT and cN stage. To test for trends Wald test was used.

P-values of < 0.05 were considered statistically significant in all studies. In all papers Stata® version 12.0 statistical software package (Stata Corp LP, College Station, Texas, USA) was used to perform the statistical analyses.

Paper II

The cohort of 2619 patients from paper I was used for this population-based study. Patients with synchronous distant metastases were excluded. Data retrieval from the SCRCR was extended with information regarding pTNM stage, local or systemic recurrence and death. pTNM stage was categorised into pTNM stage I-II or III. Outcome measures included local recurrence rates, DFS and OS. DFS was calculated using the time interval from primary surgery to local or systemic recurrence or death from any cause and OS using the time from primary surgery to death from any cause.

Statistical analysis

Differences in proportions were analysed using the Chi-square test and for continuous variables Student's t test were used. The Kaplan-Meier method was used to assess rates of local recurrence, DFS and OS and differences between groups were analysed with the log rank test. To determine the effect of co-variables on outcome, Hazard ratios (HR) were calculated by univariable Cox regression analyses. In a multivariable model co-variables with a significance level of < 0.1 were included. Age and comorbidity was stratified into dichotomous variables and further analysed separately by univariable and multivariable Cox regression. Wald test was used for trends.

Paper III

This study included 100 consecutive patients who underwent elective abdominal rectal cancer surgery from January to June 2010 in the Stockholm-Gotland region and had undergone a pretherapeutic MRI according to the SCRCR. Preoperative and pretherapeutic MRI reports and investigations and also information on adherence to protocol standards in rectal cancer MRI were obtained for all patients from nine different hospitals. The images were retrospectively re-evaluated by a radiologist specialised in pelvic MRI and the results of the re-evaluation were compared to the information in the original reports. Twenty of these MR images that were judged necessary to discuss, were re-evaluated a second time by an experienced MRI-radiologist specialised in rectal cancer MRI. Information on patient characteristics, preoperative treatment and surgery were retrieved from the SCRCR.

According to a previous classification, all tumours were classified into early, intermediate or locally advanced based on the original report and the re-evaluation separately (Table 9)²²⁷. The tumour stage based on the original report and the re-evaluation were related to both preoperative treatment selected (no preoperative treatment, 5 x 5 Gy or CRT) and to recommendations from the Swedish guidelines for colorectal cancer³. As in the first two studies, patients included in the Stockholm III trial were considered as selected for short course RT¹⁹⁹.

Table 9. Tumour stage description based on clinical findings and MRI.

Tumour stage category		
Early	Intermediate	Locally advanced
Distance from anal verge > 5 cm T1-T3b	Distance from anal verge > 5 cm T3c/d	T4
Distance from anal verge ≤ 5 cm T1-T3a	Distance from anal verge ≤ 5 cm T3b	Positive lateral lymph nodes
N0	T4 with peritoneal, or vaginal involvement only	MRF positive
MRF clear	N1/2 MRF clear	

Statistical analysis

A paired t-test was used to analyse differences in continuous variables. Limits of agreement were assessed with Bland-Altman plots. Differences in paired proportions were determined with McNemar's test. To analyse inter-rater agreement between the original report and re-evaluation, categorical variables were analysed with Cohen's Kappa coefficient (κ). Cohen's kappa was also used for comparison between the decided and recommended preoperative treatment based on the tumour staging of the original report and re-evaluation. Agreement was determined as: no ($\kappa = 0$), slight ($\kappa > 0 - 20$), fair ($\kappa = 0.21-0.40$), moderate ($\kappa = 0.41-0.60$), good ($\kappa = 0.61-0.80$) or excellent ($\kappa = 0.81-1.00$).

Paper IV

All patients undergoing surgery with a curative intent because of locally recurrent rectal cancer at Karolinska University Hospital between January 2003 and December 2013 were eligible for this study. Among these, all patients who had a pelvic MRI both before surgery for the primary tumour and the local recurrence were included. From the medical records information was retrieved concerning patient characteristics, pre- and postoperative treatment for the primary tumour, primary surgery, distant metastases before the local recurrence and surgery for the local recurrence. For outcome analyses, data obtained included histopathological reports and information regarding end of follow-up, death and distant and local re-recurrence after surgery for the local recurrence.

Pelvic MR examinations were collected for the local recurrence, before any therapy for the primary tumour and if available also after preoperative treatment for the primary tumour. A MRI-specialised radiologist re-evaluated all MRI images and when judged necessary, another radiologist specialised in rectal cancer MRI performed a second re-assessment. The radiologists were blinded for the previous evaluation of the MRI for the local recurrence when re-evaluating the primary tumour MRI. The pre-treatment primary tumour MRI was re-evaluated regarding tumour characteristics and nodal status and if a MRI after preoperative treatment was available, mrTRG and tumour volume was assessed. The location of the local recurrence at MRI was categorised according to the Memorial Sloan Kettering classification⁸⁴. The primary tumours were classified using the same three-graded description as in study III (Table 9) and related to given preoperative treatment²²⁷.

Measures of outcome included local re-recurrence, DFS, defined as the time from surgery for local recurrence to re-recurrence (local or systemic) or death from any cause and OS, defined as time from surgery for local recurrence to death from any cause.

Statistical analysis

The Chi-square test was used to assess differences in proportions. Rates of OS, DFS and local re-recurrence were estimated with the Kaplan-Meier method and differences by means of the log rank test. Risk factors for non-radical surgery of the local recurrence and predictors of the localisation of the local recurrence were analysed with univariable logistic regression. Predictors of local re-recurrence, DFS and OS after surgery for local recurrence were determined in a univariable Cox regression analysis. Wald test was used to test for trends.

Ethics

The regional Ethical Review Board at Karolinska Institutet approved all studies.

RESULTS

Paper I

Among the 2619 patients included, 68.3 % (1789 patients) received preoperative (C)RT. This proportion increased over time ($p < 0.001$) (Figure 5). The median age was 69 years (range 27-100 years).

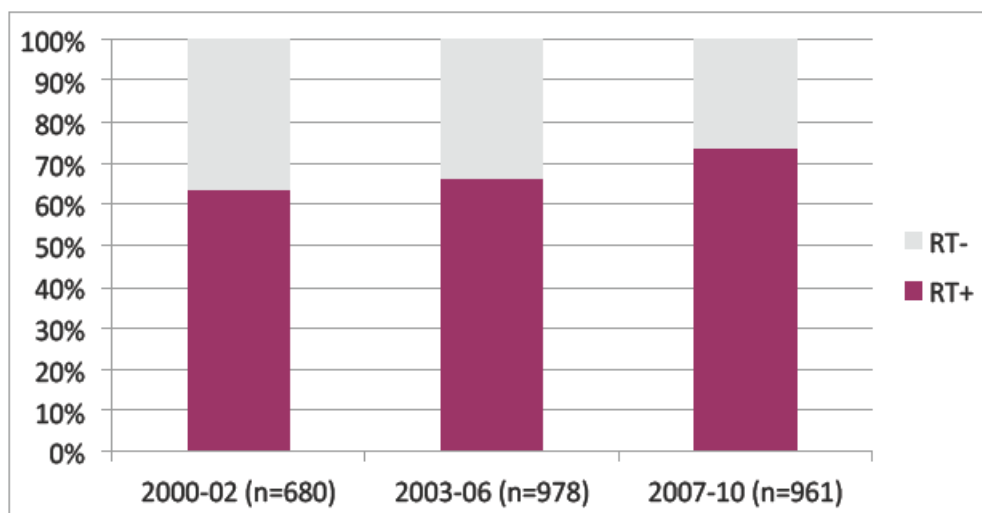


Figure 5. Proportion of rectal cancer patients receiving preoperative radiotherapy (RT) according to period of time 2000-2010 ($p < 0.001$).

In Table 10 the correlation between clinical characteristics and preoperative treatment is shown. Omission of preoperative RT or CRT was more common among elderly and in patients with comorbidity, especially in patients ≥ 80 years (adjusted OR 0.05; 95 % CI 0.04-0.07) and with a CCI score ≥ 2 (adjusted OR 0.29; 95 % CI 0.21-0.39). Women were less likely to receive preoperative (C)RT in the unadjusted analysis (OR 0.84; 95 % CI 0.71-0.99) but the difference was not statistically significant in the multivariable model. The proportion of patients undergoing surgery at high volume centres increased over time (46.9 % 2007-2010 vs. 37.2 % 2000-2002; $p < 0.001$).

Table 10. Clinical characteristics in patients undergoing elective abdominal surgery for rectal cancer 2000-2010 and odds ratios for receiving preoperative (chemo-)radiotherapy ((C)RT) from multivariable logistic regression analyses (n = 2619).

	Total (n = 2619)	(C)RT (n = 1789)	Multivariable logistic regression	
			OR (95 % CI)	p
Age at operation				< 0.001
<65	936	788 (84.2)	1.00	
65-79	1208	889 (74.0)	0.56 (0.45-0.70)	
≥80	475	112 (23.6)	0.05 (0.04-0.07)	
Sex				0.28
Male	1562	1091 (69.8)	1.00	
Female	1057	698 (66.0)	0.90 (0.74-1.09)	
CCI score				< 0.001
0	2101	154 (73.5)	1.00	
1	247	129 (52.2)	0.55 (0.40-0.76)	
≥2	271	115 (42.4)	0.29 (0.21-0.39)	
Tumour height (cm)				< 0.001
0-5	774	598 (77.2)	1.00	
6-10	1022	715 (70.0)	0.56 (0.44-0.73)	
11-15	817	474 (58.0)	0.27 (0.21-0.36)	
Hospital volume				0.40
<40 cases/year	1456	946 (65.0)	1.00	
≥40 cases/year	1163	843 (72.5)	1.09 (0.89-1.33)	
Year of surgery				0.001
2000-2002	680	434 (63.8)	1.00	
2003-2006	978	648 (66.2)	1.19 (0.94-1.52)	
2007-2010	961	707 (73.6)	1.61 (1.25-2.07)	

In the subgroup analysis of the 2007-2010 cohort, 961 patients were identified. After exclusion of 107 patients who received treatment outside recommendations by guidelines or who had distant metastases, 854 patients remained for analysis. Of those 786 (92.0 %) patients discussed at a pretherapeutic MDT, 75.2 % (n = 591) were selected for preoperative (C)RT whereas this proportion was 44.1 % (n = 30) among those not discussed at a MDT. In total, 233 (27.3 %) patients were selected to no preoperative treatment, 499 (58.4 %) to preoperative short course RT and 122 (14.3 %) to preoperative CRT. In univariable logistic regression analyses a higher ASA score (III-IV) was strongly associated with less preoperative short course RT (OR 0.30; 95 % CI 0.19-0.50) and CRT (OR 0.19; 95 % CI 0.09-0.38) while no statistically significant difference in preoperative treatment was seen in patients with a BMI over or under 25. In the multivariable model higher age, CCI score and

tumour level and less advanced cT and cN stage were correlated to less preoperative short course RT whereas only a less advanced cT and cN stage were statistically significantly associated with less preoperative CRT. There were no statistically significant differences between genders concerning preoperative RT or CRT compared to no preoperative treatment.

Because of missing data regarding tumour level, cT and cN stage, only 734 of the 854 patients could be categorised according to the three-tier tumour stage description. Table 11 displays the distribution of those patients according to tumour stage and in relation to selected preoperative treatment. Of the 34 patients selected for no preoperative treatment despite intermediate or locally advanced tumours, 24 patients had a CCI score of ≥ 2 or were ≥ 80 years. None of the remaining 10 patients had been diagnosed with pelvic malignancies the last 13 years prior to the rectal cancer diagnosis, thus limiting the possibility of previous pelvic irradiation. Among the 33 patients with locally advanced tumours selected for preoperative short course RT, 28 (85 %) were > 65 years or had a CCI score ≥ 1 . In the group of 318 patients with early tumours the median age among the 175 (55 %) patients selected to preoperative (C)RT was 67 years compared to 76 years in the 143 (45 %) patients selected to no preoperative treatment ($p < 0.001$). In the early tumour stage group 180 patients had cT1-2 tumours and of those 77 (43 %) were selected to preoperative treatment.

Table 11. Preoperative treatment according to tumour stage in rectal cancer patients undergoing elective abdominal rectal cancer surgery 2007-2010 ($n = 734$).

Tumour stage	Preoperative treatment		
	No	RT	CRT
Early	143 (45.0)	170 (53.5)	5 (1.6)
Intermediate	26 (8.4)	239 (77.1)	45 (14.5)
Locally advanced	8 (7.5)	33 (31.1)	65 (61.3)

Paper II

One patient who had surgery in 2011 and 300 patients with distant metastases by the time of surgery were excluded from the first study cohort of 2619 patients. Among the remaining 2300 patients, 1617 (70.3 %) received preoperative (C)RT. The 3-year local recurrence, DFS and OS rates were 4.7 %, 68.6 % and 80.2 %, respectively and all outcome measures improved over time ($p < 0.001$) (Figure 6).

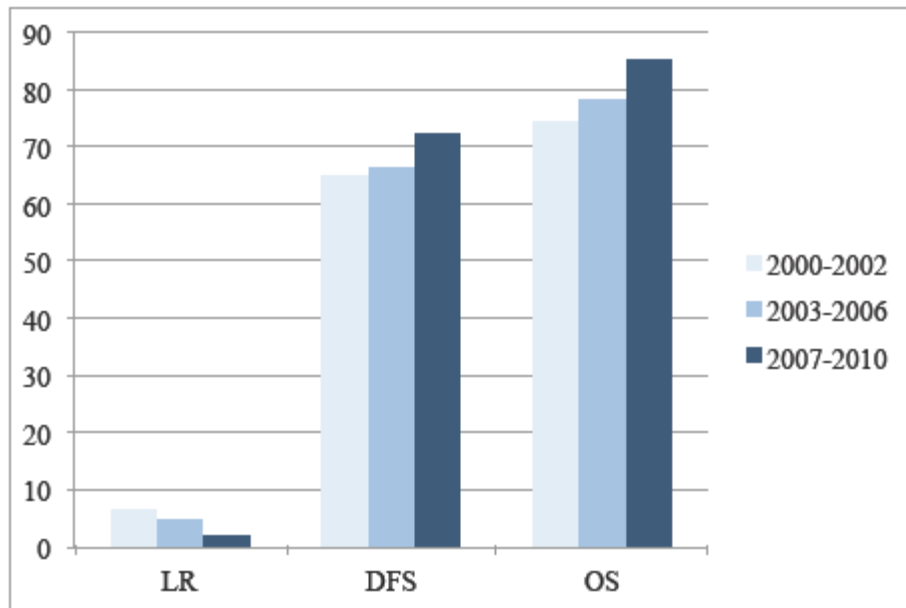


Figure 6. Rates (%) of local recurrence (LR), disease-free survival (DFS) and overall survival (OS) in relation to time period for rectal cancer patients undergoing surgery 2000-2010 ($p < 0.001$).

In Figure 7 the Kaplan-Meier curve for DFS in relation to if preoperative (C)RT was delivered or not is displayed. In univariable Cox regression analyses preoperative (C)RT were associated with better DFS (OR 0.65; 95 % CI 0.57-0.73) and OS (OR 0.53; 95 % CI 0.47-0.60).

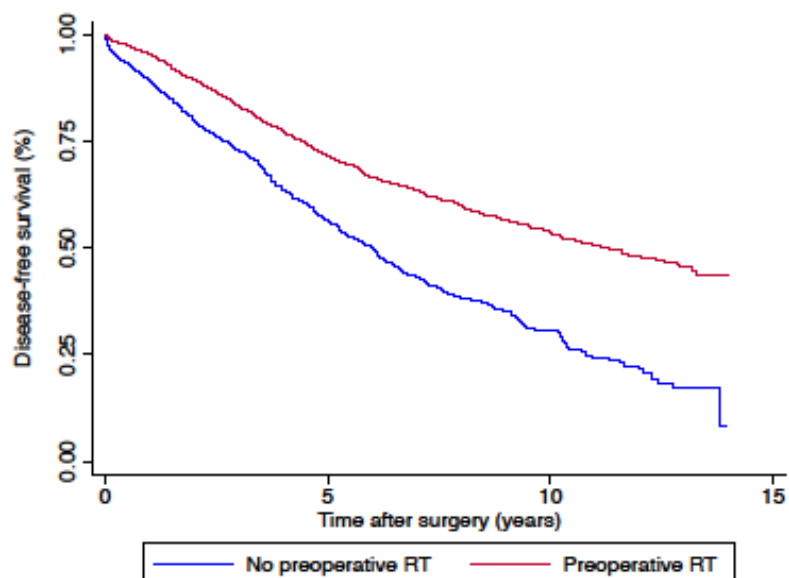


Figure 7 Kaplan-Meier analysis of disease-free survival according to delivered preoperative radiotherapy (RT) or no preoperative treatment. Log rank $p < 0.001$.

In multivariable Cox regression analyses, however, preoperative (C)RT did not significantly affect outcomes with regards to DFS and OS (Table 12). Advanced age, male sex, comorbidity, and a more advanced pTNM stage were predictors of inferior DFS and OS whereas a lower tumour level was associated with inferior OS only. Only low tumour level, more advanced pTNM stage (III) and time period were predictors of local recurrence but there was a trend towards lower local recurrence rates in patients who received preoperative (C)RT (OR 0.66; 95 % CI 0.41-1.05).

Table 12. Multivariable regression analyses of clinical characteristics affecting local recurrence rate, disease-free survival (DFS) and overall survival (OS) in rectal cancer patients undergoing elective abdominal surgery 2000-2010 (n = 2300).

	No. of patients (%)	Adjusted HR (95 % CI)		
		Local recurrence ^a	DFS ^b	OS ^c
Preoperative (C)RT				
No	683 (29.7)	1.00	1.00	1.00
Yes	1617 (70.3)	0.66 (0.41-1.05)	0.99 (0.85-1.15)	0.87 (0.74-1.01)
Age at operation				
<65	798 (34.5)	1.00	1.00	1.00
65-79	1069 (46.5)	0.89 (0.58-1.36)	1.37 (1.18-1.60)	1.68 (1.43-1.97)
≥80	433 (18.8)	1.25 (0.69-2.27)	2.60 (2.14-3.17)	3.52 (2.87-4.32)
Sex				
M	1364 (59.3)	1.00	1.00	1.00
F	936 (40.7)	0.80 (0.56-1.16)	0.82 (0.73-0.93)	0.79 (0.69-0.89)
CCI score				
0	1852 (80.5)		1.00	1.00
1	214 (9.3)		1.58 (1.32-1.89)	1.55 (1.29-1.87)
≥2	234 (10.2)		1.83 (1.53-2.18)	2.02 (1.69-2.42)
Tumour height^d				
0-5	697 (30.4)	1.00		1.00
6-10	893 (38.9)	0.46 (0.31-0.70)		0.77 (0.67-0.90)
11-15	705 (30.7)	0.42 (0.26-0.66)		0.77 (0.65-0.90)
pTNM stage^d				
I-II	1404 (62.2)	1.00	1.00	1.00
III	852 (37.8)	2.41 (1.66-3.50)	2.09 (1.85-2.36)	2.00 (1.76-2.26)

^a Adjusted for preoperative (C)RT, age, sex, tumour height, time period, pTNM stage, adjuvant chemotherapy

^b Adjusted for preoperative (C)RT, age, sex, comorbidity, time period, pTNM stage and adjuvant chemotherapy

^c Adjusted for preoperative (C)RT, age, sex, comorbidity, tumour height, time period and pTNM stage

^d Data missing on pTNM stage (n = 44) and tumour height (n = 5)

In a separate multivariable Cox regression analysis of OS, patients were stratified for age and CCI score (Table 13). Irradiated patients with a CCI score ≥ 1 had statistically significantly better OS following compared to non-irradiated patients (OR 0.65; 95 % CI 0.49-0.87). Preoperative (C)RT did not significantly improve OS in patients ≥ 80 years. However, in younger patients preoperative (C)RT was correlated to better OS (OR 0.74; 95 % CI 0.61-0.89).

Table 13. Stratified multivariable Cox regression analyses regarding overall survival in relation to preoperative treatment in patients undergoing rectal cancer surgery 2000-2010.

Multivariable Cox regression		
	HR (95 % CI)	P
Age^a		
< 80		0.001
No preoperative RT	1.00	
Preoperative RT	0.74 (0.61-0.89)	
≥ 80		0.566
No preoperative RT	1.00	
Preoperative RT	1.08 (0.82-1.42)	
Charlson Comorbidity Index^b		
0		0.828
No preoperative RT	1.00	
Preoperative RT	0.98 (0.81-1.19)	
≥ 1		0.003
No preoperative RT	1.00	
Preoperative RT	0.65 (0.49-0.87)	

Paper III

Of 100 consecutive patients eligible, pretherapeutic MR images were available in 94. In 86 % among the remaining patients, the MRI examinations were considered to have met predefined accepted standards. In the original reports the proportion of missing data were 34 % for T stage, 34 % for EMVI stage, and 10 % for MRF involvement. For patients with visible tumours according to the re-evaluation (n = 90) the proportion of missing data regarding the extent of extramural growth was 50 %. Absent data for N stage and lateral lymph node metastasis was considered as negative findings. The agreement amongst the original MRI report and the re-evaluation was good for T stage category ($\kappa = 0.71$), moderate for N stage

category ($\kappa = 0.42$) and excellent for EMVI status ($\kappa = 0.86$) and MRF involvement ($\kappa = 0.88$).

When categorising the tumours into early, intermediate and locally advanced according to Table 9, 28 of the original reports were missing data, making this tumour stage grouping impossible. In the 66 patients possible to analyse, the agreement between original reports and re-evaluation was moderate ($\kappa = 0.46$) and only 42 (64 %) of those patients were categorised into the same tumour stage group in the re-evaluation and the original reports (Table 14).

Table 14. Agreement between tumour stage based on the original MRI reports and the re-evaluation ($\kappa = 0.46$), n (%).

Tumour stage (re-evaluation)	Tumour stage (original report)		
	Early	Intermediate	Locally advanced
Early	9 (69)	3 (23)	1 (8)
Intermediate	12 (43)	14 (50)	2 (7)
Locally advanced	2 (8)	4 (16)	19 (76)

Of all 94 patients, two had atypical preoperative treatment and were excluded from further analysis. Among the remaining 92 patients, 20 patients were selected to no preoperative treatment, 57 to preoperative short course RT and 15 to CRT. The agreement between recommended preoperative treatment according to the re-evaluation and the treatment decided on was fair ($\kappa = 0.33$) (Table 15). The proportion of patients receiving overtreatment was 18 % and undertreatment 24 %, according to this comparison. The agreement between recommended preoperative treatment according to the original report and received preoperative treatment was slight ($\kappa = 0.12$).

Table 15. Agreement between recommended preoperative treatment according to the re-evaluation of MR-investigations and selected preoperative treatment ($\kappa = 0.33$), n (%).

Preoperative treatment recommended	Preoperative treatment selected		
	No	RT	CRT
No	11 (44)	13 (52)	1 (4)
RT	5 (12)	31 (80)	3 (8)
CRT	4 (14)	13 (46)	11 (39)

Paper IV

A total of 76 patients underwent surgery with a curative intent because of locally recurrent rectal cancer during the study period. After exclusion of 20 patients in whom MRI before primary surgery was unavailable and two patients in whom surgery was indicated by a re-recurrence, 54 patients remained for analyses. The median age at the time of surgery of the local recurrence was 65 years (range 42-82 years). Forty-two (78 %) patients received preoperative (C)RT prior to primary surgery and of those, 20 patients underwent a second MRI after preoperative treatment. Of the primary tumours, 10 (19 %) were categorised as early, 13 (25 %) as intermediate and 30 (57 %) as locally advanced according to the MRI re-evaluation. One patient had a primary tumour that was not possible to detect on MRI. Preoperative CRT was only given to 10 out of the 30 patients with locally advanced tumours and in total 24 (45 %) were undertreated regarding preoperative (C)RT for the primary tumours according to the Swedish national guidelines for colorectal cancer.

Some 13 (24 %) of the patients had suspected lateral lymph node metastases on MRI before primary surgery. On the MRI of the local recurrence, the lateral compartment of the pelvis was involved in 31 (57 %) of the patients. In a univariable logistic regression analysis, a right-sided involved lateral lymph node was associated with an ipsilateral local recurrence (OR 5.50; 95 % CI 1-18-25.53). This relationship could not be demonstrated on the left side. Nor could a statistically significant association be shown between involved lateral lymph nodes *per se* and a laterally located local recurrence (OR 3.17; 95 % CI 0.76-13.20).

In 35 (65 %) of the patients a R0 resection of the local recurrence was accomplished. None of the primary tumour MRI characteristics predicted for a R0 resection of the local recurrence in an unadjusted logistic regression analysis. However, in those 20 patients in whom tumour regression was assessed with a second MRI following preoperative treatment, a tumour volume decrease of ≤ 70 % was correlated to fewer R0 resections (OR 0.07; 95 % CI 0.01-0.84). A TRG of 4-5 was also associated with a lower rate of R0 resection, although without statistical significance (OR 0.14; 95 % CI 0.02-1.14).

The 3-year local re-recurrence rate, DFS and OS after surgery for local recurrence were 41 %, 26 % and 57 %, respectively. In a univariable Cox regression analysis a lateral recurrence predicted for an inferior outcome in terms of OS (HR 3.03; 95 % CI 1.50-6.12) and DFS (HR 2.23; 95 % CI 1.19-4.18). However, none of the primary tumour MRI characteristics were statically significantly associated with worse outcomes.

DISCUSSION

Survival and local recurrence rates in rectal cancer patients have improved rapidly during the past decades due to advances in surgery and the introduction of preoperative (C)RT. Also, some of the patients with recurrent or metastatic disease in whom palliative treatment previously remained as the only alternative can now be treated with a potential for cure. Although improvements have been made with minimally invasive surgical techniques, nerve-sparing surgery, enhanced perioperative management and refined radiation technique, rectal cancer treatment is still associated with substantial morbidity. Preoperative treatment selection in the rectal cancer MDTs is often complex and optimal decision-making requires reliable information regarding both tumour growth and patient characteristics. This thesis aimed to investigate some of the aspects influencing treatment decision in rectal cancer management.

The findings from several trials of halved local recurrence rates following preoperative short course RT irrespective of quality of surgery performed, have largely impacted rectal cancer treatment in Sweden^{181, 186, 188}. Indeed, in paper I the proportion of irradiated patients increased from 2000 to 2010 and in the most recent time period (2007-2010) this proportion was 74 %. The vast majority of those patients were selected for short course RT. Whether as much as three fourths of rectal cancer patients undergoing abdominal surgery is best served by preoperative (C)RT could be discussed. In the trials showing a benefit of preoperative RT, the gains were mainly evident in stage II-III disease where the risk of local recurrence is greater than in stage I rectal cancer^{180, 186}. In the subgroup analysis of the 2007-2010 patients in paper I, 55 % of patients with early cancers and 43 % with T1/2N0 tumours were decided for preoperative (C)RT. Interestingly, patients in the early group selected for preoperative (C)RT were significantly younger than patients selected for immediate surgery. It could be speculated that some patients in this group were inadequately selected for more aggressive treatment because of young age. Although limited by the absence of information regarding predictive factors influencing preoperative treatment decisions such as MRF involvement, EMVI status, presence of involved lateral lymph nodes and T 3/4 substage, the results of this paper indicated overuse of preoperative (C)RT. It is important to keep the negative effects of (C)RT in mind when choosing treatment strategies for rectal cancer patients^{173, 190, 217}.

Although to a lesser extent, some of the papers in this thesis also indicated undertreatment among certain patient categories. In the 2007-2010 subgroup analysis of paper I, 34 (8 %) of the 416 patients with intermediate or locally advanced tumours did not receive any preoperative treatment. In 10 of these patients neither age, nor comorbidity nor previous pelvic irradiation could explain this finding. Furthermore, in paper III the recommended preoperative treatment according to the original reports and the selected preoperative

treatment was only slight ($\kappa = 0.12$). Also, of the 54 patients included in paper IV, only 10 of the 30 patients received preoperative CRT despite locally advanced primary tumours and in total, 45 % of the patients obtained less intense preoperative treatment than indicated by the Swedish national guidelines for colorectal cancer. The patients in this study were relatively young and likely not burdened by comorbidity since they subsequently underwent surgery for the local recurrence. Hence, advanced age or comorbidity does not explain the large proportion of patients that did not receive preoperative (C)RT. In this group of patients it cannot be ruled out that at least some of the local recurrences could have been avoided, had optimal pre-therapeutic decisions been made prior to surgery for the primary tumour.

In a report from the Dutch Surgical Colorectal Audit, 88 % of the rectal cancer patients received preoperative (C)RT according to the recommendations in the Dutch guidelines and in 66 % of the patients with T1N0 tumours preoperative RT was delivered despite not indicated²³⁷. Several other population-based investigations have reported suboptimal guidelines adherence and also inferior outcomes in rectal cancer patients in whom compliance to guidelines was inadequate^{239, 254, 255}. Age and comorbidity are known risk factors for guidelines violation and omission of preoperative (C)RT in rectal cancer management^{232, 237, 239, 254}. In paper I, both age and comorbidity were strong predictors of delivery of preoperative RT. Among patients with a CCI score of ≥ 2 or age ≥ 80 years only 42 % and 24 %, respectively, received preoperative (C)RT whereas the proportion receiving (C)RT in the population was 68 %. To abstain from preoperative (C)RT may be correct in the management of the patients with severe comorbidity or advanced age considering the acute toxic effect and life expectancy in this group of patients^{241, 244, 256}. However, in this study the proportion of patients receiving preoperative treatment was significantly lower also among the patient between 65 – 79 years or with mild comorbidity (CCI score = 1). Although chemoradiation may not be feasible in frail patients, it has not been proven that short course radiation in these patients correlates to more acute toxic effects compared to in younger patients without comorbidity^{235, 244, 245}. Publications from the Stockholm III trial have shown that 5 x 5 Gy with a delay of 4-8 weeks before surgery compared to 5 x 5 Gy and immediate surgery, increases the rate of pCR, decreases the rate of postoperative complications and has similar rates of local recurrence^{199, 200}. In patients with locally advanced tumours who are not fit for preoperative CRT, short course RT with delayed surgery may thus be considered¹⁹⁸.

Preoperative RT has been shown to increase local control in rectal cancer patients > 75 years²⁴². The 3-year local recurrence rate in paper II was 4,7 %, which is consistent with a previous report from the SCRCR²⁵⁷. Despite a relatively large study cohort, the low number of local recurrences made statistical analyses regarding the impact of preoperative (C)RT in relation to age and comorbidity unfeasible. The OS and DFS for patients more than 65 years and patients with a CCI score of ≥ 1 were significantly lower. However, stratified analyses demonstrated a benefit of preoperative RT in patients with comorbidity (CCI score ≥ 1) regarding OS (adjusted HR 0.65; 95 % CI 0.49-0.87) while preoperative RT in patients ≥ 80

years did not significantly influence OS rates. Efficient treatment selection ultimately decreases differences in long-term outcomes between patients. That is, patients with more advanced tumours should receive more intense preoperative treatment and optimally this will improve local control and possibly also long-term survival. Hence, the results could be interpreted so that management regarding preoperative treatment selection in the elderly was adequate. The patients ≥ 80 years who actually received RT possibly had more advanced tumours. On the other hand, patients with comorbidity received preoperative RT to a lesser extent and this may reflect inadequate preoperative treatment selection.

Since TME surgery was introduced and fully adopted, the effect of preoperative RT on local control has not been translated into improved survival outcomes other than for subgroups of patients¹⁸⁸. Long-term results from the Dutch TME trial showed a better 10-year OS in patients with stage III tumour with a negative CRM after preoperative 5 x 5 Gy followed by surgery compared to surgery alone (50 % vs. 40 %; $p = 0.032$)¹⁸⁰. Paper I showed an increased use of (C)RT throughout the study period and within the same study cohort, only excluding stage IV patients, the rates of local recurrence, DFS and OS improved concurrently. There are several factors possibly contributing to the improvements in long-term outcomes. Improved treatment selection due to enhancements in clinical tumour staging with MRI, the introduction of MDT conferences, optimised TME surgery and enhanced perioperative care may explain better outcomes. However, it cannot be ruled out that the increased usage of preoperative (C)RT contributed to improved survival, at least in subgroups of patients. Indeed, the adjusted analysis showed a tendency of better OS following preoperative (C)RT (OR 0.87; 95 % CI 0.74-1.01). On the other hand, all patients included in paper I and II underwent abdominal surgery. According to a report from the SCRCR including all rectal cancer patients in Sweden, the proportion of non-resected patients increased from 17.5 % in 2001-2006 to 25.8 % in 2007-2010 ($p < 0.001$)²⁵⁷. A different selection to surgery could possibly influence the outcomes among patients included in paper I and II.

It has previously been reported that the proportion of patients receiving preoperative RT for rectal cancer is lower among women than in men^{258, 259}. A recently published study also showed that incomplete dosage of preoperative RT was more common in women whereas age and comorbidity did not predict treatment completion²⁶⁰. Contrary to the findings above, adjusted analysis in paper I could not display any gender inequalities regarding delivery of RT (OR 0.90; 95 % CI 0.74-1.09), although completion of irradiation could not be controlled for. In paper II however, male sex predicted for worse OS and DFS, even when age and comorbidity were adjusted for. The pelvic anatomy differs between genders with regards to both organ content (uterus, ovaries, prostate, vesicles) and the width of the pelvic cavity. Therefore, surgery of the narrower male pelvis is considered to be more arduous, especially in patients with low tumours. A higher proportion of preoperative irradiation for low tumours among men than women may be justified in order to accomplish tumour regression, enhance quality of TME, reduce CRM involvement and thereby improve oncological outcomes.

A prerequisite for optimised treatment selection at the pretherapeutic MDT conferences is adequate information regarding tumour growth. MRI is the standard tool for assessment of T stage in rectal cancer but several other predictors of resectability, local and systemic recurrence can also readily be assessed with MRI. In the Stockholm-Gotland area of Sweden repeated educational efforts have been made to improve the performance and reporting of MRI in rectal cancer. In paper III the compliance to predefined standards of MRI examination was 86 %. The information analysed in this study was based on MRI investigations performed in 2010. Although this was relatively recently, the rapid increase in knowledge regarding the importance of the information from pretherapeutic MRI possibly has improved the performance regarding MRI for rectal cancer since then.

In a study by Al-Sukhni *et al.*, 128 pretherapeutic narrative MRI reports were reevaluated. Not even 40 % of these reports were complete with regards to cT stage, cN stage and MRF (CRM) involvement²⁶¹. Aiming at standardised scanning technique and systemised reporting in rectal cancer MRI, the MERCURY study group developed a proforma-based tool²⁶². To increase completeness of pretherapeutic tumour staging and aid treatment-decisions at the MDTs, an adaption of this protocol was introduced in Sweden in 2014. Thus, the somewhat discouraging results in paper III regarding completeness of reporting of important tumour characteristics such as T stage and EMVI could partly be explained by the absence of a structured reporting system during the study period. Also, although the accuracy and importance of pretherapeutic T staging with MRI was known in 2010, the prognostic significance of mrEMVI was not fully embraced^{72,73}.

Ninety % of the original reports reported regarding MRF involvement and the agreement between the original reports and the re-evaluation was excellent ($\kappa = 0.88$) for this factor. It appears as if the knowledge concerning the predictive value of an involved MRF has had a large impact on rectal cancer MRI reading⁷⁰. However, sufficient quality in the assessment of T is not yet maintained concerning the relatively low level of agreement between the original reports and re-evaluation, and also the large proportion of missing data for T stage and extent of extramural growth. The assessment of nodal status on MRI is flawed by relatively low sensitivity and specificity⁵⁷. Although this in part could explain the poor agreement for N stage, a better congruence was expected. Further education and radiological workshops is warranted in order to improve MRI interpretation and reporting.

MRI staging of good quality can make treatment strategies more adequate and improve outcomes with respect to number of complete resections, rates of local recurrence and survival²⁶³. In paper III, the inadequacies in the original reports translated into only moderate agreement between original reports and the re-evaluation when tumours were staged into early, intermediate and locally advanced. The fact that only 66 patients could be stage grouped in this analysis because of missing data in the original reports decreases the reliability of the agreement measurement but of the classifiable patients, 24 (66 %) were inadequately categorised. Moreover, the poor agreement ($\kappa = 0.12$) between treatment

recommended according to the original reports and the treatment actually received, raises concern. Inadequate MRI staging may have caused unnecessary morbidity because of overtreatment as well as inferior outcomes among undertreated patients. When comparing the delivered with the suggested treatment from the re-evaluation, the agreement was better ($\kappa = 0.33$), though far from satisfactory. Preoperative treatment selection is not guided solely by MRI staging. Frailty could be a reasonable cause to abandon guideline recommendations resulting in undertreatment for some patients. To explain the overtreatment displayed in paper III is more difficult. Optimised MRI staging is of vital importance to ensure proper decision-making.

Evaluation of MRI interpretation quality would optimally include correlation to postoperative histopathology as the reference standard. However, the tumour properties of the resected specimen are affected by preoperative treatment. Since no other radiological modality more accurately can assess local tumour growth in rectal cancer, re-evaluation by experts in rectal cancer MRI reading remains as the best available alternative.

To explore predictive factors for outcome in patients undergoing treatment for locally recurrent rectal cancer is difficult. With TME surgery and preoperative (C)RT, local recurrence rates of about 5 % have been shown and among the patients with local recurrences the majority receive palliative treatment only, because of disseminated disease or unresectable tumours^{180, 192, 264}. Thus, few patients with locally recurrent rectal cancer are considered for surgery and the study cohorts available are small. Furthermore, the selection criteria regarding resectability differ among centres managing locally recurrent rectal cancers, which make comparison of studies reporting outcome difficult. Also, no uniform classification of local recurrence exists and the heterogeneity among these tumours requires individualised treatment-decisions. Paper IV primarily aimed to investigate whether there are tumour characteristics at the primary tumour MRI predictive for long-term outcome after surgery for local recurrence but no such association could be revealed. Naturally, many factors after the staging of the primary tumour could influence the results after surgery for the local recurrence. Patient characteristics such as age and comorbidity, adjuvant treatment and quality of surgery of the primary tumour and the local recurrence, distant metastases before local recurrence and the biological properties of the tumours may explain differences in outcome. Due to a small study population these factors were not possible to control for in the statistical analyses. The small study population itself implies that although statistical significance was not obtained it cannot be excluded that some of the factors analysed can show predictive values in a larger setting. The evidence regarding management of locally recurrent rectal cancer is generally based on retrospective data from single-centre cohort studies. To further increase knowledge in this field, an international register with prospectively registered data and multicentre investigations is warranted.

A R0 resection is a prerequisite to improve long-term outcome in locally recurrent rectal cancer¹⁵⁹. In the series of patients in paper IV, 65 % underwent a R0 resection, which is in

line with previous reports^{156, 157, 159}. There was an association between response to preoperative (C)RT for the primary tumour and the rate of radical resection of the recurrence. Possibly, there are features regarding tumour biology that predict for both response to preoperative treatment and the ability to achieve successful treatment of the local recurrence and that this information could be used in the treatment selection for the local recurrence. Two recent reviews have evaluated re-irradiation in patients with locally recurrent rectal cancer^{265, 266}. It was concluded that despite the absence of randomised trial and the heterogeneous treatment regimens regarding both (C)RT and surgery in the included investigations, re-irradiation can be recommended for selected patients with acceptable safety and favourable outcomes regarding R0 resection rate. The information on primary tumour response to (C)RT may be useful in this selection.

In a study by Syk *et al.* no correlation could be detected between lateral lymph node involvement on primary tumour MRI and later local recurrence. This report was based on only 33 patients and more than 40 % of the primary tumours were located in the upper rectum²⁶⁷. On the contrary, other investigations have reported on an association between enlarged lateral lymph nodes (≥ 5 mm) and a lateral local recurrence^{67, 268}. Fujita *et al.* showed that among patients randomised to only TME surgery the rates of lateral and overall local recurrence were higher than in patients that also underwent LLND¹³⁷. However, in this trial none of the patients received preoperative (C)RT. In paper IV a lateral lymph node on primary tumour MRI was significantly associated with an ipsilateral local recurrence but only on the right side. As only 13 out of 54 patients had suspected lateral lymph nodes in this study it is difficult to draw any firm conclusion from this finding. Several authors have used size as a predictor for lateral lymph node involvement and different cut offs such as 5, 8 and 10 mm have been suggested^{67, 137, 269}. In paper IV only morphological criteria (irregular border, presence of mixed signal intensity) were used, based on experience from the MERCURY study group⁶⁸. The optimal criteria for lateral lymph node metastasis remain to be defined with regards to sensitivity and specificity. Also, the downstaging effect on lymph nodes following preoperative (C)RT constitutes a major problem when histopathological evaluation of pretherapeutic MRI is undertaken.

All investigations in this thesis have been made using observational data. Retrospective observational cohort studies have their main advantages in the ability to use existing data and in a short time analyse the exposure and outcome of many patients over a long period of time. However, these studies are associated with a risk of bias and confounding influencing the outcome and thereby affecting the internal validity. The data in the SCRCR are prospectively registered with almost complete coverage and reported with very good validity. Therefore, the risk of selection bias or information bias is limited and to decrease the risk of confounding, multivariable analyses were used in paper I-II. The reporting to Swedish National Patient Register is mandatory regarding inpatient care and coverage is good, but even though evaluation of this register has shown a rather good validity there is a risk of misclassification

bias because of inadequacies in the diagnosing of disease. Also, since the coverage of outpatient data in the Swedish National Patient Register is lacking in completeness only data on inpatient care was used and therefore there could be patients included in paper I-II with significant comorbidity not recorded in the CCI classification. Although the CCI based on diagnosis is merely an approximation of physical function, correlation to ASA score, that possibly reflects physical function better, was good. The external validity of the results of paper I-III in the thesis is concluded to be good since the data used is population-based. The small number of patients with local recurrences made other study design than the retrospective observational used in paper IV, difficult.

CONCLUSIONS

Overall conclusion

There is room for improvements regarding MRI performance and interpretation, and also regarding the selection to preoperative therapy in rectal cancer patients, especially among patients with comorbidity.

Specific conclusions

The use of preoperative treatment increased over time. Advanced age and comorbidity were strong predictors for omittance of preoperative treatment and even patients with only mild comorbidity and in the beginning of aging received substantially less (C)RT. Signs of overtreatment and to a lesser extent also undertreatment were revealed.

Local recurrence rates, DFS and OS improved over time. Age and comorbidity predicted for worse survival outcomes. An improvement in OS following preoperative treatment was seen in patients with comorbidity but not among the elderly.

Compliance to MRI protocol standards was incomplete. Missing data and inadequacies in original MRI reports made complete preoperative tumour staging impossible, leading to a risk of impaired treatment selection.

A significant number of patients with operated local recurrences received less preoperative treatment for the primary tumour than recommended by guidelines. A tumour volume shrinkage on MRI after preoperative (C)RT for primary rectal cancer predicted for a higher rate of R0 resection of the local recurrence. However, no associations between MRI characteristics of the primary tumour and long-term outcomes after surgery for locally recurrent rectal cancer were found.

FUTURE PERSPECTIVES

Notwithstanding the successful development regarding local recurrences and survival outcomes up until now, there are many areas that warrant further improvements in rectal cancer management. Systemic disease remains to be a problem, adverse effects of surgical and oncological treatment still are considerable and the proportion of rectal cancer patients in whom curative treatment is judged unfeasible, is not negligible. With more therapeutic options available and an increasing life expectancy, treatment selection is becoming more complex and the need for a multidisciplinary approach even more important. Objective measure of physical function and evidence on how to best treat frail patients is needed for an individualised treatment-decision.

Detection of rectal tumours at an earlier stage allows for a less aggressive treatment strategy and may improve outcomes. Faecal blood tests used in screening programmes are highly specific while sensitivity is more unsatisfactory. Endoscopy on the other hand, is resource demanding and non-adherence remains a challenge. Circulating tumour cells or fragments of tumour DNA in the blood can possibly be of importance in the future as a less invasive screening alternative. Potentially these liquid biopsies also can evaluate treatment effect, identify high-risk tumours and be used to detect recurrence.

Adequate tumour response assessment after preoperative treatment is increasingly important in an era of rising interest in organ preservation. MRI has shown promise in the assessment of complete response but there are further improvements to be made regarding certain imaging features such as nodal involvement. Numerous regimens of organ preservation programs have been proposed with various preoperative treatments, indications for patient inclusion depending on tumour properties, the use of TEM and surveillance. More evidence is warranted before organ preservation can be generally recommended for certain patients.

Optional radiation techniques beside conventional external RT have emerged. With contact brachytherapy, Intensity-Modulated RT (IMRT) or proton therapy, radiation can be delivered more precisely to the tumour thereby minimising damage to normal, adjacent tissue. However, the clinical benefit with regards to toxicity, late adverse effects and oncological outcomes needs to be further investigated. Laparoscopy has shown short-term benefits in rectal cancer surgery. For more recently introduced minimal invasive techniques such as robotic surgery and ta-TME the evidence is still limited and more knowledge is needed. This applies for both the long-term benefits of these techniques regarding oncologic outcome and late adverse effects. Re-irradiation of locally recurrent rectal cancer appears to be feasible but optimal dose and fractionation remains to be elucidated. To increase knowledge concerning multimodal treatment of local recurrences, international cooperation with prospective registration of data and multicentre investigations are required.

SAMMANFATTNING PÅ SVENSKA

Kolorektalcancer (cancer i tjock- och ändtarm) är den tredje vanligaste cancerformen i världen och fler insjuknar i västvärlden än i Afrika och Asien. Hos en tredjedel av patienter med kolorektalcancer är tumören belägen i rektum. Varje år diagnosticeras 2000 svenskar med rektalcancer och förutom hög ålder och manligt kön har man sett att rött kött, lågt intag av fibrer, alkohol, rökning, övervikt och inflammatorisk tarmsjukdom ökar risken. Ärftlighet ses hos en femtedel av alla insjuknade. Vanliga symptom vid rektala tumörer är trötthet på grund av anemi (blodbrist), rektal blödning, förändrade avföringsvanor och ändtarmssmärter.

Den botande behandlingen består av kirurgi där man tar bort rektum. Historiskt har rektalcancerkirurgi varit förknippat med dålig överlevnad, hög risk för lokalt återfall och mycket komplikationer. Förnyad operationsteknik (TME), där också hela det fettskikt som omgärdar rektum tas bort, har förbättrat prognosen avsevärt. Den relativa 5-årsöverlevnaden är idag närmare 70 % i Sverige. Trots förbättrad teknik är långtidsbiverkningar av kirurgin, som påverkan på sexualfunktion och urin- och avföringsinkontinens vanligt. Operationerna kan göras öppet eller med titthålsteknik. I en mindre andel av patienterna med tidiga tumörer kan tumören tas bort lokalt och rektum kvarlämnas.

Strålbehandling (RT) kan ta död på mikroskopiska canceransamlingar i anslutning till tumören, exempelvis i lymfkörtlar, och åstadkomma tumörkrympning vilket ökar chansen att åstadkomma radikal kirurgi. Vid avancerade tumörer kombineras preoperativ RT med cellgiftsbehandling (CRT). Preoperativ (C)RT i kombination med TME har minskat risken för ett lokalt återfall till ca 5 %. Dock finns komplikationer också till RT. Övergående påverkan med diarréer, illamående, trötthet, infektioner och hudproblem är vanliga. På lång sikt förefaller komplikationer associerade med rektalcancerkirurgin vara ännu vanligare hos patienter som också fått RT.

Patienter med konstaterad tumör i ändtarmen genomgår rektoskopi för att kartlägga tumörnivån och vävnadsprov tas för att bekräfta diagnosen. En datortomografi av buk och bröstorg utförs för att utesluta fjärrmetastaser. För att bedöma tumörens lokala växtsätt görs en magnetresonanstomografi (MRT). Ett flertal faktorer på MRT kan förutsäga risken för tumöråterfall och chansen att åstadkomma radikal kirurgi. Riktlinjer för val av behandlingsregim baseras på MRT, där tumörerna kan indelas i tidiga, intermediära och lokalt avancerade och dessa olika tumörstadier rekommenderas direkt kirurgi, preoperativ RT respektive preoperativ CRT. Beslut om preoperativ behandling och kirurgi tas vid multidisciplinära teamkonferenser (MDT-konferenser) där både tumör- och patientfaktorer påverkar behandlingsvalen.

Hög ålder och komorbiditet (samsjuklighet) utesluter ofta patienter från deltagande i kliniska studier. Därför är dessa patientgrupper dåligt studerade och rekommendationer för hur de bäst

ska behandlas saknas. Denna avhandling undersökte hur patientfaktorer samt tumörfaktorer utifrån MRT-undersökningar påverkar de preoperativa behandlingsvalen vid rektalcancer.

I delarbete I studerades hur ålder och komorbiditet påverkade val till preoperativ RT. Data för samtliga 2619 patienter som opererades för rektalcancer i Stockholm-Gotland 2000-2010 inhämtades från det svenska kolorektalcancerregistret. Uppgifter om komorbiditet inhämtades från Socialstyrelsens patientregister. 68 % av alla patienter fick (C)RT innan operation och användningen ökade över tid. Bland patienter med komorbiditet erhöll endast 47 % preoperativ (C)RT och motsvarande andel bland äldre patienter var 24 %. En relativt stor andel av patienter med tidiga tumörer fick RT och en liten andel av patienter med mer avancerade tumörer fick ingen preoperativ behandling alls.

Delarbete II syftade till att utreda hur val av preoperativ behandlingsstrategi hos äldre och sjuka påverkade långtidsprognosen. För denna studie användes uppgifter på 2300 patienter från patientgruppen i delarbete 1 utan tecken till fjärrmetastaser vid operation. Preoperativ (C)RT påverkade inte överlevnad eller återfallsfrekvens totalt eller bland de äldre men hos patienter med komorbiditet sågs en bättre överlevnad efter preoperativ (C)RT.

Delarbete III studerade standarden på utförande, tolkning och rapportering av MRT vid rektalcancer och i vilken mån detta påverkar behandlingsval. MR-undersökningar på 94 patienter som opererades 2010 från studiegruppen i delarbete I inhämtades. MR-undersökningarna utvärderades och jämfördes med ursprungsutlåtandet. Följsamheten till riktlinjer för MRT-utförande var ofullständig. På grund av bristfällig information i originalutlåtandet kunde tumörstadielinje endast göras i 70 % av patienterna och överensstämmelsen mellan originalutlåtanden och eftergranskningen var inte tillfredsställande. Detta föreföll påverka val av preoperativ behandlingsstrategi.

I delarbete IV undersöktes om faktorer vid MR-undersökning för primär rektalcancer kan användas för att förutsäga prognosen efter operation av lokalt tumöråterfall. Behandlingsvalen vid primärtumören studerades också. 54 patienter som opererats för ett lokalt återfall av rektalcancer på Karolinska Universitetssjukhuset 2003-2013 och som hade genomgått MRT för primärtumören inkluderades. MR-undersökningarna eftergranskades och ur patientjournalerna inhämtades uppgifter om uppföljning. Vid analysen hittades inga faktorer på den första MR-undersökningen som ökade risken för död eller ett nytt återfall efter operationen för det lokala återfallet. Däremot korrelerade en bra respons på preoperativ (C)RT för primärtumören till en större andel radikalt opererade lokala recidiv. Även i denna studie fanns tecken till underbehandling avseende preoperativ (C)RT av primärtumören.

Sammanfattningsvis kunde denna avhandling visa att den information som används och de beslut som tas vid MDT-konferenser kan förbättras avseende val till preoperativ behandling och att detta kan påverka långtidsprognosen vid rektalcancer.

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