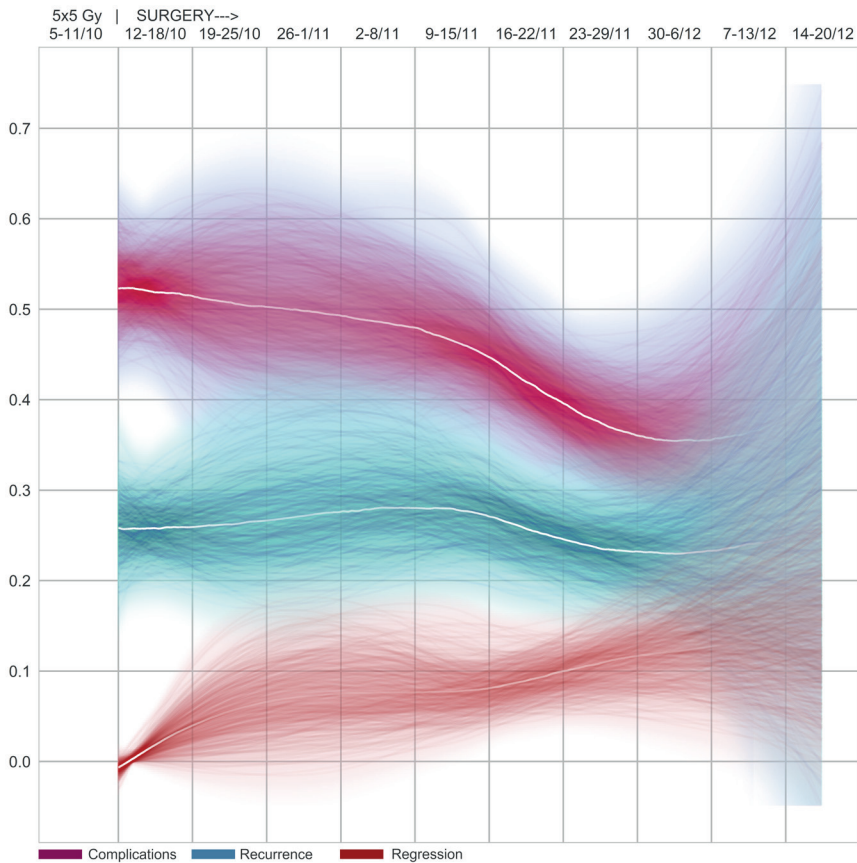


Preoperative radiotherapy in rectal cancer - Aspects on fractionation and timing of surgery



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PREOPERATIVE RADIOTHERAPY IN RECTAL CANCER

- Aspects on fractionation and timing of surgery

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- Aspects on fractionation and timing of surgery

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"It's the terror of knowing what this world is about"
D. Bowie, F. Mercury

To Dana, Evelina and David

Abstract

Neo-adjuvant radiotherapy (RT) in rectal cancer (RC) reduces the risk for local recurrence (LR). The optimal fractionation or time to surgery is not determined. The focus areas of this thesis are different RT-courses and timing of surgery in patients with RC. The Stockholm III trial forms the basis of the studies included in the thesis. Between 1998 – 2013, patients with primarily resectable adenocarcinoma of the rectum were randomly allocated to three different RT-courses. SRT - 5 Gy x 5 and surgery within one week, SRT-delay- 5 Gy x 5 and surgery after 4-8 weeks or LRT-delay - 2 Gy x 25 and surgery after 4-8-weeks. Including centres could choose to randomise patients between three courses or between the two courses with 5 Gy x 5. Primary endpoint was time to LR, secondary end points included distant metastases (DM), survival, tumour regression and adverse events. All patients have been registered in the Swedish ColoRectal Cancer Registry.

Paper I. All 840 patients randomised in the Stockholm III trial were analysed after a minimum follow up of 2 years. 357, 355 and 128 patients were allocated to SRT, SRT-delay and LRT-delay respectively. The three armed randomisation was analysed separately and the patients randomised to any of the courses with 5 Gy x 5 were pooled and analysed in a short course RT comparison. About 6-7% of the patients with a delay to surgery required hospitalisation between start of RT and surgery due to RT-induced toxicity. In total, 25 patients had a LR within the follow up time, without statistical significant differences between the groups. The cumulative incidence of DM, overall survival (OS) and recurrence free survival (RFS) did not differ between the groups. We found a statistical significant reduction of post-operative complications in SRT-delay compared to SRT (OR 0.61 [95% CI 0.45–0.83] $p=0.001$).

Paper II. The aim this study was to evaluate the post-operative complications in relation to the exact overall treatment time (OTT). Patients were categorized according to OTT and fractionation. Patients that received 5 Gy x 5 were divided into four groups; Group A: 7 days, B: 8-13 days, C: 5-7 weeks, D: 8-13 weeks. Patients that received 2 Gy x 25 were divided in two groups; Group E: 9-11 weeks and F: 12-14 weeks. Main outcome was post-operative complications defined as any-, surgical- or infectious complication. Adjusted odds ratios (any complication) were; A vs. B OR (95% CI); 0.72 (0.40-1.32) $p=0.289$, C vs. B 0.50 (0.30-0.84) $p=0.009$, and D vs. B 0.39 (0.23-0.65) $p<0.001$. There were no statistical significant differences between group E and F.

Paper III. In this study, all available histopathology slides from the resected tumours have been reassessed by one pathologist. Tumour regression was the main outcome and secondary outcomes were histopathological characteristics and the correlation between tumour response and survival. Patients randomised to SRT-delay showed more tumour regression compared to the other arms. A complete pathology graded tumour regression (pCR) was seen in about 10% of the patients after SRT-delay. Patients with pCR had improved OS and time to recurrence, compared to patients with lower regression grades. Hazard Ratio pCR vs no-pCR: OS: 0.51 (0.26–0.99) $p = 0.046$, TTR: 0.27 (0.09–0.86) $p = 0.027$.

Paper IV. Long-term follow up of the Stockholm III trial after a minimum follow-up of 5 years. The endpoints from paper I were analysed. The incidence of LR was 11 of 357 (3,1%), 13 of 355 (3,7)%, 7 of 128 (5,5%) in SRT, SRT-delay and LRT-delay. Incidence of DM was 88 of 257 (24,7%), 82 of 355 (23,1%), 38 of 128 (29,7%). The median OS was 8.14 (7.23-9.98), 10.18 (8.45-11.68) 10,53 (6.95-11.34) years in SRT, SRT-delay and LRT-delay without statistical differences between the groups, log-rank SRT vs. SRT-delay $p=0.162$ (short course RT comparison), SRT vs. LRT-delay $p=0.738$ (three armed randomisation).

In conclusion, we found no statistical differences between the arms regarding oncological outcomes (LR, DM, OS, RFS). SRT-delay is an alternative with less post-operative complications and higher possibility of pCR compared to SRT. LRT-delay demands more RT-resources without any other obvious gain.

List of scientific papers

- I. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial**
J. Erlandsson, T. Holm, D. Pettersson, Å. Berglund, B. Cedermark, C. Radu, H. Johansson, M. Machado, F. Hjern, O. Hallböök, I. Syk, B. Glimelius, A. Martling
The Lancet Oncology
2017;18; 336-346
- II. Postoperative complications in relation to overall treatment time after neo-adjuvant radiotherapy in patients with rectal cancer**
J. Erlandsson, D. Pettersson, B. Glimelius, T. Holm, A. Martling
British Journal of Surgery
Accepted for publication March 2019, In press.
DOI:10.1002/bjs.11200
- III. Tumour regression after radiotherapy for rectal cancer – Results from the randomised Stockholm III trial**
J. Erlandsson, E. Lörinc, M. Ahlberg, D. Pettersson, T. Holm, B. Glimelius, A. Martling
Radiotherapy and Oncology
2019;135;178-186
- IV. Long term outcomes in the Stockholm III trial on different radiotherapy regimens for rectal cancer**
J. Erlandsson, S. Fuentes, T. Holm, B. Glimelius, A. Martling
Manuscript

List of abbreviations

AJCC	American joint committee on cancer
APE	Abdominoperineal excision
AR	Anterior resection
ASA	American Society of Anaesthesiologists
CI	Confidence interval
CT	Computed tomography
CRM	Circumferential resection margin
CRC	Colorectal cancer
CRT	Chemoradiotherapy
DFS	Disease-free survival
DM	Distant metastases
eCRF	Electronic clinical registration form
ELAPE	Extralevator abdominoperineal resection
EMVI	Extramural vascular invasion
ESMO	European society of medical oncology
Gy	Gray
GI	Gastrointestinal
HR	Hazard ratio
KM	Kaplan-Meier
LR	Local recurrence
LRT	Long course radiotherapy
LET	Linear energy transfer
MDT	Multidisciplinary team conference
MRF	Mesorectal fascia
MRI	Magnetic resonance imaging
OR	Odds ratio
OTT	Overall treatment time
OS	Overall survival
PN	Perineural invasion
RC	Rectal cancer
RFS	Recurrence/relapse free survival
RT	Radiotherapy
SCRCR	Swedish colorectal cancer registry

SDI	Sociodemographic index
TEM	Transanal endoscopic microsurgery
TNM	Tumour Node Metastasis
TME	Total mesorectal excision
TRG	Tumour regression grade
TTR	Time to recurrence
QoL	Quality of Life
W&W	Watch and wait

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Background

Epidemiology

Colorectal cancer (CRC) is the second most common cancer in Sweden in both females and males and more than 6000 individuals are diagnosed yearly. Rectal cancer (RC) accounts for about one third of the cases corresponding to an incidence of about 19.9 and 27.6 / 100 000 persons in women and men respectively. The mortality rate has been stable around 5 and 10 /100 000 persons in women and men respectively.^{1,2} Globally, it is the third most common cancer after bronchus/lung- and breast cancer. Yearly about 1.7 million new cases are diagnosed worldwide. There is a variation in incidence depending on sociodemographic index (SDI). Countries with the highest SDI has the highest incidence in contrast to countries in the lowest SDI-quintile, where CRC is the eighth most common cancer.³ Data from the GLOBOCAN database have been analysed in terms of CRC by Arnold et al.⁴ Globally three different patterns of incidence and mortality were observed. Increases in both mortality and incidence were seen in some countries in Eastern Europe, Latin America and Asia. In the Northern European countries, UK, Netherlands, Canada and a few more countries there was an increase in incidence but a decline in mortality. A third group was countries with a decline in both incidence and mortality such as the US, New Zealand, Australia and Iceland. The different patterns are highly correlated to the human development index (HDI), see Figure 1 for details. In Sweden, the incidence and mortality have been more or less stable for the last 15 years.² The reduction of mortality may in some countries be an effect of the implementation of guidelines and thereby optimising the treatment for CRC. The introduction of screening programs might explain the decline in some countries. The increase in incidence is probably related to changes in life style factors in countries with lower HDI.

Risk factors

It has been proposed that the attributable risk of dietary factors on CRC are almost 50 %.⁵ Many life style factors and dietary habits have been explored with the ambition to explain the causes of CRC.⁶ Smoking is clearly associated with CRC and the correlation might be stronger in rectal than

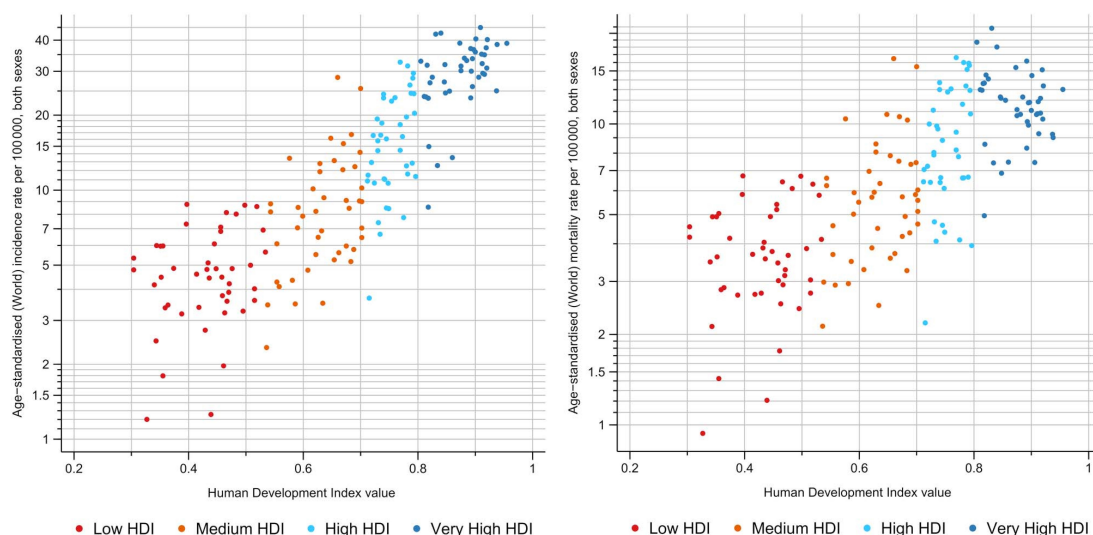


Figure 1. Age-standardised incidence and mortality rate of colorectal cancer by human development index (HDI). Reprint with permission from Arnold et al.⁴

in colon cancer.^{7,8} Both high weight and high Body Mass Index (BMI) are linked to risk for CRC.⁹ Alcohol consumption show a dose-response relationship in the aspect of developing both colorectal adenomas and CRC.^{10,11} High intake of red or processed meat is significantly associated with a higher risk of CRC. However, the association seems stronger for cancers in the colon rather than in the rectum.^{12,13} High intake of milk products have shown to be protective, but the association is weak and it is not clear which nutrients, i.e lactose, vitamin D or dietary calcium, that would be responsible for the risk reduction.^{12,14-16} Other protective factors might be high intake of dietary fibres, although the ideal source of fibre is not determined.¹⁷ High physical activity has been shown to reduce the risk for colon cancer, but the effect on RC is not as convincing.^{18,19} Further, a meta-analysis concluded that physical activity results in better CRC related survival. However, the included studies had different definitions of physical activity and the optimal cut-off level was not determined.²⁰

Inflammatory bowel disease, both Crohn's and ulcerative colitis are well known risk factors for developing CRC.^{21,22} A considerably increased risk for gastrointestinal (GI) cancer is seen in patients with onset of disease in childhood. Hazard ratio (HR) (95 % confidence interval (CI)) 18 (14.4-22.7).²³

Hereditary risk

In about 5% of the patients with CRC, a specific genetic mutation is found. However, for individual patients with inherited tumour syndromes, there is a substantial risk of developing CRC with a life time probability of 50-100%, depending on type of syndrome.²⁴ The hereditary CRC syndromes are divided into polyposis or nonpolyposis syndromes based on the number and histology of polyps in the bowel. Familial adenomatous polyposis (FAP) is recognized by a large amount of polyps throughout the colon, with a high risk of CRC. Up to 1/3 of FAP cases are de novo mutations, otherwise FAP is an autosomal dominant inherited mutation with a 100 % penetration by the age of 40.²⁵ Other polyposis syndromes include Peutz-Jegher and juvenile polyposis, among others. The main proportion of nonpolyposis CRC are patients with Lynch syndrome with a life time risk of CRC of about 50 %.

Swedish ColoRectal Cancer Registry

In 1995 the Swedish Rectal Cancer Registry was founded. After a merge with the Swedish Colon Cancer Registry in 2007 there has been one registry, the Swedish ColoRectal Cancer Registry (SCRCR). All registry data are recorded prospectively by the surgeons, pathologists and oncologists responsible for the patient. All CRC are reported, except for autopsy findings. The national coverage is estimated to be >97 %.²⁶ Recorded data include basic patient characteristics, preoperative tumour data (since 2007), neo-adjuvant therapy, type of surgery, post-operative complications, pathology report and adjuvant treatment. Recurrence data and long-term toxicity are reported at one, three and five years after surgery. Data on survival are linked to the Swedish population registry. The SCRCR has been validated at several times.²⁶⁻²⁸ In the latest validation, the agreement between registry data and medical charts was 90 % on average.²⁸ The post-operative course was the least valid parameter with only about 63 % agreement. Although, high ratio of correct values, some variables have a large amount of missing data, especially preoperative staging.

Anatomy

The rectum is the most distal part of gastrointestinal tract. The dentate line demarks the transition of columnar glandular epithelium of the bowel to the squamous epithelium of the anal canal. At present, cancers with a distal extension ≤ 15 cm from the anal verge (measured by rigid sigmoidoscopy) are considered as RC according to the European Society of Medical Oncology (ESMO)-guidelines and the Swedish national care programme.^{29,30} The definition has somewhat varied over time and potential important differences exist in the inclusion criteria in influential trials, both regarding height in cm and measurement technique. For instance, in the Swedish Rectal Cancer Trial the definition was “below the sacral promontory, as shown on lateral projection on barium enema”.³¹ The Dutch TME trial and the German CAO/ARO/AIO-04 trial included patients with tumours with a height limit of ≤ 12 cm, but another German trial had the cut-off level at ≤ 16 cm.³²⁻³⁴ A more anatomical definition is used by the American Joint Committee on Cancer (AJCC) which states “Approximately 12 cm in length, the rectum extends from the fusion of the taenia to the puborectalis ring.”³⁵ One problem of using a fixed cm measurements is that the individual length and distance from anal verge to anatomical landmarks varies in relation to BMI, age, gender and weight.³⁶ The rectum lies infra peritoneally, with the lowest peritoneal reflection in the anterior aspect, the pouch of Douglas. Below this level, between the rectum and the posterior vaginal wall or prostate in female and male respectively the Denonvilliers’ fascia is found. The exact embryonal origin is undetermined and the optimal dissection plane in this area is also somewhat debated. If dissection is performed anterior of the fascia there is a risk of nerve injury, but it is of uttermost importance to dissect in front of the perirectal fascia.³⁷ The rectum is covered with a fatty envelope containing vessels for arterial supply, venous and lymphatic drainage together with lymph nodes. This is today known as the mesorectum. A term introduced by Heald when he introduced the “total mesorectal excision” (TME) in 1982.³⁸ Whether the mesorectum really is a true mesentery of the rectum or not has been questioned, but the surgical terminology of a mesorectum remains unthreatened.³⁹ The mesorectum is covered with the endopelvic fascia or the mesorectal fascia (MRF).

The main arterial blood supply comes from the superior rectal artery (SRA) – the end branch of the inferior mesenteric artery (IMA), and the inferior rectal artery (IRA) –branch from the internal iliac arteries. With highly reported differences in frequency (12-97 %) the middle rectal artery (MRA) – which arises directly from the internal iliac arteries, also supplies the rectum.⁴⁰ Lymphatic drainage follows the arteries. Understanding of lymphatic drainage is of most importance since cancer spread through lymph nodes and vessels is a major cause of treatment failure in RC.⁴¹

Clinical presentation

The median age to be diagnosed with RC is about 70 years. Less than 5 % of patients are younger than 50 years.⁴² However, recent data suggests that CRC in the younger population is increasing around the world.^{43,44} Initial symptoms of include local signs in form of rectal bleeding or mucinous discharge and/or pain, change of stool habits, or faecal incontinence. General symptoms may include abdominal pain or discomfort, weight loss, fatigue and anaemia. In case of distant metastases other adjacent symptoms may occur. In a modern European patient cohort, about 22-26 per cent of patients have metastatic disease at time of diagnosis.⁴⁵ Acute symptoms at time of diagnosis, such as bowel obstruction or perforation are seen in up to 15 % of patients with RC.

The frequency is probably higher in colon cancer. Patients requiring emergency interventions have a poorer outcome.^{46,47} With increasing implementation of screening programs a larger proportions of patients will be diagnosed with earlier tumours and with less symptoms.⁴⁸

When RC is suspected a digital rectal examination should be performed to assess the size and mobility of the tumour, and to describe the relationship to other pelvic structures. A biopsy is needed to confirm invasive adenocarcinoma. Although rare, other malignancies might be found in the rectum, such as neuroendocrine tumours, sarcomas, lymphomas, melanomas or metastases from other organs.⁴⁹ Anal cancer is a type of squamous cell carcinoma with growth in and around the anal canal and can in some cases present as a rectal mass. A rigid sigmoidoscopy should be performed to further assess the tumour and to measure the distance from the anal verge and to classify the tumour in to low (0-5 cm), middle (6-10 cm) or high (11-15 cm).²⁹ This subgrouping guides the further decisions regarding treatment. In addition, a complete investigation of the colon with colonoscopy or CT colonoscopy is warranted since synchronous tumours are reported in 5-10 %, a missed second cancer requires additional surgery and might affect long-term outcomes.⁵⁰

Table 1 TNM-classification of colorectal cancer, 8th edition.

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

Adapted from from Amin et al.³⁵

Staging of rectal cancer

RC should be staged according to the TNM classification system, T-tumour, N-node and M-metastases. Staging is performed preoperatively to be able to choose the optimal treatment for the individual patient. The preoperative staging is summarized in a “clinical stage” indicated with *c* in front of TNM stage, i.e. *cT2N1M0*. Post-operative (pathology graded) stage has a strong prognostic value and is used for risk stratification and to guide decisions on adjuvant treatment. The pathology stage is indicated with the prefix *p*, i.e. *pT3bN1M0*. If neo-adjuvant therapy has been given, an *y* is used in front of the *p*. The TNM system is revised by AJCC and Union for International Cancer Control. The 8th edition was released in December 2016.³⁵ The 7th edition is recommended in Swedish National Programme. The differences between the 7th and 8th editions are small regarding RC.⁵¹ Important changes include; in situ tumours (Tis) are referred to as intramucosal adenocarcinoma, T and N categories have not changed but isolated tumour cells <20 cells in lymph nodes should be considered as N0, and micro metastases (>20 cells or size of >0.2 < 2 mm) are N1.⁵² The TNM-system is designed for postoperative staging, but are used also for preoperative cStage. However, no preoperative method can categorize patients with the same high resolution as the histopathological examination (Table 1).

T-stage

The invasion depth of the cancer tumour into the bowel wall decides the T-stage. The patient’s prognosis is worse with higher T-stage.^{53,54} In Figure 2, T1 to T3 are illustrated. T4 tumours are invading through the bowel wall and can be subtyped in T4a – only growth through the serosa, and T4b, growth into other organs.

N-stage

The number of metastatic lymph nodes is the base for the N-classification. Only regional lymph nodes are considered when deciding N-stage, metastatic nodes in other regions are seen as distance metastases. In RC, the regional nodes are perirectal, along the sigmoid/inferior mesenteric arteries, in the pre- and lateral sacral spaces, along the internal iliac artery, around the sacral promontory, and along the rectal arteries. Tumour deposits are foci of metastatic disease in the perirectal fat. They may represent discontinuous spread or venous invasion with extravascular spread or a metastatic lymph node destroyed beyond all recognition by tumour growth. These deposits are classified as N-stage disease (N1c).

M-stage

The M-stage describes the presence of distant spread of the tumour to other organs, peritoneal cavity or extra regional lymph nodes.

Preoperative staging

The preoperative investigations focus at three areas. The local growth of the tumour, the nodal spread and metastatic situation.

Tumour and nodal assessment

In the Western world magnetic resonance imaging (MRI) assessment of RC is mandatory and the treatment decisions are highly affected by the result. The use of MRI has been introduced as a

standard of care since the early 2000s, when it could be shown that the MRI-staging had a high correlation with the pathology assessment.⁵⁵ MRI can accurately stage both T- and N-stage. Nodal assessment and the subsequent staging is based on the number of nodes suspicious for malignancy. The shape, rather than the size, combined with irregular borders and a mixed signal intensity is indicative of metastatic nodes.⁵⁶ Other important clinical findings that can be assessed are the relationship to the MRF, which corresponds to the future resection plane, or the circumferential resection margin (CRM). A positive or threatened mri-MRF is considered in most guidelines to be an indication of chemoradiotherapy (CRT). Extramural vein invasion (EMVI) has been stressed to be a significant risk factor by the Royal Marsden group. EMVI+ patients had odds ratio (OR) (95 % CI) 5.68 (3.75-8.61) and 3.91 (2.61-5.86) of having synchronous or developing distant metastases after surgery, respectively.⁵⁷ MRI have been considered to have a higher predictive value regarding CRM and T-stage compared to N-stage in a review and meta-analysis from 2012.⁵⁸

Metastases

Computed tomography (CT) of the thorax and abdomen, including the pelvis is used mainly to detect metastatic disease. The possibility of detecting hepatic metastases is good, with high sensitivity and specificity using CT-scan.⁵⁹ A focused MRI of the liver might be used when lesions cannot be categorized by CT-scan, due to the higher specificity.⁶⁰ Pulmonary metastases are harder to diagnose, and figures of 4-42 % of pulmonary lesions cannot get a final diagnosis, and only 25 % of lesions found on chest CT turn out to be metastases.^{61,62}

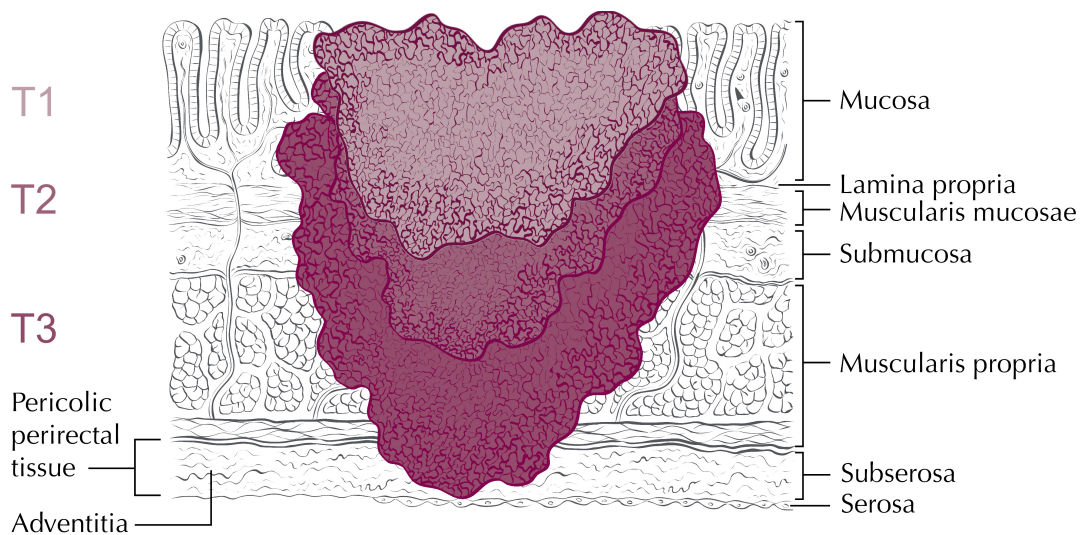


Figure 2. Illustration of tumour invasion depth (T) stage 1-3 according to international TNM-classification. Reprint (modified) with permission from AJCC cancer staging atlas.⁵¹

Post-operative staging

The pathology assessment of the surgical specimen is the foundation of the postoperative staging. The (y)p Stage, based on T- and N- stages is presented in Table 2. Other parameters that should be reported are tumour infiltration in vessels, nerves, the distance to the CRM and differentiation of the tumour.

Characteristic	Stage
Tis N0 M0	0
T1-2 N0 M0	I
T3 N0 M0	IIA
T4a N0 M0	IIB
T4b N0 M0	IIC
T1-2 N1 M0 / T1 N2a M0	IIIA
T3-4a N1 M0 / T2-3 N2a M0 / T1-2 N2b M0	IIIB
T4a N2a M0 / T3-4a N2b M0 / T4b N1-2 M0	IIIC
Any T Any N M1a	IVA
Any T Any N M1b	IVB
Adapted from Amin et al. ³⁵	

Positive venous invasion, V0/1, and especially extramural venous invasion, EMVI +/- is associated with poorer outcomes regarding survival and distant metastases, and patients with the latter have been reported to have similar outcomes as ypStage III tumours.⁶³ Tumour infiltration of the lymphatic vessels, L 0/1, might predict future lymph node metastases, but in RC the association is weaker than in colon cancer.⁶⁴ Perineural invasion (PN) has been defined as tumour growth in, around and through peripheral nerves.⁶⁵ The definition is however somewhat debated and subsequently the diagnosis might not be totally comparable between studies. Albeit, PN+ has been reported as an independent bad prognostic factor, also in patients who had neo adjuvant therapy.^{66,67}

Resection margins

An involvement of the CRM after RC surgery is a strong risk factor for local recurrence (LR). Quirke et al. analysed 52 specimens and found that in patients with involved CRM the LR incidence was 85 %.⁶⁸ This association has later been confirmed in other studies.⁶⁹ Today, a positive CRM is often defined as a margin of ≤ 1 mm. An assessment of the quality of the TME-specimen in regards of the MRF has been proposed to be a part of the standard pathology report. By categorizing the plane of surgery into three levels based on a macroscopic evaluation Quirke et al. showed that the quality of surgery predicts LR.⁷⁰ Further, an incomplete TME is also associated with higher rates of distant metastases (DM).⁷¹ Spread of RC proximal and distally is also possible, the proximal resection margin is seldom a problem since the bowel is resected at least at the level of the arterial ligation. The distal margin should be at least 1-2 cm in low – middle RCs under the condition that a complete TME is performed. In high RC, a partial TME might be performed and then 5 cm margin is required.^{72,73}

Grading of differentiation

It has been known for decades that oncological outcomes are associated with the grade of differentiation in CRC.⁷⁴⁻⁷⁶ Previous commonly used classifications included well-moderate-poor differentiation. Due to high interobserver variability a two tier classification was recommended from the WHO, high-grade- vs- low-grade cancer with a cut off level at 50 % glandular formations.^{77,78} Other differentiation patterns include the mucinous type, defined by > 50% extracellular mucin. The signet ring cell adenocarcinoma is rare (<1 % of RC) and has a poorer prognosis.⁷⁹ Finally, an extremely rare type is the medullary cancer with an estimated incidence of 5-8 cases / 10 00 CRC.⁸⁰

Residual tumour

Classification of the residual tumour status (R) is important since it strongly correlates with LR, DM and survival.⁸¹ The classification is R0 – no residual tumour, R1 – Microscopic residual tumour, R 2 – Macroscopic residual tumour.

Tumour regression grading

There are several different grading systems for assessing tumour regression after neo-adjuvant (C)RT in patients with RC, (Table 3). They have been adapted and modified from a system initially described for upper GI-cancers. Mandard et. al. found that the tumour regression grade (TRG) was a significant predictor of disease free survival (DFS) in 93 patients with oesophageal cancer.⁸² Dworak et. al. proposed a 5 tier system in RC, which has been commonly used.⁸³ Ryan et. al introduced a three-tier system. This grading system was considered to be more reproducible than the 5- tier system, advocated by others.⁸⁴ Vecchio et. al found that TRG according to Mandard predicted overall survival (OS) and DFS and the “TRG-system” was used by some authors.⁸⁵ Other systems, such as the 3 tier Rectal Cancer Regression Grade and its modified version (m-RCRG) system have also been used.^{86,87} AJCC later adopted a 4-tier system.³⁵ In one comparison, none of the commonly used regression grading systems predicts recurrence free survival (RFS) or OS better than the standard ypStage.⁸⁸ One major issue with all the regression grading systems is that the interobserver variation is high. It has been reported κ -scores of 0.72-0.74 for the TRG and mRCRG systems between two observers.⁸⁶ In other settings the κ -scores for Mandard, Dworak and mRCRG were 0.28, 0.35 and 0.38 respectively.⁸⁹

Downstaging of the tumour and high grade regression are associated with improved oncological outcomes in many series but outcomes after a near-complete response are conflicting.⁹⁰⁻⁹⁵ Another issue that most of the regression grading systems only focuses on the downstaging of the tumour and no formal assessment of metastatic lymph-nodes is done. This has been suggested to be important by some authors that found lymph node regression grade to be a prognostic determinant.⁹⁶ Other studies found that a pathologically grade complete response (pCR) only is beneficial in patients with cStage III disease.⁹⁷

	Dworak⁸³	AJCC³⁵	Mandard⁸²	Ryan⁸⁴
No regression	No regression (TRG 0)	-	Absence of regressive change (TRG 5)	-
Minimal	Dominant tumour mass with obvious fibrosis and/or vasculopathy (TRG 1)	Minimal or no tumour cells killed (TRG 3: poor response)	Residual cancer outgrowing fibrosis (TRG 4)	Significant fibrosis outgrown by cancer, or no fibrosis with extensive residual cancer (TRG 3)
Moderate	Dominantly fibrotic changes with few tumour cells or groups (TRG 2)	Residual cancer outgrown by fibrosis (TRG 2: minimal response)	Fibrosis outgrowing residual cancer (TRG 3)	Residual cancer outgrown by fibrosis (TRG 2)
Near complete	Very few tumour cells in fibrotic tissue with or without mucous substance (TRG 3)	Single or small groups of tumour cells (TRG 1: moderate response)	Rare residual cancer cells (TRG 2)	-
Complete	No tumour cells, only fibrosis (TRG 4)	No viable cancer cells (TRG 0)	No residual cancer (TRG 1)	No viable cancer cells, or single cells, or small groups of cancer cells (TRG 1)

MDT-conference

The multidisciplinary team conference (MDT) gathers all specialties involved in the care of the patient with RC. Typically, team members are colorectal surgeons, radiologists, oncologist, pathologists and specialized nurses. Patients are often discussed both pre- and postoperatively, or during treatment, i.e if an evaluating MRI is performed during neo-adjuvant treatment. The aim of the MDT-conference is to improve the care and outcomes of the patients. With increasing knowledge of treatments of RC, it is impossible for the single clinician to be up to date in all subspecialties in the chain of care. In Sweden it is mandatory according to the National guidelines to discuss patients with CRC in a MDT-conference. The introduction of MDT-boards has probably resulted in better preoperative staging and better adherence to guidelines. No improved hard outcomes, such as OS or DFS have been proven in studies. However, patients discussed at MDT boards had more MRI performed, more complete staging and fewer CRM-positive resections.⁹⁸⁻¹⁰⁰

Stratified neo-adjuvant treatment

Treatment recommendations or decisions from the MDT-board are in many cases based on a risk stratification from the perspective of LR. This is natural since LR historically has been the main issue in patients with RC. In Sweden, for the last two decades patients' tumours have been stratified in to three risk groups, the good, the bad and the ugly.¹⁰¹ Still today, this is the basis for the selection of preoperative treatment, (Figure 3). Some extensions have been made, especially regarding patients with mriEMVI+, that are considered to be at high risk and should be given radiotherapy (RT).¹⁰² In the recent ESMO-guidelines tumours are categorized in five groups instead, RT is reserved for patients with "bad"- tumours or worse, under the condition that LR rates are $\leq 5\%$.²⁹ In Japan CRT is reserved for low-medium tumours deemed unresectable, otherwise lateral node dissection is more commonly used.¹⁰³ In the US, the NCCN-guideline strongly advocate CRT to all patients except T1-T2 N0 tumours.¹⁰⁴

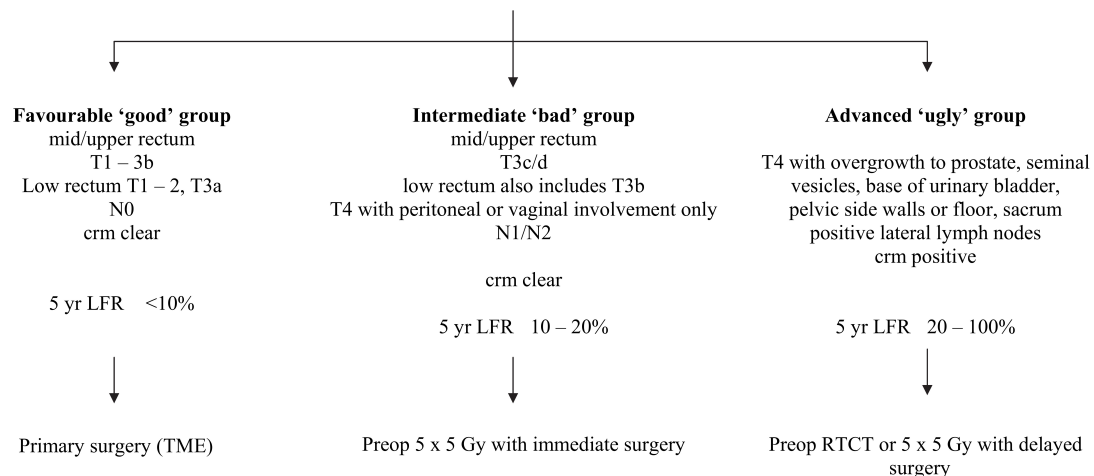


Figure 3. MRI-based stratification of neo-adjuvant treatment according to Blomqvist & Glimelius. Reprint with permission.¹⁰¹

Radiotherapy

The definition of radiation is the transmission of energy in the form of waves or particles through space or in a medium. Particles includes protons, electrons, ions (like carbon) and pions. In clinical RT, electromagnetic radiation is used. The carrier of the radiation is the photon, which not is considered a particle. Radiation can be either ionizing or non-ionizing. The energy level of the particles decides the effect. Ionizing radiation has the ability (enough energy) to break chemical bonds and ionize atoms and molecule, directly or indirect. The effect on human tissue depends on the type of radiation and exposed tissue. The linear energy transfer (LET) is the amount of energy a particle deposits in local ionizations per unit path length (measured in keV/ μm), i.e the amount of damage in the track of the particle. The biological effect in tissue is naturally a result of the LET level. High LET radiation types are neutrons, protons and heavy charged particles. Low LET types are for instance X-ray and gamma radiation. The absorbed radiation dose is expressed in Gray (Gy) which is equal to joules/kg.¹⁰⁵

The energy deposited in the tissue leads to ionization, with the subsequent conversion of free radicals from atoms and molecules. The radiation induces several molecular signalling pathways in the cells and tissues including DNA-repair, cell cycle arrest, apoptosis, proliferation, inflammation and fibrosis. These steps are the response to the RT and the effect is that irradiated cells are killed and replaced with scar tissue. The effect may be direct or indirect. Ionizing effect on DNA or cell membrane will lead to a direct effect. Other effects include the inability of mitosis. The effect of RT is highest when the cell is in the proliferation cycle, especially during mitosis. Thus, tissues with high proliferation rate are more sensitive to RT. Malignant tumours are characterized by a rapid growth, and are theoretically more sensitive to RT.

Cell death is usually defined as loss of “clonogenic” capability, i.e the ability to reproduce. Cells with damaged DNA may however divide and grow for some time before the cell division capability stops. There are different patterns of cell death after RT. Necrosis, where the death is uncontrolled and highly inflammatory. When cells are programmed to die it is called apoptosis and the cells breaks down in a controlled manner without inducing any inflammation. Certain radiosensitive cancer forms respond with a lot of apoptosis, e.g. lymphomas and neuroblastomas. Another form of cell death is the “mitotic catastrophe” which occurs when cells cannot segregate their chromosomes during mitosis. The DNA-damage is not lethal until mitosis takes place, and this is one reason why tumour regression sometimes takes several days or weeks after end of RT.

Fractionation of RT is in most cases biologically superior to single-fraction RT. Four R's have classically been used to describe the biology of fractionation. Repair – normal tissue must repair the DNA-damage, which takes time. Reoxygenation – the tumours need to re-oxygenate, central parts of the tumour might have impaired blood flow. Redistribution – the cells must have time to move forward in the cell cycle in order for RT to have the best effect. Repopulation – Cells repopulation varies during RT, a kick-off time is often described at a certain point when repopulations accelerates. Also normal tissues must have time to repopulate. A fifth R can also be used, “Radio sensitivity”. A common model to describe cell death clinically is the Linear-Quadratic model.

$$SF_D = e^{-(\alpha D + \beta D^2)}$$

SF = surviving fraction, D = dose, α = the unreparable damage, independent of fraction and dose rate. β = the repairable damage, dependent on dose and fractionation.

The α/β ratio differs between tissues. Low ratio tissues have high abilities to repair, in contrast to tissues with low repair abilities (high α/β ratio). The former is relatively resistant to small fractions and the latter is sensitive to small fractions, (Figure 4 A). The knowledge of different ratios is important to decide the optimal fractionation. Typical high α/β tissues are most tumours. Most normal tissues have a low α/β ratio. With the knowledge of α and β values the biologically effective dose (BED) can be calculated and it's possible to compare different RT-schedules. It is also possible to estimate what doses that are accepted in tissues and organs surrounding the tumour or target. The difference between the “tumour control probability” (TCP) and the normal tissue complication probability (NTCP) can be referred to as a therapeutic window, (Figure 4B). Based on the reason above, it is logic to fractionate RT. Tumours take more damage than surrounding cells. Different tumours have different ratios, breast and prostate cancer are considered low α/β tumours. The α/β ratio and BED of different RT-schedules are in RC somewhat debated.¹⁰⁶ Analysing retrospective data have proven to be difficult due to different fractionation schedules and overall treatment time (OTT). It has been suggested that RC has values closer to prostate cancer which also is a adenocarcinoma.¹⁰⁷ An α/β of 10 Gy has been used, initially derived from head neck cancers (squamous cell carcinoma).^{108,109} One study concluded that RC probably has a “moderately low α/β ratio”.¹¹⁰

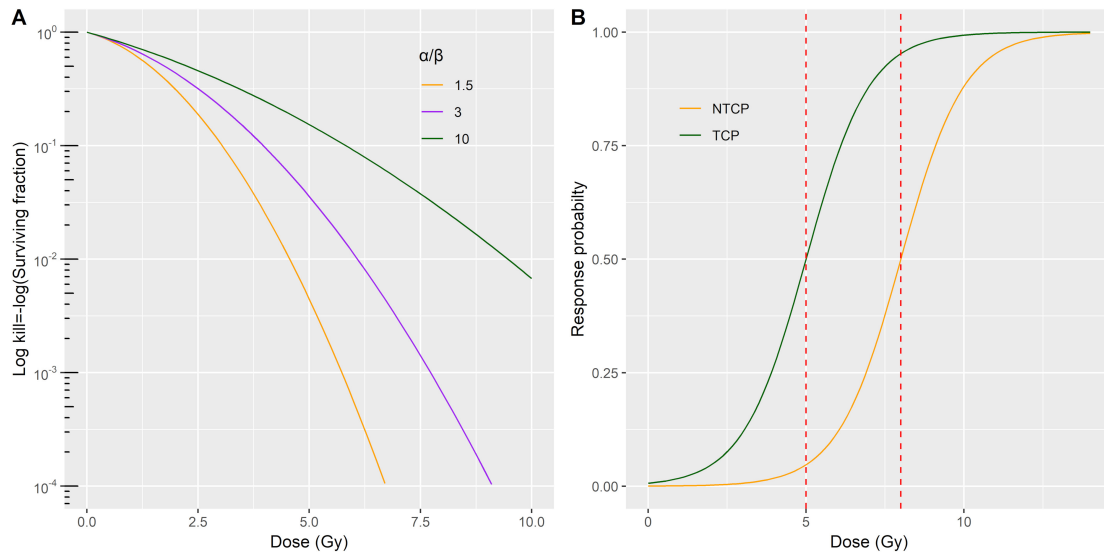


Figure 4. Relationship between cell death and dose. A) Surviving fraction of cells in three hypothetical tissues with different α/β ratios. B) The relationship between tumour control and normal tissue. NTCP-normal tissue complication probability, TCP – tumour control probability.

Radiotherapy in rectal cancer

Today, the aim of RT in RC is to reduce the number of LR. During the years, many RT regimens with different schedules of fractionation have been used. At present, two different courses are dominating. Either a conventionally fractionated long-course of 1.8-2 Gy x 25-28 with delayed

surgery (LRT-delay), most often combined with chemotherapy (CRT). An alternative is a short course, 5 Gy x 5 (SRT). In the European countries, neo-adjuvant RT is most commonly used.

More than 60 % of Swedish patients with RC were treated with neo-adjuvant RT in 2015, with a registered national variation of 26-92 %.¹¹¹ The use of RT also varies around the globe, and even in the Nordic countries.^{112,113} In the US neo-adjuvant CRT is the dominant therapy.¹¹⁴ Although widely used and well-studied, the optimal fractionation or timing of surgery is not agreed upon.¹¹⁵

Fractionation and timing of surgery

Attempts to treat or palliate patients with RC with irradiating radium sources trace back at least to the early 1900s with reports on tumour regression and turning inresectable tumours available for surgery.^{116,117} Initial experiences from RT in squamous cell carcinomas were explored in RC. Initially, adenocarcinomas of the rectum were considered to be radio resistant. Later it was found that the tumour regression takes longer time and a complete regression can occur up to 3 months after RT.¹¹⁸

The first randomised trials that could show fewer LR after preoperative RT enrolled patients in the late 1970s and early -80s.^{119,120} The rationale of using preoperative RT instead of postoperatively is based on results from several trials. The Uppsala trial randomly assigned patients to preoperative SRT or postoperative 2 Gy x 30 and it was stated that preoperative RT was better tolerated and more effective.¹²¹⁻¹²³ Later, the Stockholm I trial showed a reduction of LR from 28% to 14 % after pre-operative short course RT (SRT) and immediate surgery, however at the price of an increased postoperative mortality.¹²⁴ The radiation was delivered in a suboptimal way and with a large target area, compared with current guidelines.³⁰ The Swedish Rectal Cancer Trial and the Stockholm II trial showed, apart from a decrease in LR, a survival benefit for patients that received preoperative SRT compared surgery alone.^{31,125,126} The Dutch TME-trial randomised patients between preoperative SRT and surgery within one week or surgery alone, simultaneously as the TME-concept was introduced and formally trained. The cumulative incidence of LR was 11 % in the non-irradiated group and 5% after pre-op RT. Thereby confirming that RT approximately halves the proportion of LR, even from low numbers after optimised surgical technique.¹²⁷

In a systematic overview published in 2001 it was concluded that preoperative RT reduces the risk of LR and death from RC.¹²⁸ However, one potential disadvantage with pre-operative treatment is that all patients are treated. When RT is delivered post-operatively instead, only patients considered to be at high risk for LR can be offered treatment. In the MRC-CR07 trial patients were randomised to preoperative SRT or to selective post-operative CRT if the circumferential resection margin was involved. The results, after a median follow up of 4 years were that the preoperative SRT group had a 61 % reduction of LR, an improvement of DFS but not in OS. HR OS 0.91 (0.73-1.13), p=0.40.¹²⁹ A German trial concluded that preoperative CRT gave less toxicity and better local control compared to postoperative CRT.³³ After a follow up of minimum 11 years of the same trial, LR rates were still significantly lower after preoperative CRT, 7.1 % vs 10.1 %, but no differences in distant failure or DFS.¹³⁰

LRT-delay and CRT

LRT-delay has been used for several years. Three trials have proven better local control with the addition of concomitant chemotherapy, compared to RT alone, but without survival benefit, except for locally advanced cancers.¹³¹⁻¹³³ Based on these trials, LRT-delay is practically abandoned in favour of CRT. 5-fluorouracil or per oral capecetabine is often used as the adjuvant chemo and is likely equal, but capecetabine is more convenient.¹³⁴ An additional boost of 5.4 Gy delivered in 3 fractions may be used in some settings, with the ambition to assure R0 resection.¹³⁵ The addition of chemotherapy increases the treatment toxicity, and could even influence the mortality. In one meta-analysis the HR for toxicity related mortality was HR 2.86 (0.99-8.26).¹³⁶ The addition of further cytotoxic agents such as oxaliplatin have been explored in several trials, but without convincing beneficial results. Two meta-analyses concluded decreased risk for DM but without any improvement of DFS or OS.^{137,138}

Short course radiotherapy

The SRT was introduced as an option to postoperative conventionally fractionated LRT, with possible practical gains.¹³⁹ The standard SRT-course is 5 Gy x 5 delivered Mon-Fri and surgery early in the following week. The SRT-course has been explored in several trials, mentioned above. The effect on LR has also been confirmed outside the randomised trials and there is a tendency of improved survival in low tumours.¹⁴⁰ Later, two trials have randomised patients to CRT or SRT in patients with T3/T4 resectable cancers, with similar study protocols. Both the trials concluded that SRT with immediate surgery are not significantly different from CRT with respect of DFS, OS or rate of LR, but with more acute adverse events in the CRT group.¹⁴¹⁻¹⁴³

The optimal time interval within the first week is however debated. In a subgroup analysis from the Dutch TME-trial elderly patients (>75 years) were found to have worse survival if operated on 4-7 days after last RT, compared to having surgery performed 0-3 days after RT.¹⁴⁴ In part, this might be explained by an impaired leukocyte response, or even a drop in leukocyte count, seen around 5 days after the last given RT fraction. This was found in retrospective studies of the Stockholm I-II trials, and also in an interim analysis of the Stockholm III.^{145,146} Other studies found a correlation between overall post-operative complications and low leukocyte ratio in the 2 first days after surgery, in irradiated patients.¹⁴⁷ However, a large Dutch registry based study analysed 2131 patients and concluded that there was a higher probability of anastomotic leaks (AL) in patients having surgery 0-3 days compared to 4-14 days after end of RT (10.1% vs 7.2 %, $p=0.018$).¹⁴⁸ In conclusion, the exact timing of surgery seems to matter in the early period, depending on the outcomes of interest.

SRT-delay

SRT-delay, 5x5 Gy and surgery 4-8 weeks after the last given fraction, was first introduced in patients not fit for CRT and the feasibility and safety have been evaluated in retrospective studies.¹⁴⁹⁻¹⁵¹ RT induced toxicity was seen in about 5-6 %, and the treatment option has been considered tolerable. Few prospective trials have explored SRT-delay, except for the Stockholm III trial. An interim analysis presented the results on feasibility in 2010.¹⁵² The patient inclusion continued and the results after, a minimum follow up of two years, were presented in 2017, as a

part of this doctoral thesis. The oncologic results were considered similar but with reduced number of postoperative complications when delaying surgery for 4-8 weeks after SRT.¹⁵³

Other studies exploring a delay after SRT include a retrospective study by Veenhof et al. who studied 108 patients, with surgery < 2 weeks or with a delay 6-8 weeks after RT. No statistical differences regarding oncological outcomes were found.¹⁵⁴ A small polish trial randomised patients between SRT with immediate surgery or a delay for 4-5 weeks. Tumour regression was seen after delayed surgery and patients with tumour regression had an improved 5-year OS.¹⁵⁵ A phase II trial concluded that the SRT-delay regimen was feasible and with acceptable toxicity.¹⁵⁶ A Japanese study compared outcomes from two centres that used a modified SRT-delay course (2.5 Gy x 2 x 5, with a concomitant radio sensitizer) or CRT. The results showed no statistical differences in RFS, OS or tumour regression.¹⁵⁷ A Lithuanian trial randomised 150 patients between SRT-delay and CRT. The conclusion was that OS did not differ significantly between the groups. However, the DFS was 59.1 % vs 75.1 % (p=0.022) favouring CRT.¹⁵⁸ A Turkish group conducted a retrospective study on 136 patients with immediate or delayed surgery with improved survival in SRT-delay.¹⁵⁹ A recent meta-analysis has pooled five of the studies mentioned above and concluded that surgery should be delayed for > 4weeks after SRT.¹⁶⁰ Notable is that the Stockholm III trial contributed with 712 of 1244 patients in the study, and patients in the other studies might not be totally comparable. In summary, the use of SRT-delay seems to have become an accepted alternative to SRT.¹⁶¹

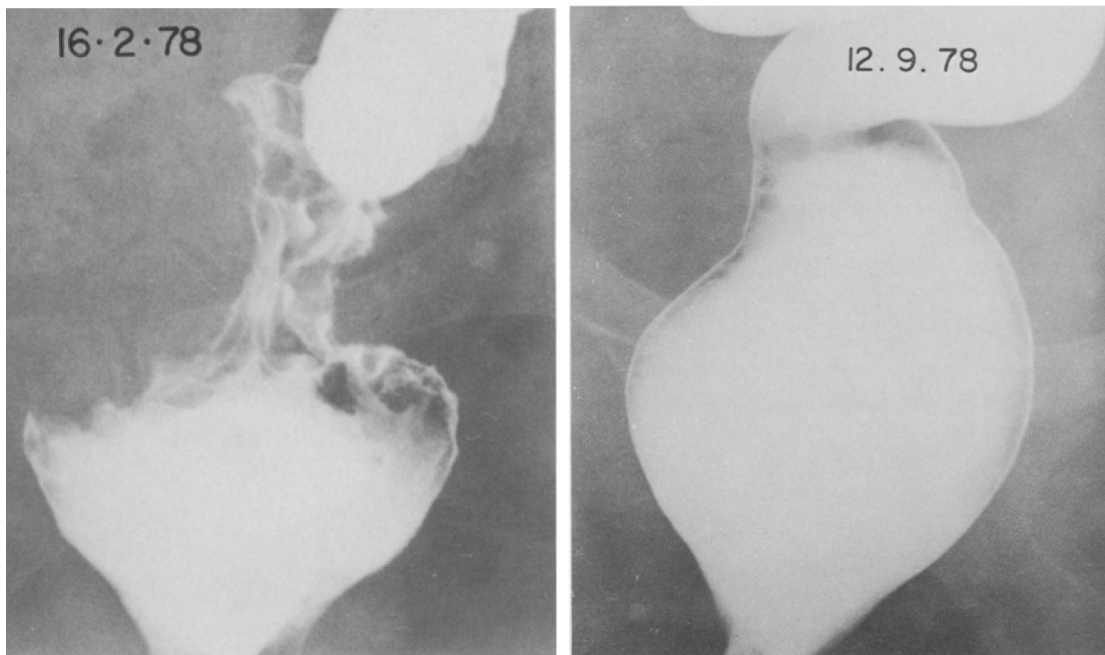


Figure 5. Complete tumour regression after seven months demonstrated by barium enema. Reprint with permission from Cummings et al.¹¹⁸

Tumour regression

RT induces cell death and a possible regression of the irradiated tumour. To achieve a pCR was previously considered to be without prognostic value.^{162,163} Today several studies have found an improved survival in patients with pCR. Whether this is a result of the tumour response per se, or an effect of a favourable tumour biology is not determined.^{164,165} The possibility of tumour regression and the correlation to the OTT has been known for decades, (Figure 5).¹¹⁸ However, considering pCR as an important outcome has more recently gained popularity and the optimal waiting time to achieve pCR has not been decided.

Tumour regression is enhanced by the addition of chemotherapy concomitant to a LRT-schedule.^{166 167} In a Swedish, Norwegian and Polish collaboration the pCR rates increased to 16 % from 7 % $p=0.04$, in patients that received LRT and fluorouracil /leuovorin, compared to LRT alone.¹³³ In a Dutch registry based study, about 15 % of patients achieved pCR if surgery was delayed for 10-11 weeks after CRT, corresponding to an OTT of more than 15 weeks, (Figure 6)¹⁶⁸ A meta-analysis on 13 studies concluded a pCR rate of almost 20 % compared to 14 % if surgery was delayed more than 6 –8 weeks.¹⁶⁹ Although the relationship graphically seems simple, i.e longer waiting time increases the likelihood of pCR, the correlation between pCR and OTT might be more complex. In the randomised French GRECCAR-6 trial the proportion of pCR after 7 weeks compared to 11 weeks after CRT was not statistically different.¹⁷⁰ Retrospective studies have found a similar pattern.¹⁷¹

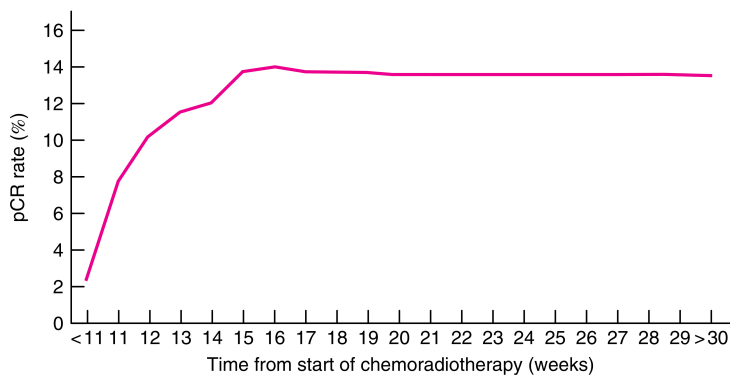


Figure 6. Cumulative complete response rate in 2203 patients after CRT. Reprint with permission from Sloothaak et al.¹⁶⁸

and even pCR, can be achieved if surgery is delayed at least 4 weeks after SRT.^{149,174-176} CRT induces more pCR than SRT, mainly because of the timing of surgery.^{142,177} Another, registry based, study found that SRT-delay was less likely to induce pCR compared to CRT, adjusted OR (95% CI) 0.3 (0.2-0.5).¹⁷¹

Organ preservation

The idea of organ preservation in the case of a complete clinical response (cCR), has evolved since it was presented from a Brazilian group.¹⁷⁸ A review of 15 studies on non-operative management after cCR failed to perform a “formal meta-analysis” due to the heterogeneity of the including studies. The regrowth rate was found to be 21 % at a mean of 16 months, of which 93% could be

It was early reported that patients receiving SRT had visible signs of tumour regression if the surgery was delayed for at least 10 days.¹⁷² Further studies concluded that no tumour regression is detectable if surgery is performed immediate after SRT.¹⁷³ However, a higher grade of tumour regression,

“surgically salvaged”. A pooled OS was estimated to be 92 %, with a follow up of 23-68 months in the included studies. The authors stated that one major problem is that few of the studies had a control group and that organ preservation is a possible option only in selected patients.¹⁷⁹ A recent case series from the US had similar results with about 90 % surgical salvage in patients with regrowth, but patients with local regrowth had a worse outcome.¹⁸⁰ Other studies have estimated the local regrowth to be 21.4 %.¹⁸¹ The concept of “Watch and Wait” has increased in popularity and an international database is established. The ambition is to collect a large number of patients with prospectively recorded data. Long-term outcomes have been presented and local regrowth rate was found to be 25 % of which 97 % were in the bowel wall.¹⁸²

Other concepts of organ preserving strategies are local excision or transanal endoscopic microsurgery (TEM) instead of TME-surgery in the case of nearly complete responses. Results from the GRECCAR collaboration seems promising, after 5 year follow up.^{183,184} The ongoing STAR-TREC trial is randomising patients with \leq T3b tumours between standard TME-surgery, CRT or SRT followed by TEM-surgery or active surveillance depending on clinical response.¹⁸⁵ In summary, substantial evidence indicates that an organ preserving approach is safe in many settings.

Less is known about patients ending up without any signs of regression. These patients will have their OTT prolonged, without any obvious gain. At present, this situation is hard to avoid. There are no good tools to predict the response after neo-adjuvant (C)RT in RC. Factors such as tumour size < 2 cm, low cT- or cN-stage, high radiation dose, delayed surgery, high pre-treatment CEA-levels and post-treatment tumour size have been identified with some possibility to predict pCR.¹⁸⁶⁻¹⁸⁸ In the field of MRI, predictive models using multiparametric MRI-information combined with clinical parameters might be able to identify non-responders.¹⁸⁹ Other groups have identified other MRI-features with the possibility to find good or complete response.^{190,191} However, these are recently published and the findings needs to be confirmed in other settings. Further, no genetic profiles have been found with the ability to predict response to CRT.¹⁹² One interesting finding is that patients with DNA mismatch repair deficiency, or MSI-H tumours, might respond well to neo-adjuvant CRT.¹⁹³ These patients are otherwise known to be bad responders to adjuvant flouropyrimidine based chemotherapy. In summary, many attempts have been made to identify predictors of pCR. Some of these factors are not of any help in the pre-treatment decision phase, such as post-treatment tumour size or delayed surgery. At present, no methods are sufficiently specific or sensitive to use for treatment stratification.

With the ambition of tumour regression and pCR, the time interval after CRT is today often prolonged. From the previous standard of 6-8 weeks up to 10-12 weeks. A randomised trial from Royal Marsden concluded that there was a higher rate of MRI-measured downstaging and pCR after 12 weeks compared to 6 weeks.¹⁹⁴ Other studies exploring the optimal interval found that there is a larger probability for tumour regression if you wait 14 weeks compared to 9 weeks.¹⁹⁵ Two observational studies from the US with data from the national cancer database analysed two cohorts with surgery between 2004-2012.^{196,197} It was suggested that 8 weeks should be the upper limit of delay after CRT. Waiting time beyond 60 days was associated with shorter survival and higher rates of positive surgical margin.

When delaying surgery, it is important to monitor the patients and the tumour's response to CRT. Otherwise, there is a risk that patients with poor response will follow the same standard course as patients with acceptable or excellent response. The evaluation of neo-adjuvant treatment with MRI was explored in the MERCURY-trial and it was concluded that TRG can be assessed by MRI and even predict survival, OS 27 % vs 72 % in no response vs. good response.¹⁹⁸ Other studies have concluded similar results.¹⁹⁹ However, the overall correlation between MRI- assessed TRG and pathology graded TRG has been found to be low in larger materials.²⁰⁰

Radiation technique

The RT technique has evolved during the years. In the Swedish national guidelines for RC treatment there is an instruction of how the RT should be planned and delivered³⁰. In short, the patients are tattooed with a reference point, to be used for field settings and target drawing. RT is given with the patient laying down. To avoid the small bowel to come in to irradiation field the drawing and treatment can be carried out with a comfortable filled urinary bladder. A dosage CT is made for target volume (TV) and dose calculation. Volumes that should be defines are: Gross Tumour Volume (GTV). The clinical target volume (CTV) is the primary tumour with 1-2 cm margin within the mesorectum, thus including the primary lymph nodes. The nearest "secondary" nodes (presacral, along the SRA and the lateral stations) are also included. CTV with the lymph nodes are called CTVN The iliacal and inguinal nodes are not included regularly. The planning target volume (PTV) includes CTVN plus an additional margin of 0.8-1.3 cm. In the Swedish guidelines organs at risk (OAR) are not needed to be defined in SRT. In the more advanced tumours ("ugly"), a boost-GTV can be added in areas where surgically resection is expected to be troublesome. The CTVN includes the external iliac vessels if the tumour overgrows the pelvic organs, such as the prostate, bladder or vagina. In the very low tumours also inguinal nodes are included. In LRT courses, OAR are defined including the bowel bag, bladder, pelvic bones and genitals.

These guidelines are currently being revised and a new version will be released this year.

Toxicity from radiotherapy

The beneficial effects of RT, i.e tumour regression and fewer LR comes at the price of acute and long-term side effects. Type of acute toxicity depends on dose and irradiated target volume. Different grading systems are used to classify the severity of adverse RT events. The European Organisation for Research and Treatment of Cancer (EORTC) published a 5-level (0-4) system in 1995 with specifications for all organ systems.²⁰¹ Organs in the radiation field are naturally organs at risk for toxicity. Other side effects can be effects on circulating white blood cells and bone marrow, as previously discussed. The acute RT effects typically subside in a few weeks. In SRT little RT toxicity is developed between the time from RT to surgery. Typical symptoms might include erythema, diahorrea, urogenital symptoms, neurological complaints or pain. In patients with planned short waiting time to surgery these symptoms rarely cause surgery to be delayed or requiring hospital admission.²⁰² Acute toxicity symptoms are more frequent in LRT or CRT compared to SRT.¹⁶⁷ The Stockholm III trial was the first trial to compare acute radiation toxicity

between SRT, SRT-delay and LRT-delay. In the arms with a delay to surgery there is time to develop toxicity symptoms, and hospitalisation was required in about 6-7% of the patients.¹⁵³

The late effects after RT are well known and include faecal incontinence, increased stool frequency and urgency, all symptoms are also associated with surgery of RC, but aggravated by RT.²⁰³ Increased GI-symptoms in general and bowel obstruction in particular have been described after RT, compared to non-irradiated patients.²⁰⁴ Patients in the Dutch TME-trial that received RT reported impaired quality of life (QoL) even after a follow up of 14 years.²⁰⁵ However, no impact on general symptoms was seen in the irradiated group. Symptoms of urinary dysfunction such as increased frequency, chronic cystitis and incontinence are more common in patients after RT.²⁰⁶ In addition, negative effects on sexual function have been found in both sexes. In males increased rates of both erectile and ejaculatory problems as well as a decreased overall sexual function have been reported.²⁰⁷ Hypogonadism has recently been reported as a potential risk after RT to the pelvis.²⁰⁸ In females, RT has been linked to dyspareunia, vaginal dryness and overall sexual dysfunction.²⁰⁹ A reduction of sexual desire has recently been described as a result of impaired androgen production from the ovaries.²¹⁰ Other long-term side effects of RT are pelvic insufficiency fractures (PIF), with chronic pelvic pain as cardinal symptom. A Danish case-control study found that 12.2 % of 1100 patients had PIF after CRT during a follow up of 36 months. High age and female gender were risk factors.²¹¹

The risk of secondary, RT induced, cancers has been explored in several studies. Patients included in two Swedish trials, recruiting patients in the 1980s and -90s were found to have an increased risk of a second cancer, RR (95% CI) 1.85 (1.23-2.78).²¹² A more recent study did not find any increased risk for a secondary cancer in irradiated patients, when analysing >13000 patients in the SCRCR with follow up of about 20 years.²¹³ In contrast, irradiated patients had a decreased risk of prostate cancer. The reduction of prostate cancers was confirmed in other studies, but they also found an increased risk for some gynaecological cancers.²¹⁴⁻²¹⁶ The latter study, also found an increased risk for lung cancer and lymphoma in irradiated patients.²¹⁶

Effect on distant failure?

In the 1970s and -80s local failure rates after RC surgery were reported to be 12 – 45 % in clinical trials, and probably higher in the population.²¹⁷ After the introduction of TME-surgery together with optimised chemotherapy and RT, the introduction of multidisciplinary conferences and other actions, the local control is now excellent and is reported to be below 5 % in low-risk tumours. Overall 3-year survival has improved from 57 % in 1995 to 62 % in 2012.²¹⁸ The distant failure in form of metastases is however still a major problem and therefore the aim should be to identify patients with high risk for distant recurrence. Since the introduction of the concept of good-bad-ugly, certain patients with cStage II and III disease will receive more aggressive treatment with appropriate neo-adjuvant treatment in form of SRT or CRT. Though neo-adjuvant treatment is effective on local control, the distant recurrence levels are not affected. This task is addressed by the RAPIDO-trial, which is closed for inclusion.²¹⁹ Patients with high-risk tumours (locally advanced – ugly) were randomly assigned to a combination of chemotherapy with high-dose capecetabine of 1000mg/m² and oxaliplatin 130 mg/m² in 6 cycles after SRT, or standard CRT

followed by adjuvant chemotherapy, with the hypothesis that the experiment group will increase the 3-year DFS from 50-60 %. The results will be available in 2020. A polish trial with a similar intention included patients with fixed cT3 or cT4 tumours and randomly assigned them to conventional CRT or three cycles of FOLFOX after SRT. No difference in R0 resection, DM, post-operative or late complications could be found but there was an improved OS in patients receiving consolidative chemotherapy.²²⁰

Surgery for rectal cancer

Except for patients with a complete tumour regression following (C)RT, surgery is required to cure patients with RC. Professor R. “Bill” Heald introduced the concept of TME in 1982 and showed excellent results regarding LR rates, even compared with modern materials with adequate preoperative staging, neo-adjuvant therapy and modern surgery. The technique consists of sharp dissection in embryological planes and excising rectum together with the whole mesorectum with blood vessels and lymph nodes as an intact specimen covered with an undamaged endopelvic fascia.³⁸ After the adaption of the TME-technique the frequencies of LR roughly halved in studies exploring RT-courses.^{33,127} Today, LR frequencies are as low as 3 % in low-risk tumours in Sweden.²

Anterior resection

Anterior resection (AR) is one of the standard procedures in surgery for RC. In patients with a cancer in the mid or low rectum, AR is the preferred technique, given that the patient tolerates an anastomosis. Preoperative impaired sphincter function or faecal incontinence are often considered a contraindication for this approach. Surgery is performed with the TME-technique and to minimise the risk of LR it is important to do a full TME and not leaving any mesorectum behind.⁷¹ The bowel is usually transected distally just above the pelvic floor. In high tumours, especially above the peritoneal reflection, a partial TME may be performed, with the ambition of better functional outcomes. However, there is clearly a risk of underestimating the need of radical surgery in the high tumours.²²¹ The continuity of the bowel is restored performing a anastomosis, most often by a circular stapling device. To reduce the number of symptomatic AL, a defunctioning stoma reduces reduce the frequency of early diagnosed leaks.²²²

Hartmann’s operation

The procedure where a part of the left colon is excised and an end- colostomy is brought up, is known as the Hartmann’s procedure, first described in the early 1920s.^{223,224} The indication of today in cancer surgery is in patients not fit for an anastomosis.²²⁵

Abdominoperineal excision

The abdominoperineal excision, (APE) and its modifications are primarily used for low RC when a radical excision cannot be guaranteed without removal of also the sphincters. In short, APE includes removing of the whole rectum, by TME-technique, including the anal canal, and consequently constructing an end stoma. Or with the words of the founder “*an abdominal anus is a necessity*”.²²⁶ Both perineal and combined abdomino-perineal approaches had been used since the 1880s but with poor results. Miles described a case series of 12 patients in the Lancet 1908, with an impressive reduction in the frequency of LR. The 42 % mortality was found acceptable, considering the natural course of the disease. The paper had an huge impact on the surgical society

and APE was considered the standard procedure in RC surgery for a long time. Today, APE is usually divided into four subtypes. The intersphincteric, conventional, extralevator (ELAPE), and the ischioanal APE.²²⁷ The intersphincteric APE is mainly an alternative to Hartmann's procedure. Instead of leaving a stapled rectal stump at the level of the pelvic floor the entire rectum with the anal canal is excised by an intersphincteric dissection. The potential advantage is that problems from the stump, such as abscesses are avoided. Differences in surgical morbidity is currently explored in a trial.²²⁸

In a conventional APE the abdominal part extends all the way down to the pelvic floor. The perineal part includes excision of the sphincters and the anal canal where after the specimen is extracted. The risk of the approach is a retraction, or waist, just above the levator muscle, with risk of threatened margins in this area. In patients with really low or advanced tumours, involving the sphincters, the outcomes were known to be inferior compared to higher tumours. With the ambition of avoiding this, the ELAPE was introduced.²²⁹ The concept is that the abdominal part ends at the level of the coccyx and the perineal excision line, from below, follows the outer edge of the external sphincter and continues below and along the levator muscles until the insertion onto the pelvic sidewall, resulting in an almost cylindrical specimen, with theoretically a greater lateral resection margin. The pelvic floor defect often requires mesh- or flap reconstruction. A superior CRM and lesser perforations after ELAPE have been confirmed in studies.^{230,231} However, the operation has been questioned by others in respect of wound healing, perineal hernias and a not convincing oncological superiority.^{232,233}

The ischioanal APE is the most extensive excision, and is indicated in patients with large locally advanced cancers involving the perineal skin or ischioanal compartment. The incision line follows the fascia of the internal obturator muscle instead of the external sphincter, as in ELAPE.

Minimal invasive techniques

The use of minimal invasive surgical techniques has gained popularity during the last two decades. The surgical community in Sweden has been a late adopter, but now about 60 % of the patients are operated with minimal invasive techniques.² The advantages with laparoscopy compared to open surgery includes reduced time to recovery, return to bowel function and length of stay. The oncological results have been considered similar.²³⁴⁻²³⁷ However, the operating time is longer and other trials have not concluded non-inferiority in terms of quality of the specimen.^{238,239} Robotic assistance is proposed to overcome some of the limitations of standard laparoscopic surgery, i.e. better 3-D visualisation and articulation of instruments. Small studies, often case series, have supported the use and efficacy, but the multicentre randomised ROLARR trial concluded that robotic assisted surgery is of no advantage in RC surgery.²⁴⁰ The main outcome was conversion rates. No data on survival or long-term outcomes are available yet. The place for robotic RC surgery still remains uncertain.

The transanal TME (taTME) combines transabdominal laparoscopic resection and a transanal TME-dissection using a gel-platform and endoscopic instruments. It can be carried out with two surgical teams simultaneously. There might be advantages in male patients with narrow pelvises or in the obese patients. However, the technique is relatively new and the oncological safety has to be confirmed in prospective studies.²⁴¹

Local excision

Since complications after RC surgery are common, techniques with the ambition of a local excision have developed. Main indication is early tumours, such as polyps or Tis, but it has also been introduced in cancers. As discussed previously the techniques may also have a place in tumours with good response after neo-adjuvant therapy.¹⁸³⁻¹⁸⁵ The simplest approach is transanal excision, often using some kind of retractor to facilitate visual exposure. The goal is a full thickness excision with 1 cm margin. With the TEM a resectoscope is used and the visualisation is improved, however the cost is high and there is a steep learning curve.²⁴² Compared to TME-surgery in T1 tumours, TEM results in significantly less morbidity and shorter length of stay, however with a higher risk for LR.²⁴³ Further, if TME-surgery has to be performed as a completion to the TEM, the embryological planes might be disrupted and the surgery need to be more extensive.²⁴⁴ The TAMIS, transanal minimal invasive surgery, uses the same concept as the TEM, but with more standard laparoscopic instruments. Other endoscopic techniques include endoscopy submucosal dissection (EMD) or the endoscopic mucosal resection (EMR).

Post-operative complications

The short term adverse events after RC surgery involves the common complications seen after any type of major surgery such as wound infections, general infections, bleeding and thromboembolic events. There have been a number of ways of reporting and register post-operative complications, the lack of conformity makes comparison between studies challenging. A system of grading complications was introduced by Clavien et. al and has been accepted by the surgical community and was introduced in the SCRCR in 2011.²⁴⁵ One of the most detrimental complications is the AL after AR. The effect is a pelvic infection, with risk of general sepsis, often requiring a second operation, and in worse case converting the AR to a Hartmann's procedure. About 2/3 of patients with AL will end up with a permanent stoma.²⁴⁶ The frequency of AL after AR is about 10 %, in defunctioned patients.^{222,247,248} Male sex, malnutrition, and high body weight increase the risk.²⁴⁹ In a pooled analysis, the use of neo-adjuvant therapy does not seem to be a strong risk factor for AL.²⁵⁰ Perineal wound complications following APE is a major problem seen in at least 20 % of the patients, in ELAPE the complications are even more common.²³⁰ The use of (C)RT substantially increases the risk of perineal wound infections.^{202,251}

Trying to minimize the post-operative complications has been the focus from several point of views. Minimal invasive techniques generally shortens length of stay and reduces peroperative blood loss and postoperative pain.²⁵² The risk reduction for major complication, such as AL or need of reintervention does not seem to differ. In the COLOR II trial 40 % of patients operated with open technique had any complication compared to 37 % operated by laparoscopy, $p=0.424$.²³⁵ Smoking cessation for at least 4 weeks prior to surgery reduces the risk of complications with almost 50%, in a mixed surgery cohort.^{253,254} Introduction of enhanced recovery programs (ERAS) have gained popularity.²⁵⁵ Among other gains such as a shorter length of stay, there is up to a 50% reduction of postoperative complications.²⁵⁶ In a meta-analysis it was concluded that the risk reduction is primarily seen in non-surgical complications, such as respiratory and cardiovascular events.²⁵⁷

Another way of optimising the patient before surgery is the concept of prehabilitation, which is a wide group of interventions with the aim of an overall improved physical state. It is proposed that these interventions improve the capacity to deal with the stress of major surgery with a subsequent improved post-operative period. Review articles have found conflicting results on these programs, mainly due to the heterogeneity of the studies and focus on single risk-factors in the included studies.²⁵⁸⁻²⁶⁰ At least, the idea of “prehab” does not seem to have any negative outcomes, and international randomised trials are ongoing.²⁶¹

Although promising evolvments have been made, the level of postoperative complications in the SCRCR has remained rather stable for the last two decades. Around 35 % of the patients are registered with some form of complication. In the last two years there might be trend towards a decline in the frequency.²

Adjuvant chemotherapy

In colon cancer there is evidence that adjuvant chemotherapy reduces the risk for recurrences, and improves survival in stage III disease. Further, adjuvant therapy is often used for patients in stage II with risk multiple risk factors.²⁶²⁻²⁶⁴ In RC, the benefits have been harder to show. A Cochrane-review concluded that OS was improved by adjuvant chemotherapy HR (95 % CI) 0.83 (0.76-0.91).²⁶⁵ However, the included trials were published between 1981-2011, before the TME-era, and only two trials included patients with neo-adjuvant treatment. A more recent meta-analysis used pooled individual patient data from trials including patients who had neo-adjuvant treatment.²⁶⁶ No benefits in OS or DFS were found, pooled estimate HR DFS 0.9 (0.77-1.07) $p=0.230$, OS 0.97 (0.81–1.17) $p=0.775$. In a sub-group analysis DFS, but not OS was improved in high tumours HR DFS 0.59 (0.40–0.85) $p=0.005$, OS 0.70 (0.44–1.14) $p=0.152$. Another meta-analysis concluded a positive effect on DFS, HR 0.79 (0.61-1.00) $p=0.0047$, analysing patients randomised after surgery, i.e were “at risk” of receiving chemotherapy ($n=753$).²⁶⁷ However, no positive effect on OS was found.

Although the level of evidence is moderate, at best, the use of adjuvant chemotherapy is rather common. The ESMO-guidelines consider it “reasonable” to consider adjuvant treatment in patients with RC but it should be assessed on individual basis. Both the American and Japanese guidelines recommends adjuvant chemotherapy in stage III RC.^{103,104}

Aims of the thesis

The overall aim of this thesis was to improve treatment and outcomes of patients with rectal cancer, by comparing preoperative courses of RT and timing of surgery. Focus has been on oncological outcomes, radiation toxicity, postoperative complications and tumour response. The specific aims of the four studies were:

- I.** To analyse the early adverse events, oncological outcomes and survival in the Stockholm III trial.

- II.** To analyse the postoperative complications in the Stockholm III trial, in relation to the exact timing of surgery.

- III.** To assess tumour regression, histopathology outcomes and correlation to survival and recurrence in the Stockholm III trial.

- IV.** To analyse the long-term oncological outcomes and survival in the Stockholm III trial after a minimum follow up of 5 years.

Patients and Methods

The Stockholm III trial

The patient cohorts in all the studies in this thesis derive from the Stockholm III trial. A summary of the studied cohorts and outcomes are presented in Table 1. On the 5th October 1998 the first patient was enrolled and last patient entry was 31st January 2013. The design was a randomised, non-blinded, multicentre, non-inferiority trial. Eligible patients had a biopsy proven adenocarcinoma of the rectum without signs of distant spread and were planned for an abdominal surgery. Exclusion criteria were severe cardiovascular comorbidity and/or previous RT to the pelvis. Patients were randomised between three different RT courses:

- 1) SRT 5 Gy x 5 and surgery within one week.
- 2) SRT-delay 5 Gy x 5 and surgery after 4-8 weeks.
- 3) LRT-delay 2 Gy x 25 and surgery after 4-8 weeks.

Including hospitals could choose to randomise patients between SRT or SRT-delay, or between all three arms. Some hospitals did not include patients in the three armed randomisation, and some hospitals did not include in all arms during periods of the year due to logistic reasons. Primary end-point was time to LR. Secondary outcomes were survival, distant metastases, 30-day mortality, postoperative complications, reoperations, sphincter saving surgery and late morbidity. Based on studies that included patients in the 1980s and 1990s the frequency of LR was estimated to be about 15 % and five-year survival 60 %. Non-inferiority, regarding the primary outcome, was too be deemed if the upper limit of a double sided 90 % CI (corresponding to a significance level of <0.05) of a HR did not exceed 1.7. To achieve a power of 80 % the total sample size was set to 840 patients. Early after study start it became obvious that the introduction of modern surgical techniques (TME) and optimised RT would affect the frequency of LR in the future. An amendment

	Cohort	Primary outcome	Secondary outcomes	Eligible patients	Included in main analysis
Study I	All patients in the Stockholm III trial	Time to local recurrence	Radiation toxicity, metastases, survival, postoperative complications	840	840
Study II	Patients with surgery and RT in the Stockholm III trial	Postoperative complications in relation to overall treatment time	Early mortality	830	810
Study III	Patients with RT, surgery and available specimens in the Stockholm III trial	Tumour regression in relation to treatment	Survival and recurrence in relation to tumour regression	730	697
Study IV	All patients in the Stockholm III trial	Time to local recurrence	Incidence of metastases, survival.	840	840

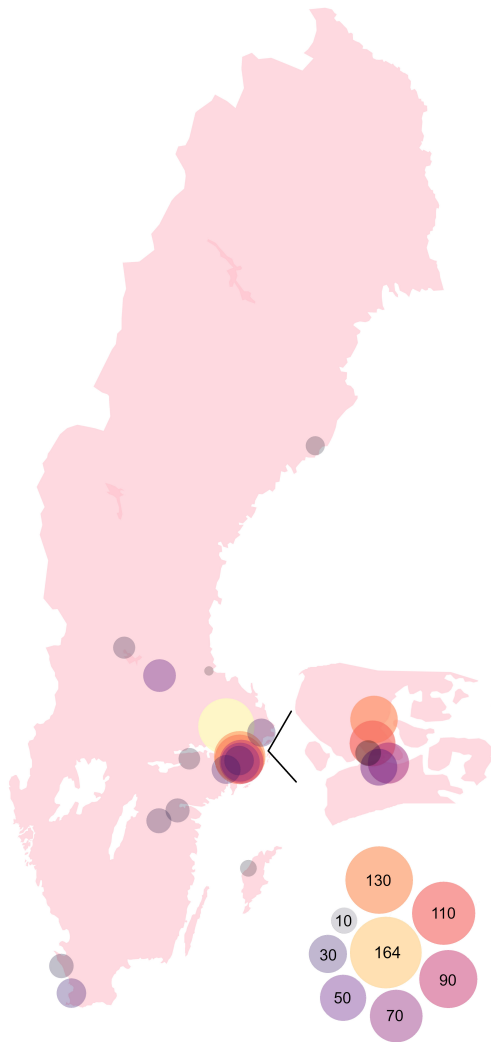


Figure 7. Graphical presentation of number of included patients/centre. Region of Stockholm is enlarged. Quantity is indicated both in colour intensity and size of bubble, number indicates upper limit per bubble. For exact number of patients please see appendix in paper I.

to the initial study protocol was made. It was concluded that the HR to determine non-inferiority would be considerably higher if the sample size was not revised. This was however accepted and the trial continued with unchanged number of patients. Further, tumour regression and quality of life were added as secondary outcomes. Patients were initially recruited from the Stockholm/Uppsala region. With time, other centres showed interest and joined the trial. A total of 18 centres included patients, (Figure 8). TME-surgery was performed as AR, APE or Hartmann's procedure. Antibiotic and thrombosis prophylaxis were administered according to local routines.

RT planning and delivery have followed the local- and national guidelines and have somewhat varied over the years. In brief, RT was delivered with a four field box technique, with high-energy photons (8-20 Gy). Individual 3-D dose planning and multileaf collimators were used at some hospitals towards the end of the trial. Target limits were drawn 3-4 cm above the anal verge or 5 cm below the tumour. The anal canal was included in the target volume only if an APE was planned. The upper limit was usually mid L5. The lateral

limits of the anteroposterior beams extended 1–1.5 cm outside the pelvic rim. The anterior limit was sufficiently ventral to cover the obturator nodes, the entire mesorectum with tumour extension and the nodes along the internal iliac vessels.

Registry data

The SCRCR was used as the electronic clinical registration form (eCRF) and data from the registry have been used in all studies. Data registration was done by the local physicians. As standard, data are reported to SCRCR; at surgery, at follow up after 1, 3 and 5 years, or when an event occurs. Due to low completeness and low comparability in certain variables in the registry, data were validated in the patients' medical charts.²⁸ All hospital records from date of surgery and the following 30-days, including the first out-patient visit were analysed with the respect of type of surgery and post-operative complications. Further, fractionation of RT and radiation toxicity were also validated. The local physicians were asked to make an extra report to the registry on patients who were in between the ordinary reporting times at time for data extraction from the SCRCR.

With help of the regional cancer centre in Stockholm, data were collected from the regional cancer centre in the Northern region of Sweden, which administrates the registry. Two data files were received at two occasions. One in 2015 and one in the autumn of 2018. In 2017 a new reporting system was introduced in the SCRCR. This resulted in difficulties in 2018 when data were to be collected for the 5-year follow up. It took several revisions and a lot of data processing and merging before the data finally were ready for analyses.

Analyses of randomised clinical trials

Randomised clinical trials (RCT)s have been considered high level of evidence for many decades. The hierarchy of scientific evidence is often described as a pyramid, with meta-analyses placed at the top, followed by RCTs. The exact hierarchy cannot be determined by study design only, one must also consider the quality of the studies.^{268,269} When incorporating clinical studies in practice guidelines there is a need of grading the quality of the underlying studies. The GRADE working group has developed recommendations on these issues, taking quality, benefits and harms and costs in to account.²⁷⁰ When starting the Stockholm III trial, the knowledge of the SRT-delay was limited and any retrospective study would have been impossible. Hence, a RCT-design was chosen.

The major advantage by randomising patients is that potential confounders are evenly distributed in the groups. When this is achieved, analyses can be carried out without adjustment for confounding factors. However, there might be problems when analysing and interpreting the data, especially when dealing with loss-to follow up or protocol violations. In the Stockholm III trial patients could violate the protocol in several ways. Patients could receive no RT at all. RT could be fractionated in another way than allocation prescribed. The timing of surgery could be wrong, both too short or too long according to randomisation, or it could fit the time interval of another arm. Further, some patients had no surgery, and a few patients had only local excisions. One way of tackling these issues are to analyse RCTs according to intention to treat (ITT). The basic idea is that all patients are analysed in the groups they initially were allocated to, independent of non-compliance or violations. Thereby avoiding too optimistic estimates when removing the “violators” and accepting that noncompliance and protocol deviations are likely to occur in actual clinical practice too.^{271,272} However, when analysing trials according to ITT and thereby categorizing patients as they got a treatment they never received, the treatment differences might be diluted. Another way of grouping patients is “per-protocol” which often is defined as only patients that received one of the allocated treatment are analysed. The third option is “as treated” analyses, where patients are analysed in the regimen they de-facto received, this is sometimes referred to as a “modified ITT”.²⁷³ Both the latter ways potentially introduce biases in the analyses and should be undertaken with caution. In the present thesis, study I and IV were analysed according to ITT. In paper II, the aim was to analyse subgroups and ITT-analyses were not applicable. The patient cohort of study III was a subgroup of the Stockholm III trial, and the main outcome was a secondary outcome in the trial, therefore patients were analysed “as-treated”.

Survival estimates

Survival estimates were calculated in study I, III and IV. OS is often considered as the most important outcome in many research areas, including adjuvant cancer trials. However, several different outcomes are used as surrogate endpoints, with somewhat varying definitions in the literature. Punt et al. conducted a review article with the ambition of a consensus definition of the most commonly used end points in colorectal adjuvant trials (Table 5).²⁷⁴ It was concluded that DFS is the most appropriate primary outcome since it includes relevant events, is robust against bias and is observed earlier than OS. Time to recurrence (TTR) was seen as the most sensitive endpoint with respect of specific benefits from treatments, due to the exclusion of non-cancer related death.

Event	Endpoint					
	DFS	RFS	TTR	TTF	CSS	OS
Locoregional recurrence	E	E	E	E	I	I
Distant metastases	E	E	E	E	I	I
Second primary, same cancer	E	I	I	E	I	I
Second primary, other cancer	E	I	I	E	I	I
Death from same cancer	E	E	E	E	E	E
Death from other cancer	E	E	C	E	C	E
Non-cancer-related death	E	E	C	C	C	E
Treatment-related death	E	E	C	E	C	E
Loss to follow-up	C	C	C	C	C	C

DFS = disease-free survival; RFS = relapse-free survival; TTR = time to recurrence; TTF = time to treatment failure; CSS = cancer specific survival; OS = overall survival; E = event; C = censor; I = ignore. Reprint with permission from Punt et al.²⁷⁴

The probably most commonly used method for survival estimates in medical statistics is the Kaplan-Meier (KM) method.²⁷⁵ The graphical presentation was originally intended for OS-analyses, a guaranteed event eventually, taking differences in follow up time in to account. Patients are censored when lost to follow up or at end of study. Hence, they contribute with information that no event occurred up to that time point. Differences in KM-curves are often tested by the log-rank test, a non-parametric test that compares the expected number of deaths (events) in one group with the total number of events when combining the groups, p-value is calculated from an approximate χ^2 -test.²⁷⁶

Cox regression

One way of comparing survival estimates is the Cox regression, a proportional-hazards model. Basically it describes mortality rates at any given time point. In the basic model, the ratio between two hazards is assumed to be constant regardless of time. The result is presented as a hazard ratio. To assess the proportionality of the hazard functions a visual inspection using Schoenfelds residuals are commonly used.²⁷⁷ The mortality rates might not be constant across categories, such as including hospital in a multicentre trial. In those situations, a stratified Cox-regression might be used, allowing for the baseline risk to vary across categories.

Cox regression, stratified on including centres has been used in study I and IV. In study III no stratification was done, due to the as-treated analyses.

Competing risks

KM-estimates have been criticised for over-estimating the risk of an event in the case of competing risks.²⁷⁸ For example, say RFS is the outcome of interest. Then LR, DM and death would be the events used for calculation of the RFS-estimate. The KM-method assumes that patients experiencing a competing risk, have the same probability of the event as patients that are censored, thus over-estimating the cumulative incidences. The ambition when taking competing risks in to account is to get results that better mirrors the reality. Several ways of dealing with this issue have been proposed. The basic idea is to use “cumulative incidence functions” that gives proportions of patients who have experienced the event, accounting for the fact that other events could have happened. The result will differ from a cause specific hazard, estimated by for instance the KM-method. Competing risks were calculated in paper I.

Other statistical methods

Pearson’s χ^2 -test is used for statistical hypothesis testing between groups with categorical data. The test is based on the difference between expected and observed frequencies in the groups. If the sample size is very small, about less than five, Fisher’s exact test should be used instead. These two tests have been used in all four studies.

For testing continuous variables, the Mann-Whitney U test (Wilcoxon rank-sum test) or the Kruskal-Wallis test were used, the latter when comparing more than two samples with non-normally distributed (skewed) continuous data. The test is based on difference in variance between the groups. Hence, it assumes equal distribution in the compared groups. These tests have been used in paper I-IV.

Binary data are often compared using logistic regression. An advantage with regression models is the possibility of adjustments with several covariates in one model, the result is most often presented as OR. Logistic regression was used in Study I, II and IV. Estimates are presented as crude and adjusted OR.

If not otherwise specified, point estimates are accompanied with 95 % confidence intervals (CI) and the statistical significance level is $p \leq 0.05$. In all studies, Stata v. 13 -14.2 (Stata Corp LP, College Station, Texas, USA) have been used for statistical calculations. Some graphs in study III-IV and the cover image were constructed using R v. 3.5.1 (R foundation for Statistical computing).

Specific considerations

Study I

All patients in the Stockholm III trial were included (n=840). Data from the SCRCR were collected with the last day of follow up of 30th March 2015, when all patients had been followed for at least 2 years since surgery. Previous interim analyses revealed a difference in tumour height and a

subsequent higher proportion of AR in the LRT-delay group.¹⁵² This, in combination with the fact that some centres did not randomise patients in the three-armed randomisation at all led to the decision to analyse patients in the three armed randomisation separately, to avoid a bias introduction. Patients randomised to SRT and SRT-delay, irrespective of randomisation were pooled and analysed in a short course RT comparison.

Primary outcome was time to LR and secondary outcomes were DM, intercurrent death, RFS and OS. These outcomes were calculated from day of randomisation to time of event. Other endpoints were radiation toxicity, defined as RT related symptoms requiring hospitalisation between start of RT and surgery. Post-operative complications within 30-days, or same hospitalisation period as the primary surgery, were also analysed. Complications were defined as any cardiovascular, surgical, infectious, neurological complication. Surgical complications were defined as any wound dehiscence, postoperative bleeding, surgical site infection, stoma-related complication, deep infection, anastomotic leak, complication, or other surgical related adverse event.

Study II

In this subgroup analysis patients were analysed as-treated. Patients were categorized in to groups based on their OTT, calculated from start of RT to day of surgery. Hence, patients without surgery or RT were excluded. Patients who received 5 Gy x 5 (SRT) were categorized into four groups. A – 7 days, B 8-13 days, C 5-7 weeks, D 8-13 weeks. Patients who received LRT-delay was categorized in two groups E 9-11 weeks, F 11-14 weeks. Groups A-D were compared separate from group E and F. Outcomes were post-operative complications. The same definition as in study I was used. In addition, any type of infectious complication was also analysed. Differences between the groups were analysed using descriptive statistical methods. OR for complications were calculated using logistic regression and presented as crude and adjusted point estimates. Variables in the adjusted model were; ASA-score (American society of anaesthesiologists), sex, old age ≥ 75 years dichotomized, and type of surgical operation. These variables were selected based on data showing that male sex, high ASA-score and APE are associated with more post-operative complications.²⁷⁹⁻²⁸² This clinical knowledge could also affect the decision on timing of surgery. Old age was considered a confounder since elderly patients might be selected to different waiting intervals, and have inferior outcomes when analysed stratified by OTT.¹⁴⁴ In the SRT-comparison, group B was defined as the reference group.

Study III

In this study, the main outcome was tumour regression in the treatment arms. All available histological slides from patients in the Stockholm III trial were retrieved from the local pathology departments that initially prepared them. Blinded to allocation, one experienced GI-pathologist have reassessed them. The regression system according to Dworak was used (0-4).⁸³ Other assessed histopathological characteristics were T-stage, N-stage, CRM, PN, EMVI, and tumour differentiation. pCR was defined as ypT0N0, given that both variables were assessable. Secondary outcomes were OS and TTR in relation to grade of tumour regression. Main analyses were conducted in the as-treated groups SRT, SRT-delay and LRT-delay. In the survival- and recurrence analyses all patients with assessable specimens were included. Based on previous studies, the most

interesting comparison was considered to be between Dworak regression grade 3 and 4. Thus, Dworak regression groups were reclassified in to three groups, 0-2, 3 and 4.

Study IV

In this study, the main outcome of interest was time to LR, after a minimum follow up of 5 years since surgery. Secondary outcomes were DM, RFS and OS. All patients (n=840) in the Stockholm III trial were included. Data were collected from the SCRCR with last day of follow up of 31st March 2018. The study was analysed according to ITT. An additional as-treated analysis was performed. Patients were categorised in to groups based on the actual treatment they received and by OTT. Since the weekday of RT-start, and the exact OTT may vary due to holidays and other reasons, the OTT defining the “as –treated groups” were: SRT 7-13 days, SRT-delay 33-67 and LRT-delay 57-94 days, thus corresponding to having surgery performed within one week or 4-8 weeks after the end of RT.

Cover image

In an attempt of summarizing this thesis in one image, inspiration was found in a beautiful ambition of describing uncertainty in statistical models by a visually-weighted regression, or “watercolour regression”.²⁸³ The concept was further elaborated and the R-script was shared online in 2012.²⁸⁴ The plots in the cover image were constructed based on these ideas and codes. In short, an unadjusted generalized linear model using the binomial distribution was fitted. Non-parametric locally weighted scatterplot smoothers (LOWESS, span=0.95) were calculated using 500 bootstrap samples from the trial data, generating the spaghetti plots. Every smoother has a high transparency (low alpha value). Hence, areas with a high density of overlapping smoothers will turn more intense and opaque, indicating a higher degree of certainty. The median smoother is indicated by a white line. The contrast to the background smoothers corresponds to the certainty of the median estimate. Every bootstrap sample is surrounded by a shade, causing the water colour effect. The shading intensity is based on density estimates of vertical cuts through the smoothers. In this graphical presentation, all bootstrap estimates are plotted. Consequently, the spaghetti with shading basically corresponds to a full CI. For the graphical presentation, only patients receiving 5x5 Gy and OTT < 11 weeks are included. Complications are the probability of any post-operative complication. Recurrence is the probability of any local- or distant recurrence at 5 years. Regression is the probability of a pCR.

Ethics

The Stockholm III trial was approved by the ethics committee at Karolinska Institute, Stockholm, Sweden.

Results

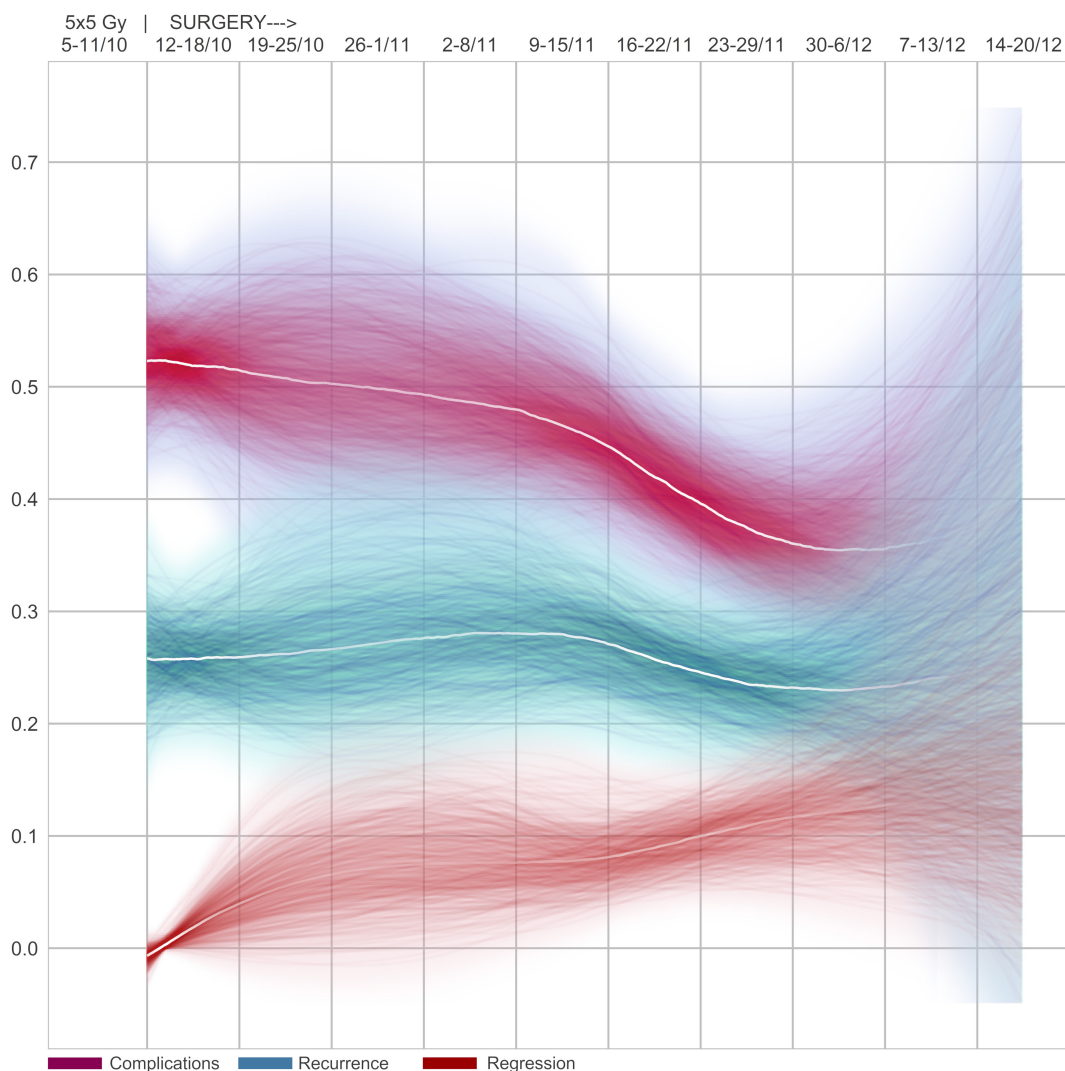


Figure 8. Proportions of three outcomes in the Stockholm III trial, by overall treatment time (OTT) calculated from radiotherapy start on 5th October 1998. Patients receiving 5x5 Gy and OTT < 11 weeks are included. Complications are any post-operative complication. Recurrence is any local- or distant recurrence. Regression is complete pathologic response.

A summary of the main results in this thesis are presented in Figure 8 (also on the cover). It is a visualisation of proportions of complications, recurrences (LR or DM) and tumour regression in the Stockholm III trial. The outcomes are presented by OTT, calculated from start of RT to surgery. The hypothetical first day of RT is 5th October 1998, as an homage to the first included patient in the trial. This is a graphical presentation of a subset of patients in the Stockholm III trial, initially planned for decorative use. For this reason, the LOESS-curves might be considered a bit under fitted, and the uncertainty overestimated due to the shading. However, the plots clearly indicate that conclusions from the Stockholm III data are most valid in patients with surgery within one week, or after 4-8 weeks after RT. In patients in between or beyond these intervals, the grade of uncertainty is higher.

Study I

In total, 840 patients were randomised in the Stockholm III trial. 385 in the three armed design and 455 in the two-armed. Basic patient characteristics were similar in all the randomised groups but there was a higher median tumour height in the LRT-delay group and consequently a lower proportion of APEs in this group, 19% vs 33% and 41%. (Table 6). About 6-7 % of the patients required in-hospital care due to side effects of RT between RT-start and surgery in SRT-delay and LRT-delay. One patient allocated to SRT was registered with RT-toxicity (protocol violator with OTT=196 days). There were statistically fewer overall- and surgical complications in SRT-delay vs. SRT in the short RT comparison, OR any complication: 0.61 (0.45–0.83) p=0.001. In the three-armed comparison the frequency of complications was lower, but not statistically significant, in SRT-delay and LRT-delay compared to SRT. In total, LR was seen in 25 of 840 patients. No statistical significant differences were found between the groups regarding LR, DM, OS, and RFS, neither in the short RT comparison, nor in the three-armed comparison, (Figure 9 and Figure 10). A summary of the oncological outcomes in the short RT comparison is presented in Figure 11.

	Three armed randomisation			Two armed randomisation	
	SRT (n=129)	SRT-delay (n=128)	LRT-delay (n=128)	SRT (n=227)	SRT-delay (n=228)
Age (years)	67 (62-74)	67 (62-75)	66 (61-73)	67 (61-74)	67 (61-74)
Gender					
Male	81 (63%)	79 (62%)	73 (57%)	137 (60%)	134 (59%)
Female	48 (37%)	49 (38%)	55 (43%)	91 (40%)	93 (41%)
Height from anal verge					
0-5 cm	50 (39%)	57 (45%)	31 (25%)	78 (34%)	68 (30%)
6-10 cm	49 (38%)	49 (39%)	60 (48%)	91 (40%)	95 (42%)
11-15 cm	30 (23%)	21 (17%)	35 (28%)	58 (26%)	63 (28%)
Type of surgery					
AR	79 (61%)	68 (53%)	93 (72 %)	139 (61%)	136 (60%)
APE	47 (36%)	53 (41%)	24 (19%)	75 (33%)	79 (35%)
Hartmann's	3 (2%)	6 (5%)	8 (6%)	14 (6%)	12 (5%)
Local excision	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)
No resection	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Data are median (IQR) or n(%). SRT=short course radiotherapy 5 Gy x 5 surgery within one week. SRT-delay = short course radio therapy, 5 Gy x 5, with a delay of 4-8 weeks to surgery. LRT-delay = Long course radio therapy, 2 Gy x 25, with a delay of 4-8 weeks to surgery. AR=anterior resection. APE=abdominal perineal excision. Reprint from Study I.					

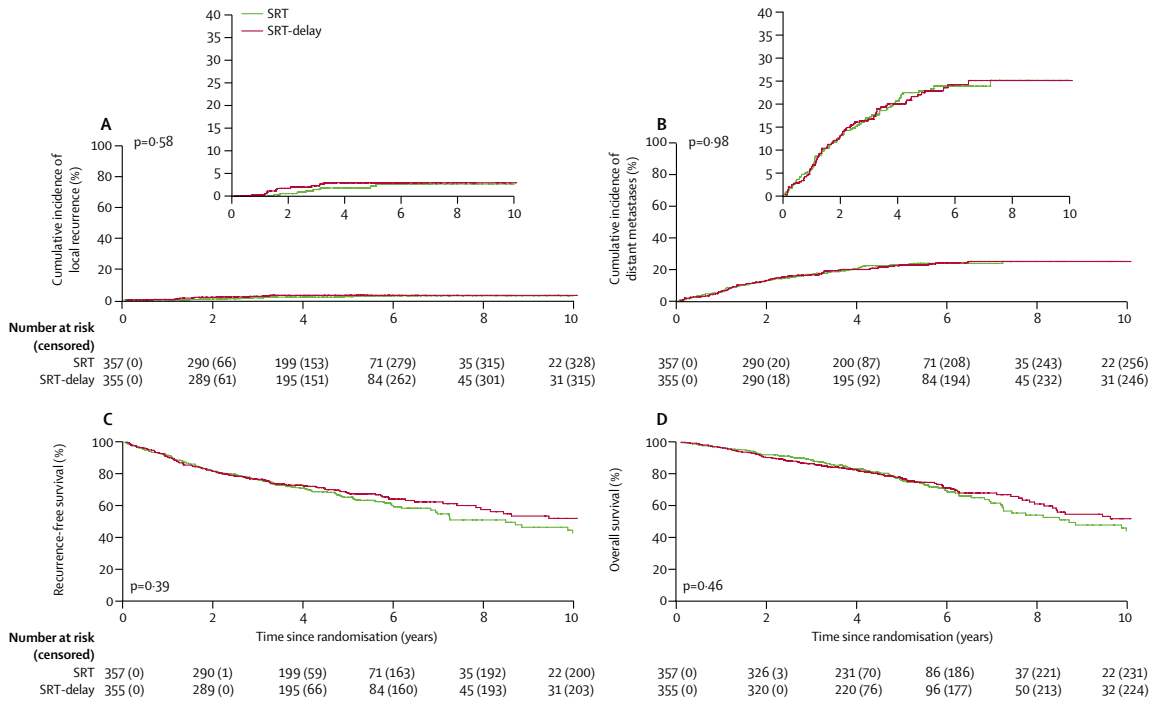


Figure 9. Outcomes in the short RT comparison. A) Local recurrences. B) Distant metastases. C) Recurrence Free Survival. D) Overall Survival. Reprint from Study I.

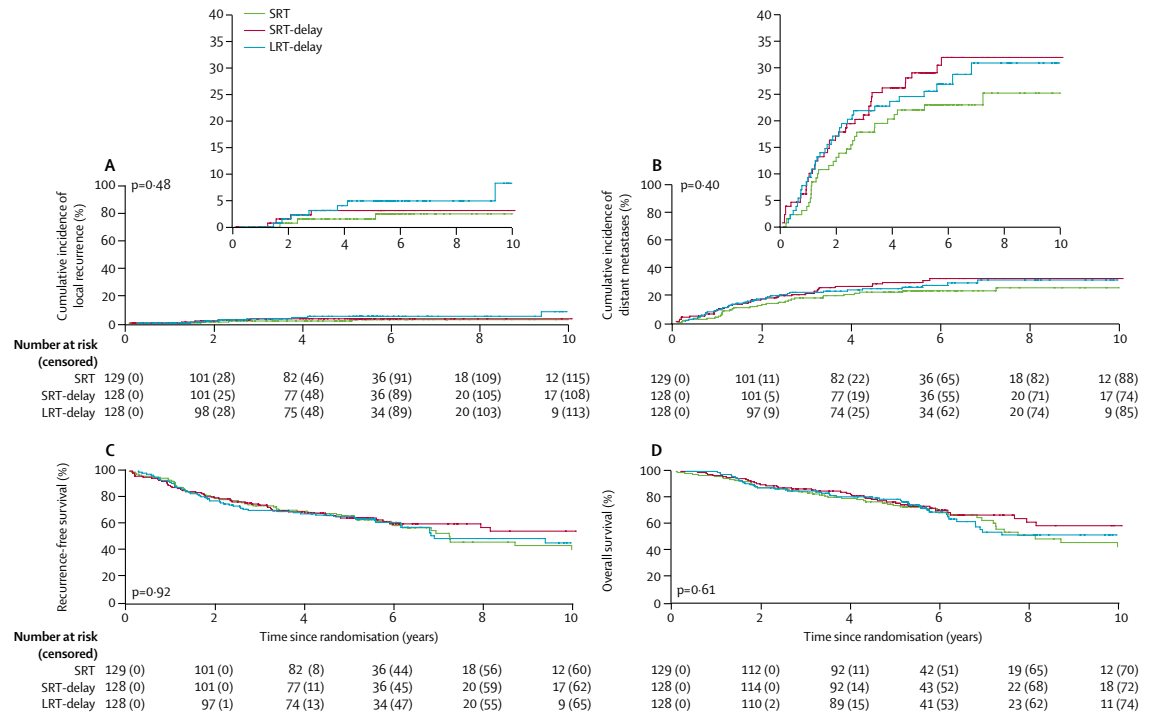


Figure 10. Outcomes in the three armed randomisation. A) Local recurrences. B) Distant metastases. C) Recurrence Free Survival. D) Overall Survival. Reprint from Study I.

Short course RT comparison

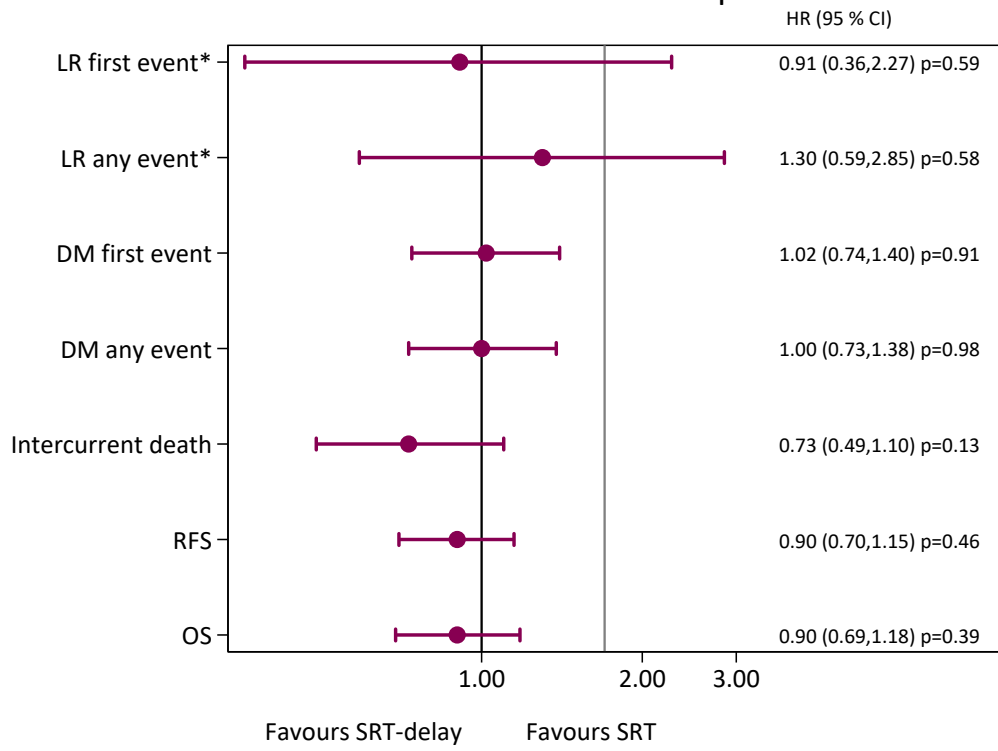


Figure 11. Summary of oncological outcomes in study I. * 90 % CI. Grey line indicates the initial non-inferiority level of 1.7. Modified from study I.

Study II

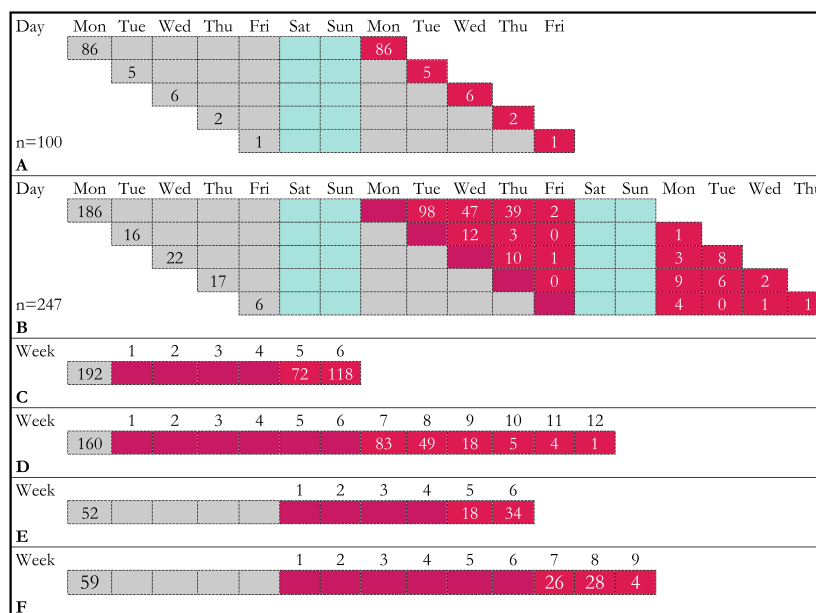


Figure 12. Number of patients by group and OTT. Grey is day of RT, blue is weekend, plum is delay, cyclamen is day of surgery. Modified from Study II.

In the Stockholm III cohort seven patients never received any RT. Two patients never had surgery and one had a local excision. These patients were excluded from this study. Further, 20 patients had OTTs in between or beyond the OTT in the pre-specified groups. Hence, 810 patients were analysed, Group A n=100, Group B n=247, Group C n=192, Group D n=160, Group E n=52, Group F n=59. The distribution of patients by OTT is presented in Figure 12. Patients excluded from the groups had no statistical significant differences in basal patient characteristics compared with the included patients. Hence, no obvious reason to violate the study protocol with respect of timing of surgery was found. Patients that received 5 Gy x 5 (Group A-D) and patients that received 2 Gy x 25 (Group E-F) were analysed separately. Baseline patient characteristics between group A-D and E-F were not significantly different. The most common post-operative complication was surgical site infection seen in about 21 % of the patients in total. In the short course RT comparison, the highest frequency of postoperative complications was found in group B (OTT of 8-13 days). The lowest complication risk was found in patients with the longest OTT, (Figure 13). We found no statistically significant differences in the proportion of complications when comparing Group E and Group F. There were very low numbers of 30- and 90-day mortality in the trial, and the frequency did not significantly differ between the groups. As a sensitivity analysis the 20 patients initially excluded from the study were put into the groups, without changing the results. When analysing the infectious complications without surgical site infections the results also remained stable.

In this study OTT was used to categorize patients. The exact date at end of RT was not known. Hence, the waiting time between end of RT and day of surgery could not be calculated. However, the weekday of RT-start was known and it is possible to estimate the end of RT, assuming that no

Postoperative complications after short-course radiotherapy by overall treatment time
Group B (OTT 8–13 days) is reference

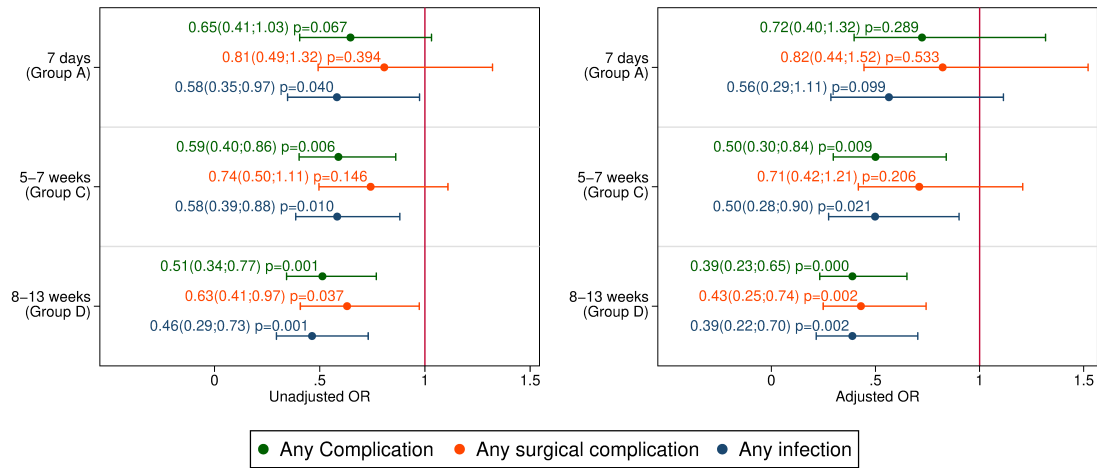


Figure 13. OR for different types of complications, by OTT Group B is reference. Reprint from Study II.

surgery is performed or RT is given on Saturdays or Sundays. It was decided not to present this “estimated end of RT” in the original paper due to the uncertainties, especially in the groups with a delay to surgery (unknown holidays or logistic reasons, etc.). This supplementary analysis on patients receiving 5 Gy x 5 is presented here. Four groups were constructed, based on time from estimated end of RT to surgery; 0-3 days n=126, 4-7 days n=221, 28-41 days n=182, 42-85 days n=170. The interpretation of the results does not differ from the main analyses in any major way. The lowest frequency of complications was seen when surgery was delayed for more than 41 days, (Figure 14). In the unadjusted analyses there was a statistical significant reduction of complications in the group with surgery after 0-3 days compared to 4-7 days, but the results did not remain stable after adjusting for covariates. In the adjusted model the reduction of infectious complications did not reach statistical significance in the group with surgery 28-41 days after SRT.

Postoperative complications after short-course radiotherapy
4-7 days (estimated) after end of RT is reference

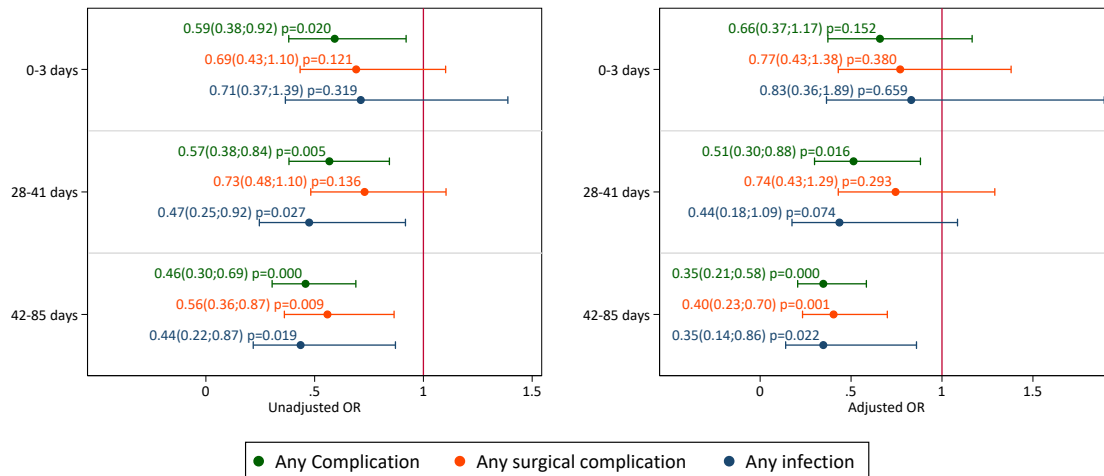


Figure 14. OR of different types of complications, by estimated end of RT.

Study III

In total, 730 (86.9 %) of 840 specimens were available for reassessment. It was not possible to assess 45 specimens due technical reasons or missing slides. Due to unclear reasons at the local pathology departments, 65 specimens were not possible to retrieve. In the as-treated groups 318, 285 and 94 patients were included in the SRT, SRT-delay and LRT-delay, respectively. Flowchart of the study and reasons for exclusions and cross-over are presented in figure 15. The ypTstage was significantly lower in the SRT-delay group compared to both SRT and LRT-delay (Table 7).

TRG 0-2 was seen in 312 of 318 (98,1%) after SRT, indicating a low downstaging effect after immediate surgery. The lowest frequency of both EMVI+ and PN+ was seen after SRT-delay. A rather high frequency of missing CRM status was noted, 179 (25.7 %) of 697 patients. A positive CRM, defined as distance of ≤ 1 mm was seen in 31 (6.0 %) of 518 of the patients, without significant difference between the groups. pCR was virtually not seen before in OTT < 3 weeks. Patients with pCR had significantly improved TTR and OS compared to no-pCR. The difference remained significant also after adjusting for old age, sex and type of surgery. HR OS 0.51 (0.26;0.99) $p=0.046$, HR TTR 0.27 (0.09;0.86) $p=0.027$. Patients with specimens assessed as TRG 4 had better OS and TTR compared to patients with TRG 0-2, (Figure 16). When comparing OS and TTR in TRG 0-2 with TRG 3 or TRG 3 with TRG 4, no statistical differences were found.

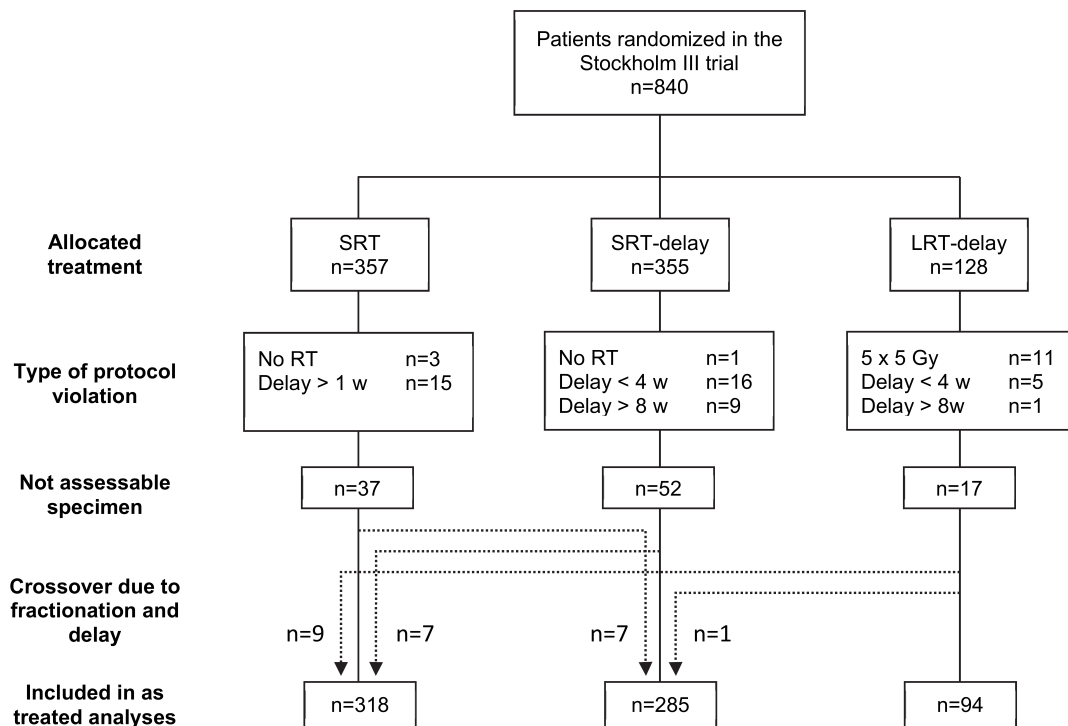


Figure 15. Flowchart of included patients in the as treated comparison. Crossover was possible when both fractionation and waiting interval matched another group. Reprint from study III.

Table 7. Pathology outcomes					
		SRT	SRT-delay	LRT-delay	p-value
N		318	285	94	
ypStage	ypStage 0 [‡]	4 (1.3%)	35 (12.3%)	3 (3.2%)	<0.0001
	ypStage I	86 (27.0%)	100 (35.1%)	27 (28.7%)	
	ypStage II	107 (33.6%)	72 (25.3%)	36 (38.3%)	
	ypStage III	109 (34.3%)	68 (23.9%)	24 (25.5%)	
	ypStage IV	4 (1.3%)	4 (1.4%)	2 (2.1%)	
	ypStage x [†]	8 (2.5%)	6 (2.1%)	2 (2.1%)	
ypT-stage	ypT0	4 (1.3%)	30 (10.5%)	3 (3.2%)	<0.0001
	ypTis	2 (0.6%)	6 (2.1%)	2 (2.1%)	
	ypT1	13 (4.1%)	34 (11.9%)	6 (6.4%)	
	ypT2	100 (31.4%)	78 (27.4%)	27 (28.7%)	
	ypT3	188 (59.1%)	124 (43.5%)	54 (57.4%)	
	ypT3 a/b	135 (42.5%)	90 (31.6%)	37 (39.4%)	
	ypT3 c/d	50 (15.7%)	33 (11.6%)	12 (12.8%)	
	ypT3 x	3 (0.9%)	1 (0.4%)	5 (5.3%)	
	ypT4	11 (3.5%)	13 (4.6%)	2 (2.1%)	
	ypT4a	3 (0.9%)	5 (1.8%)	1 (1.1%)	
	ypT4b	6 (1.9%)	4 (1.4%)	1 (1.1%)	
	ypTx [†]	2 (0.6%)	4 (1.4%)	0 (0.0%)	
ypN-stage	ypN0	199 (62.6%)	211 (74.0%)	66 (70.2%)	0.046
	ypN1	76 (23.9%)	48 (16.8%)	15 (16.0%)	
	ypN2	37 (11.6%)	23 (8.1%)	11 (11.7%)	
	ypNx [†]	6 (1.9%)	3 (1.1%)	2 (2.1%)	
EMVI+	Yes	124 (39.0%)	75 (26.3%)	35 (37.2%)	0.005
	No	192 (60.4%)	204 (71.6%)	59 (62.8%)	
	N/A	2 (0.6%)	6 (2.1%)	0 (0.0%)	
PN+	Yes	67 (21.1%)	25 (8.8%)	13 (13.8%)	<0.0001
	No	249 (78.3%)	254 (89.1%)	81 (86.2%)	
	N/A [†]	2 (0.6%)	6 (2.1%)	0 (0.0%)	
Differentiation*	Adenoma	1 (0.3%)	4 (1.6%)	0 (0.0%)	0.028
	High	15 (4.8%)	24 (9.4%)	6 (6.6%)	
	Moderate	251 (79.7%)	201 (78.8%)	79 (86.8%)	
	Low	22 (7.0%)	10 (3.9%)	0 (0.0%)	
	Mucinous	25 (7.9%)	16 (6.3%)	5 (5.5%)	
	Signet ring	1 (0.3%)	0 (0.0%)	1 (1.1%)	
	N/A [†]	1 (0.3%)	4 (1.6%)	0 (0.0%)	
CRM	>1 mm	228 (92.3%)	193 (96.0%)	66 (94.3%)	0.26
	≤ 1 mm	19 (7.7%)	8 (4.0%)	4 (5.7%)	
	N/A [†]	71	84	24	
Dworak	TRG 0	29 (9.1%)	20 (7.0%)	4 (4.3%)	<0.0001
	TRG 1	233 (73.3%)	124 (43.5%)	42 (44.7%)	
	TRG 2	50 (15.7%)	92 (32.3%)	37 (39.4%)	
	TRG 3	2 (0.6%)	16 (5.6%)	7 (7.4%)	
	TRG 4	4 (1.3%)	29 (10.2%)	3 (3.2%)	
	N/A [†]	0 (0.0%)	4 (1.4%)	1 (1.1%)	
pCR		1 (0.3%)	29 (10.4%)	2 (2.2%)	<0.0001

Numbers are n (%) if not otherwise specified. N/A not assessable. *ypT0 not included. [†]Not included in statistical calculation. [‡]Includes ypT0 and ypTis, Reprint from Study II.

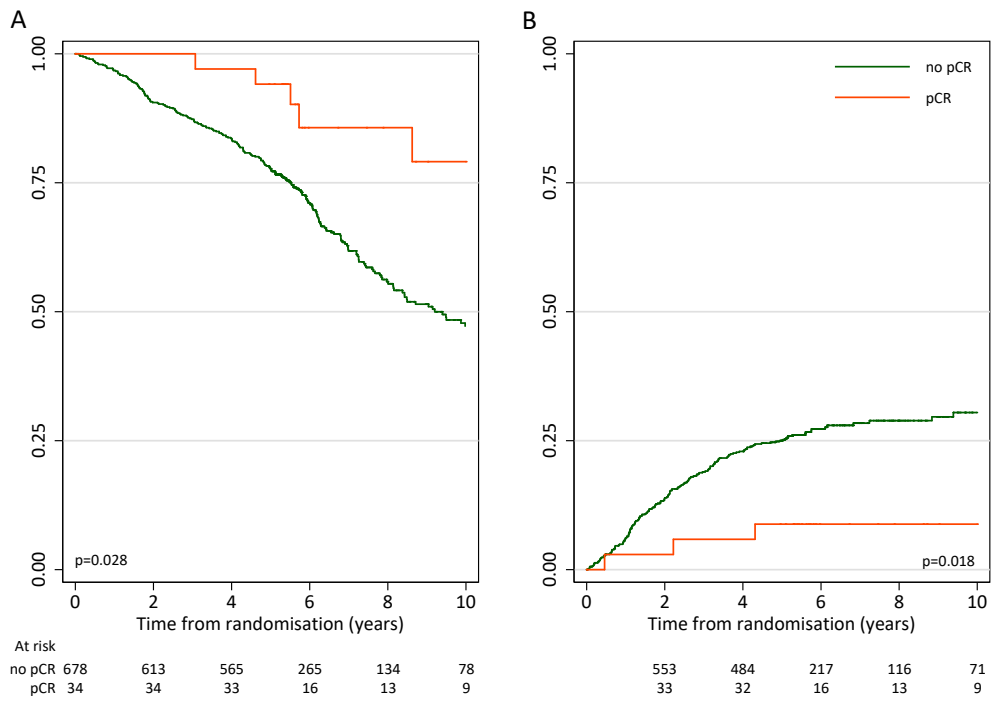


Figure 16. Kaplan-Meier estimates by pCR, pathologically graded complete response, all patients with assessable ypT and ypN stages. A Overall survival. B Time to recurrence. Reprint from Study III.

Study IV

All 840 patients initially randomised in the Stockholm III trial were included in this study. Analyses were performed according to ITT. The three-armed randomisation was analysed separately and the patients randomised to 5 Gy x 5 +/- delay to surgery were analysed in a pooled short course RT comparison. Patient distribution by OTT is presented in figure 17. The median follow-up (IQR) in the SCRCR was 5.7 (5.3-7.6) years. Two patients were lost to follow up in the SCRCR after 2.5 years (SRT-delay) and 1.8 years (LRT-delay) respectively, for unclear reasons. The median follow-up time regarding OS was (IQR) 9.8 (7.7-12.6) years.

Number of failure events in the three-armed comparison and pooled short RT comparison are presented in Table 8 and Table 9 respectively. Median OS (95 % CI) in the three armed randomisation was 8,14 (6.94-11.24), 10,34 (8.16-12.76) and 10,53 (6.95-11.34) years in SRT, SRT-delay and LRT-delay respectively, (Figure 18). In the short RT comparison, the median OS (95 % CI) was 8.14 (7.23-9.98) and 10.18 (8.45-11.68) years in SRT and SRT-delay respectively, (Figure 19). No statistical significant differences were seen regarding the oncological outcomes between the groups.

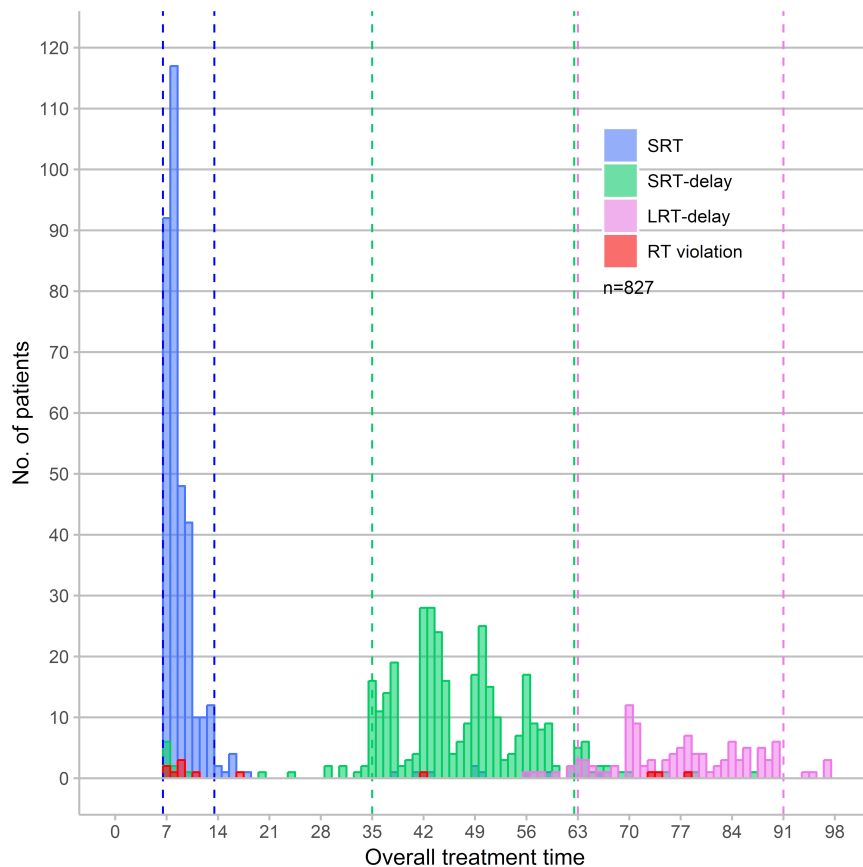


Figure 17. Number of patients by overall treatment time, grouped by allocated treatment. Patients without surgery, RT or OTT >13 weeks are excluded from figure (n=13). Bar colour indicates allocated treatment by randomisation. RT-violation – patients allocated to LRT-delay that received 5x5 Gy. Dashed lines corresponds to predefined time intervals within the treatment courses. Intention to treat groups includes all patients independent of protocol violation. As treated groups includes all patients within dashed lines +/- a few days.

Table 8. Oncological outcomes and survival in the three armed randomisation.					
	SRT	SRT-delay	LRT-delay		
n	129	128	128		
Any death	65 (50.4)	58 (45.3)	56 (43.8)		
Intercurrent death	37 (28.7)	24 (18.8)	23 (18.0)		
MET	31 (24.0)	38 (29.7)	38 (29.7)		
LR	3 (2.33)	4 (3.13)	7 (5.47)		
	SRT (ref)	SRT-delay	p	LRT-delay	p
OS	1.0	0.75 (0.51-1.09)	0.137	0.88 (0.61-1.29)	0.512
RFS	1.0	0.90 (0.61-1.21)	0.589	0.99 (0.63-1.30)	0.956
Distant metastases	1.0	1.47 (0.90-2.42)	0.123	1.23 (0.76-1.99)	0.39
Local recurrence*	1.0	1.18 (0.33-4.15)	0.830	2.23 (0.70-7.14)	0.236

Data are n(%) or HR(95 %) if not otherwise specified.*90 % CI

Table 9. Oncological outcomes and survival in the short RT course comparison			
	SRT	SRT-delay	
n	357	355	
Any death	200 (56.0)	211 (59.44)	
Intercurrent death	84 (23.5)	68 (19.2)	
DM	88 (24.7)	82 (23.1)	
LR	11 (3.1)	13 (3.7)	
	SRT (ref)	SRT-delay	p
OS HR	1.0	0.84 (0.66-1.06)	0.146
RFS HR	1.0	0.85 (0.68-1.06)	0.144
Distant metastases	1.0	0.94 (0.69-1.27)	0.692
Local recurrence*	1.0	1.31(0.66-2.61)	0.518

Data are n(%) or HR(95 %) if not otherwise specified.*90 % CI

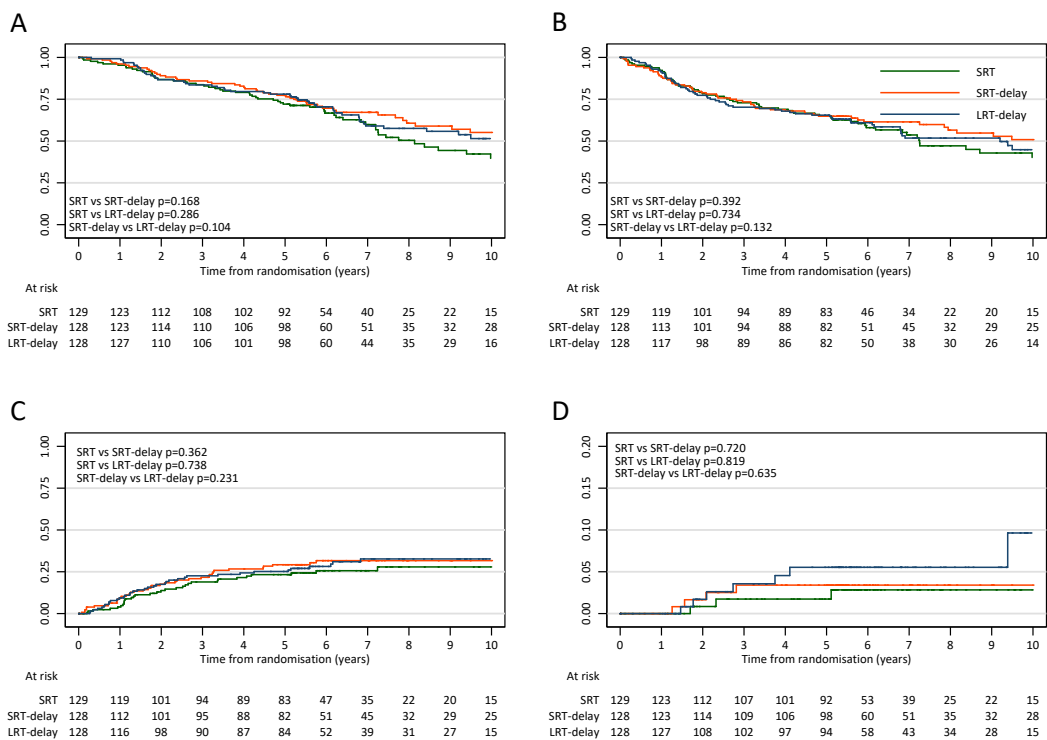


Figure 18. Oncological outcomes in the three armed comparison. A Overall survival B Recurrence Free Survival, C Distant metastases D Local recurrence. p is log-rank test.

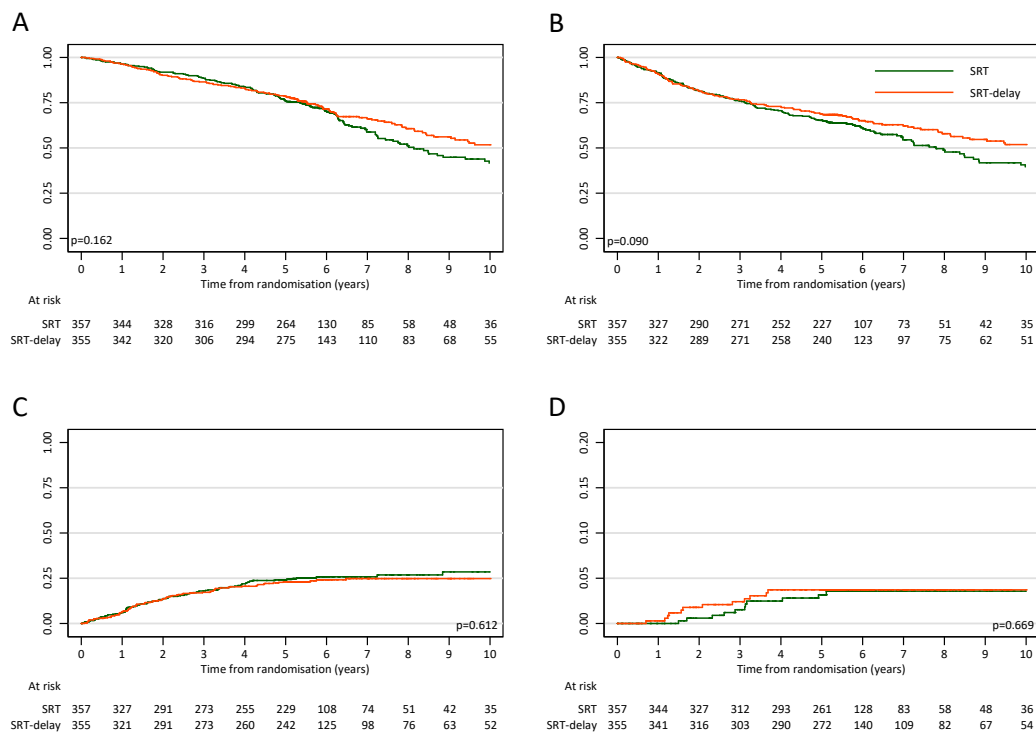


Figure 19 Oncological outcomes in the short RT comparison. A Overall survival B Recurrence Free Survival, C Distant metastases D. Local recurrence. p is log-rank test.

Discussion

Long inclusion period

The Stockholm III trial was planned and initiated in a time when LR rates were considerably higher compared with today. Previous trials had shown an improved local control with RT compared to surgery alone and preoperative RT had been proven to be superior to post-operative ditto.^{122,124-126} Naturally, the most important aspect of any new trial on adjuvant treatment in RC was to be certain that the experimental treatment was as good as the standard treatment with respect of LR. The choice of a non-inferiority design and time to LR as primary end-point, was the most obvious and interesting thing to do. In Sweden, two RT-courses were used for RC, 5 Gy x 5 or 2 Gy x 25. Randomisation between them with one additional experimental arm with a delay to surgery after 5x5 Gy was chosen. The trial had a long inclusion period of 14.7 years. During the trial a lot of evidence evolved regarding the importance of TME-surgery, good quality of the surgical specimen, histopathological risk factors, MRI-guided stratification of neo-adjuvant treatment and improved MRI-staging.^{55,70,71,101,127} Further, the feasibility and safety of the SRT-delay regimen was explored and described outside the trial.¹⁴⁹⁻¹⁵¹ Later, the addition of chemotherapy to LRT-courses was proven to improve local control and improve survival in unresectable tumours.¹³¹⁻¹³³ During the latter part of the trial SRT was suggested to have similar oncological outcomes compared to CRT in T3/T4 tumours, which also had been showed in a Polish trial.^{141,142} However, the comparison between SRT and SRT-delay in a prospective setting had not been explored. When the interim analyses had proven safety and a possibility of tumour regression even after SRT-delay, more centres joined the trial and the recruitment got easier.^{152,174} The long inclusion period evidently has implication when interpreting the results from the Stockholm III trial. However, patients have been included in the trial and randomised to all arms during the whole time period. Thus, the effect on outcomes would be small on relative estimates. In study II and IV outcomes were stratified on inclusion period, without changing the results in any major way.

One weakness in the Stockholm III trial is the lack of data on preoperative staging. In the original protocol, the use of preoperative MRI was vaguely advocated and data were not prospectively registered. MRI-staging became standard around 2003 and was introduced as a variable in the SCRCR from 2007. Hence, it is not easy to describe the study population with respect of baseline tumour stage. However, T-stage could be estimated from the ypStage. It has previously been described that no downstaging is seen in patients with an OTT<10 days after SRT.^{172,173} In the Stockholm III trial ypTstage was ≥ 3 in about 2/3 of the patients with OTT ≤ 10 days, and this is probably the closest estimate of the true value that can be calculated.

SCRCR

The SCRCR was used as the eCRF. Although the registry has been validated and many variables are proven to be reliable there is still a risk of missing data.²⁸ Post-operative complications, radiation toxicity, type of surgery and some more variables were manually controlled in the patients' medical charts. The analyses of LR and DM are based on registry data, and there might be a risk of missing events in the registry.²⁷ The regular definition on "follow-up" in the SCRCR is that the patient have

been examined with appropriate radiology and by the responsible physician. If this not have been possible, a telephone call and a thorough assessment of the medical chart should have been carried out. We have asked the including centres to make additional reports on patients in the trial, thereby forcing extra audits of the medical charts. When data were collected to the first study, we noted that several centres had very few events registered in the SCRCR on patients included during the last 2-3 years. We asked the including centres to double check around 110 patients without any registered events, no additional events were identified. The levels of LR and DM in the study are also in line with what is expected. In general, there are both advantages and disadvantages with using quality registries as the eCRF. The main upside is the limited extra work for including centres, which may lead to a higher degree of participation, especially at centres without research facilities. The down side might be lower completeness of data. Further, the collection of data from the SCRCR for study IV was complicated by a new reporting system. In the case of Stockholm III, this must be considered as a minor problem since we have full control of the included patients and most events were before 2017. However, this might be an issue that threatens the validity of future studies based on SCRCR.

Complications and toxicity

In study I we explored the frequency of adverse events after RT and surgery in all three arms. We found significantly lower frequency of post-operative complications if surgery was delayed after 5 Gy x 5, but also increased RT-induced toxicity in these patients. Pre-operative RT-toxicity was seen in about 6-7 % of the patients in SRT-delay and LRT-delay. Naturally, some of the “post-operative” complications seen after SRT with immediate surgery is an effect of RT-toxicity. We have not tried to classify the post-operative adverse events as an effect of RT or surgery. In absolute figures, the total amount of complications is lower after SRT-delay compared to SRT (even with RT-toxicity included). However, since no grading of the severity of post-operative complications has been done, comparison of the total load of adverse events must be done with caution. Grade 3-4 RT induced toxicity must not be compared with surgical site infections or easily treated urinary tract infections.

The Australian trial comparing SRT and CRT found no difference between the treatment groups regarding post-operative complications (53.2 % in SRT vs. 50.4% in CRT)¹⁴³. In our material the post-operative complication rate was 50 % in SRT, 38 % in SRT-delay and 39 % in LRT-delay. When comparing these trials one could get the impression that the rate of complications is similar in CRT and SRT with immediate surgery. However, other studies found that CRT did not increase the risk for post-operative morbidity compared to surgery alone in a propensity-matched population, 29.3 % vs 31.3%.²⁸⁵ One meta-analysis exploring effect of neo-adjuvant therapy on morbidity concluded that CRT does not increase the post-operative complications, but morbidity is high after SRT with immediate surgery.²⁸⁶ Thus, timing of surgery matters.

In study II we aimed at describing the post-operative complication profile in-detail by OTT. Other studies have described that surgery should be performed early in the waiting interval, due to poor leukocyte response if OTT is prolonged more than 10 days.^{145,146} In a sub-group of the Dutch TME trial it was shown that elderly patients even had worse survival if surgery was performed in the end

of the first week, but this was not found in a verification set of patients, analysed in the same study.

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We found that the lowest rate of any-, surgical or infectious complications was seen if surgery was delayed for at least 6 weeks after end of RT. No obvious benefit was found if surgery was performed early (0-3 days from RT, or OTT 7 days) One limitation of this study was that the last day of RT was not known. Therefore, patients were grouped based on OTT instead of “time from last RT fraction”. As a sensitivity analysis data were analysed with the estimated last day of RT, without changing the results in a major way. Other limitations included that data on comorbidities were highly limited. We used the ASA-score in the multivariate analysis as a surrogate for concurrent disease. Further, data on ASA-score was only available after 2007. Thus, the adjusted models are based on data from fewer patients than the crude model. Other missing variables that would be of interest are BMI and smoking status. Both which are known to affect the post-operative outcomes.

Would this lack of data affect the interpretation of the main result? First, a confounder must be associated with both the outcome and the exposure. It is not sure that the “missing comorbidities” would affect both the OTT and the post-operative outcome. Second, there were no statistically differences in baseline characteristics between the OTT-groups, indicating that the missing data are equally distributed in the OTT-groups. One other issue that not have been formally tested, is if the risk reduction varies over different “risk-stratas”. High risk patients will naturally gain more in absolute numbers, but speaking in relative terms, the risk reduction is probably similar for both high- and low-risk patients. To conclude, there are less complications if surgery is delayed but some of the effect might be explained by residual confounding.

Are post-operative complications an end-point of importance? Apart from prolonging length of stay, increasing hospital costs and causing patient discomfort, it has been proposed that patients with severe post-operative complications have inferior oncologic outcomes. Mainly explained by a prolonged interval to, or disqualification of adjuvant chemotherapy.^{279,287} However, many of the studies exploring outcomes after complications have included both colon and rectal cancers in the comparisons. In studies that specifically analysed patients with RC, the results are conflicting.²⁸⁸⁻²⁹⁰ In the Stockholm III trial no difference of severe complications such as AL or rate of reoperations was found between the treatment groups. In conclusion, the reduction of complications in the arms with the delay to surgery is not likely to affect the long-term oncological outcomes.

Tumour regression

In the Study III it was concluded that SRT-delay induces more pCR and higher tumour regression grades compared to SRT and LRT-delay. OS and TTR are improved in patients with pCR and TRG 4. The higher rate of tumour regression in SRT-delay compared to SRT is expected since there is no time for the tumour to regress if surgery is performed within one week.^{172,173} The comparison between SRT-delay and LRT-delay has not, to our knowledge, been explored in prospective studies before. The superiority of 5 Gy x 5 might be somewhat surprising since the BED has been considered to be similar in SRT and LRT. However, even if the α/β ratios are not

fully understood in RC, the results in our study must be interpreted with care. There are more “high” tumours in LRT-delay and there might exist some residual confounding factors. The very small number of TRG 4/pCR in LRT-delay did not allow for any multivariate analyses.

In our material, TRG 3 had more similar outcomes compared to TRG 0-2, even though the histopathological findings were more like TRG 4. Other studies have found that near complete or moderate tumour response is associated with improved survival.^{88,92} One study found a positive association only in cStage III patients.⁹⁷ Other studies found a more stepwise relationship in all TRG-grades, with better survival in higher TRG.^{91,291} Further, one study with focus on the near pCR patients concluded that these patients have at a higher risk for recurrence than expected.⁹⁵ The results from the Stockholm III trial indicates that patients with TRG 3 does not have the same excellent outcomes as patients with TRG 4/pCR. This might have implications in decisions on follow up or adjuvant treatment decisions.

One issue with this study is the long inclusion period. The way surgical specimens have been handled, dissected and prepared for microscopic examination have changed during the years. However, this effect is seen in all three randomisation arms and is not likely to affect the relative estimates. One strength in the study is that all slides have been assessed by one pathologist, which removes the interindividual variation. This have in other settings have been proven to be a major problem.⁸⁹

Oncological outcomes and survival

In Study I and IV, OS, RFS, incidences of LR and DM were not statistically different between the arms. There are some limitations in these estimates. First, the excellent incidence of LR make the non-inferiority design problematic. The initial upper CI-limit to deem non-inferiority (HR=1.7) was included in the CI of the point estimate. However, this was anticipated early after trial start and was accepted in the protocol amendment. The final conclusion regarding LR in the long-term follow up of the Stockholm III is that we are 90 % confident that SRT-delay is not 2.6 times worse than SRT. Under other circumstances this would might not be accepted as a decent level to claim non-inferiority. However, with the low levels of LR of today, the sample size needed to deem non-inferiority at the 1.7 level, would be considerably higher compared to the Stockholm III trial.

When analysing DM, the results are very similar in SRT and SRT-delay. Regarding OS and RFS there is a tendency of better outcomes in SRT-delay than in SRT, however not reaching statistical significance. RFS was chosen as one of the survival outcomes and not DFS, suggested by Punt et al.²⁷⁴ To calculate DFS, data on second cancers are needed which are not registered in the SCRCR. These results are on average in the whole cohort and there might be subgroups of patients with deviating outcomes.

Is it safe to delay surgery?

In these four papers we have shown that a delay to surgery has potential benefits. Post-operative complications are reduced and there is chance of downstaging and even pCR. The oncological outcomes in terms of LR, DM and survival are similar in the arms. However, there are some arguments against delaying surgery. First, in patients without tumour regression – TRG 0, the OTT is prolonged without any obvious gain. It is not easy to decide if this delay is harmful or not.

Patients with TRG 0-2 have inferior OS and TTR compared to patients with TRG 4. Many of the patients with high grade TRG also have longer OTT. In a supplementary analysis we included patients only with a delay to surgery, with the ambition to include only patients “at risk” for tumour regression. This did not change the results in a major way. TRG 0-2 was still associated with worse outcomes and this is probably due to different tumour biology. Further analyses of the effect of delaying surgery in subgroups based on tumour regression is not possible. The outcome is an effect of the exposure (delayed surgery). Second, patients that are considered for post-operative adjuvant treatment will have their start of chemotherapy delayed with several weeks. A possible negative effect on oncological outcomes in these patients, cannot be neglected. However, as discussed previously, the use of adjuvant chemotherapy in RC is controversial.

On the other hand, the interval between RT and surgery might be useful. There is time to optimise patients before surgery. Interventions of interest include smoking cessation, adjustment of cardiovascular medication, physical exercise and other types of prehabilitation. Further, logistic planning might be facilitated by a longer OTT, when it is possible to plan patients to certain procedures such as laparoscopic, robotic or open resections.

Future perspectives

During the last decades, outcomes for patients with RC have improved. Better preoperative staging, neo-adjuvant (C)RT and improved surgical technique have made it possible to achieve LR frequencies <5%. With modern intensive care and surgical technology perioperative mortality is rare. Some topics are however still of scientific interest.

Patient selection

There are evolving evidence that organ preserving strategies are safe and well tolerated.^{164,292} This has many implications for further research. One of the major questions are if we should irradiate more or less. In Sweden Watch and Wait (W&W) programs are based on cherry-picking, i.e the indications of RT are not changed. Patients with a near CR might enter a W&W program, all other will follow the standard program, which in most cases equals TME-surgery. The risk of expanding the indication for RT constitutes of overtreatment in patients without a cCR. In the new Swedish guidelines, the opposite direction is chosen (work in progress). The indication of RT is more restricted and fewer patients will receive neo-adjuvant RT. A study on choosing pathway would be interesting. The STAR-TReC trial, where patients are randomised to TME-surgery or organ-preserving strategy, is an interesting approach to deal with this issue.

In contrast to picking the winners, prediction of RT-response would be of most value. Focus has been on finding patients with excellent response, without finding any good predictive markers. Another approach might be to find patients with little probability of response, to be able to find a group of patients where RT can be avoided and/or to keep the OTT as short as possible.

Quality of Life

In the Stockholm III trial the median OS was about 10 years. With increasing survival, it is important to assure that all treatments are evaluated in the aspect of QoL. Patients without recurrences in the Stockholm III trial have been assessed by telephone interviews and questionnaires regarding QoL, and data is currently being analysed.

Tumour regression

At least two aspects of TRG assessment are important future research topics. First, the TRG assessment by MRI as an evaluation of treatment. MRI is now used as a screening tool to determine if patients are eligible for W&W programs or if surgery should be performed instead. It is important that radiologists and surgeons to have knowledge about the MRI, clinical and endoscopic findings in patients with potential cCR. Most data and reports come from highly specialised centres around the world. Today in Sweden, eligible patients are recommended to be referred to expert centres. However, the first screening is done at local hospitals, and the implementation of such practice much be followed by a scientific evaluation. Second, postoperative TRG-assessment suffers from large inter-individual variations. An attempt to minimise this has been presented by the pathologists in Leeds. The method is not yet fully published, but previous data indicates that the proportion of tumour cells in relation to stroma may predict survival.²⁹³ In short, the aim of the method is to decide the percentage of viable tumour cells using a digitalised assessment of the

“tumour density”. Some of the histopathological slides from patients in the Stockholm III trial have been examined and results are currently being analysed.

Radiation techniques

Technologies around RT are constantly being evolved including, MRI-based dose-planning, VMAT (volume based arc therapy), modern linear accelerators and proton radiation. These new techniques have the possibility of more effective RT with less acute and long term toxicity. Implementation of these techniques must be correlated with clinical outcomes in patients, and in collaboration with surgeons operating these patients.

Conclusions

Overall conclusion

Delaying surgery with 4-8 weeks after SRT in patients with RC appears safe regarding oncological outcomes and survival, with reduced number of post-operative complications. No benefits were found in LRT-delay.

Specific conclusions

- There were significantly less post-operative complications in SRT-delay compared to SRT. Radiation induced toxicity was seen in about 6-7 % in both the arms with a delay to surgery. The frequencies of LR were low, irrespective of allocated treatment. There were no statistically significant differences in the incidences of LR or DM in the arms. RFS and OS were similar in the arms.
- The lowest risk of post-operative complications was seen in the group with longest OTT (5-13 weeks) after SRT. There were no obvious advantages with surgery very early in the short interval after SRT.
- SRT-delay induces tumour regression and pCR more effectively compared to SRT and LRT-delay. pCR or TRG-4 are associated with improved OS and TTR.
- In the long-term follow up of Stockholm III, there were no statistically significant differences in the cumulative incidence of local- or distant recurrence. Median OS (95 % CI) was 8.14 (7.23-9.98), 10.18 (8.45-11.68) and 10.53 (6.95-11.34) years in SRT, SRT-delay and LRT-delay respectively, without statistically significant differences between the groups.

Sammanfattning på svenska

Tjock och ändtarmscancer drabbar mer än 6000 personer/år i Sverige och är den näst vanligaste cancerformen hos både män och kvinnor. Ca 1/3 av fallen är ändtarmscancer, vilket innebär att tumören sitter på mindre än 15 cm avstånd från ändtarmsöppningen. Den viktigaste behandlingsformen för att uppnå bot är kirurgi. Operationen innebär oftast omfattande bukkirurgi där hela, eller del av ändtarmen tas bort tillsammans med omkringliggande blod- lymfkärl och lymfknutor. Det finns två dominerande operationstyper. Antingen kan man rekonstruera tarmkontinuiteten genom en skarv – anastomos. Om detta inte är möjligt för att tumören växer för nära ändtarmsöppningen görs en s.k. rektumamputation som innebär att även ändtarmsöppningen opereras bort. I dessa fall måste en permanent stomi anläggas. Den relativa 3 årsöverlevnaden är 87 % hos patienter utan fjärrspridning (metastaser). Det är känt att risken för lokalrecidiv kan minskas med omkring hälften om strålbehandling ges innan operation, s.k. neoadjuvant radioterapi. Strålbehandling kan delas upp i många små enheter (fraktioner) eller färre, större fraktioner. Varje fraktions absorberade strålningsdos mäts i enheten Gray (Gy).

Denna avhandling belyser väntan till kirurgi efter olika typer av strålbehandling vid ändtarmscancer. Grunden till arbetet är Stockholm III studien. En stor multicenter studie som mellan 1998-2013 lottade 840 patienter till tre olika strålbehandlingsregimer.

SRT	5 stråltillfällen á 5 Gy och operation inom 1 vecka.
SRT-delay	5 stråltillfällen á 5 Gy och operation efter 4-8 veckor.
LRT-delay	25 stråltillfällen á 2 Gy och operation efter 4-8 veckor.

Samtliga patienter har följts upp i det Svenska KoloRektalCancerRegistret.

I **arbete I** analyserades samtliga patienter i studien efter att de följts i minst 2 år efter operation. De utfall som analyserades var akut strålningsbiverkan, postoperativa komplikationer, tid till lokalrecidiv, metastaser, total överlevnad och sjukdomsfri- överlevnad. Resultaten visade att SRT-delay och LRT-delay hade ungefär lika stor andel patienter som behöver sjukhusvård till följd av strålningsbiverkan, ca 6-7 %. I grupperna med väntan till kirurgi var det lägre andel patienter som drabbades av någon komplikation efter kirurgin. Skillnaden var störst och statistiskt säkerställd när man jämförde SRT och SRT-delay. Andelen som fick lokalrecidiv var mycket låg och det fanns inga skillnader mellan behandlingsarmarna. Total- och sjukdomsfri överlevnad var lika i armarna. Konklusionen var att det är säkert att fördröja kirurgin efter strålbehandling med dessutom minskad risk för postoperativa komplikationer.

Arbete II studerade de postoperativa komplikationerna i detalj. Syftet var att studera om det fanns några tidsintervall som kunde kopplas till extra bra eller dåliga utfall. Gruppen som fått kort strålbehandling (5 Gy x 5) delades upp i fyra grupper baserat på den totala behandlingstiden mellan strålstart och operation. Grupp A: 7 dagar, Grupp B 8-13 dagar, Grupp C 5-7 veckor och Grupp D 8-13 veckor. Resultaten visade att den minsta risken för komplikationer fanns i gruppen med

längst väntan till kirurgi, Odds Kvot någon komplikation, Grupp D vs. Grupp B (95 % Konfidens Intervall): 0.39(0.23;0.65) $p < 0.001$, efter att ha justerat för störfaktorer.

I **arbete III** analyserades de bortopererade tumörernas svar på strålning. Det är möjligt under mikroskopiundersökningen att gradera hur mycket en tumör har krympt ihop efter strålbehandling. En 5 gradig skala användes. 0 – Inget tumörsvar alls, 1 – dominerande tumörmassa utan ärrbildning, 2-dominerande ärrvävnad med endast lite tumörceller, 3- väldigt få tumörceller, 4- inga kvarvarande tumörceller endast ärrvävnad. Samtliga tillgängliga operationspreparat har eftergranskats av en patolog som inte visste vilken typ av behandling patienten hade fått. Resultaten visade att SRT-delay var den grupp som hade störst sannolikhet att ha tumörer med komplett tumörsvar (TRG 4), vilket skedde i ca 10 % av fallen. Patienter som hade komplett tumörsvar hade en klart förbättrad överlevnad och mindre risk för canceråterfall (både lokalt och metastaser) jämfört med grupperna som hade TRG 0-2.

Syftet med **arbete IV** var att studera långtidsutfallen i de olika behandlingsarmarna i Stockholm III studien. Data på återfall och överlevnad hämtades ånyo från registret när samtliga patienter följts i minst 5 år från kirurgi. Resultaten i arbete I bekräftades. Alltså, inga statistiskt säkerställda skillnader avseende lokalrecidiv, metastaser eller överlevnad hittades mellan armarna. Total medianöverlevnaden i armarna (95 % konfidensintervall) var: SRT 8.14 år (7.23-9.98), SRT-delay 10.18 år (8.45-11.68) , LRT-delay 10,53 år(6.95-11.34)

Sammanfattningsvis framstår det säkert att fördröja kirurgi efter 5 Gy x 5. De postoperativa komplikationerna kan minska, men till priset av akuta strålningsbiverkningar. Om kirurgin fördröjs 4-8 veckor efter strålning kan ca 10 % av tumörerna helt försvinna, dessa patienter har bättre överlevnad än övriga.

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