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PREOPERATIVE RADIOTHERAPY IN RECTAL CANCER

ASPECTS OF DIFFERENT REGIMENS

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CONTENTS

ABSTRACT

In Sweden approximately 2000 patients are annually diagnosed with a rectal cancer. The main treatment of the cancer is surgery. Radiotherapy (RT) is used as an adjuvant treatment in >60% of these patients to improve local control and in some patients to downsize a primary non resectable tumour to facilitate surgery. However RT has drawbacks as acute adverse events due to RT, increased risk of postoperative complications and mortality and late side-effects from RT. To optimise RT schedules regarding oncological and negative effects the Stockholm Colorectal Cancer Study Group initiated the Stockholm III Trial in 1998 to compare different fractionations of RT and the importance of timing to surgery. The trial is randomising patients with primary resectable tumours to one of three treatment schedules: short-course RT with immediate surgery (SRT); short-course RT with delayed surgery (SRT-delay); long-course RT with delayed surgery (LRT-delay).

In Paper I, III and IV patients randomised in the on-going Stockholm III Trial were studied. In Paper II were patients having SRT-delay outside the Stockholm III Trial in the Stockholm-Gotland region studied.

The papers conclude that the Stockholm III Trial is a feasible study with acceptable compliance to the protocol. Acute adverse events due to RT were low both within the Stockholm III Trial as well as after the SRT-delay schedule outside the trial.

In Paper II, patients outside the Stockholm III Trial had SRT-delay, a schedule still without strong scientifically support, mainly due to primary non-resectable tumours and co-morbidities. The short-term outcome of the treatment was in line with established schedules.

RT has been shown to impair the postoperative leucocytosis after surgery and increase complications and mortality. A depression of the bone marrow due to RT is one potential reason of these findings. In Paper III allocated treatment were related to postoperative complications and the leucocyte reaction to RT, measured as a ratio between leucocyte counts (LC) postoperative days 1 or 2 and the preoperative LC. Patients with low ratios had more complications compared to patients with intermediate and high ratios irrespective of RT regimen. Patients having SRT had more patients with low LC-ratios and more complications compared to the two other arms. There was no association between preoperative low (<4.0) LC and postoperative complications.

Short-course RT has been considered not to have a downstaging effect, however with surgery immediately after the end of RT. In Paper II with surgery delayed there were lower stages and less involved margins after the RT when the clinical stages and margins were compared to the pathological stages and resection margins, indicating downstaging. Also in Paper IV, comparing the arms with short-course RT, a downstaging effect were indicated when the patients in the SRT-delay arm had significantly lower TNM Stages and T-stages and in addition more tumour regression compared to patients in the SRT randomisation arm.

LIST OF PUBLICATIONS

I D. Pettersson, B. Cedermark, T. Holm, C. Radu, L. Påhlman, B. Glimelius, A. Martling

Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer.

(British Journal of Surgery. 2010; 97(4): 580-587)

II D. Pettersson, T. Holm, H. Iversen, L. Blomqvist, B. Glimelius, A. Martling

Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer.

(British Journal of Surgery. 2012 Apr;99(4):577-583)

III D. Pettersson, B. Glimelius, H. Iversen, H. Johansson, T. Holm, A. Martling

Postoperative impaired leucocyte counts in the randomised Stockholm III Trial of different radiotherapy regimens in rectal cancer.

(Submitted)

IV D. Pettersson, E. Lörinc, T. Holm, H. Iversen, B. Cedermark, B. Glimelius, A. Martling.

Tumour regression and pathological outcome in the randomised Stockholm III Trial of different radiotherapy regimens in rectal cancer.

(Manuscript)

ABBREVIATIONS

AJCC	American Joint Committee Against Cancer
APR	Abdominoperineal resection
AR	Anterior resection
CI	Confidence interval
CRM	Circumferential resection margin
CRT	Chemoradiotherapy
CT	Computed tomography
EORTC	European Organisation for Research and Treatment of Cancer
Gy	Gray
HP	Hartmann´s procedure
HR	Hazard ratio
LC	Leucocyte counts
LR	Local recurrence
LRT-delay	Long-course radiotherapy with delayed surgery
MDT	Multidisciplinary team conference
MRF	Mesorectal fascia
MRI	Magnetic resonance imaging
OR	Odds ratio
OTT	Overall treatment time
PET	Positron emission tomography

RCC	Regional Cancer Center
RCT	Randomised controlled trial
RT	Radiotherapy
RTOG	EORTC Radiation therapy oncology group
SCCSG	The Stockholm Colorectal Cancer Study Group
SRCT	The Swedish Rectal Cancer Trial
SRT	Short-course radiotherapy
SRT-delay	Short-course radiotherapy with delayed surgery
TEM	Transanal endoscopic microsurgery
TME	Total mesorectal excision
TNM	Tumour-Node-Metastasis stage
UICC	International Union Against Cancer
ypCR	Complete pathological response after neoadjuvant therapy

INTRODUCTION AND BACKGROUND

General Background

Colorectal cancer is the third most common cancer type worldwide in men and the second in women. The incidence varies with high incidences in Europe, North America and Australia and low ones in South-Central Asia and Africa[1].

In Sweden approximately 6000 patients are diagnosed with a colorectal cancer every year. For each sex, colorectal cancer is the third most common cancer after breast cancer and skin cancer for women and prostate cancer and skin cancer for men[2]. Due to different treatment strategies, types of surgery and disease outcome, colorectal cancer is often divided into colon cancer and rectal cancer. The rectal cancer, defined as a cancer within or partly within 15 cm from the anal verge, accounts for about a third of the colorectal cancers[2]. Rectal cancer itself is the seventh most common cancer for each sex and the eighth for the combined sexes.

The aetiological factors behind colorectal cancer are complex and heterogeneous. Risk factors are hereditary syndromes, increasing age, male sex, previous colorectal polyps or cancers and inflammatory bowel disease. In addition, environmental factors such as red meat, a high-fat diet, low fibre intake, obesity, diabetes mellitus, smoking and high consumption of alcohol have been shown to play an important role in the aetiology[3, 4]. Studies have shown that incidence rates in groups emigrating from a low incidence rate country to a high rate country equal or surpass the new rate within a generation.

Before a cancer has developed, the tumour has passed through several steps from a benign tumour to a malignant adenocarcinoma[5]. The most common colorectal polyp, the hyperplastic one, is not a major precursor of cancer. Instead, adenomas are the most important precursor lesions. Only a fraction of adenomas progress to cancer, a transition called the adenoma-carcinoma sequence. This transition takes years to decades to occur[6].

The Swedish Rectal Cancer Registry

The Swedish Rectal Cancer Registry was started in 1995 on an initiative of the Swedish National Board of Health and Welfare and since 1996 includes all healthcare regions in Sweden[7]. It is mandatory for surgeons and pathologists to report to one of the six Swedish Regional Cancer Centres (RCCs). The RCC registers and also validates the data before reporting to the RCC in Umeå, which compiles the data in a national registry. The registry has developed with an increasing number of variables over the years. Today it includes data on preoperative staging, multidisciplinary team conferences, neoadjuvant therapy, surgery performed, postoperative course, postoperative staging, postoperative oncological therapy, any surgery on metastases, recurrences, metastasis and follow-up. The registry links its data to the Swedish Cancer Registry and the Registry of Causes of Death.

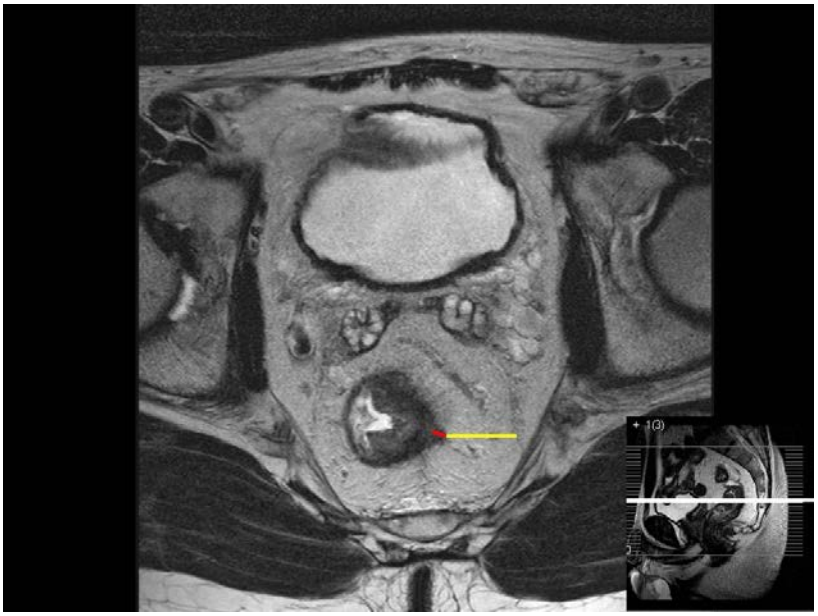
The Swedish Rectal Cancer Registry has an almost 100% coverage and is continuously validated through research projects.

Clinical Staging

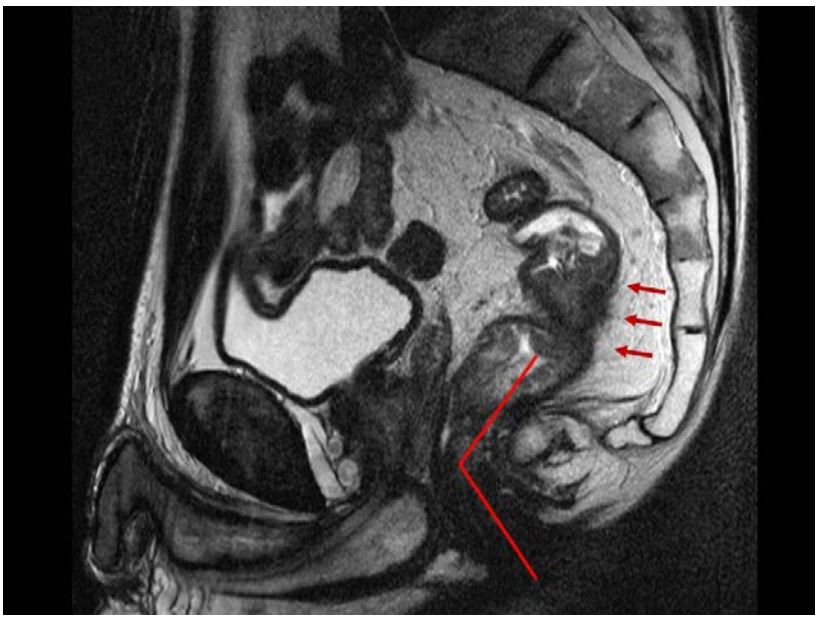
The diagnosis of an adenocarcinoma in the rectum is made by a biopsy of the tumour. Before the decision for a recommended treatment, the disease is clinically staged. The local tumour staging includes digital examination, rigid sigmoidoscopy, magnetic resonance imaging (MRI) of the pelvis and, in some cases, also endorectal ultrasound. The digital examination provides information on the distance from the anus to the tumour and whether the tumour is fixed or not. A fixed tumour at digital examination indicates a locally advanced tumour with overgrowth to adjacent organs in the pelvis. The rigid sigmoidoscopy determines the distance from the anus to the tumour, extent of intraluminar growth and provides an opportunity for biopsies. The pelvic MRI is today the gold standard for the modality of local tumour staging. MRI gives a good prediction of the tumour stage, i.e. the depth of tumour growth in the rectal wall; however, with a known risk of overstaging both tumour and nodal stage[8]. In addition, MRI is very accurate in predicting a tumour with an involved or threatened mesorectal fascia or growth to other structures in the pelvis (Figure 1).

Regarding distant metastasis, computed tomography (CT) of the abdomen and a chest x-ray are recommended in many treatment programmes. Today CT is often also used for the examination of the chest, which detects also smaller abnormalities. The drawback is detection of false positive nodules or metastases, which might result in a delay of the process towards a treatment decision. If the

Figure 1. Magnetic resonance images (MRI) of the pelvis.



Transaxial T2-weighed MR-image showing a semi-annular tumour in the mid rectum. The red line indicates how the extent of extramural tumour growth is measured. The yellow line indicate how the closest distance from extramural tumour to the mesorectal fascia is measured (white thick line on the sagittal small image in the right lower corner indicate the level of the section within the pelvis).



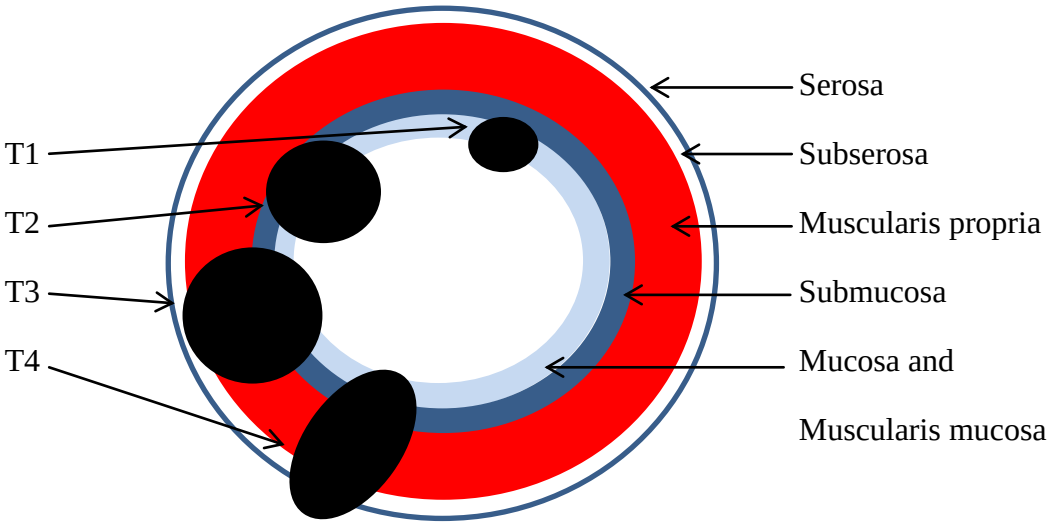
Sagittal T2-weighted MR-image in the midline of the pelvis in a male patient with rectal cancer (red arrows). The red lines indicate how the distance from the lower border of the anal verge is measured.

Images published with the kind permission of Dr. L. Blomqvist

abdominal CT shows structures in the liver of uncertain type, contrast-enhanced ultrasound is the next modality of choice to determine if there is a metastasis or not.

A relatively new method is combined CT with positron emission tomography (CT-PET). The PET modality is based on differences in metabolism between normal tissue and the tumour. A positron-emitting radio-nucleotide, often attached to a glucose analogue, flouro-deoxy-glucose (FDG), which is used as a tracer. The tracer accumulates in tissues with a high rate of metabolism, such as inflammatory tissue, heart, brain, kidneys and liver. Also colorectal metastases have a high metabolism, which enables the modality also to detect small lesions. There is a risk of false positive results due to the accumulation in the normal tissue mentioned above. The PET technique combined with CT gives both metabolic and anatomic information which is important in the diagnostics of metastases. CT-PET is not a modality for an early stage tumour. However, in patients with suspected metastases, up front the treatment decision for curative or palliative intention or, in recurrences, the CT-PET is valuable.

Figure 2. T Stage and invasion depth of the tumour in a bowel wall.



Tumour-Node-Metastasis Staging

An international common system for staging of the cancer disease is important. It is used for comparisons between prognoses of different tumour stages, outcomes of different treatments, outcomes in different countries or differences over periods of time and provides support in the decisions on disease treatment.

The Tumour-Node-Metastasis (TNM) classification of malignant tumours is a system originally developed by the International Union Against Cancer (UICC) in the 1950s. The American Joint Committee on Cancer (AJCC) also used the TNM system with some initial variations. The two systems have been unified since 1987. The TNM classification is revised continuously and the latest seventh edition was published in 2009[9, 10].

The TNM system is based on three major pillars:

T-stage: which describes the extent of the primary tumour and its depth of invasion. In colorectal cancer the invasion into and through the layers of the bowel wall sets the stage (Figure 2).

N-stage: which describes the involvement of regional lymph nodes.

M-stage: which describes distant metastases, including non-regional lymph nodes.

For each malignancy, except for CNS malignancies, the TNM system defines the stages. The definitions for colorectal cancer are shown in table 1, 2 and 3. In the revision of the TNM system to the seventh edition, further subclassifications were added. Due to subsequent stage migrations compared to earlier editions[11], many pathologists chose to continue the use of the sixth edition[12, 13]. Hence both the sixth and seventh definitions are shown in the table.

Table 1. Tumour-Node-Metastasis Classification

AJCC 5th and 6th Edition		*AJCC 7th Edition*	
	Primary Tumour (T)		
TX	Primary tumour cannot be assessed	***TX***	Primary tumour cannot be assessed
T0	No evidence of primary tumour	***T0***	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria	***Tis***	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa	***T1***	Tumour invades submucosa
T2	Tumour invades muscularis propria	***T2***	Tumour invades muscularis propria
T3	Tumour invades through the muscularis propria into subserosa or into non-peritonealised pericolorectal tissues	***T3***	Tumour invades through the muscularis propria into subserosa or into non-peritonealised pericolorectal tissues
T4	Tumour directly invades other organs or structures and/or perforates visceral peritoneum.	***T4***	Tumour directly invades other organs or structures and/or perforates visceral peritoneum.
		T4a	Tumour penetrates to the surface of the visceral peritoneum
		T4b	Tumour directly invades or is adherent to other organs or structures
	Regional Lymph Nodes (N)		
NX	Regional lymph nodes cannot be assessed	***NX***	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	***N0***	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes	***N1***	Metastasis in 1–3 regional lymph nodes
		N1a	Metastasis in one regional lymph node
		N1b	Metastasis in 2–3 regional lymph nodes
		N1c	Tumour deposit(s) in the subserosa, mesentery, or non-peritonealised pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes	***N2***	Metastasis in 4 or more regional lymph nodes
		N2a	Metastasis in 4–6 regional lymph nodes
		N2b	Metastasis in 7 or more regional lymph nodes
	Distant Metastasis (M)		
MX	Distant metastasis cannot be assessed.	***MX***	Distant metastasis cannot be assessed.
M0	No distant metastasis	***M0***	No distant metastasis
M1	Distant metastasis	***M1***	Distant metastasis
		M1a	Metastasis confined to one organ or site (for example, liver, lung, ovary, non-regional node)
		M1b	Metastases in more than one organ/site or the peritoneum

Table 2. Subclassification of T3 tumours

Subclassification of T3 tumours	
T3a	Minimal invasion: <1mm beyond the borders of the muscularis propria
T3b	Slight invasion: 1-5mm beyond the borders of the muscularis propria
T3c	Moderate invasion: >5-15mm beyond the borders of the muscularis propria
T3d	Extensive invasion: >15 mm beyond the borders of the muscularis propria

During the development of the TNM system additional variables have been added. Tumour located within lymphatic vessels, veins and perineural invasion have been reported as independent adverse prognostic factors. Regarding lymphatic and venous invasion, there are some controversies due to several other studies being unable to show the association in multivariate analyses. In addition, differentiation of a lymphatic vessel from a small vein is difficult, for which reason all thin-walled vessels are to be presumed to be a lymphatic vessel by convention. This has resulted in some studies reporting lymphatic and venous invasion together. The literature concludes, however, that invasion of vessels is of prognostic importance[14, 15].

The factors are coded as follows[9]:

Lymphatic invasion:

LX Lymphatic vessel invasion cannot be assessed.

L0 No lymphatic vessel invasion.

L1 Lymphatic vessel invasion.

Venous invasion:

VX Venous invasion cannot be assessed.

V0 No venous invasion.

V1 Microscopic venous invasion.

V2 Macroscopic venous invasion.

Perineural invasion:

Present

Absent

Not recorded

Over the period of initial assessments, treatments and reassessments, the disease is often staged several times for the evaluation of treatments and, if needed, to adjust the treatment plan. To define when the staging is done, different prefixes are used.

c Stage based on clinical data.

p Stage based on pathological data.

y Indicates treatment as radiotherapy (RT) and/or chemotherapy during or prior to the staging, e.g. ypTNM[16]

r Clinical or pathological staging at the time of retreatment for recurrence or disease progression

a Autopsy data

Table 3. The AJCC system of classification of rectal cancer.

	TNM Stage, 7th Edition				***TNM Stage 5th and 6th Edition***		
	T	***N***	***M***		***T***	***N***	***M***
0	Tis	N0	M0	***0***	Tis	N0	M0
I	T1-2	N0	M0	***I***	T1-2	N0	M0
II	T3-4	N0	M0	***II***	T3-4	N0	M0
IIA	T3	N0	M0	***IIA***	T3	N0	M0
IIB	T4a	N0	M0	***IIB***	T4	N0	M0
IIC	T4b	N0	M0				
III	Any T	N1-2	M0	***III***	Any T	N1-2	M0
IIIA	T1-2	N1/N1c	M0	***IIIA***	T1-2	N1	M0
	T1	N2a	M0				
IIIB	T3-T4a	N1/N1c	M0	***IIIB***	T3-4	N1	M0
	T2-T3	N2a	M0				
	T1-T2	N2b	M0				
IIIC	T4a	N2a	M0	***IIIC***	Any T	N2	M0
	T3-T4a	N2b	M0				
	T4b	N1-N2	M0				
IVA	Any T	Any N	M1a	***IV***	Any T	Any N	M1
IVB	Any T	Any N	M1b				

Resection margins

After resection of the primary tumour one of the most important assessments is whether the tumour is completely removed or not. During the surgery the surgeon judges the macroscopic radicality or residual tumour (table 7). In the pathological assessment the circumferential resection margin (CRM), defined as the shortest distance between the surface of the specimen and tumour tissue, is determined. A distance equal to or shorter than one millimetre is regarded as positive (CRM+) and a longer distance as negative (CRM-). Some authors have proposed a change in the cut-off point to 2 mm[17]. This increased risk was found in a series with a median 35-month follow-up and 2-year rates of local recurrence (LR) and could not be reproduced in other trials[18].

In general, the risk of LR decreases and the prognosis improves when the CRM distance increases[19, 20]. The TME surgery (see page 26) has resulted in less involved margins in resectable tumours and the use of neoadjuvant treatment has also reduced LR. However, the CRM is still one of the most important prognostic factors[21] preserving radical surgery as the most important aim of the treatment.

During the preoperative assessment and staging the pelvic MRI is used to assess the distance corresponding to the planned CRM or the distance from the tumour to the mesorectal fascia (MRF), which in standard surgery for primary resectable tumours is the plane of dissection posteriorly and laterally[22]. A positive MRF is defined as a distance equal to or shorter than one millimetre and a negative MRF as a distance exceeding one millimetre.

Multidisciplinary Team Conference

The multidisciplinary team (MDT) conference is an important step towards achieving an optimal treatment strategy and is recommended in many countries[23]. The treatment of rectal cancer involves many disciplines of medicine represented at the MDT conference by surgeons, oncologists, radiologists, pathologists and specialised nurses. The structured discussion of a patient, which defines the MDT conference, is aimed at individualising and hence optimising the treatment for each patient and improving the prognosis[24]. At a preoperative MDT conference the tumour staging, co-morbidities and social factors, together with the patient's own wishes, are considered and a treatment recommendation is made. If preoperative treatment such as RT or a combination of RT and chemotherapy is

needed, the initial contacts with the oncological departments are often made at the conference already.

Patients with more advanced tumours and receiving long-course preoperative treatments or patients with a delay between the RT and the surgery are often re-assessed after the neoadjuvant treatment. They are also often discussed again at an MDT conference giving the participants an opportunity to follow the course and also to revise the strategy if needed.

Postoperatively, the MDT conference assesses the pathology report and the patient's clinical course to decide if any postoperative treatment is needed and how the patient is to be followed up.

Preoperative Treatment

After the primary assessment of the disease the MDT conference recommends a treatment strategy. In some clinical situations the prognosis of the disease is improved if the patient receives preoperative or neoadjuvant oncological treatment. These situations, according to the present recommendations, are shown in Figure 3.

In patients with tumours classified as favourable[25] or 'good', the risk of a local recurrence is low and preoperative treatment with RT is regarded as overtreatment, e.g. the risk of an adverse event caused by the neoadjuvant treatment and its effects exceeds the oncological benefit of the RT.

A primary resectable tumour, classified as an intermediate[25] or 'bad' tumour, is recommended to undergo preoperative RT with the aim of reducing LR.

In advanced[25], 'ugly' tumours the aim is also to reduce the size of the tumour before the surgery to facilitate a radical procedure. Current recommendations are CRT. Besides standard treatment schedules and randomised trials, other customised strategies are also used, i.e. if the patient is unfit for CRT[26-28].

Figure 3. Neoadjuvant treatment of rectal cancer according to clinical stage. Modified from Blomqvist/Glimelius[25]

Favourable 'good' group	***Intermediate 'bad' group***	***Advanced 'ugly' group***
Mid-/upper rectum T1–3b Low rectum T1–2, T3a	Mid-/upper rectum T3c/d Low rectum also includes T3b T4 with peritoneal or vaginal involvement only	T4 with overgrowth to prostate, seminal vesicles, base of urinary bladder, pelvic side walls or floor, sacrum
N0	N1/N2	Positive lateral lymph nodes
CRM clear	CRM clear	CRM positive
⇩	⇩	⇩
Primary surgery	Primary 5x5 Gy with immediate surgery	Preoperative CRT or 5x5 Gy with delayed surgery[1]

CRT: chemotherapy to 50.4 Gy in 1.8 Gy fractions with 5-fluorouracil. 5 x 5 Gy with delayed surgery is used in patients not fit for CRT.

Radiotherapy

Radiotherapy in rectal cancer has been shown to reduce the rate of local recurrences and, in occasional studies, also increases the survival[29-36]. The RT has its oncological use in the preoperative setting when the tumour is primarily inoperable and requires down-sizing to facilitate surgery and in primary operable tumours to kill tumour cells in the periphery of the tumour for improved local control. Postoperative RT has been shown to have an inferior effect compared to preoperative RT[31]. Postoperative RT might be used in patients with positive circumferential resection margins if there was no preoperative RT. In some patients the entire tumour mass disappears after RT, a so-called complete pathological response. In most of these patients the segment where the tumour was initially diagnosed is resected. This surgery is motivated by the risk of tumour deposits in both the bowel wall and lymph nodules. However, some studies report a good outcome after a "wait-and-watch" strategy[37].

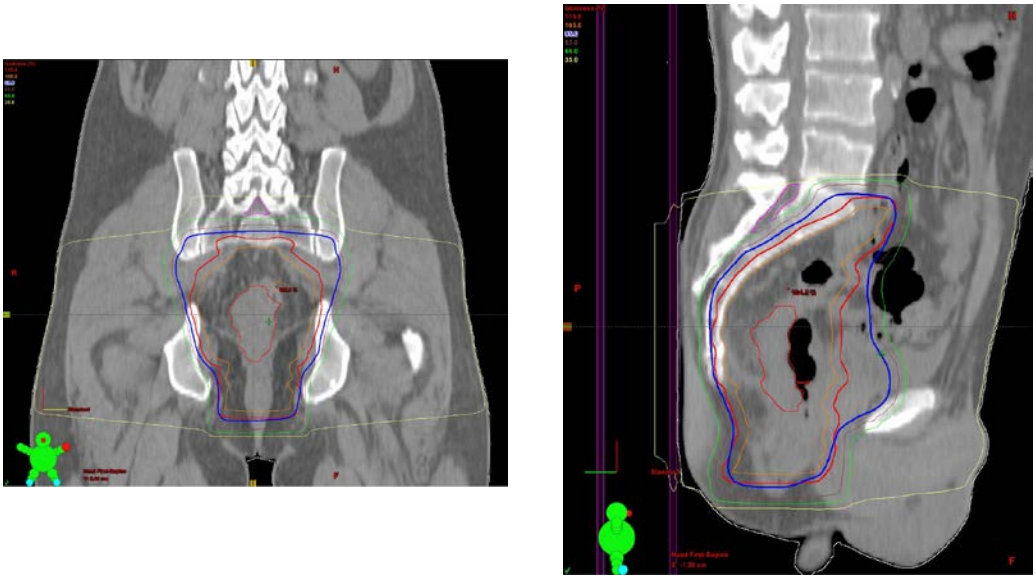
The aim of the RT is to obtain a cell-killing effect in as many tumour cells as possible without damaging any normal tissue. The latter is hard to achieve, but must be pursued by optimising the delivery of RT. There is an important difference between tumour cells and normal cells in which tumour cells have an impaired ability to repair the RT-induced damage. In addition, cells in the mitotic phase have the highest sensitivity to RT. Tumour cells have a higher proliferation rate, i.e. they have a large proportion of cells in mitosis, resulting in higher sensitivity to RT compared to normal tissue. These are two of the most important reasons why RT works as an oncological treatment without too much collateral damage in normal tissue.

If the DNA damage is extensive, the cell will die when it is trying to divide. However, it can survive and function if it is not trying to divide. In cells with high proliferation rates, e.g. in the skin, bowel mucosa or the bone marrow, the symptoms appear early (days to weeks). In types of cells with a low proliferation rate, e.g. in the liver or kidneys, the symptoms appear after a longer period of time (months).

The tolerance in normal tissue, mainly regarding late side effects, limits the dose that can be given to a tumour. The dose is dependent on the target and surrounding organs and the aim of the RT (for cure or adjuvant or palliative purposes). In order to give irradiated cells in normal tissue a chance to repair and to optimise the impact of RT in the tumour, the dose is administered in smaller quantities, i.e. fractionation. The interdependence between total dose, dose per fraction, fractions per day, treated volume and other factors is complex. The clinical oncologists use theoretical models, but also their clinical experience, to optimise the treatment schedules. The pros and cons of different schedules are an ongoing debate, also including how to use RT in rectal cancer in the best of ways. One concern regarding hypofractionated RT, e.g. 5 Gy x 5, is a theoretically increased risk of late adverse events compared to conventional, long-course, fractionations. However, even though the long-term effects after SRT are well known, the long-term effects after long-course RT have not been explored to the same extent. In two relatively short-term comparisons between SRT and CRT after four years in randomised trials, there were no differences between the treatment arms regarding long-term side effects[38, 39].

The debate and development of RT schedules continues, including the data from the ongoing trials.

Figure 4. Dose plan on images from a computed tomography (CT) for a rectal cancer with the lower border 6 cm from the anal verge



Inner red lines: tumour borders.

Orange lines: clinical target volume.

Outer red lines: planned target volume.

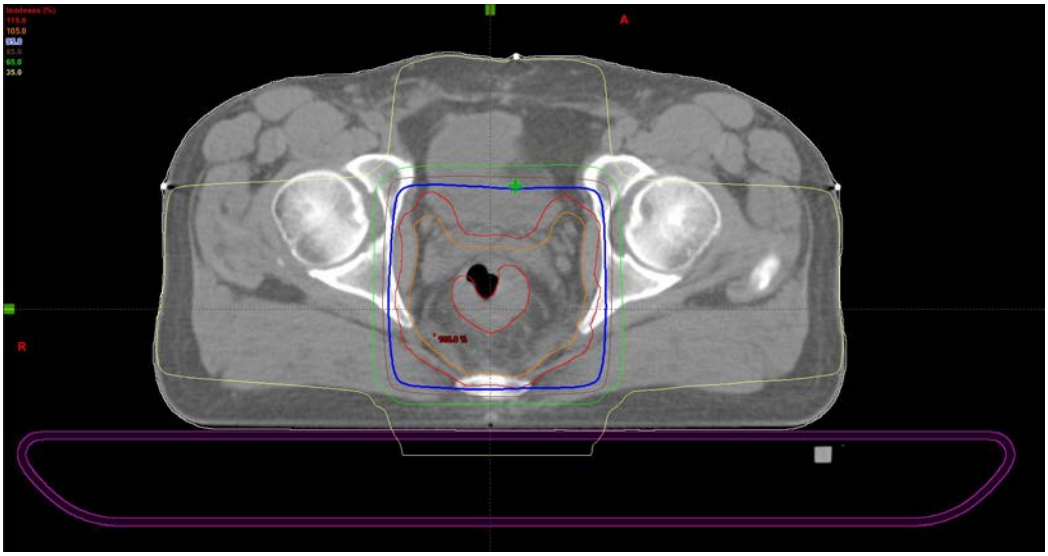
Blue lines: isodose, 95% of maximum dose.

Green lines: isodose, 65% of maximum dose.

Yellow lines: irradiated volume.

Purple lines: organs at risk, with this field the sacral nerve roots.

Doubled purple lines on axial and sagittal images: surface of the CT gurney.



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Important Studies on Radiotherapy in Rectal Cancer Treatment

Current research on preoperative, especially short-course, RT in primary resectable rectal cancer is based on some key trials performed during the last few decades. The studies listed and described below are a selection of the studies important to this thesis.

The Uppsala Trial

To address the question of whether RT should be given pre- or postoperatively, patients with a primary resectable tumour in the rectum or the recto-sigmoidal junction were randomised to short-course preoperative RT (5 x 5.1 Gy during one week) or postoperative long-course RT (30 x 2 Gy during eight weeks). Patients randomised to postoperative long-course RT had the RT only if the pathological stage was TNM stage 2 or 3. Patients with stage 1 were only followed. Between 1980 and 1985 471 patients were randomised. The trial reported a lower rate of LR in the preoperative RT group (12% vs 21%), the postoperative RT was not as well tolerated as the preoperative RT and there was no difference in survival after a mean follow-up of 6 years. The trial concluded that adjuvant RT should be given preoperatively[31].

The Stockholm I Trial

The Stockholm Colorectal Cancer Study Group (SCCSG) was set up in 1980 with the aim of improving the treatment of colorectal cancer. SCCSG initiated the same year a randomised multicentre trial on rectal cancer and RT, the Stockholm I Trial. Hospitals in Stockholm County, the island of Gotland and Malmö City recruited, until the end of recruitment in February 1987, 849 patients with primary resectable rectal cancers without distant metastasis for randomisation to either short-course RT (5 x 5 Gy) and surgery within a week or to surgery alone. Exclusion criteria were earlier RT to the pelvic area or a scheduled local excision of the tumour.

The trial showed a significant reduction of LR in the RT group compared to the surgery-alone group (16% vs 30%). The RT group had, however, a higher risk of postoperative mortality within 30 days after surgery, i.e. 8% compared to 2% in the surgery-alone group. The increased risk was mainly found in elderly patients, > 75 years old, due to cardiovascular events. Also the risk of postoperative complications was higher in the RT group, mainly due to wound sepsis[40]. The

recurrence-free interval was significantly prolonged and the mortality related to rectal cancer decreased in the irradiated group. There was no difference in the overall mortality between the groups[34].

The Stockholm II Trial

In 1987, immediate after the closure of the Stockholm I Trial, SCCSG launched the Stockholm II Trial which randomised 557 patients up to May, 1993. Hospitals in Stockholm County and the island of Gotland participated in the trial. The Stockholm II Trial had nearly the same protocol as the first trial, with some changes aimed at reducing the postoperative morbidity and mortality in the RT group while maintaining the reduction of LR. Firstly, due to the increased risk of postoperative mortality in the older irradiated patients, an upper age limit at 80 years was included. Secondly, the RT technique was changed with a decreased target volume and the most cranial RT volumes were excluded. In addition, the more modern four-field box technique was adopted instead of the older anterior and posterior parallel opposed portals. These adjustments evened the risk of postoperative mortality, within 30 days, between the randomisation groups (2% in the RT group compared to 1% in the surgery-alone group). The almost 50% reduction of LR in patients having curative surgery in the RT group was maintained with 14% in the RT group and 27% in the surgery-alone group after a median follow-up time of 8.8 years. The overall survival for patients who had curative surgery was improved in the RT group. In addition, death due to rectal cancer was reduced[33].

The Swedish Rectal Cancer Trial

In March 1987, parallel to the Stockholm II Trial, the randomised multicentre Swedish Rectal Cancer Trial (SRCT) was launched randomising patients from 70 Swedish hospitals. The setup was identical to that of the Stockholm II Trial and until the closure of SRCT in February 1990, 1168 patients were enrolled in the SRCT, 316 of which were also included in the Stockholm II Trial.

The trial showed a reduction in LR in line with the two Stockholm trials (11% in the RT group, compared to 27% in the surgery-alone group) without any difference in postoperative mortality. In addition, the trial showed for the first time an increased overall five-year survival rate (58% vs 48%) and a cancer-specific survival rate at nine years among patients who had curative surgery (75% vs 65%) for the RT group compared to the surgery-alone group[32].

The TME Trial

Several trials, like the ones described above, have shown a reduction of LR after preoperative short-course RT. However, in all of these trials the positive effect of RT was observed after surgery using what is today an obsolete technique including partly blunt dissection in the pelvis. Heald described in 1982 a new sharp dissection technique aimed at removing the rectum, including an intact mesorectum covering the tumour[41]. This total mesorectal excision (TME) technique reduced the frequency of LR[42]. To assess whether RT also reduces LR after TME surgery or just compensates for poor surgery, the Dutch Colorectal Cancer Study Group initiated the TME Trial. The trial was a randomised multicentre one enrolling 1861 patients between January 1996 and December 1999. The patients were randomised to RT and TME surgery within a week *or* to TME surgery alone[30].

Several important articles have been published from the trial. The main findings are: the irradiated group had more postoperative complications than the surgery-alone group[43]. The RT group had better local control in patients who had macroscopic radical surgery, with still more than 50% reduction of LR after a 10-year follow-up (5% vs 11%). In addition, the RT group had a higher cancer-specific survival if the surgery was radical. However, in the RT group other causes of death were increased, outweighing the cancer-specific benefits so as to result in an overall survival at the same level as for the surgery-alone group. This is interpreted as a consequence of adverse events arising from the RT. Finally, RT cannot compensate for poor, non-radical surgery[44].

The Stockholm III Trial

In 1998 the SCCSG initiated its third trial, the Stockholm III Trial. This trial was aimed at studying the effects of different RT fractionations and the timing to surgery after RT with the primary endpoint LR and secondary endpoints acute and long-course adverse events due to RT, postoperative complications, downstaging and quality of life. The Stockholm III Trial is a multicentre randomised controlled trial allocating patients with a primary resectable cancer to one of three preoperative treatment arms: short-course RT (5 Gy x 5) with surgery within a week (SRT); short-course RT and surgery delayed four to eight weeks (SRT-delay) or long-course RT with surgery delayed four to eight weeks (LRT-delay). Exclusion criteria are previous RT to the pelvic or abdominal regions, signs of severe ischaemic disease or symptoms of severe arteriosclerosis.

A hospital or patient can choose to participate in the three-armed comparison or in a two-armed comparison of the relevance of timing of surgery (SRT and SRT-delay).

The Stockholm III Trial is still ongoing. With the aim of 840 randomised patients, today (April 2012) the trial has included 770 patients. Two pre-planned interim analyses have been made, which are presented in Papers I and IV in the present thesis.

Trials comparing Radiotherapy and Chemoradiotherapy

In Europe the two most common schedules for preoperative treatment are either short course RT (5 Gy x 5) during one week and surgery within a week or long course RT (1.8–2 Gy x 25) with concomitant chemotherapy (CRT) and surgery delayed for four to eight weeks. Today the latter schedule is normally used when the tumour is clinically judged to be locally advanced or 'ugly'.

In 1993 the European Organisation for Research and Treatment of Cancer (EORTC) initiated the EORTC 22921 Trial to study whether addition of chemotherapy to RT increased the effect of RT and whether chemotherapy improved survival. Up to 2003 it randomised 1011 patients with resectable T3 and T4 tumours to one of four treatment arms: preoperative long-course RT (1.8 Gy x 25); preoperative CRT; preoperative RT and postoperative chemotherapy; preoperative CRT and postoperative chemotherapy. In all arms the surgery was delayed. The trial reported that adding chemotherapy to RT induces more downstaging and downsizing, reduces LR (17% in the RT only group vs about 9% in all chemotherapy arms), but did not improve survival[45, 46].

Parallel to the EORTC 22921, the French trial FFCD 9203 randomised 733 patients according to a similar protocol, but without any arms with postoperative chemotherapy. The trial reported more acute toxicity in the CRT arm, less LR after 5 years (8% vs 16%) and more pathological complete responses (11% vs. 4%) in the CRT arm. There was no difference in overall survival[47].

Braendengen et al. reported from the LARCS Trial, which randomised from 1996 to 2003 207 patients with primary non-resectable tumours to either preoperative RT (2 Gy x 25) with concomitant chemotherapy and postoperative adjuvant chemotherapy or to long-course RT only. The trial concluded that CRT improved local control, time to treatment-failure and cancer-specific survival compared to long-course RT alone[48].

The MRC CR07 and NCIC-CTG C016 Trial was a large multicentre, randomised trial comparing preoperative RT (5 Gy x 5) with selective postoperative CRT (1.8

Gy x 25) for patients who had positive resection margins. 1350 patients were randomised from 1998 to 2005. Most patients in both groups with stage III disease received adjuvant chemotherapy. The trial showed lower LR rates (4.4% vs. 10.6% after 3 years) and a prolonged disease-free survival in the preoperative RT group[39].

The Polish Trial randomised between 1999 and 2002 312 patients with resectable T3 or T4 tumours to preoperative RT (5 Gy x 5) and surgery within a week or to CRT (1.8 Gy x 28) with surgery 4–6 weeks later. Again, acute adverse events due to RT were more common in the CRT group (18% vs 3%) compared to the RT group. There were no differences in sphincter-preserving surgery, postoperative complications, LR, disease-free survival or late RT toxicity between the two treatment arms[38, 49, 50].

Adverse Events after Radiotherapy

The benefit of RT is a decrease in LR and, in some settings, induction of downsizing and downstaging. However, the cost for these benefits is the risk of adverse events, both acute and in the longer perspective. The National Cancer Institute (NCI) defines an adverse event as follows: '*An adverse event is any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.*' As in the case with postoperative complications, an international uniform system to define and grade adverse events due to oncological treatment is missing. Instead, there are several systems such as the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) (Table 4) and Common Toxicity Criteria (CTC)[51], the EORTC Radiation Therapy Oncology Group (RTOG) toxicity criteria[52] and several more. In some areas such as late adverse events, the NCI CTCAE has adopted the RTOG criteria, but there are still differences between the systems. In the Swedish Rectal Cancer Registry there is today no form for registration of variables regarding the oncological treatment, although this has been discussed. NCI also advocates the use of *adverse events* instead of the commonly used *toxicity*.

Table 4. General guideline to grades of adverse events according to CTCAE v4.0

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

Adverse events due to RT depend on the target and its surrounding organs. In rectal cancer the small intestines, urinary bladder, uterus, ovaries, prostate, sacral plexa and anal sphincters are often within the RT volume. After short-course RT with immediate surgery, acute adverse events are relatively rare partly due to the fact that the irradiated organ is removed before the development of such symptoms as proctitis or diarrhoea.

Acute adverse and well-documented effects of the RT in rectal cancer are skin erythema, fatigue, nausea, proctitis, diarrhoea and neurological pain[43, 53-55]. In most patients the symptoms are mild when the surgery is not delayed[43, 49] and disappear soon after the end of the RT. In some cases there are more severe symptoms demanding admission to a hospital for treatment.

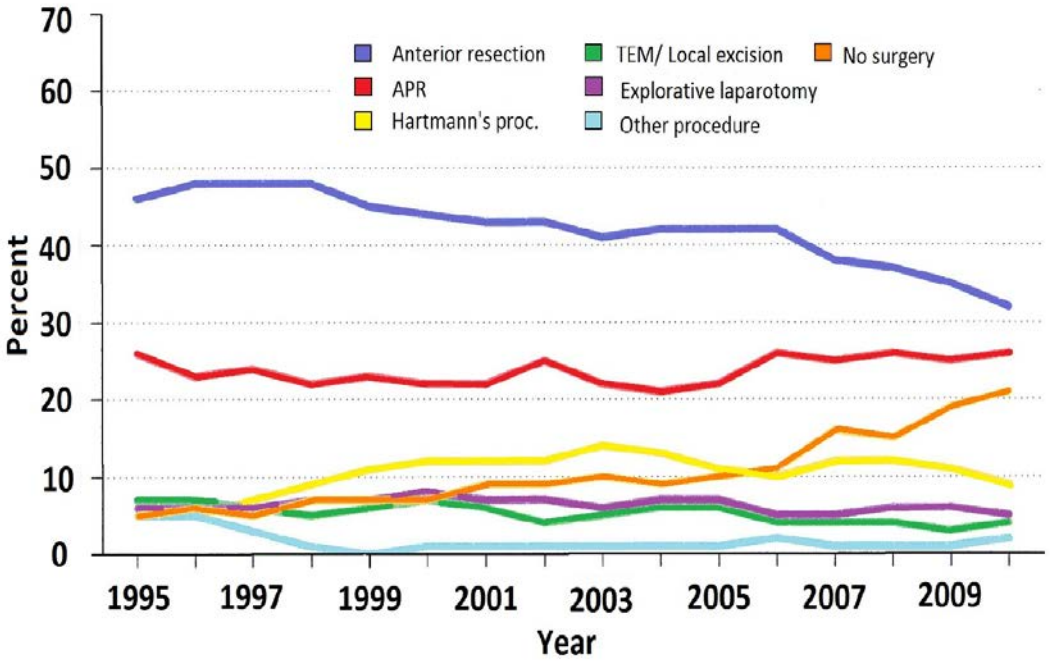
Late adverse effects of RT in rectal cancer are an impaired sphincter function, sexual dysfunction, an increased risk of postoperative intestinal obstruction, femoral neck and pelvic fractures, venous thromboembolism and secondary malignancies[56-60]. Long-term follow-ups of randomised trials report an increased risk of admission to hospital for irradiated patients the first six months after RT, but thereafter their risk is at the same level as for non-irradiated patients. The increased risk of fractures and cardiovascular disease in the first Stockholm trials[59, 61] has decreased to a tendency in more recent trials[62, 63], probably due to a smaller abdominal RT volume and better shielding of the sacrum and hips.

Surgical Treatment

Surgery is the most important part in the treatment of a rectal cancer. Some 75% of the patients diagnosed with a rectal cancer in 2010 had some type of resection of the tumour[64]. A radical resection of the tumour is of the greatest importance for reducing the risk of an LR and for surviving the disease. In some rare cases a complete pathological response (ypCR) after the neoadjuvant treatment leads to a decision to abort any planned surgery and instead wait and see. The strategy is still most controversial and debated[37]. In Sweden during 2010 some 21% of the diagnosed patients did not have any surgery, a slowly increasing proportion (Figure 5). However, most of these patients did not have surgery for other reasons than ypCR, such as metastatic disease receiving oncological palliative treatments only or patients not fit for surgery due to age and co-morbidities.

The gold standard for rectal cancer surgery today is TME surgery. As described earlier, the introduction of TME surgery with a careful sharp dissection along 'the holy plane' of the mesorectal fascia has reduced the rates of LR in several reports [65-67]. At the same time TME surgery preserves the pelvic autonomic nerves and thereby reduces the risk of bladder or erectile dysfunction.

Figure 5. Type of surgery in Sweden during 1995 to 2010



Anterior Resection

An anterior resection (AR) includes resection of the rectum by mobilisation of the rectosigmoid colon and its mesentery, division of the inferior mesenteric artery and the sigmoid colon, mobilisation of the rectum by dissection according to the TME technique in the pelvis to either the pelvic floor or to 5 centimetres distal to the tumour, division of the distal rectum and removal of the specimen and, finally, creation of a colorectal anastomosis.

The procedure is sphincter-sparing and restores the continuity of the bowel after resection of the rectum. One major risk of the procedure is that of a postoperative anastomotic leakage and concurrent septicaemia. Risk factors for an anastomotic leakage are preoperative RT, male sex, low anastomosis and intraoperative adverse events[68]. A randomised trial, the RECTODES Trial, showed a decreased risk of a symptomatic anastomotic leakage in patients randomised to a defunctioning loop stoma after AR compared to patients randomised to AR only[69]. In Sweden 75% of the patients who had an AR during 2010 also had a defunctioning stoma. In women the proportion was smaller than in men (79% vs 70%) probably because the male pelvis is considered to be more difficult to dissect. The overall proportion of defunctioning stomas increased rapidly after the RECTODES results were reported and differences between the Swedish regions were evened[64].

AR is the most common type of surgical procedure for rectal cancer, accounting for approximately 45% of the procedures with a resection of the tumour during 2010 in Sweden[64]. The proportion of ARs is decreasing, probably due to a greater awareness of the effects of the sometimes poor sphincter function after an AR. The so-called anterior resection syndrome, including urgency, incontinence and an increased frequency of defecation, sometimes causes considerable suffering for the patients. For patients with preoperative poor sphincter function, incontinence or a disability, a Hartmann´s procedure or an abdominoperineal resection is often the better choice[70].

Abdominoperineal Resection

An abdominoperineal resection (APR) is used in the most distal tumours or if poor postoperative sphincter function is expected. In 2010 37% of the procedures in Sweden were APRs[64]. The procedure includes the same TME approach in the pelvic dissection as in AR. In the distal part, however, the anal canal and part of the pelvic floor are also included in the resection. Even though the oncological outcomes after rectal cancer surgery have improved over time, the results after an

APR have remained poor. The high rates of LR after APR are probably caused by technical difficulties resulting in tumour perforations and positive resection margins. This has recently resulted in a change of the approach to the perineal dissection to a more radical one where the abdominal dissection stops earlier and the perineal dissection is wider compared to the standard procedure[71]. With this approach, the specimens are more cylindrical than specimens after the standard technique, which often had a waist at the level of the pelvic floor. The extended resection increases the distance to the tumour and reduces the rates of tumour perforations and positive margins[72]. This approach leaves, however, a larger defect in the pelvic floor which often requires some kind of reconstruction with myocutaneous flaps or a biological mesh.

APR is associated with more postoperative complications than AR due to perineal wound infections. This risk is increased after RT[73-75].

Hartmann's Procedure

Hartmann's procedure (HP) is performed as an AR but without the restoration of bowel continuity. Approximately10% of patients with rectal cancer had an HP during 2010 in Sweden[64]. Indications for an HP instead of an AR are, as earlier mentioned, poor sphincter function or incontinence. In addition, co-morbidities and advanced age, where severe complications such as anastomotic leakages might be lethal, are indications.

Local Excision

In small early cancer tumours or in some patients not fit for an abdominal procedure, a local excision of the tumour is an alternative. A transanal submucosal or full- thickness excision is normally possible in the lower and middle parts of the rectum. In the middle and upper rectum transanal endoscopic microsurgery (TEM) is an option. This procedure uses a special proctoscope with fitting instruments and gas insufflation in the rectum which give the surgeon better control and subsequently potentially better resection margins to the tumour. A major disadvantage of the procedures is that the mesorectum with its lymph nodes is left behind with a subsequent high risk of LR. In a future perspective, if better methods of preoperative nodal staging emerge, local excisions might be a good alternative for stage I disease.

Postoperative complications

Rectal cancer surgery with an abdominal approach is a major procedure with a high risk of postoperative complications ranging from simple wound infections to death. The rate of overall postoperative complications after AR, APR or HP in Sweden is almost 30%[64]. In controlled trials the reported proportions of patients having a complication is even higher. In the TME Trial and the Stockholm III Trial the total overall complications were over 40%. However, in the EORTC 22921 and FFDC 9203 trials the complication rates were less than 25%. One reason for the diverting complication rates is the use of different definitions of which complications to report. In the Swedish Rectal Cancer Registry both severe complications, such as anastomotic leakages or pelvic abscesses and simple wound infections, are reported. In other trials, such as the EORTC 22921 and the FFDC 9203, only more severe complications are reported.

Table 5. The Clavien-Dindo classification of postoperative complications.

Grade	***Definition***
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic or radiological interventions. Acceptable therapeutic regimens are drugs such as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention.
IIIa	Intervention not under general anaesthesia.
IIIb	Intervention under general anaesthesia.
IV	Life-threatening complication (including CNS complications) requiring IC/ICU management.
IVa	Single organ dysfunction (including dialysis).
IVb	Multiorgan dysfunction.
V	Death of a patient.
Suffix 'd'	If the patient suffers from a complication at the time of discharge the suffix 'd' (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

This lack of uniform definitions and grading systems hampers the comparisons between different trials, centres and over time. In 1992 Clavien proposed a system for classification of complications[76]. This system has developed with the latest revision in 2004[77] by Dindo et al. and is used today in many studies (Table 5). The Clavien-Dindo system has been incorporated since a few years back in the Swedish Rectal Cancer Registry and provides future Swedish studies a more distinct instrument for the evaluation of complications.

Immunological Response to Treatment

Preoperative RT is known to increase the risk of postoperative complications. The biological mechanisms are, however, still not fully understood. Machado et al. hypothesised in 2000 an association between RT and leucopenia after observing an increased number of irradiated patients with preoperative leucopenia in their clinic[78]. Marijnen et al. proposed an association between RT, increased systemic cytokines and postoperative complications when they reported an increased mortality rate in patients in the TME Trial having surgery more than three days after RT[79].

The hypothesis of leucopenia as a reason for increased postoperative complications is based on the fact that approximately 40% of the adult bone marrow lies in the head and neck of the femoral bone and within the bony pelvis. These areas are to some extent affected by RT to the pelvis, which results in depressed bone marrow. This might lead to preoperative leucopenia and an impairment of postoperative leucocytosis, which is normally seen within 24 hours after surgery[80].

In Malmö Johnson et al. reported from a retrospective study suppression of leucocytes and an impaired postoperative response in patients having preoperative RT, both short and long-course, compared to non-irradiated patients. The patients with an impaired leucocyte response also had more postoperative complications[81].

Hartley et al. also conducted a retrospective study where all patients received short-course RT, but they did not see any association between the levels of pre- or postoperative leucocyte counts and postoperative complications. However, in patients without complications, the postoperative leucocyte response was better than in patients with complications, which was in line with the results reported by Johnson[82].

Fokstuen et al. made a retrospective study of irradiated patients randomised in the Stockholm I and II Trials regarding pre- and postoperative leucocyte levels which

confirmed the earlier findings of the relationship between leucocyte response and complications. In addition, the study reported an increased mortality if the response was poor on postoperative day 1 and if the time from the start of RT to surgery exceeded ten days.

To conclude, a poor postoperative leucocyte response appears to be a bad prognostic factor regarding postoperative complications and, in one study, also mortality. The immunological mechanisms are, however, not fully understood.

Pathology

After removal of the tumour the specimen is assessed by a pathologist, which is an assessment of great importance. Firstly, the outcome of the assessment is the basis for the recommendation of a postoperative MDT conference regarding follow-up and adjuvant treatment because the outcome is of great importance for the prognosis. Radical surgery, e.g. residual tumour, or not; positive margins or not; histopathological grade; TNM-stage all have an impact on the prognosis. Secondly, the assessment also gives feedback to surgeons, oncologists and radiologists on the surgery, effects of neoadjuvant treatment and preoperative radiology, respectively.

Staging

Postoperative staging is done according to the TNM staging system in the same way as the preoperative staging by macroscopic and microscopic assessments (Table 1, 2 and 3). Compared to the initial clinical staging, the pathological staging can use more of the subclassifications due to the higher resolution of a microscope compared to the radiological imaging.

Tumour Regression

Tumour regression or tumour response is an assessment measuring the impact of neoadjuvant treatment on the tumour. The effect of RT, with or without concurrent chemotherapy, results in tumour cell death, fibrosis and, in some cases, a reduced size of the tumour, so-called down-sizing. In some studies tumour

regression has been shown to have prognostic significance regarding disease-free survival, especially in patients with a complete pathological response (ypCR)[83-85].

Using the microscope, the pathologist can assess the tumour response as proportions of tumour cells and fibrosis and then grade it according to one of the existing grading systems (Tumour Regression Grade (TRG) according to Mandard[86], Rectal Cancer Regression Grade according to Wheeler[87], TRG according to Ryan[88] or Regression Grade according to Dworak[89]). As in the case of postoperative complications, the lack of a uniform grading system is a drawback for comparisons between studies which have used different grading systems. In Sweden there is no recommendation in the national treatment guidelines for this assessment. However, the Dworak system (Table 6) is used in Stockholm County as well in the interim analysis of the Stockholm III Trial (Paper IV).

Table 6. The Dworak system of tumour regression

Grade 0	No regression
Grade 1	Dominant tumour mass with obvious fibrosis and/or vasculopathy
Grade 2	Dominant fibrotic changes with few tumour cells or groups (easy to find).
Grade 3	Very few (difficult to find microscopically) tumour cells in fibrotic tissue with or without mucous substance.
Grade 4	No tumour cells, only fibrotic mass (total regression or response)

Histopathological Grading

The most common histological type of rectal cancer is the adenocarcinoma, followed by mucinous (colloid) adenocarcinoma with more than 50% mucinous and signet-ring carcinoma. Medullary, squamous cell, adenosquamous, small-cell and undifferentiated carcinomas are rare. In the Swedish National Treatment Guidelines, adenocarcinomas are graded according to the WHO 2002 classification based on the degree of gland formation as: well, moderately, poorly and undifferentiated. Mucinous and signet ring cancers are classified as poorly differentiated cancers. Poor and undifferentiated tumours are adverse prognostic factors[15, 90].

Circumferential Resection Margins

The circumferential resection margin (CRM) has been described earlier in Resection Margins, page 19.

Residual Tumour

In 1977 the AJCC introduced the Residual Tumour Classification which describes the primary tumour after the surgery. In the 3rd edition of the TNM Classification in 1987 the current classification was introduced, which is preserved in later editions (Table 7). The R classification now also includes discontinuous extension of the tumour as a distant metastasis and differentiates microscopic and macroscopic residual tumours. With the adaptation of CRM assessments there is some potential confusion regarding radicality (Table 8). A new expanded R classification has been proposed by Wittekind et al., but it has not yet been implemented[91].

Table 7. Residual tumour classification.

RX	Presence of residual tumour cannot be assessed.
R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour

Table 8. Comparison of CRM status and R classification

CRM status	***Pathological findings***	***R Classification***
CRM-positive	Direct involvement of CRM	R1
CRM-positive	CRM ≤ 1 mm but > 0 mm	R0
CRM-negative	CRM > 1 mm	R0

Table modified from Wittekind et al[91].

Adjuvant Therapy

Postoperative adjuvant chemotherapy in rectal cancer is a subject of debate and in Sweden it is not recommended outside clinical trials[90]. However, in some parts of the world, such as the United States, adjuvant treatment is often recommended. The rationale for this recommendation is based on the similarity in the macroscopic and microscopic appearance and the response to chemotherapy in metastatic disease in rectal and colon cancer[92]. The support from randomised trials for this treatment in rectal cancer is weak. Supportive trials are old and involve blunt surgery and often no neoadjuvant treatment. In more recent trials the addition of postoperative chemotherapy has not improved overall survival[46, 93]. However, a recent Cochrane report concludes that data support postoperative chemotherapy in patients who had curative surgery in non-metastasised disease[94] but without the ability to determine in which stages the effect is most favourable. The report recommends further a randomised trial with modern chemotherapy agents.

Follow-up

After surgery the patient is usually included in follow-up programmes. Except for the first follow-up for control of the postoperative course, the value of follow-up programmes has been debated for patients who have had curative surgery. Nevertheless, most international societies recommend some kind of follow-up aimed at finding LR, distant metastasis and metachronous colorectal tumours as early as possible. Early detection of the recurrent disease is believed to improve survival. However, the evidence for this is weak and is the source of the debate. A recent review[95] reports improved overall survival if the follow-up is intense, but only one single study out of the four included RCTs[96] supporting the findings in two other reviews[97, 98]. The main result of the review is, however, weak evidence for the benefit of surveillance due to small and heterogeneous studies. As a result of the debate, a large randomised multicentre trial, the COLOFOL Trial, started to randomise patients in 2005 to either a high-frequency control programme with follow-ups every six months up to three years after surgery or to a low-frequency schedule with follow-ups one and three years after surgery. The primary outcomes are 5-year overall and cancer-specific survival and secondary outcomes are quality of life and the cost-effectiveness of the follow-up. The trial has been closed for randomisation since 2011.

In Sweden the national recommendations had been to include patients in the COLOFOL Trial or to use the low-intensity schedule.

AIMS OF THE THESIS

The *overall* aim of the thesis was to improve the treatment and outcome in patients with rectal cancer.

The *specific* aims were:

- To assess feasibility, compliance, acute adverse events due to RT and postoperative complications in relation to RT regimens within the Stockholm III Trial.

- To describe indications, early toxicity, RT response and short-term outcome after short-course RT with delayed surgery in patients outside the Stockholm III Trial.

- To compare postoperative leucocyte responses in the three different RT regimens in the Stockholm III Trial and to assess the relationship between leucocyte response and postoperative complications.

- To compare the pathological outcome in the two short-course RT randomisation arms in the Stockholm III Trial with a special focus on T-stage, involved resection margin and tumour regression.

PATIENTS AND METHODS

All patients in this thesis were diagnosed with an adenocarcinoma in the rectum. The origin of the study population for each study is presented in Table 9.

Table 9. Patients included in the studies of the thesis.

Paper	*Inclusion period*	*Origin of study cohort*	*Study cohort*	*Number of patients*
I	1998-2005	The Stockholm III Trial	The first 303 consecutively randomised patients	303
II	2002-2008	All inhabitants in the Stockholm-Gotland region	Patients with rectal cancer having short-course preoperative RT with surgery delayed more than four weeks; outside the Stockholm III Trial	112
III	1998-2010	The Stockholm III Trial	Patients included in the Stockholm III Trial with data on leucocyte counts perioperatively	585
IV	1998-2010	The Stockholm III Trial	Patients randomised in the Stockholm III Trial to the SRT and SRT-delay arms with pathology specimens available for re-assessment	398

The Stockholm III Trial

As previously stated, the SCCSG initiated the Stockholm III Trial in 1998 to study differences in fractionations of preoperative RT in primary rectal cancer and the importance of the timing to surgery after the RT. The Stockholm III Trial is still ongoing. With the aim of including 840 randomised patients, today (April 2012) the trial has included 770 patients.

Patients entering the study are required to have a biopsy-confirmed clinically resectable adenocarcinoma within 15 cm from the anal verge (measured with a rigid sigmoidoscope) and to be scheduled for a resection using an open abdominal procedure. Pretreatment assessments are made according to regional treatment programmes. Patients with a preoperative diagnosis of distant metastases, locally advanced unresectable tumour or patients with tumours scheduled for local excision are excluded. Patients who have previously received RT to the abdominal or pelvic region or have had signs of severe ischaemic heart disease or symptoms of severe arteriosclerosis are also excluded.

The patients are randomised to one of three treatment arms: short-course RT (five doses of 5 Gy given during one week) and surgery within a week after the end of the RT (SRT); short-course RT as in the SRT arm and surgery delayed four to eight weeks after the end of RT (SRT-delay) or long-course RT (25 doses of 2 Gy given during five weeks) with the surgery delayed four to eight weeks after the end of RT (LRT-delay).

A patient or a hospital can choose to randomise between all three arms or between the two arms with short-course RT (SRT and SRT-delay).

During the years of randomisation the number of participating hospitals has increased. Today, April 2012, patients are included from the seven hospitals in the Stockholm-Gotland region, the University Hospital in Uppsala, the hospitals in Falun and Mora and the Mälarsjukhuset Hospital in Eskilstuna, the University Hospital in Linköping and the Vrinnevi Hospital in Norrköping, as well as the University Hospital in Umeå, the Skåne University Hospital, Malmö, and the Helsingborg Hospital.

Paper I

The study in Paper I was the first pre-planned interim analysis of the Stockholm III Trial including the initial 303 consecutively randomised patients. Registry data on all patients were validated and new variables were added by means of a retrospective review of the medical records. The new variables were data on compliance with the study protocol and adverse events after RT.

The level of the tumour, i.e. the distance from the anus to the lower limit of the tumour, was categorised into low (< 6 cm), mid (6–10 cm) and high (> 10 cm) levels. Patients having an adverse event after RT were identified through the inpatient registry where patients who were admitted to a hospital between the start of RT and the surgery were identified and the medical records were reviewed and symptoms recorded. The adverse events correspond to RTOG toxicity criteria grades 3–4.

Statistical Analyses

Distributions were compared using the $\chi 2$ test of independence or Fisher's exact test. The Kruskal-Wallis test was used for comparisons of age between the study groups.

In the analysis of event-specific rates, patients were considered to be at risk of the studied event until death, emigration or end of follow-up. Event-specific hazards modelling was carried out using Cox's proportional hazards regression model. Potential confounding factors, such as age, sex, tumour stage and level, type of surgery, two- or three-armed trial and randomising hospital, were controlled for by including these factors in the models. Results are presented as odds ratios (ORs) with corresponding 95 per cent confidence intervals (CIs). *P* values refer to Wald statistics tests. All analyses were made on the basis of intention to treat.

Paper II

The study was a retrospective cohort study with both prospectively reported and retrospectively added registry data. All patients during the study period in the Stockholm-Gotland region diagnosed with a rectal cancer and having short-course RT and a resection of the tumour after more than four weeks after RT were identified in the Swedish Rectal Cancer Registry. Patients included in the Stockholm III Trial and those having preoperative chemotherapy were excluded.

The registry data were validated and additional data were added by means of a review of the medical records. Added data regarded reasons for the therapy schedule, the short-term outcome after RT and data on MRI re-assessment after RT but before surgery.

Statistical Analysis

Distributions were compared using the exact McNemar test of paired proportions or the Wilcoxon signed rank test.

Paper III

In this study patients in the Stockholm III Trial randomised up to November 2010 were identified. Prospectively recorded data from the Swedish Rectal Cancer Register were validated and new variables were added by means of a review of the medical records. Added variables were data on leucocyte counts (LCs), if available, preoperatively and postoperatively on days 1 and 2. The preoperative value was recorded only if it was determined after completed RT and within two weeks before surgery. Patients for whom no laboratory data were found were excluded from the study.

In the calculation of the ratio of postoperative and preoperative LCs, the value for postoperative day 1 was used. If this value was not available, the value for day 2 was used. Patients lacking data for this calculation were excluded from this analysis. For the analysis and presentation of the LC ratios (339 cases), three equally large groups (of 113 cases each) were created with low, intermediate and high ratios, respectively. The cut-off values were defined by the cases in the intermediate group with the lowest (1.21) and highest (1.58) ratios.

Overall treatment time (OTT) was defined as time from start of RT to surgery. The relationship between OTT, LC ratio and postoperative complications was analysed in a subgroup analysis of the SRT and SRT-delay groups irrespective of randomisation arm.

Statistical Analysis

Differences in distribution between treatments, various categorical clinical variables and complications were tested using Fisher's exact test. For continuous variables distributional differences were tested using the Mann-Whitney U-test.

The odds for complications were studied using unconditional logistic regression. Results from these models are presented as ORs together with 95% CIs. P-values from the models refer to the Wald test. Interactions were tested by including product terms in the model.

Paper IV

This study was the second pre-planned interim analysis of the Stockholm III Trial. Only the two randomisation arms with short-course RT were analysed. Patients randomised up to November 2010 were identified. Demographic data, allocated treatment arm, received RT and data regarding surgery were extracted from the Swedish Rectal Cancer Register. All available slices from the pathological specimens were retrieved for blinded reassessment by one pathologist. If the reassessment was impaired by technical difficulties, such as damaged slices or pale staining, the stage or circumferential resection margin (CRM) was recorded as *not assessable*. Cases where single whole-mount sections of the tumour were missing were excluded from the analysis of CRM.

The tumour node metastasis (TNM) staging system (6^{th} edition) was used for staging.

At pathological assessments, the CRM was defined as positive if the tumour involved the CRM or was found at 1 mm or less from the margin. If the distance from the tumour to the margin exceeded 1 mm, the CRM was judged to be negative. The Dworak system of tumour regression was used for the assessment of regression (Table 6).

Statistical Analysis

Differences in distribution between the randomisation arms regarding the pathological outcome treatment were tested using Fishers exact test or the Mann-Whitney test.

Ethics

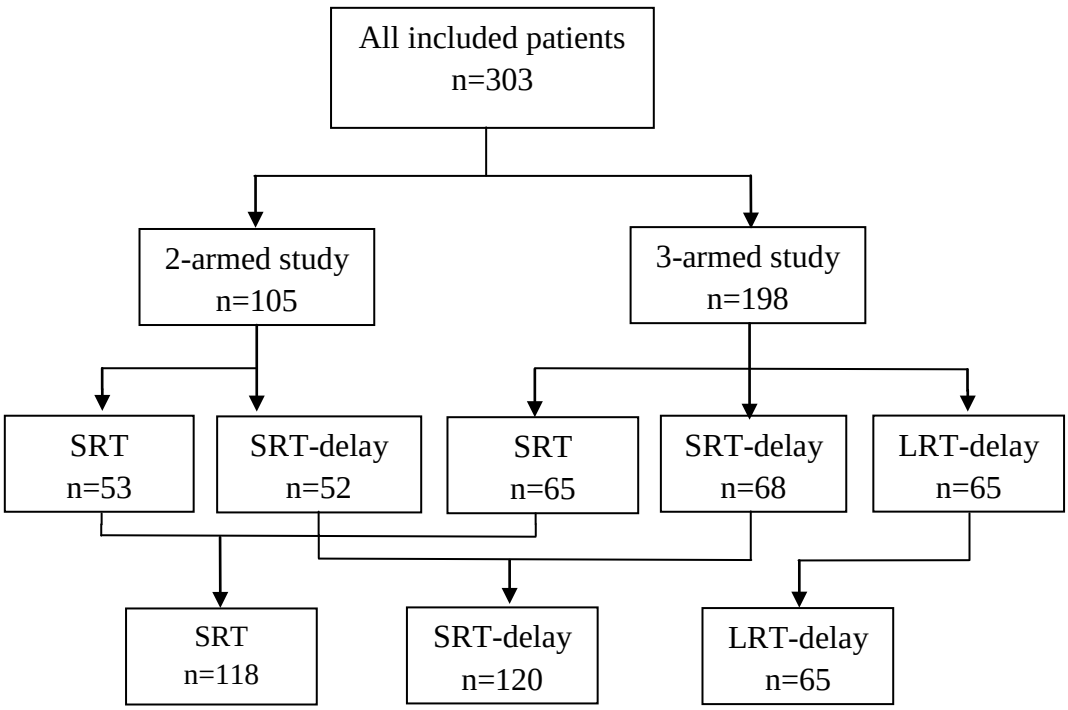
All studies were approved by the regional ethical review boards.

RESULTS

Paper I

The Stockholm III Trial randomised the first patient in October 1998. In December 2005 303 patients had been randomised in the trial. Due to the option to either randomise between three or two arms, the distribution of patients was not balanced between the treatment schedules. The distribution of the patients is shown in Figure 6. There were no differences in clinical characteristics between patients randomised in the two-armed comparison and those who were randomised in the three-armed comparison. Henceforth the results are presented including both the two and three-armed comparisons.

Figure 6. Distribution of patients between the two and three-armed comparisons and into the analysed groups.



Patient characteristics such as age and gender proportions were similar in all three treatment arms.

Violations of the study protocol regarding eligibility were seen in two patients, each for the SRT and LRT-delay arms, and one in the SRT-delay arm. All violations, except for one, were presence of distant metastases at randomisation. One patient had a locally advanced, primary non-resectable tumour at randomisation. Reasons for the violations were inclusion in the trial before the primary clinical assessment was finished.

Seventeen patients, seven, six and four in the SRT, SRT-delay and LRT-delay arms, respectively, did not receive their allocated treatments according to the study protocol. Physical limitations were the main reason. In the arms with delayed surgery, three patients had obstruction symptoms resulting in surgery scheduled earlier than prescribed by protocol. There were no statistical differences between the randomisation arms regarding the protocol violations.

Acute adverse events due to RT were seen only in the arms with delayed surgery. In the SRT-delay group, five patients (4%) and in LRT-delay, three (5%) were admitted, mainly due to vomiting and diarrhoea with dehydration, but also due to constipation and lower back pain and, in one patient, due to extensive vaginal bleeding.

The LRT-delay arm had a smaller proportion of low tumours than the other arms (25% vs 35% in the SRT and 37% in the SRT-delay groups) and a larger proportion of high tumours (35% vs 27% and 22% in the SRT and SRT-delay arms, respectively.) The difference was not, however, statistically significant *(P* = 0.309).

The differences in tumour level were reflected in the type of surgery. In the LRT-delay group the proportion of APR was smaller than in the two other groups (20% vs 30% in the SRT and 33% in the SRT-delay groups) and the proportion of AR was larger (72% vs 64% and 59% in the SRT and SRT-delay arms, respectively). The differences were not statistically significant, however *(P* = 0.381).

Patients having an AR in the LRT-delay arm had a defunctioning stoma in a greater extent than patients in the other arms (62% vs. 41% in the SRT and 35% in the SRT-delay arms, *P* = 0.016).

Table 10. Postoperative complications

	SRT n=118	***SRT-delay n=120***	***LRT-delay n=65***	***P value***
Postoperative complications	55 (47)	48 (40)	21 (32)	0.164
Type of complication*:				
Surgical	33 (28)	30 (25)	13 (20)	0.493
Cardiovascular	4	5	0	0.367
Infection	13 (11)	10 (8)	7 (11)	0.751
Other	12 (10)	9 (8)	1	0.098

Values in parenthesis are percentages. *More than one type of complication might be recorded for each patient.

Both overall and surgical complications were numerically most common in the SRT arm; however, the difference was not statistically significant. Complications are shown in Table 10.

In a multivariable analysis, the odds for postoperative complications, compared to the SRT arm, were 0.90 (95% CI 0.49 to 1.62, $P = 0.713$) for the SRT-delay arm and 0.81 (0.36 to 1.79; $P = 0.598$) for the LRT-delay arm.

A subgroup analysis of postoperative complications in the SRT arm in relation to the overall treatment time (OTT), i.e. the time from start of RT to surgery, showed significantly more complications in the subgroup with an OTT interval of 11–17 days compared to patients with an OTT less than 10 days or more than 17 days (Table 11).

Table 11. Postoperative complications in patients randomised to short-course RT and immediate surgery (SRT) in relation to actual time to surgery after the start of RT.

	≤10d (n=75)	***11-17d (n=37)***	***>17d (n=6)***	***P value***
Postoperative complications*	29	24	2	0.036
Surgical complications	17	15	1	
Reoperation	5	6	1	
Cardiovascular	2	2	-	
Infection	6	7	-	
Other	7	4	1	
Surgical complications*				
Wound infection	17	15	1	
Intra-abdominal infection	-	1	-	
Haemorrhage	1	1	-	
Anastomotic leak†	5 of 48	5 of 24	0 of 3	
Wound dehiscence	1	1	1	
Complications due to defunctioning stoma	1	-	-	
Other	2	2	1	
Postoperative mortality 30 and 90 days	-	1	-	

*More than one type of complication might be recorded for each patient. †AR only.

Paper II

From January 2002 to December 2008 112 patients in the Stockholm-Gotland region were diagnosed with a rectal cancer, received short-course RT without concurrent chemotherapy and had surgery more than four weeks after the start of RT outside trials. The patients included constituted approximately nine per cent of all patients having preoperative RT in the Stockholm-Gotland region during the study period.

Fifty-six patients had a positive MRF at the preoperative MRI, 50 of which were cT4 tumours. Three patients with cT4 and an additional five patients had distant metastases.

Main reasons for the choice of treatment varied and are shown in Table 12. The treatment decisions were made at an MDT conference for 82 patients (73%).

Table 12. Main reasons for short-course preoperative RT with delayed surgery.

	n=112
Primary non-resectable disease	43
Co-morbidity and/or frailty	21
Unintentional*	13
Administrative causes	10
Miscellaneous[†]	9
Reason not found	16

*Delay of planned immediate surgery owing to leucopenia after RT and other acute diseases. [†]Patient's choice; hope of down-staging non-locally advanced tumour; delayed salvage surgery after non-radical transanal resection in one patient.

RT was administered as planned in all but two patients. Acute adverse events due to RT resulting in admission to a hospital, corresponding to RTOG toxicity criteria grades 3–4, were noted in six patients (5%), all grade 3.

Sixty-two patients were reassessed by an MRI after RT and before surgery after a median of 4 weeks (range 2–14 weeks) after the end of RT. In 46 patients (74%) tumour regression was reported.

The surgery was performed after a median period of seven weeks (range 4–17 weeks) after the end of RT. In 51 patients (45%) an AR was performed, in 49 patients (44%) an APR, in 11 (10%) a Hartmann procedure and in one patient a total colectomy. Thirty-six of the patients having an AR (71%) also had a defunctioning stoma.

Forty-three patients (38%) had some type of postoperative complication, 32 of which (29%) had a surgical complication. One patient died within 30 days and two others within 90 days (3%).

The pathology assessment showed a complete pathological response in nine patients (8%). The clinical staging was compared to the pathological outcome in patients where both data were available. TNM stage, T stage, N stage and margin involvement (50% vs 14%; $P < 0.001$) were significantly lower in the pathological assessment. Seven patients had a higher T stage and 13 patients had a higher TNM stage in the pathological assessment compared to the clinical assessment.

Paper III

From trial start in October 1998 until November 2010 the Stockholm III Trial had included 657 patients, 585 of which had data on perioperative LC for analysis. The included patients were allocated to the SRT, SRT-delay and LRT-delay arms comprising 244, 246 and 95 patients, respectively. As in Paper I, fewer patients were randomised to the LRT-delay arm than to the other arms due to the option of randomisation to the two-armed comparison. There were no differences in proportions of excluded patients between the randomisation arms.

Patients in the SRT arm had significantly more postoperative complications than in the two other treatment arms. The relative risk of an overall postoperative complication was lower in the SRT-delay and the LRT-delay arms than in the SRT arm (SRT-delay, 0.59, 95%, CI 0.41 to 0.84; LRT-delay, 0.63, 0.39 to 1.02¸ $P = 0.011$). The same pattern was seen in surgical complications (SRT-delay, 0.66, 0.45 to 0.97; LRT-delay, 0.61, 0.36 to 1.04), but not statistically significant *(*$P = 0.054$). Nor did infection complications differ significantly (Table 13).

Table 13. Postoperative complications by randomisation arm

	SRT n=244	***SRT-delay n=246***	***LRT-delay n=95***	***P-value***
Postoperative complications	128 (52)	97 (40)	39 (41)	0.010
Type of complication*				
Surgical	87 (36)	66 (27)	24 (25)	0.058
Cardiovascular	7 (3)	10 (4)	-	0.13
Infection	38 (16)	23 (9)	14 (15)	0.091
Other	22 (9)	18 (7)	4 (4)	0.32

Values in parenthesis are percentages. *More than one complication might be recorded for each patient.

The median LC ratio was lower in the SRT arm *(P* < 0.001) with more patients with a low ratio and fewer patients with a high ratio compared to the two other arms *(P* < 0.001).

There was no significant association between a low preoperative LC (< 4.0) and postoperative complications.

Patients with a poor LC response had the highest proportion of complications (57% vs. 47% and 36% in the groups with intermediate and good response respectively. P=0.01.). There were no differences in proportions of complications between the three randomisation arms in each interval

An analysis of the OTT, LC ratio and postoperative complications in the SRT and SRT-delay arms showed a decreasing proportion of low LC ratios with increasing OTT (Table 14). If the OTT was more than 35 days, the risk of having a complication decreased. When the risk of a complication was adjusted for LC ratios the differences between OTT categories decreased. None of the risks in odds ratios were significant.

Table 14. Overall treatment time (OTT) by leucocyte ratio and by postoperative complications after short-course radiotherapy (SRT and SRT-delay groups)

		Leucocyte ratio (%)			
		<1.21	***1.21-1.58***	***>1.58***	***P-value***
OTT*					
≤10	(n=101)	55 (55)	33 (33)	13 (13)	
11–35	(n=40)	17 (43)	8 (20)	15 (38)	
36–49	(n=74)	13 (18)	29 (39)	32 (43)	
≥50	(n=72)	16 (22)	25 (35)	31 (43)	<0.001
Total	(n=287)[†]	101	95	91	

	Postoperative complications					
	Overall Events (%)	***OR (95% CI)***	***P-value***	***Surgical Events (%)***	***OR (95% CI)***	***P-value***
OTT*						
≤10	53 (52)	1.0		37 (37)	1.0	
11–35	22 (55)	1.1 (0.5–2.3)		13 (33)	0.8 (0.4–1.8)	
36–49	31 (42)	0.7 (0.4–1.2)		18 (24)	0.6 (0.3–1.1)	
≥50	29 (40)	0.6 (0.3–1.1)	0.23[‡]	19 (26)	0.6 (0.3–1.2)	0.29
Total	135 (47)			87 (30)		

Abbreviations: OR, Odds ratio; CI, confidence interval. *Overall treatment time (i.e. time from start of RT to surgery) in days; [†]One patient in the SRT arm did not receive RT and was excluded in this analysis.

Paper IV

The initial selection in this study was the same as in Paper III. Out of the 657 randomised patients in November 2010, 398 in the SRT and the SRT-delay treatment arms with available specimens were reassessed. In the SRT arm, 203 patients, and in the SRT-delay arm, 195 patients were included in the analyses. The pathological outcome is shown in Table 15 and 16.

Table 15. Pathological outcome, stage

	SRT (n=203)	***SRT-delay (n=195)***	***P-value***
TNM stage (yp)			
0	2 (1)	24 (12)	0.008
I	59 (29)	59 (30)	
II	62 (31)	42 (22)	
III	66 (32)	53 (27)	
IV	5 (3)	6 (3)	
x*	9 (4)	11 (6)	
T-stage (yp)			
T0	4 (2)	26 (13)	<0.001
T1	10 (5)	19 (10)	
T2	60 (30)	49 (25)	
T3**†			
T3ab	79 (39)	59 (30)	
T3cd	37 (18)	24 (12)	
T3x	3 (1)	1 (1)	
T4**†			
T4a	1 (0)	4 (2)	
T4b	3 (1)	3 (2)	
Tx*	6 (3)	10 (5)	
N-stage (yp)			
N0	128 (63)	132 (68)	0.26
N1	47 (23)	40 (21)	
N2	24 (12)	18 (9)	
Nx*	4 (2)	5 (3)	

*Not included in statistical tests. †Subcategorising was not used in statistical tests.

Table 16. Pathological outcome, margins and regression

	SRT (n=203)	***SRT-delay (n=195)***	***P-value***
Tumour regression			
Grade 0	17 (8)	13 (7)	<0.001
Grade 1	140 (69)	90 (46)	
Grade 2	36 (18)	53 (27)	
Grade 3	2 (1)	8 (4)	
Grade 4	3 (1)	20 (10)	
Grade x*	5 (2)	11 (6)	
CRM			
Positive	10 (7)	9 (7)	1.00
Negative	137 (93)	121 (93)	

*Not included in statistical tests.

There were differences in the distributions of TNM-stage, T-stage and tumour regression between the treatment arms. In addition, the proportion of complete pathological responses was larger in the SRT-delay arm *(P* < 0.001).

The proportion of positive CRMs did not differ between the treatment arms.

DISCUSSION

The present studies have shown the Stockholm III Trial to be a feasible study with acceptable compliance with the study protocol. The experimental SRT-delay schedule was as safe as the established SRT and LRT-delay schedules regarding acute adverse events, both within and outside the Stockholm III Trial. The SRT schedule with immediate surgery resulted in a poorer postoperative LC response and had more postoperative complications than the other schedules. The SRT-delay schedule had lower ypTNM and ypT-stages and more tumour regression than SRT with immediate surgery.

In the three papers with patients from the Stockholm III Trial, Papers I, III and IV, the patients were recruited from a randomised controlled trial (RCT). Advantages of an optimal RTC are elimination of bias, including both known and unknown confounders, leaving the allocated treatment as the remaining difference between the randomisation groups. Drawbacks are that RCTs are time-consuming and expensive. In all four papers data were retrieved to some extent retrospectively. The use of retrospective data from medical records introduces the risk of bias, mainly information and selection bias. However, any information bias as misclassification in Papers I, III and IV should be non-differential, i.e. the type and extent of errors are the same in all randomisation arms. There were no differences between the randomisation arms in missing data which reduced the risk of selection bias.

Compared to the initial plan, the prolonged time for inclusion of patients in the Stockholm III Trial has been a problem. In 2005 the first interim analysis was performed after 303 patients were included. According to the initial plan, the trial would have been closed to further inclusion after including 840 patients at this time. After the interim analysis and the presentations of the data in different forums, the inclusion rate has increased again. The present hope is to reach the goal of 840 included patients during 2012. However, during the almost 14 years for inclusion some parameters have changed in the treatment of rectal cancer. Firstly, the 5-year LR incidence has decreased to approximately 7% [64]compared to the estimation of 15% in the power calculations for the Stockholm III Trial in 1998. This reduction mainly creates a potential power problem within the trial regarding the primary endpoint of LR. Secondly, the recommendations for which patients who should be offered preoperative RT have changed. During the initial period of the trial some patients with lower stages, who today would be judged as

'good' (Figure 3) and who are recommended surgery without any neoadjuvant treatment, also had RT. In addition, some of the patients, today judged as 'ugly' (Figure 3), did not have CRT and received RT only instead. The change in recommendations and potential differences in stage at the primary assessment between patients over time within the trial might, to some extent, affect the external validity. However, the relative differences in the outcomes between the randomisation arms are not affected by a change over time, i.e. the mix of clinical stages should be the same in all randomisation arms. Despite the potential problems due to the prolonged inclusion time, the Stockholm III Trial is a feasible study with acceptable compliance with the study protocol. Most important is that it is still unique in its setting and will continue to produce important data on relative differences in RT fractionation and the timing to surgery after SRT.

Adverse Events

The SRT-delay arm is an experimental RT schedule described earlier only outside trials in retrospective studies[26, 27], in a case report where, however, the patients also had preoperative chemotherapy[99] and, more recently, in a small RCT[100]. The schedule has its origin in sporadic observations in patients who had SRT but had had the planned immediate surgery delayed for some reason. Some of these patients had a pathologically complete response or a downsized tumour. In addition, there were few acute adverse events. In the Stockholm III Trial acute adverse events are one of the secondary endpoints. Both in the first interim analysis, Paper I, as well in the study on patients having SRT-delay outside the Stockholm III Trial, Paper II, the acute adverse events were low in number in patients having short-course RT with delayed surgery. In Paper I the adverse events from RT were seen only in patients having delayed surgery, which is to be expected owing to the fact that in SRT the irradiated organ is resected before severe acute symptoms have time to develop. The percentages having an adverse event according to the definition set were 4% and 5% in the SRT-delay and LRT-delay arms, respectively. In Paper II 5% of the patients had an adverse event due to RT. Other randomised trials have reported levels of acute adverse events between 3 and 6% for LRT-delay[47, 48] and 2 to 3% for SRT[38, 43, 49, 101]. In retrospective studies of patients having SRT-delay, Hatfield et al. reported that 5% of the patients were admitted after RT and Radu et al. reported 9% adverse events[26, 27]. In these studies the patients had poor performance status and were unfit for CRT, for which reason the risk of being admitted is expected to increase compared to patients in the Stockholm III Trial. The method used in Papers I and II for identification of the adverse events probably underestimates the true numbers due to the fact that patients with grade 3 symptoms having their treatment in the outpatient care setting are not identified. To conclude, the experimental schedule SRT-delay is probably as safe regarding acute adverse events as the established schedules. To give a perspective, in CRT acute adverse

events are more common where randomised trials have reported incidences of grade 3–4 between 15% and 28%[47, 48, 101].

Postoperative Complications

The experimental SRT-delay schedule also seems to have a favourable risk of postoperative complications compared to the SRT schedule with immediate surgery and at the same level as the LRT-delay schedule. As mentioned in the Introduction, a comparison of the proportions of patients having a complication between different trials is difficult due to different definitions of complication and differences in protocols on what to report. If the RT schedules are compared within the Stockholm III Trial, Papers I and III showed the highest risk of complications in the SRT arm. Paper III also showed an association between a poor postoperative LC response and a higher risk of a complication, which supports findings in earlier studies[81, 82, 102]. The SRT arm had the highest proportion of patients with a poor LC response after surgery, which might be one explanation of the difference in complication rates. There were no differences between the randomisation arms in proportions of complications within each group of LC response (poor, intermediate or good). That is to say, if the postoperative leucocyte response is poor, the risk of a complication is the same irrespective of the preoperative treatment.

In the first interim analysis, Paper I, the SRT arm had the highest proportion of postoperative complications. The difference from the two other arms was numerical, but not statistically significant. In a subgroup analysis of the SRT arm, the patients were grouped and analysed according to OTT. In the group having an OTT of ten days or less, the complications were at the same level as for the two other randomisation arms, i.e. approximately 40%. In the group with an OTT between 10 and 17 days, 65% of the patients had a postoperative complication. In Paper III where the numbers of randomised patients were higher, the picture was the same (≤ 10 days: 49% vs. 11–17 days: 60%, data not shown). The difference was not statistically significant in any of the comparisons. However, the findings support the data from Hartley et al., who reported a significantly increased risk of a complication if the OTT was higher than both 10 and 13 days but disappeared if the OTT cut-off was set at 20 days[103]. A retrospective study of the Stockholm I and II Trials showed an increased risk of mortality if the OTT was more than 10 days, supporting results in the TME Trial[79, 102]. However, in Paper III a comparison of OTT, LC ratios and complications in the two arms with SRT was made (Table 14). In this selection, there was no difference in complications between the OTT intervals ≤ 10 days and 11–35 days. Stratification into smaller intervals of OTT was not statistically feasible due to there being few patients in some intervals. A type II error, i.e. lack of power, is a potential explanation for a difference not being significant. Another explanation is off course the absence of a true difference between the OTT intervals regarding complications.

To conclude, data indicate an association between OTT and postoperative complications where an OTT somewhere between 10 and 20 days increases the risk of postoperative morbidity and mortality. The same data indicate that the risk decreases again if the surgery is delayed for several weeks after RT. The increased risk seems to be associated with an impaired postoperative leucocyte response due to RT. Our understanding of the impact of RT on the leucocyte response and its association with cytokine cascades remains incomplete. Until we have a good method for predicting complications and the means to prevent them, the useful option is to optimise the doses and fractionations to reduce complications with a preserved oncological effect.

Pathological Response

SRT has been regarded as a fractionation without the ability to induce tumour regression and downstaging[104]. In the regular SRT schedule the surgery is performed immediately after the end of RT with too short a time for downsizing and/or downstaging to occur. However, in the Swedish Rectal Cancer Trial and the Stockholm II Trial an imbalance in stage between RT and surgery only schedules were reported, with lower stages if the patients had SRT[32, 105]. In other trials less involved lymph nodes were reported after SRT[105, 106]. More recently, three retrospective studies, including Paper II, have shown a downstaging effect after SRT with the surgery delayed for more than four weeks after RT[26-28]. In the study by Hatfield et al., regression was seen in 82% of patients being reassessed by MRIs after RT. Two patients (8%) had complete pathological response. In the study by Radu et al., a complete pathological response was seen in two of the 24 patients (8%) without metastasis undergoing surgery. In Paper II 74% showed signs of tumour regression at reassessment after RT on MRI, the ypTNM and ypT-stages being significantly lower than the clinical stages and with a significantly lower proportion of involved margins after SRT-delay. All studies indicated a downstaging effect also after hypofractionated RT. These data were supported by the results in Paper IV where SRT-delay had lower stages and more regression compared to SRT with immediate surgery.

In Paper IV the better pathological outcomes in the SRT-delay group did not include any difference in positive margins compared to the SRT group which may have been expected. Possible explanations are few ‘ugly’ tumours and low proportions of positive CRM in both arms, i.e. the study suffers from a lack of power regarding this outcome. In Paper II, however, 50% of the patients had a positive MRF compared to 14% positive for CRM after SRT-delay, again indicating the downsizing and downstaging effect of SRT-delay.

The importance of negative margins after surgery has been shown in several studies[19-21]. In primary resectable tumours without threatened MRF, tumour regression *per se* is not considered today to be an important factor. However, also the regression grade might be a prognostic factor, mainly in advanced tumours.

One study of patients having CRT reported less positive nodes in patients with high-grade regression compared to patients with poor regression[84]. Further studies have shown good tumour regression to be a positive prognostic factor regarding overall and disease-free survival[107-109]. Some of the authors suggest that regression grade should be a routine assessment for both comparison between treatments and also to support the decision as to whether the patient needs adjuvant treatment or not. In Sweden, tumour regression is not a variable included in the new quality protocols suggested by the Swedish Society of Pathologists.

Conclusions

The experimental RT schedule in the Stockholm III Trial, SRT-delay, has been shown to be a feasible treatment with a low incidence of acute adverse events, fewer postoperative complications and with a potential downstaging effect, compared to the established schedule of SRT with immediate surgery. The schedule has already been recommended as a treatment in locally advanced tumours where the patient is not fit for CRT. However, the long-term outcomes after the RT schedule are not yet known. RT stimulates the cells to divide, the so called repopulation. In some cases the repopulation also starts with an increased proliferation rate[110]. Therefore, there is theoretically an increased risk of distant metastasis due to the repopulation of irradiated cells. A small Polish trial randomised patients with locally advanced tumours to either surgery seven to ten days after SRT or to delayed surgery four to five weeks after the end of RT. The study reports, after a five-year follow-up, better survival in the group with delayed surgery (73% vs 63%, $P = 0.24$). The results are promising but not yet sufficient for a recommendation for use of SRT-delay outside trials or in the special clinical situations, as mentioned before. Hopefully, the Stockholm III Trial will reach the inclusion aim during the current year and later on also provide information regarding long-term outcomes for LR and survival.

Parallel to the Stockholm III Trial, a new trial was launched last year, the RAPIDO Trial. RAPIDO randomises patients with locally advanced tumours to either standard CRT or to the experimental arm with SRT followed by six cycles of combination chemotherapy (capecitabine and oxaliplatin) during 16 weeks and, finally, surgery after another four to six weeks. The trial might include the patients with advanced tumours who are no longer included in the Stockholm III Trial and will provide data on the SRT-delay schedule in combination with chemotherapy.

CONCLUSIONS

- The Stockholm III Trial is a feasible trial with acceptable compliance with the protocol. The incidence of acute adverse events due to RT was low. SRT with immediate surgery had a tendency to more postoperative complications. This increased risk was mainly due to patients with an OTT between 11 and 17 days.

- The reasons for the use of SRT-delay outside the Stockholm III Trial in the Stockholm-Gotland region varied, including primary unresectable disease and co-morbidities. Acute adverse events due to RT were few in number. Postoperative complications were acceptable. SRT-delay induces downstaging/downsizing.

- An impaired postoperative LC response increases the risk of postoperative complications. Patients included in the SRT schedule with immediate surgery had a higher risk of impaired LC response and more postoperative complications.

- Short-course RT induces tumour regression and downstaging of the tumour if the surgery is delayed for 4–8 weeks after the end of RT.

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