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Optimising Radiotherapy in Rectal Cancer Patients

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Abstract

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Rectal cancer is the eight most common cancer diagnosis in Sweden in both men and women, with almost 2000 new cases per year. Radiotherapy, which is an important treatment modality for rectal cancer, has evolved during the past decades. Diagnostic tools have also improved, allowing better staging and offering information used to make well-founded decisions in multidisciplinary team conferences.

In a retrospective study (n=46) with locally advanced rectal cancer (LARC) patients, unfit for chemoradiotherapy, patients were treated with short-course radiotherapy. Delayed surgery was done when possible. Radical surgery was possible in 89% of the patients who underwent surgery (80%). Grade IV diarrhoea affected three elderly patients. Target radiation volume should be reduced in elderly or metastatic patients.

In a prospective study (n=68) with LARC patients, magnetic resonance imaging (MRI) and 2-^{18}F-fluoro-2-D-deoxyglucose (FDG) positron emission tomography (PET) were used to determine if FDG-PET could provide extra treatment information. Information from FDG-PET changed the stage of 10 patients. Delineation with FDG-PET generally resulted in smaller target volumes than MRI only.

Seven of the most advanced LARC patients in the above cohort were used for a methodological study to determine if dose escalation to peripheral, non-resectable regions was feasible. Simultaneous integrated boost plans with photons and protons were evaluated. While toxicity was acceptable in five patients with both protons and photons, two patients with very large tumours had unacceptable risk for intestinal toxicity regardless of modality.

In the interim analysis of the Stockholm III Trial (n=303, studying radiotherapy-fractionation and timing of surgery in relation to radiotherapy) compliance was acceptable and severe acute toxicity was infrequent, irrespective of fractionation. Short-course radiotherapy with immediate surgery tended to give more postoperative complications, but only if surgery was delayed more than 10 days after the start of radiotherapy.

Quality-of-life in the Stockholm III Trial was studied before, during and shortly after treatment using the EORTC QLQ-C30 and CR38 questionnaires. Surgery accounted for more adverse effects than radiotherapy in all groups. Postoperatively, the poorest quality-of-life was seen in patients given short-course radiotherapy followed by immediate surgery. No postoperative differences were seen between the two groups with delayed surgery.

Keywords: Rectal cancer, locally advanced, radiotherapy, FDG-PET, peripheral boost, protons, quality-of-life

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Pentru familia mea

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Radu C, Berglund Å, Påhlman L, Glimelius B. "Short-course preoperative radiotherapy with delayed surgery in rectal cancer - A retrospective study." *Radiotherapy and Oncology* 2008 June; 87 (3) 343-349.

II Brændengen M, Hansson K, Radu C, Siegbahn A, Jacobsson H, Glimelius B. "Delineation of gross tumour volume (GTV) for radiation treatment planning of locally advanced rectal cancer using information from MRI or FDG-PET/CT: A prospective study." *International Journal of Radiation Oncology Biology Physics* 2011 Nov; 81(4): e439-445.

III Radu C, Norrlid O, Brændengen M, Hansson K, Isacsson U, Glimelius B. "Integrated peripheral boost in preoperative radiotherapy for the most advanced non-resectable rectal cancer patients." *In manuscript*.

IV Pettersson D, Cedermark B, Holm T, Radu C, Påhlman L, Glimelius B, Martling A. "Interim analysis of the Stockholm III trial of preoperative RT regime for rectal cancer." *British Journal of Surgery* 2010 Apr; 97 (4) 580-587.

V Radu C, Johansson B, Pettersson D, Martling A, Glimelius B. "Health-related quality of life during treatment in the Stockholm III Trial, evaluating different preoperative radiotherapy regimens for rectal cancer." *In manuscript*.

Contents

Abbreviations

LARC	Locally advanced rectal cancer
TNM	Tumour-node-metastasis (classification)
TME	Total mesorectal excision
pCR	Pathological complete remission
mrf	Mesorectal fascia
5-FU	5-fluorouracil
QoL	Quality of life
EORTC	European Organisation for Research and Treatment of Cancer
QLQ-C30	EORTC QoL questionnaire – Core 30
QLQ-CR38	EORTC QoL questionnaire – Colorectal 38
CT	Computerized tomography
MRI	Magnetic resonance imaging
PET	Positron emission tomography
FDG	2-^{18}F-fluoro-2-D-deoxyglucose
SUV	Standardized uptake value
RT	Radiotherapy
CRT	Chemoradiotherapy
SCRT	Short-course radiotherapy
LCRT	Long-course radiotherapy
SCRT group	Short-course radiotherapy with immediate surgery
SCRT-delay group	Short-course radiotherapy with delayed surgery
LCRT-delay group	Long-course radiotherapy with delayed surgery
Gy	Gray
GTV	Gross tumour volume
CTV	Clinical target volume
PTV	Planning target volume
OAR	Organs at risk
3D-CRT	Three-dimensional radiotherapy
IMRT	Intensity-modulated radiotherapy
RBE	Relative biological effectiveness
DVH	Dose volume histogram

Introduction

Colorectal cancer is the third leading cause of cancer-related death in the Western world and the incidence is slowly increasing. Approximately every third colorectal cancer starts in the rectum. While in early stages of rectal cancer surgery alone is enough for cure, in more advanced rectal cancer, radiotherapy (RT) or chemoradiotherapy (CRT) is needed to improve local tumour control and cure. Different RT regimens have been used. It has been shown that preoperative RT is superior to postoperative RT and that this should be standard [1-3]. The choice of RT or CRT in rectal cancer is made based on imaging from computerised tomography (CT) and magnetic resonance imaging (MRI) [4]. Deriving maximum information from radiological investigations can further improve treatment results.

Different preoperative regimens are studied in an on-going multicentre phase III-trial (the Stockholm III Trial) to find the optimal fractionation and timing of surgery. Patients with primary resectable rectal cancer are randomized to short-course preoperative RT (5 x 5 Gy, SCRT) followed by surgery within 1 week or after 4–8 weeks, or long-course preoperative RT (25 x 2 Gy, LCRT) with surgery after 4–8 weeks. The overall time from discovery of a more advanced rectal cancer until follow-up can be both long and filled with anxiety. Rectal cancer treatments may also have consequences both in the short and long run. Evaluation of quality-of-life (QoL) is therefore important.

Background

Anatomy of the rectum

The rectum is the lowest portion of the large intestine. It begins in the upper pelvis and ends at the anus. It lies mainly within the muscular and fatty tissue of the pelvis. The blood supply of the upper two thirds of the rectum drains into the liver whereas the lower third also drains to the lungs. This explains why the liver is often the first site of spread of colon cancer. Lung metastases are relatively more common in rectal cancer than in colon cancer. There are lymph nodes (Figure 1) immediately surrounding the rectum that drain into other lymph nodes cranially and laterally and subsequently higher in the abdomen, thus putting patients at risk of developing metastases there.

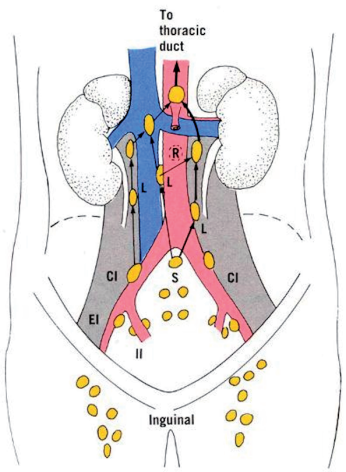

Figure 1. Lymph node drainage

Most lymphatic vessels from the pelvis drain into groups of nodes associated with the iliac arteries and their branches. The external iliac lymph nodes receive vessels from the inguinal nodes, external genitalia, vagina, and cervix; and they thereafter drain into the common iliac nodes. Internal iliac and sacral lymph nodes receive afferents from all the pelvic viscera (e.g., cervix, prostate, and rectum) and from the perineum, buttock, and thigh; they then drain into the common iliac nodes and nodes along the superior rectal artery.

Common iliac lymph nodes drain the two preceding groups and send their efferents to the lumbar group of aortic nodes, which also receive the afferents of the testis and ovary. The lower part of the anal canal and also the external genitalia drain into the inguinal nodes.

Rectal cancer can spread by haematogenous metastasis, regional lymph node metastasis, perineural growth, intraluminal metastasis and by direct extension through the bowel wall.

Epidemiology

Incidence and trends

Annually there are close to 2000 cases of rectal cancer diagnosed in Sweden. Almost all cases (90-95%) are adenocarcinoma (Figure 2). Together with colon cancer it is the second most common cancer both in men (preceded by prostate cancer) and in women (preceded by breast cancer).

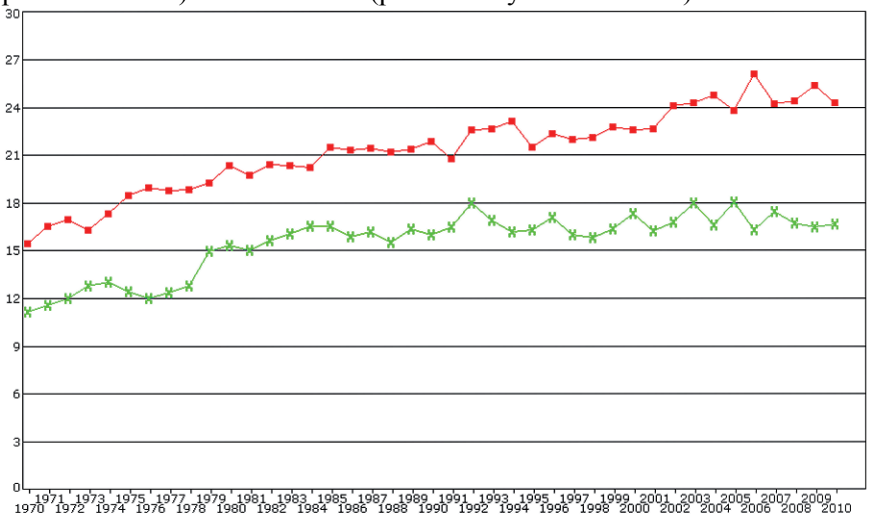

Figure 2. Incidence of rectal adenocarcinoma per 100 000 inhabitans in Sweden between 1970-2010, red male and green female (Socialstyrelsen)

The number of cases of rectal cancer and colon cancer has increased steadily over the past 30-year period. After correction for the increased population and the increasing age of the population there is only a slight increase in the age-standardized incidence.

Rectal cancer mainly affects the elderly in the population with a median age of 74; about 75% of cases occur after the age of 65. Only about 5% of patients are younger than 50 years. It is diagnosed more often in males. Slightly more than half of the patients are cured from their rectal cancer and this group has the same mortality as the general population.

Aetiology

The actual cause of rectal cancer is unclear. However, the following risk factors for developing rectal cancer are known: increasing age, smoking, family history of colon or rectal cancer, high-fat diet and/or a diet mostly from animal sources and limited physical activity.

An often forgotten risk factor for death due to rectal cancer is the lack of screening. Routine cancer screening of the colon and rectum is the best known way to detect rectal cancer at an early stage.

Rectal cancer mostly occurs after transformation within adenomatous polyps. About 85% are sporadic, and the rest have an inheritable component. Predisposing factors include chronic ulcerative colitis and granulomatous colitis; the risk of cancer increases with the duration of these disorders. Other risk groups are patients who have been previously treated with RT.

Symptoms

Colorectal adenocarcinoma grows slowly, and there is a long interval before the tumour is large enough to cause symptoms. Symptoms depend on lesion location, type, extent of growth and complications.

Rectal cancer can cause many symptoms that require a person to seek medical care. However, rectal cancer may also be present without any symptoms. The most common presenting symptom is bleeding with defecation. Whenever rectal bleeding occurs, even with obvious haemorrhoids or known diverticular disease, coexisting cancer must be ruled out. Tenesmus or a sensation of incomplete evacuation may be present. Pain is common with perirectal involvement. Obstruction and unexplained weight loss are also symptoms that need further investigations. Any change in bowel habits in adult patients should alert physicians to the possibility of an underlying colon or rectal tumour. Some patients first present with symptoms and signs of metastatic disease (e.g. hepatomegaly, ascites, supraclavicular lymph node enlargement).

Diagnosis and staging

If a tumour in the rectum is discovered by any of the staging procedures mentioned, a biopsy needs to be performed. The histopathological examination of the biopsy is part of the tumour staging and gives information about tumour type and grade of dysplasia.

The stage describes the extent of the cancer in the body. It is based on how far the cancer has grown into the wall of the intestine, whether or not it has reached nearby structures, and whether or not it has spread to the region-

al lymph nodes or distant organs. The stage of a cancer is one of the most important factors in determining prognosis and treatment options.

Staging usually includes digital examination, rectoscopy with biopsy, colonoscopy, ultrasound, CT and MRI. Transrectal ultrasonography is mostly used in early tumours to determine the extent of infiltration into the muscle wall.

CT scans with contrast are mostly used to determine if there is a spread in thorax or abdomen. It is also used for RT planning. CT scanning is an effective method to detect and map the occurrence of metastasis or relapse after completion of surgery. The development of CT scans gives us better precision, spatial resolution and speed study.

MRI of the pelvis can be used to preoperatively evaluate if the tumour is confined to the bowel wall, has spread into the mesorectal fat or grows close to or involves the mesorectal fascia (mrf) or infiltrates adjacent organs in the pelvis. Based upon this staging surgeons know if it is possible to radically resect the tumour without any preceding therapy. Mesorectal and other regional lymph nodes can be shown but the method still has limitations in diagnostic accuracy when it comes to assessing whether these contain tumour growth or not. The investigation of locally advanced and large pelvic tumours with MRI is of great value for treatment planning, and MRI is now standard in all such cases.

Positron emission tomography (PET) using 2-^{18}F-fluoro-2-D-deoxyglucose (FDG) can visualize the enhanced glucose utilization in tumour tissue. The amount of FDG accumulated is proportional to the rate of glucose utilization. The Standardized Uptake Value (SUV) was introduced as a semi-quantitative measure of ^{18}F -FDG uptake. Over the past few years FDG-PET/CT has become an additional modality in tumour mapping. The information from PET and RT studies is increasing rapidly, especially in head and neck cancer [5,6], lung cancer [7] and Hodgkin´s lymphoma [8]. There are few studies describing rectal cancer and delineation of gross tumour volume (GTV) with the help of PET and none that have made comparisons to up-to-date staging including pelvic MRI, with the exception of one very recent publication [9]. One limitation of PET is the lack of contrast resolution for soft-tissue structures, which can lead to inter- and intra-observer variations in delineation of GTV [10,11]. This is evident in the difficulty of agreeing upon the best methodology for PET imaging [12-14] and upon how to use it in GTV delineation. Even if CT scanning remains the clinical standard for volume definition and dose calculation, PET/CT has potential to better define limits and thus minimize dose to organs at risk (OAR) and to possibly increase dose to target volumes.

The most commonly used staging system for colorectal cancer is that of the American Joint Committee on Cancer (AJCC), sometimes also known as the TNM system. It is regularly updated. TNM5 (Table 1), from 1997, was mostly used in the studies described in this thesis. It has recently (2010) been

replaced by TNM7 (TNM6 from 2002 never came to more widespread use in Sweden).

Table 1. American Joint Committee on Cancer (AJCC) TNM5

	Primary Tumour (T)
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissues
T4	Tumour directly invades other organs or structures and/or perforates visceral peritoneum
	Regional Lymph Nodes (N)
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes
	Distant Metastasis (M)
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

TNM5				**Dukes**
Stage 0	Tis	N0	M0	
Stage I	T1	N0	M0	A
	T2	N0	M0	
Stage II	T3	N0	M0	B
	T4	N0	M0	
Stage III	Any T	N1	M0	C
	Any T	N2	M0	
Stage IV	Any T	Any N	M1	D

Another factor that affects survival is the differentiation (grade) of the cancer, which is a description of how similar the cancer looks to normal colorectal tissue when seen under a microscope. Differentiation can be low, moderate or high.

Prognosis

The chance of curative treatment depends entirely on tumour stage at diagnosis. Of patients with rectal cancer stage I over 95% are presently cured, in

stage II 80% and stage III around 50%. The chance of cure in rectal cancer patients with metastases (stage IV) is very small and varies between 0-12%. From a statistical point of view, patients with a rectal cancer can be regarded as cured after 7 years of follow-up with no relapse [15].

The 5-year cancer-specific survival rate for rectal cancer patients diagnosed during 1995-2003 was 62%. Based on different tumour stages, the relative 5-year survival for patients in Stages I, II, III and IV was 95.1%, 78.3%, 55.4% and 3.1% respectively [16].

Treatment

Treatment of rectal tumours depends on the stage of the cancer. Surgery is of the utmost importance. To achieve long-term survival it is mandatory that the rectal tumour can be removed radically. An exception can be very early tumours managed with radical RT only [17]. This is rarely practiced in Sweden. RT and/or chemotherapy increase the patients' chances of remaining tumour-free.

The decision to forego surgery is more dependent on the patient's overall health than the tumour spread. However, better medical and oncological treatments have challenged the surgical tradition in patients with primarily metastatic disease. Nowadays combinations of RT and chemotherapy in palliative patients with metastases can be sufficient and surgery is not always mandatory.

Surgical treatment

Tumour size, extent and distance from the anus for rectal cancer is crucial for the choice of surgical procedure, but other important factors that should also be taken into consideration are the patient's age, presence of co-morbidity and sphincter function.

Surgery for rectal cancer is more difficult than surgery for colon cancer. Well-trained and experienced surgeons should perform it. Preferably two experienced surgeons, working together as a team should perform surgery.

Three approaches are possible when striving for curative surgery of rectal cancer:

- Anterior resection with anastomosis, with or without a colonic reservoir
- Anterior resection without anastomosis (Hartmann's surgery) and
- Rectal excision with permanent colostomy (abdomino-perineal resection)

Total mesorectal excision (TME) is gold standard, and has been shown to be the surgical technique of choice, to substantially reduce local recurrences [18-20]. The technique involves a precise dissection in an anatomically well-defined plane outside the mrf down to the pelvic floor. In higher tumours, the same precise dissection outside the mrf must be done, but the entire mesorectum down to the pelvic floor is not always removed.

Other forms of more limited surgery may be indicated where the intent is palliative (although in some cases it can result in cure). These include various forms of local, endoanal or transsacral operations. These are more and more often done using special equipment (trans-anal endoscopic microsurgery).

Oncological treatment – radiotherapy and chemoradiotherapy

For decades, rectal cancer has been clinically categorized as primary resectable (primary surgery for cure being possible) or non-resectable, where some form of pre-treatment is required to enable adequate radical surgery. The boundary between these two options has not been sharp but instead highly dependent on the surgeon's skills.

Nowadays with better staging methods and multidisciplinary team conferences we can discuss which approach is best for the individual patient. The terminology of the European Rectal Cancer Consensus (EURECA) project [21,22] is used, dividing rectal cancer into three groups: early, intermediate and locally advanced (also designated “T4 non-resectable”). The terms “good”, “bad” and “ugly” have also been used for these three groups [23] dividing rectal cancer patients into three risk groups:

- -“Good”: early cancers where the risk of local failure is very low and thus with no need of pre-treatment (30-40%),
- -“Bad”: tumours considered intermediate where the risk of local recurrence is increased and motivates pre-treatment with RT (40-60%),
- -“Ugly”: locally advanced rectal cancers (LARC) where the risk of not being able to perform radical surgery is so high that it motivates pre-treatment with RT and/or chemotherapy with a delay before surgery to allow downstaging/downsizing (10-15%) [24]

This definition is adjusted to the therapy tradition in Sweden and predicts the local failure risk (Table 2). RT alone is capable of eradicating some small localized rectal tumours [17] while its effect on larger tumours is limited by normal tissue tolerance.

RT alone in early rectal cancer (the “good” group) might be a feasible alternative to local excision in patients with poor performance status or for those who refuse surgical treatment. Organ preservation might be achieved

with RT alone (boost) or with CRT. This approach needs careful follow-up and surgery if the tumour does not regress completely or relapses.

Table 2. MRI-directed pre-operative evaluation practised presently in Uppsala and Stockholm, Sweden, modified after Blomqvist et al. [23]

Favourable "good" group	**Intermediate "bad" group**	**Advanced "ugly" group**
mid/upper rectum T1-3b low rectum T1-2	mid/upper rectum T3c/d low rectum also includes T3a/b	T4 with overgrowth to adjacent organs and structures, positive lateral lymph nodes
N0	N1/N2	any N
mrf clear	mrf clear	mrf positive
5-years LFR** < 10%	5-years LFR** 10-20%	5-years LFR** 20-100%
Primary surgery (TME) or organ preserving (RT/CRT)	Preoperative SCRT with immediate surgery (TME)	Preoperative CRT or SCRT with delayed surgery

*The algorithm does not primarily address the risk of systemic disease, although this risk also increases with the presence of many of "the risk factors", however, not necessarily parallel to the local failure rate (LFR). The grouping is thus different in the RAPIDO Trial, where also the risk of systemic disease is considered. Mesorectal fascia (mrf) or the corresponding structures at or below the levator level < 1mm is positive.
**Calculated in the group of patients planned for surgery, i.e. irrespective of the surgical outcome. The figures are valid if the surgeon is an experienced rectal cancer surgeon and no pre-treatment is given.

Rectal cancers are rarely so sensitive to RT that they can be eradicated without damaging surrounding tissues. OARs for radiation injury are the small bowel, urinary bladder, anal sphincter, ureters, femoral heads and nerves. The first and primary indication for RT in addition to surgery is to prevent local recurrences and, secondary to improve survival. The loco-regional RT cannot influence the risk of microscopic spread beyond the primary site.

Several randomized trials have shown that RT given pre- or postoperatively reduces the risk of local recurrence. The tumour cell killing effect at a given radiation dose is best if the RT is given preoperatively [25-27].

Results from three large Swedish studies and a Dutch-Swedish study show that preoperative SCRT reduces local recurrence risk by 50-70% both in combination with TME and with non-TME surgery [28-32]. Meta-

analyses have shown that preoperative RT increases 5-year overall survival and reduces the risk of local recurrence in patients with resectable rectal cancer [33,34].

Preoperative RT has been predominantly used in Europe. In the U.S., postoperative RT has most frequently been used. The advantage of postoperative RT is that you know the tumour stage and can treat only the group which is most in need of treatment, previously stage II and III, now with positive circumferential margin. Internationally a conventionally fractionated RT with doses of 1.8 to 2 Gy daily up to a total dose of 45 to 50.4 Gy in about five weeks has been used. This treatment is usually combined with chemotherapy [35].

Local failure rates in intermediate tumours (the "bad" group) with both TEM surgery and preoperative RT have been dramatically reduced. Preoperative SCRT with immediate surgery is presently the standard choice in this group based upon the results of the randomized studies.

Different RT treatments, with or without chemotherapy, have been studied in several randomized trials. Chemotherapy added to RT could act as a radiosensitizer. It has been shown that conventionally fractionated RT combined with chemotherapy increases local tumour control and possibly also survival [36-39]. Oral capecitabine or UFT / leucovorin has an effect comparable to intravenous 5-FU used in the randomized trials and is presently preferred because of convenience. Furthermore it has been shown that preoperative CRT improves local tumour control and possibly improves disease-free survival when compared to postoperative CRT [2]. A Polish trial has shown that preoperative SCRT is comparable to preoperative CRT treatment with regard to local tumour control and survival [40]. The same findings were more recently reported also in an Australasian study [41]. A randomized British trial showed that local tumour control and disease-free survival is better with preoperative SCRT than postoperative CRT given to patients with positive mrf or other high-risk criteria for local recurrence [3]. When RT is given together with chemotherapy both acute and late side effects can become more pronounced. Dose-reductions are frequently necessary which could possibly affect overall outcome.

There is a major disagreement in the literature on what is considered a locally advanced rectal cancer, or LARC. The intermediate ("bad") group is internationally popularly termed LARC and is the group included in most recent trials evaluating different CRT protocols. In Sweden and Norway, the term LARC is reserved for the ugly tumours and corresponds to the tumours that previously were considered "inextirpable". Braendengen et al. [38] showed that local control can be achieved in about 82% of the LARC patients provided they are treated with preoperative CRT consisting of 5-fluorouracil (5-FU) and 50 gray (Gy) followed by attempts at radical surgery. A subgroup of these patients has very advanced tumours with over-

growth to e.g. the lateral pelvic sidewalls and upper part of the sacrum (here designated “ugly-ugly”).

Studies have indicated that increased RT-dose is advantageous[42], and some groups have tried to find strategies for giving total doses of 66 Gy in 2 Gy fractions or more without compromising OAR [43-46]. The pelvis and perineum are especially difficult areas to irradiate because of the proximity of the urinary bladder, small intestine and internal genital organs, and risk for both acute and late toxicity must be considered. The irradiated volume of small bowel may be reduced by creating a conformal dose distribution that tightly matches the usually horseshoe-shaped planning target volume (PTV) of rectal cancer, using techniques such as intensity-modulated RT (IMRT) [47-49].

RT techniques have improved in time with more sophisticated modalities such as IMRT with photons or even protons. Treatment planning and methods of fixation of the patient have also evolved. The dose distributions obtained from IMRT treatments are superior to those obtained from three dimensional conformal RT (3D-CRT), which in turn are better than only radiating with two beams without computer planning. To make the best use of the improved RT techniques optimising the fractionation schedules and combining with sensitising drugs should be considered.

Three-dimensional imaging is a very important aspect of RT. The primary tumour volume is defined as the GTV. The clinical target volume (CTV) includes the GTV and a margin around it for assumed sub-clinical disease. The PTV includes the CTV and a margin around it to account for organ movement and patient set-up errors. The dose delivered to PTV represents the dose intended for CTV and ensures that the prescribed dose is delivered to the CTV [50,51]. Normal tissues in the area are designated OARs.

The optimisation of a 3D-CRT treatment plan is made by varying beam energy and beam weight or by applying beam modulators such as wedge filters. For an IMRT planning the computer optimisation determines all these factors. IMRT delivery techniques have developed dramatically since the end of the 1980s.

Protons have special physical characteristics that allow the dose to be delivered precisely in the culmination of their so-called Bragg peak, after which the dose is close to zero. When directed at a target, there will be dose delivered as protons enter the body, but not behind the tumour target, after they have stopped. By proper selection of beam directions, this minimizes irradiation of healthy surrounding tissues. The biological effect of a proton beam is close to those of photons although the protons have higher relative biological effectiveness (RBE) compared to photons. For clinical use the RBE for protons is considered to be about 1.1 [52].

The Stockholm III Trial

SCRT is considered standard treatment in Sweden and in many other countries in the intermediate "bad" group, but it may induce both acute and late morbidity, and has been claimed to cause more late morbidity than LCRT [53]. Late toxicity from SCRT has been extensively reported [54-57], whereas reports about late toxicity from pre- or postoperative LCRT with or without chemotherapy are more scarce [55].

A multicentre randomized trial started in 1998 to address the issues about the best fractionation but also the best timing of surgery in relation to RT (Clinicaltrials.gov registration number NCT00904813). The trial started before MRI was used as a diagnostic standard and the intent was to include early and intermediate tumours. It is still on-going and nowadays includes mostly patients from the "bad" group. Patients can be randomized to SCRT followed by surgery within 1 week (hereafter SCRT group) or after 4–8 weeks (hereafter SCRT-delay group), or LCRT (hereafter LCRT-delay group) with surgery after 4–8 weeks. A hospital can choose to participate in the three-armed comparison (SCRT, SCRT-delay or LCRT-delay) or a two-armed comparison of early vs. delayed surgery after SCRT (SCRT or SCRT-delay) (Figure 3).

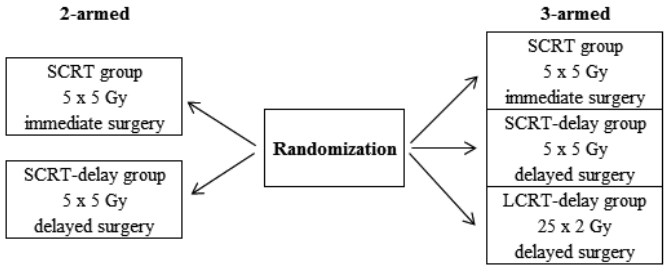

Figure 3. Randomization within the Stockholm III Trial

Primary endpoint in the trial is time to local recurrence. Secondary endpoints are acute and late toxicity, postoperative morbidity, QoL and overall survival. It aims to include 840 patients. In February 2012, 758 patients had been included and accrual is continuing.

Quality of life (QoL)

Health-related QoL has been studied in many trials and patient-reported outcomes have become standard in many oncological trials. The side effects from rectal cancer treatment can be substantial, and both acute and chronic. QoL is therefore important both in the short-term and long-term perspec-

tives. Late consequences from rectal cancer surgery have been well described [58].

Birgisson et al. [55] found in a meta-analysis that the most common late adverse effects of RT were bowel obstruction, bowel dysfunction (faecal incontinence) and sexual dysfunction. Several different RT regimens were included in the meta-analysis, offering some insight into how complications correlated with fractionation and dosage. Overall, in the more recent studies which used better radiation techniques and smaller target volumes, the rates of adverse events were lower. The number of studies that have evaluated long-term effects are, however, rather limited, preferentially restricted to the SCRT trials and no conclusions as to the best schedule can be drawn. Unfortunately, to date, no specific markers have been identified that might help predict which patients have higher risk of acute RT toxicity.

In another overview [57] the authors discuss the different late side effects from RT and CRT and conclude that it is important to focus on high-quality assessments of treatment impact on general health, bowel, urinary and sexual function.

QoL can in colorectal cancer, alongside with other instruments, be measured with a cancer-specific core instrument as the European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire (QLQ-C30) [59], and with a colorectal-specific QoL questionnaire as the EORTC Colorectal QoL Questionnaire (QLQ-CR38) [60].

Aims

- to retrospectively investigate the outcome of SCRT with delayed surgery in elderly and co-morbid patients with LARC unfit for standard therapy with CRT with respect to palliation, resection rate, survival and adverse effects. (Paper I)

- to investigate the usefulness of PET/CT for RT target definition and detection of systemic disease in LARC patients. (Paper II)

- to investigate in a model study the feasibility of dose- escalation to peripheral areas of CRT in the locally most advanced rectal cancer patients with non-resectable tumours. (Paper III)

- to investigate the feasibility of SCRT with delayed surgery and compare this to SCRT followed by immediate surgery and LCRT treatment with delayed surgery within the Stockholm III Trial. (Paper IV)

- to investigate QoL during the preoperative treatment and immediate postoperative period of patients within the Stockholm III Trial. (Paper V)

Materials and methods

Paper I

Between January 2002 and December 2005, 247 patients with rectal cancer have been irradiated at the Department of Oncology in Uppsala. Seventy of these received SCRT with delayed surgery and 21 patients, all with a resectable cancer, were randomized within the Stockholm III Trial. The remaining 49 patients were treated outside of the trial. Three of these had a resectable cancer (cT2-3NXM0), but were for various reasons treated outside of regular clinical protocols. All three patients later had surgery and two of them had a pathological complete remission (pCR). The clinical records of the remaining 46 patients with non-resectable primary tumour (cT4) were retrospectively evaluated for the patients treated with SCRT outside of the Stockholm III Trial.

With the exception of two patients, all patients were adequately staged with pelvic (35 MRI, 9 CT), lung (chest x-ray or CT) and liver imaging (usually CT) at diagnosis. All patients were re-staged 4 – 6 weeks after the end of the RT. Most assessments were made at a multidisciplinary team conference.

The RT was given with 5 Gy in 5 fractions during 5 consecutive workdays according to department routines. With the exception of a few individuals, all patients underwent dose-planning CT and an individualized CTV was done, including the GTV with margins and regional lymph nodes, depending upon tumour location.

Paper II

From 2007 to 2009, 77 consecutive patients with LARC ("ugly") were prospectively screened for inclusion in the study at two university hospitals in Sweden (Karolinska in Stockholm and Akademiska in Uppsala). All patients were planned for treatment following the standard guidelines in the actual institution, independent of inclusion in this study. The patients consented to undergo a PET/CT investigation and all examinations were evaluated at the multidisciplinary team conferences to be of sufficient quality for staging. Sixty-eight patients were eligible (technically adequate imaging and an interval between the routine CT and MRI investigations and the PET/CT of maximally 60 days).

The MRI images were not matched with the CT and were reviewed on a separate screen. The CT examination from the PET/CT, done in supine position and in the radiation treatment position, was used as CT simulation to define the active tumour and target volumes. Standard GTV was delineated using information from clinical examination, CT and MRI (GTV-MRI). Thereafter a "GTV-PET" was defined in the fused PET/CT, and the target volume delineations were compared for total volume, overlap and mismatch. Pathological uptake considered to represent metastases was also registered. No autocontouring was used. We adjusted the background intensity to what we considered "normal" based on general FDG uptake in the liver. Areas with elevated FDG uptake not explained by normal anatomical structures were considered as tumour tissue. No adjustment of the GTV-MRI was done after incorporating FDG-PET/CT information.

Paper III

Out of the 77 patients in paper II, 7 had very advanced tumours (all cT4a) with overgrowth to non-resectable structures (pelvic side walls including lumbo-sacral plexus or sacrum above S3) and were therefore selected for this dose escalation study. GTV-boost was delineated around these overgrowth regions within a peripheral part of the GTV-tumour. Target volume definition (according to Radiation Therapy Oncology Group-guidelines [61]) and OAR were outlined once on the same PET/CT-scan for both photon and proton planning. Intestinal cavity (the region where small bowel loops might be found during treatment) was defined according to studies done by Sanguineti and Fiorino [62,63]. We favour using intestinal cavity rather than small bowel loops as it is impossible to account for intestinal movement.

Photon and proton plans with simultaneously integrated boost were optimised to deliver 45 Gy to the lymph nodes, 50 Gy to the delineated tumour and 62.5 Gy to the boost-areas in 25 fractions. To estimate the robustness of the plans for changes in intestinal gas filling, the gas in the PTV was delineated for all patients. Both proton and photon plans were then recalculated with the gas replaced by water equivalent material.

Comparison of intestinal cavity volumes with the volumes recommended by Fiorino et al. [63] and Roeske et al. [64] were done to evaluate the acute toxicity (diarrhoea and other gastrointestinal toxicity) of the small bowel.

Late toxicity (obstruction/perforation/fistula) of the small bowel was estimated from the dose volume histograms (DVH) of intestinal cavity with the Lyman-Kutcher-Burman's model and the effective volume method with the parameters (TD_{50} = 55 Gy, n=0.15, m=0.16) [65-67].

Paper IV

Interim analysis of the Stockholm III Trial. The trial includes "resectable" rectal cancer patients with adenocarcinoma who are randomized between three preoperative arms. Doctors and patients can choose between inclusion

in a 2-armed or 3-armed study. Most hospitals participate in the 3-armed study, but at some hospitals a patient can also be included in the 2-armed comparison. The first 303 patients treated between 1998 and 2005 were analysed as part of a first planned interim analysis.

In the early years of the study, no individual tumour target was drawn, but this practice became more common with time at most centres. The upper beam limit was typically at the middle of the L5 vertebrae at the start of the study and lowered to L5-S1 or the middle of S1 in later years.

The patients underwent anterior resection, abdomino-perineal resection or Hartmann's procedure. The standard operation included TME. Patients randomized to the SCRT with direct surgery were scheduled for surgery 1–7 days after the completion of RT. In the delayed surgery groups operation was planned for 28–56 days after the completion of RT.

Paper V

Patients included in the Stockholm III Trial were asked if they wanted to participate in a QoL-study during treatment. The study commenced 2 years after the start of the main study. From January 2001 to the end of January 2010 total accrual in the Stockholm III Trial was 454 patients at hospitals participating in the QoL-sub-study. At the end of January 2010, 304 patients (67%) were included in the QoL-study and completed forms at 5 different stages (time-points) of their treatment. QoL has been assessed by the QLQ-C30 and QLQ-CR38, developed and validated by the EORTC.

According to the questionnaire manuals [68], missing values were dealt with as follows; if at least one-half of the items on a scale were completed, the scale score was divided by the number of items present. If less than one-half of the items were completed, the scale was considered missing.

The QLQ-C30 contains 30 questions, and it is subdivided into five functional levels (physical, role, emotional, cognitive, and social), nine symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), and one global health status and quality of life (global QoL) scale. Subscale-scores are transformed to a score ranging from 0 to 100. A high score for a functional scale represents a high level of functioning, and a high score for the global QoL scale represents a high QoL. In contrast, a high score for a symptom scale represents significant symptomatology for the patients.

The QLQ-CR38 consists of 38 questions: 19 questions are completed by all patients, and the remaining 19 are divided into groups of questions relevant for subsamples of patients only (i.e., male or female, patient with or without a stoma). The CR38 is subdivided into four functional scales (body image, sexual functioning, sexual enjoyment, and future perspective) and eight symptom scales (micturition problems, gastrointestinal tract symptoms, chemotherapy side effects, defecation problems, stoma-related problems,

male and female sexual problems, and weight loss). Scoring is equal to that for the QLQ-C30.

Clinical guidelines for interpretation of QLQ-C30 subscales presented by Cocks et al. [69] were used. Cocks meta-analysis provides mean difference intervals for “trivial, small, medium and large” clinical changes for all subscales except emotional functioning due to the medium estimate being lower than the estimate for small effects.

Statistical analyses

Descriptive statistics were used in paper I, II and III. T-test for paired data was used in paper II.

The sample size in the Stockholm III Trial (paper IV) was set to 840 patients to obtain a statistical power of 80% to demonstrate equality in local recurrence rates (15% after 5 years) between the two short-course treatments. The study has a statistical power of 70% with the addition of the long-course treatment. Distributions, in paper II, were compared with the chi-square test of independence or Fisher's exact test. The Kruskal–Wallis test was used for comparison of age between the study groups. In the analysis of event-specific rates, patients were considered to be at risk of the studied event until death, emigration or end of follow-up. Event-specific hazards modelling were carried out using Cox's proportional hazards regression model. Results are presented as odds ratios with corresponding 95% confidence intervals.

In the QoL-study (paper V), patient characteristics at baseline were compared using chi-square test, t-test and analysis-of-variance (ANOVA) for both the included patients and for those who did not enter the study. Differences in QoL between treatment arms were evaluated at baseline, after one week of RT, 3-8 weeks after the last RT fraction but before surgery and postoperatively after 4-8 weeks, 8-13 weeks and later than 13 weeks, respectively by ANOVA with repeated measures. Treatment by time interactions were analysed primarily in the 3-armed randomization sub-group (n=158). The Least Significant Difference Test (LSD) was used for pairwise comparisons among means in case of statistically significant treatment by time interactions. When QoL was compared between the SCRT groups only (SCRT and SCRT-delay), all randomized patients into those groups were analysed (n=247).

Results

Paper I

We identified 3 different groups of patients who were treated with SCRT and delayed surgery. The first group (A) had non-resectable, non-metastatic rectal cancer (T4NXM0). Of the 24 patients in group A, 13 were of a very high age (chronological and biological above 80 years) with some co-morbidity, 7 had high age and severe physical co-morbidity and 4 had severe psychiatric and/or a social situations preventing prolonged RT (± chemotherapy). In group B (T4NXM1, n = 9), the patients had predominantly loco-regional disease and were not candidates for palliative combination chemotherapy, usually because of high age and co-morbidities. The patients in the third group (C, n = 13) had T4 tumours with synchronous distant metastases and were candidates for up-front chemotherapy, a few with the intention to have surgery of both the primary and the secondaries if sufficient regressions at both sites were seen. The patients in the first two groups (A + B) were elderly (median 79 and 76 years, respectively), and had clinically significant co-morbidity. In group (C), the median age was 63 years.

The SCRT was well tolerated by most patients, but grade IV diarrhoea was recorded in three elderly patients. One patient in group (C) died from neutropenic fever caused by preceding chemotherapy. Retrospectively, the interval between chemotherapy and radiation was too short for this patient.

Many patients were reported to have a reduction of local symptoms after the treatment was given. Delayed surgery was performed in all but nine patients. Radical surgery (R0 + R1) was performed in 22 (92%) (group A), 4 (44%) (group B) and 6 (46%) (group C) patients, respectively. A pCR was seen in four patients (two in group A and two in group C). Metastatic surgery was possible in 2 patients, one of them have been recurrence-free 31 months after diagnosis. No postoperative deaths occurred. Overall survival is shown in figure 4.

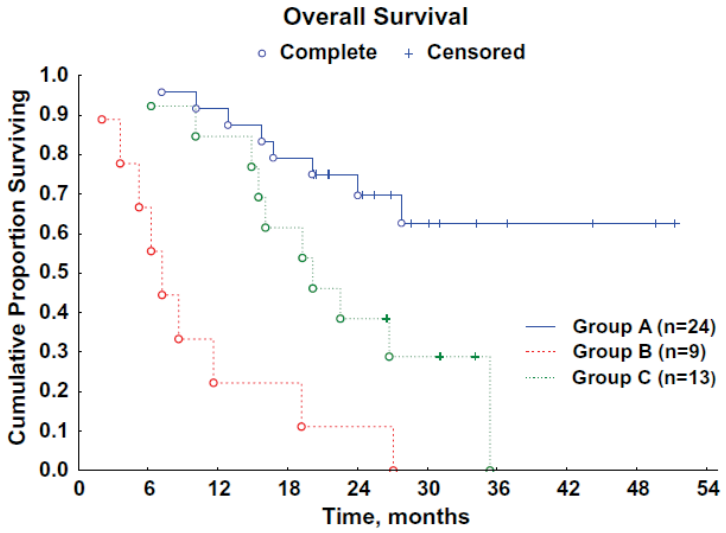

Figure 4. Overall survival from the radiation therapy (5 x 5 Gy) in the three groups; A: T4NXM0 with contraindications to radiochemotherapy, B: T4NXM1 treated for palliation with contraindications to radiochemotherapy and combination chemotherapy, and C: T4NXM1, treated up-front with combination chemotherapy and later with 5 x 5 Gy.

Paper II

Fifteen percent of the tumours were located in the upper third of the rectum, 44% in the middle third and 41% in the lower third. About one quarter had clinical stage cT3, all mrf+, and three quarters cT4. Sixteen percent in cT3 had N+ disease and 51% in cT4. Thirty-two percent in total had distant metastases, but only 4% in the cT3 group.

Median volume of GTV-MRI was larger than GTV-PET, 111 cm^3 versus 87 cm^3 ($p<0.001$). In many cases the GTV-MRI contained the GTV defined on the PET/CT images as sub-volumes, but when calculating a "GTV-total" after adding GTV-PET to GTV-MRI, the volume increased with median 11% (range 0.5-72%). New lesions or altered interpretation of a lesion outside the regional tumour area were seen in 15% of the patients using PET/CT (Table 3). One patient was restaged from cT3 to cT4, and one patient was downstaged from M1 to M0, having no FDG uptake in enlarged and thus suspect lymph nodes close to the renal artery.

Table 3. Changes in pre-treatment stage using PET/CT after standard clinical and radiological evaluation

Lesions	n	%
T3 to T4	1	2
N0 to N+	3	4
N0M0 to N+M1	3	4
M0 to M1	2	3
M1 to M0	1	2
Changes in total	10	15
No change	58	85

Paper III

Proton and photon plans reached equally good conformity to the three PTVs. The mean volume for the intestinal cavity was 913 cm^3 (range, 615-1157 cm^3). One of the patients (no 57, with the largest tumour and inguinal metastasis, where the CTV included more than 40% of the intestinal cavity) had unacceptably high doses to the intestinal cavity at all measured levels. Patient no 55, with the GTV-boost adjacent to the intestinal cavity, also had high doses to the intestinal cavity for both plans and unacceptable dose in the photon plan with 53.6 Gy. The rest of the patients' intestinal cavity doses were acceptable (dose levels under those recommended by Fiorino [63]), with proton plans generally being superior for doses under 45 Gy (Figure 5). The estimated probability for late toxicity at the endpoint obstruction/perforation/fistula was acceptable except for the two most advanced patients described above.

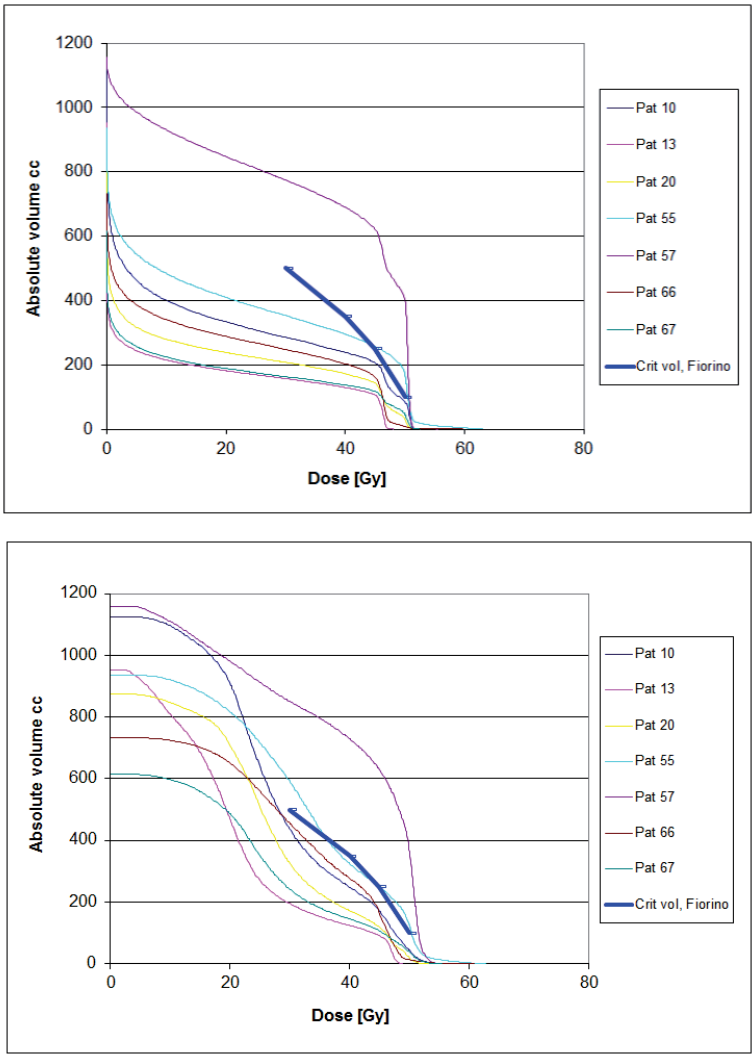

Figure 5. Dose volume histogram (DVH) for intestinal cavity for protons (top) and photons (bottom) with critical volumes recommended by Fiorino mapped

The proton plans spared the bladder better than the photon plans; with a maximum of 56.3 Gy for the photon plan in patient no 57. Advantages of protons were seen also for the femoral heads with a maximum dose of 48.5 Gy for the photon plan in patient no 57. The integral dose (i.e. deposited energy) to the body, with PTV-regional excluded, was estimated by multiplying the average dose with the volume. The proton plans mean integral dose (109 J) was about half of the mean integral dose from the photon plans (222 J).

Nerve roots and S1-S5 vertebrae doses were higher in patients with tumour growth into S1-S2, which was expected, with a maximum of 61.7Gy

and 63.1Gy respectively. Photons gave a slight advantage compared to protons in these areas.

Paper IV

Of the 303 patients, 118 patients were randomized to the SCRT group, 120 to the SCRT-delay group and 65 to the LCRT-delay group. Five patients (1.7%) were ineligible. Demographic data were similar between groups although patients in the LCRT-delay group tended to have more high tumours (35% vs. 22.5-27.1%) and there were few protocol violations (5-6%). Eight patients (2.6%) developed radiation-induced acute toxicity; 5 patients (4.2%) in the second group and 3 patients (5%) in the third group. There were no differences in tumour clearance between the three groups. There were no significant differences in postoperative complications between groups (46.6%, 40.0% and 32% in groups 1, 2 and 3 respectively; $P = 0.164$), however, patients in the LCRT-delay group had the lowest rate of complications and reoperations. Patients randomized to SCRT with immediate surgery, but with surgery 11–17 days after the start of RT, had the highest complication rate (24 of 37) (Table 4). No differences between the treatment groups in postoperative mortality (within 30 and 90 days) were found.

Table 4. Postoperative complications in patients randomized to SCRT and surgery within a week in relation to actual time of surgery after the start of RT

	≤ 10 days ($n = 75$)	11–17 days ($n = 37$)	> 17 days ($n = 6$)	P‡
Postoperative complications*	29	24	2	0·036
Surgical complications	17	15	1	
Reoperation	5	6	1	
Cardiovascular	2	2	0	
Infection	6	7	0	
Other	7	4	1	
Surgical complications*				
Wound infection	17	15	1	
Intra-abdominal infection	0	1	0	
Haemorrhage	1	1	0	
Anastomotic leak†	5 of 48	5 of 24	0 of 3	
Wound dehiscence	1	1	1	
Complications due to defunctioning stoma	1	0	0	
Other	2	2	1	
Postoperative death	0	1	0	

*More than one type of complication might be registered for each patient. †Anterior resection only. ‡Fisher´s exact test.

Paper V

There were no statistically significant differences in clinical characteristics between patients randomized in the study compared to those participating in the Stockholm III Trial but not in the QoL-sub-study. Tumour localisation differed between the randomized 3-armed sub-group with fewer low rectal tumours in the LCRT-delay group and fewer high rectal tumours in the SCRT-delay group. Statistically fewer defunctioning stomas were done in the latter group. Postoperative complications were more frequent in the SCRT group than in the SCRT-delay group.

Baseline QoL differed slightly between groups with the best scores in the LCRT-delay group and lowest scores in the SCRT group. Statistically significant differences were seen in emotional (p=0.014) and cognitive (p=0.019) functioning, fatigue (p=0.004) and in micturition symptoms (p=0.034). The only significant difference seen between the SCRT group and SCRT-delay group was a higher baseline score in cognitive functioning for the SCRT-delay group (p=0.045).

After one week of RT there were statistically significantly more symptoms from the gastrointestinal canal (p=0.004) and more defecation problems (p=0.018) in the SCRT groups (SCRT and SCRT-delay) having received 25Gy compared with the LCRT group having received 10-12Gy. Furthermore there were statistically significant changes over time in all groups with positive changes in future perspective and negative changes in sexual functioning and enjoyment and RT-induced micturition.

Post-RT comparison between the delay groups showed a slightly poorer QoL after RT compared to baseline. The only statistically significant differences between the groups were seen in diarrhoea (p=0.04) and future perspective (p=0.01) with a better scoring for the LCRT-delay group.

After surgery QoL decreased significantly in many aspects in all three groups. The SCRT group had statistically significantly lower QoL in several aspects when compared to both other groups at first postoperative comparison (PO1, 4 to 8 weeks after surgery, Table 5). No significant differences in QoL-scores were seen between SCRT-delay and LCRT-delay patients.

At the second postoperative evaluation (PO2, 8 to 13 weeks after operation) no statistically significant differences between the SCRT groups were seen when comparing with baseline scores. Mean score differences in QLQ-C30 showed mostly small to moderate negative clinical changes and positive clinical changes in constipation and diarrhoea. Statistically significant differences between the SCRT groups were seen when comparing PO2 to PO1, with larger improvements in the SCRT group. Almost all subscales improved in both groups between the periods.

The recovery was even better in postoperative period 3 (PO3, more than 13 week from surgery, only the SCRT group). Only trivial or small negative clinical changes remained when comparing to baseline scores and statistically significant positive changes were seen in emotional functioning, constipation and future perspective. When comparing PO3 to PO2 general improvement was seen with small positive clinical changes in global health status and role functioning.

Table 5. EORTC QLQ-C30 scores comparison between baseline and postoperative period 1 (PO1 = 4-8 weeks) in the 3-armed subgroup, arm A (SCRT), B (SCRT-delay) and C (LCRT-delay) (only p-values <0.05 are shown)

EORTC QLQ-C30:			Baseline	PO1 (4-8w)	Cocks clinical estimate*	ANOVA - repeated measures			
						Over time		Arm over time	
Overall	Arm	n	Mean (SD)	Mean (SD)		F	p	F	p
Global health status	A	44	70.8 (20.9)	49.2 (18.4)	- L	51	<.001		
	B	47	69.0 (21.8)	59.7 (20.3)	- S				
	C	36	75.7 (18.3)	60.4 (21.1)	- L				
Functioning scales									
Physical	A	44	88.8 (15.9)	57.2 (21.1)	- L	164.6	<.001	9.5	<.001
	B	47	89.8 (13.5)	74.0 (16.0)	- M				
	C	37	87.8 (17.7)	70.6 (18.7)	- M				
Role	A	42	77.8 (28.4)	25.0 (29.0)	- L	141.4	<.001	5.4	.006
	B	47	85.8 (24.8)	54.8 (32.3)	- L				
	C	35	85.7 (25.0)	55.2 (29.9)	- L				
Emotional	A	44	73.1 (22.8)	72.2 (17.6)					
	B	47	80.5 (20.3)	83.3 (16.4)					
	C	36	80.8 (17.1)	81.7 (21.3)					
Cognitive	A	44	82.2 (23.4)	76.9 (20.4)	- S				
	B	47	89.7 (17.9)	90.6 (16.2)	---				
	C	36	92.6 (17.6)	89.4 (20.0)	- S				
Social	A	44	86.0 (21.5)	59.8 (30.4)	- L	44.9	<.001		
	B	47	87.9 (21.1)	73.9 (27.1)	- M				
	C	35	85.7 (22.9)	73.3 (21.8)	- M				
Symptom scales									
Fatigue	A	44	24.2 (22.0)	60.6 (24.0)	- L	147.8	<.001	5.6	.005
	B	47	19.6 (20.6)	38.8 (21.0)	- L				
	C	36	14.8 (21.6)	40.0 (23.6)	- L				
Nausea and vomiting	A	44	2.7 (8.0)	13.3 (22.0)	- M	9.3	.003	3.1	.049
	B	47	1.4 (5.8)	6.4 (16.1)	- S				
	C	37	3.6 (14.8)	3.6 (8.0)	---				
Pain	A	44	15.9 (25.1)	41.7 (32.0)	- L	42.2	<.001	3.5	.034
	B	48	13.9 (19.2)	23.1 (25.2)	- S				
	C	37	11.7 (17.9)	28.8 (24.1)	- M				
Dyspnoea	A	42	14.3 (19.7)	37.3 (28.7)	- L	25.2	<.001	5.6	.005
	B	46	10.1 (15.5)	16.3 (21.2)	- S				
	C	35	8.6 (20.4)	15.2 (20.4)	- S				
Insomnia	A	43	29.5 (27.4)	38.0 (28.7)	- S				
	B	46	24.6 (27.6)	23.6 (25.0)	---				
	C	36	22.2 (23.9)	26.9 (29.6)	- S				
Appetite loss	A	44	7.6 (20.2)	35.6 (30.8)	- L	48.8	<.001	3.5	.035
	B	47	9.9 (19.6)	21.6 (28.8)	- S				
	C	36	4.6 (14.1)	21.3 (27.8)	- M				
Constipation	A	44	12.1 (20.4)	8.3 (14.6)	---	6	.015		
	B	46	19.6 (30.3)	8.7 (23.8)	+ S				
	C	35	10.5 (22.5)	4.8 (14.3)	+ S				
Diarrhoea	A	44	23.5 (28.4)	14.4 (23.2)	+ M	8.3	.005		
	B	46	21.0 (28.4)	14.5 (27.8)	+ S				
	C	35	23.8 (28.7)	10.5 (21.0)	+ M				
Financial difficulties	A	42	10.3 (27.0)	19.8 (27.6)	- S				
	B	46	7.2 (19.8)	10.1 (24.2)	---				
	C	36	10.2 (31.7)	8.3 (24.4)	---				

*Cocks guidelines for mean difference clinical estimate for trivial (---), small (S), medium (M) and large (L) changes with negative (-) or positive (+) changes

Discussion

In the more advanced, non-resectable rectal cancers ("ugly" group), conventional LCRT (1.8–2 Gy x 25–28), presently combined with chemotherapy [39], is used as a reference regimen aiming at tumour regression in order to safely allow a radical resection. In the light of rapid symptom relief and tumour regressions seen in several patients in the on-going Stockholm III Trial using SCRT with delayed surgery, this treatment was provided to patients with advanced rectal tumours but not fit for CRT. Further, patients at many sites worldwide treated with SCRT plus immediate surgery and found non-resectable were explored one or two months later, and then found to be resectable. In some patients no tumour was present. Many, including ourselves, were impressed by the regressions seen, and a retrospective study was initiated to get an idea of how frequently this occurred in this group of poor prognosis patients.

In paper I, the retrospective evaluation shows that the SCRT schedule can result in substantial downstaging/downsizing in patients with a locally advanced non-resectable T4 rectal cancer, and a radical resection can be achieved in a majority of the patients at surgery median 6–7 weeks after the RT. Standard treatment for these patients is CRT with delayed surgery, but this preoperative treatment was contraindicated in all patients. In this group of very high-risk patients, SCRT is thus an attractive alternative, to be implemented as routine care. In the light of its apparently high efficacy and potentially very low toxicity, it may, however, also be an attractive alternative to explore in patients with less advanced tumours. This is also done in the Stockholm III Trial. Outside of a clinical trial, SCRT with delayed surgery should not be used in these patients since pros and cons are not fully known. Similar retrospective studies have since been done in Stockholm [70] and Leeds [71], with similar outcomes.

The use of SCRT in patients with advanced disease locally and distant metastases, not suitable for any intensive anti-tumour therapy, also appears to be attractive. The survival in this group is short, prompting short treatments. Concerns of late toxicity are also irrelevant. Some of these patients had severe diarrhoea, albeit temporary. This can likely be reduced if the radiation target is limited to the GTV, excluding any prophylactic radiation to regional lymph nodes. This was not done during the retrospective phase, but is now recommended.

The group with non-resectable primary tumour and distant metastases, but without contraindications to intensive tumour therapy, can be treated with SCRT with the addition of intensive systemic chemotherapy shortly after. This has been explored in a Dutch prospective phase II study, the M1-study, so far only reported as an abstract [72]. In the 48 patients with primary resectable rectal cancer and limited, potentially resectable distant metastases, SCRT was given first followed by 5 months of capecitabine, oxaliplatin and bevacizumab. Results were favourable with minimal RT-toxicity. The concept of treating with SCRT followed by combination CRT is now explored in a randomized phase III trial (RAPIDO, Clinicaltrials.gov registration number NCT01558921) in patients with primary high-risk rectal cancer (basically "ugly").

In paper II the goal was to optimize delineation of GTV in patients with LARC. For these LARC patients (previously often designated "non-resectable") CRT is a required preoperative therapy to have a reasonable chance of achieving negative resection margins if mutilating surgery is to be avoided. We showed that PET/CT adds clinically important information to the pre-treatment staging and to the RT planning procedure in several patients. New lesions or change of stage were seen in 15% of the patients when they were evaluated with PET/CT. Findings of extra-mesorectal or extra-pelvic FDG uptake can not only modify the TNM staging, but also result in a change in treatment from curative to palliative, or the reverse. In this series, a therapeutic change would have been relevant for 7 of 68 patients, or in 10% of the total material.

The mismatch between tumour volumes defined by different techniques has been discussed by Roels et al. [73]. One explanation is a better differentiation between tumour and benign tissue using FDG-PET/CT. Detection of small positive lymph nodes and registration errors when using different non-integrated imaging modalities are other explanations. The results are often related to a large and overestimated GTV-MRI. In the present study no GTV-PET volume was, however, projected completely inside the GTV-MRI.

The contouring method used in the present study is based on visual assessment of MRI and PET/CT images, defining tumour by the intensity of FDG uptake adjusted by using window and level in the treatment planning system. The clinical oncologist and radiologist did the delineation together, taking into account all information in the different imaging modalities. This approach has strength in the teamwork of the two specialists, emphasizing the FDG-uptake in relation to clinical information and tumour distribution on CT and MRI. However, FDG-PET/CT is an operator dependent method with a risk of inter-observer variability defining GTVs. In the present study MRI images and PET/CT were not fused, and the interval between MRI and PET/CT varied up to 58 days, due to different reasons at the clinics involved. Patients with an "ugly" tumour (MRI-classified at the multidisciplinary team

meeting) were offered the opportunity of a FDG-PET/CT examination for research purposes. We are aware that the delay between the MRI and PET/CT may have resulted in a mismatch between the imaging modalities, and the tumour could potentially have increased in size or changed in shape.

Contouring of GTV derived from PET/CT is a critical step and should include the most optimal technical and clinical information. Different delineation methodologies have been described, and reviews [12,13] and procedure guidelines [14] for tumour PET imaging have been recently published.

From our original study material of 77 patients with LARC (all "ugly"), the "ugly-ugly" (with overgrowth to non-resectable structures), constituted just under 10% of the patients. In the randomized trial with 209 LARC patients [38], between 10 and 15% had very advanced tumours at retrospective evaluation of the patient cohort. Even though the patients are rare, the consequences can be dire if local control is not achieved.

In paper III we report that for the seven patients with the most locally advanced rectal cancers seen during a recent 2-year period in the Stockholm-Uppsala region, both photons and protons could have been used for the treatment including the peripheral boost. Protons gave similar coverage of treatment target whilst sparing the small intestine for five out of seven patients. The remaining two patients had very large tumour volumes and their respective risk of acute and late treatment toxicity was high regardless of whether photons or protons had been used. It must be emphasized that the cases included in this model study are more extensive than most tumours that are at presentation classified as cT4.

Since the 1990s, efforts have been made to explore if the special properties of protons can be utilized in clinical RT of patients with rectal cancer [74-77]. One problem with protons as a treatment modality in rectal cancer is the changeability of the target volume due to internal organ motion, organ filling and bowels containing gas. RBE at the end of the Bragg peak extends the effective range of the protons [78] which in the case of intestinal gas means that the distal edge of the Bragg peak will be located in the bowels and increase the risk of toxicity. The finite range of protons makes the proton plans more sensitive than photon plans if the density distribution in the patient changes from the planning CT. Gas in the bowels will not be present at the same location, or with the same volume, in all 25 fractions. We cannot exclude the possibility that a small degradation of the target coverage could occur.

Severe diarrhoea and other gastrointestinal toxicity can be a cause of undesired breaks or early termination of CRT. Several authors have reported toxicity of the small bowel at the low to medium dose ranges 5-30 Gy [79-81]. Derived models to calculate the probability for severe diarrhoea have large uncertainties [76,80] but can still give a hint of the complications to expect. That it is impossible to predict intestinal movement adds to this difficulty. Another problem when using models to calculate toxicity risks is that

they do not take into account the additive and sometimes radio-sensitizing effect of chemotherapy. We are aiming at limiting the doses to the small bowel as described by Fiorino et al. [63] and Roeske et al. [64], which also is recommended in the QUANTEC rapport [82]. Fiorino is using intestinal cavity as OAR rather than small intestine for RT in prostate cancer and Roeske is using peritoneal space as OAR in cervix cancer for both RT and CRT.

In the planned first interim analysis of the Stockholm III Trial (paper IV) we could demonstrate acceptable feasibility and patient compliance, irrespective of radiation regimen. Patients randomized to SCRT and immediate surgery tended to have a higher postoperative complication rate. The highest rate of complications was found if surgery was carried out more than 10 days after the start of RT, that is, the patient waited for more than 3–5 days for surgery (depending on whether or not the RT was given during one calendar week) after the last RT fraction. The major reason for a short delay was probably administrative and not patient related. The TME trial [32] also found increased postoperative mortality among elderly patients if surgery was delayed for more than 3 days [83]. Furthermore, unexpectedly high complication rates after SCRT were reported in retrospective studies of patients with a short delay to surgery at a British centre [84,85]. Similar findings, namely more complications in individuals who for some reason had their surgery postponed, were seen in a retrospective analysis of patients in the Stockholm I and II-trials [86].

In order to achieve low complication rates, these results indicate that surgery should be performed immediately after SCRT, within approximately 5 days after the last RT fraction, or be delayed for more than 4 weeks. The results are all derived from retrospective analyses and could thus be criticized. They are however consistently seen in all materials investigated and reported so far. It cannot be excluded that some patients who have their surgery delayed are at risk for complications. The reasons are otherwise not known, but could be associated with a lack of adequate response of leucocytes to the surgical trauma [86-88].

Patient inclusion in the Stockholm III Trial has been much slower than expected. The actual number of potentially eligible patients is not known. However, during the same interval, approximately 1200 patients received preoperative RT for rectal cancer in the Stockholm, Uppsala and Dalecarlia regions, including the 303 patients included in this trial. The reasons why only about 25% of the patients selected for preoperative RT were included can only be speculated upon. Inclusion rates vary substantially between hospitals.

When the Stockholm III Trial was launched the statistical calculations were based on the primary endpoint, time to local recurrence, with an expected 5-year incidence of 15%. With a statistical power of 80%, it was estimated that 840 patients were needed to show similarity in local recurrence

rates between the two short-course treatment arms. However, since 1998 the recurrence rate has improved considerably in Sweden, owing to implementation of the TME technique. Recent population-based data from the Swedish Rectal Cancer Registry have shown a local recurrence rate of 9.5% overall and 6.1% in irradiated patients [16]. Thus, the trial is probably underpowered regarding the primary endpoint. The acute and late toxicities of the treatments will thus be of greatest relevance. Of importance is also another secondary endpoint, the relative efficacy of the different radiation schedules. The second interim analysis, scheduled when at least 200 patients have been randomised to each of the two SCRT study arms, will focus on the downstaging/downsizing effect of SCRT in the delay arm.

The main finding in paper V is that the SCRT group reports poorer QoL in several domains than the two RT groups who have delayed surgery. In the interim analysis of the Stockholm III Trial (paper IV), it was found that the SCRT group had more postoperative complications than the other groups, and thus it is likely that the poor QoL reflects increased postoperative complications. When studying the SCRT group further in paper IV, a clear difference could be seen between those patients who were operated within 10 days after the start of RT and those operated more than 10 days after RT. The latter patients had significantly more postoperative complications. This has also been reported by others [86]. To determine the possible role of postoperative complications on QoL, we excluded from the analysis all the patients in the SCRT group operated later than 10 days from the start of RT. There were fewer statistically significant differences (data not shown) but the SCRT group still showed lower QoL-scores compared to the other two groups. Possibly, delay groups have longer time to adapt to the treatment situation, thus accommodating the symptoms, and therefore score higher than those who have immediate surgery.

Our data indicates that surgery has a more immediate negative impact on QoL than RT, with the largest clinical negative changes in global health, physical, role and social functions, fatigue, appetite loss, body image, chemotherapy side effects, male sexual dysfunction and weight loss. This is in line with previous findings by Stephens et al. [89] who presented QoL for the randomized MRC-CR07 trial comparing preoperative SCRT with selective postoperative chemoradiotherapy in patients with resectable rectal cancer. They concluded that for male patients the main adverse effect is sexual dysfunction, primarily from surgery but further increased by SCRT. We too could see higher scores for male sexual dysfunction and that the level of dysfunction increased more after surgery and continued to be high postoperatively, although our time perspective was much shorter.

This QoL-study had four specific aims. With regards to the first, we can conclude that SCRT seems to have a slightly more negative impact on gastrointestinal symptoms and defecation problems than LCRT after one week of treatment. This comes as no surprise since the radiation dose received is

much higher after SCRT (25 Gy) than after LCRT (10-12 Gy). The results support the clinical impression that patients tolerate the first week of treatment quite well although they may begin experiencing gastrointestinal, defecation and micturition problems.

The second aim was to compare QoL after RT but before surgery between the delay arms. The SCRT-delay group had significantly more diarrhoea 3-8 weeks after completion of RT than the LCRT-delay group. Knowing this, appropriate interventions can be planned for these patients to minimise discomfort and possible dehydration due to treatment toxicity. The retrospective studies analysing outcome of SCRT with a delay (paper I, Hatfield et al. [71] and Pettersson et al. [70]) have not reported any major adversities, but the design was not ideal to detect temporary problems. Neither was our choice of time points optimal to detect problems seen during the first two weeks after RT.

The third aim was to appraise QoL 4-8 weeks after surgery. As described above, the most important finding in this study is that patients treated with SCRT followed by immediate surgery have significantly poorer QoL 4-8 weeks after surgery than do others. This links in with the fourth aim, which was to describe the situation 2-4 months postoperatively. The SCRT group that had immediate surgery shows recovery at this point in time and no longer has poorer QoL than the group with delayed surgery. This is reassuring and adds to our knowledge about the different treatments. The patients seem to recover gradually but after 3 months from surgery there are still some negative changes compared to baseline scores. Knowing that toxicity eventually resolves has important implications both for patients and for physicians [56,90].

Unfortunately there are weaknesses with studies in which accrual is slow. The Stockholm III Trial is still recruiting patients more than ten years after it was started. During this time, staging and treatment standards have changed gradually. In the interim analysis of the trial (paper IV) 303 patients treated from 1998 to 2005 (overlapping paper V) were evaluated. In paper V covering the period 2001-2009, an increased use of defunctioning stoma (anterior resection only) was seen. This might be due to an increased popularity of this technique in later years [91,92]. During the recruitment period MRI has become standard in the pre-treatment investigations and radiology has thus improved. It is possible that all of these changes are reflected in the patients' QoL-scores and thus study results are influenced by the passing of time.

Other problems to be aware of are the methodological difficulties in collection of the QoL-data. A proportion of patients did not enter the QoL-substudy of the Stockholm III Trial. The main reason for this was that patients were not offered participation due to temporary interruptions of the study at all three sites in the beginning of the time period because of lack of staff engaged in the QoL-study. This, together with patients not agreeing to study inclusion, has affected accrual negatively. The patients available for analysis

nevertheless constitute one of few populations of prospectively studied rectal cancer patients with regards to early QoL-aspects. No statistically significant differences were seen between the study patients and the Stockholm III Trial patients who did not enter the QoL-sub-study.

There were significant differences in the baseline scores that were statistically addressed as they may possibly influence the later QoL-measurements. Specifically the LCRT-delay patients had significantly higher QoL-scores than other patients. A possible explanation is that the baseline questionnaire was completed after randomization. Another possibility is the higher percentage of middle and upper tumours in the SCRT-delay group and the LCRT-delay group. Patients with higher tumours have a larger chance of being offered surgery that does not give them a permanent stoma, and this could be mirrored by higher QoL-scores.

Conclusions

Treating LARC patients with SCRT and delayed surgery is highly feasible, has definite anti-tumour activity and is well tolerated in general, although a few cases of serious toxicity were seen. Target volume should be reduced in very old patients and when the disease is metastatic. Elderly patients should be monitored carefully with regards to severe diarrhoea. Special care should be taken with patients with neutropenia. Treatment logistical advantages were seen.

FDG-PET/CT adds information to the standard target delineation procedure of LARC, resulting in a potentially smaller GTV, but a larger GTV "total" using the union of GTV-MRI and GTV-PET. New or differently evaluated lesions were seen in up to about 15% of the patients, potentially changing the treatment strategy. The use of FDG-PET/CT can be clinically motivated in the 10-15% of the most locally advanced rectal cancers ("ugly-ugly"). For most rectal cancers to be irradiated, the added value is likely too small to motivate its use.

Adding a boost to the peripheral area of organ infiltration is possible using either intensity modulated photon or proton rays. In our study sample of seven patients, using protons gave five out of seven patients an advantage with regards to dose in OAR. Finding ways to overcome disadvantages with protons such as lack of robustness, availability and expense will be important if this treatment is to become more widespread.

SCRT and immediate surgery tended to be associated with more postoperative complications than the other schedules in the on-going Stockholm III Trial. However, this increased risk was found mainly in patients having surgery more than 10 days after the start of RT. Surgery should take place as soon as possible after SCRT, but no later than 10 days after the start of RT, or be delayed for at least 4 weeks in order to minimize toxicity. The on-going Stockholm III Trial will answer the potential benefit of the different schedules.

Slightly more symptoms from gastrointestinal canal and more defecation problems in the SCRT groups after one week of RT were seen. Preoperative diarrhoea was slightly more common in the SCRT group with delay. Postoperatively, the poorest QoL was seen in patients given short-course RT followed by immediate surgery. No postoperative differences were seen between the two groups with delayed surgery. Surgery accounted for more

adverse effects than RT in all groups. All patients gradually recovered after surgery but did not reach the same level of QoL as before treatment.

Future perspectives

The centralisation of rectal cancer to surgical centres has improved surgical results for this entity of patients. Advances in imaging have improved tumour staging and now offer the possibility of better assessments at the multidisciplinary team conferences. Preoperative RT is since 30 years standard of care in Sweden in many patients with rectal cancer and continues to evolve, which raises hope for future improvements with regards to toxicity, local tumour control and, ultimately, survival.

Important future areas of research include optimising radiation treatment with protons. The advantages of protons are obvious, and the possibility of sparing surrounding tissues is especially important in pelvic tumours. There are, however, robustness issues that need to be explored if proton treatment is to become an everyday option for the most advanced rectal cancer patients. With both photon and proton treatment, offering integrated simultaneous boosts is one way of increasing anti-tumour activity that deserves more attention.

A main problem in particularly the advanced cases ("ugly") but also in the intermediate group ("bad") is that we have managed to diminish the local problem to very low levels with good radiation and skilled surgery. However, we still lose many patients in these groups in distant spread, despite the liver and lungs being free of disease at diagnosis. This indicates that there is a high risk of developing distant metastases, which are occult at diagnosis. The standard of care for this group is CRT during 5 weeks, surgery after another 8-10 weeks and then recovery from surgery in 4-6 weeks. Since the chemotherapy is suboptimal during the CRT period to kill systemic tumour cells deposits, it takes almost 5 months until appropriate adjuvant combination chemotherapy will be delivered, and during this time period the occult metastases can grow. In a recently launched trial, the RAPIDO Trial (Rectal Cancer and Pre-operative Induction Therapy Followed by Dedicated Operation), the standard of care schedule with adjuvant chemotherapy is tested against SCRT and then combination chemotherapy for 5 months, and finally surgery. The hypothesis in this trial is to improve 3-year disease-free survival with early neo-adjuvant chemotherapy.

The on-going Stockholm III Trial is approaching its proposed accrual and will hopefully answer which of the different preoperative RT regimens is the best treatment for the intermediate "bad" group. The QoL-sub-study is still recruiting patients and will address crucial issues of treatment tolerability

from the patients' perspective. Further QoL follow-up has been initiated and intends to explore long-term toxicity, 4 and 10 years after treatment.

Summary in Swedish

Optimering av radioterapi vid rektalcancer

Ändtarmscancer är den åttonde vanligaste cancerformen hos svenska män och kvinnor och drabbar ungefär 2000 personer per år. De senaste tjugo åren har stora ansträngningar gjorts för att förbättra behandlingsresultaten vid sjukdomen och den andel patienter som helt botas har ökat. De patienter som lever med sin cancersjukdom och inte kan bli botade är i behov av behandling som effektivt minskar symptom och, om möjligt, förlänger överlevnaden. Även för dessa personer har behandlingsresultaten förbättrats.

En hörnsten i behandlingen av ändtarmscancer vid sidan om operation är strålbehandling. Strålbehandling ges till patienter med mer avancerade tumörer i syfte att minska risken för återfall lokalt, dvs. i bäckenet. Strålbehandling kan också krympa tumören så att det blir lättare att kirurgiskt avlägsna den. I denna avhandling har fem arbeten gjorts som alla handlar om olika aspekter av strålbehandling vid ändtarmscancer – hur behandlingen kan förbättras ytterligare, hur den upplevs av patienterna och hur antalet botade patienter kan öka om den används på rätt sätt.

I arbete 1 studeras patienter med lokalt avancerad ändtarmscancer som av olika skäl inte tål lång strålbehandling (varje vardag under fem veckor) tillsammans med cytostatika. De behandlades därför med strålbehandling varje vardag i en vecka. Patienterna var mestadels äldre, hade ofta andra svåra sjukdomar eller hade spridning av sin cancer. Syftet med studien var att se hur väl det fungerade att ge fem dagars strålbehandling och att därefter operera patienterna efter 6-8 veckors väntan. Studien visade att detta tolererades väl, gav god symptomlindring och att 37 av 46 patienter kunde bli opererade. Tre av de äldre patienterna drabbades av svår diarré efter strålbehandlingen, vilket är viktigt att veta eftersom de därmed utgör en grupp som skall kontrolleras noga efter sådan behandling. Studien visar att det finns en möjlig behandling att erbjuda äldre eller sköra patienter som inte tål standardbehandling (lång strålbehandling i kombination med cytostatika) och som kan ge goda behandlingsresultat i denna grupp av patienter.

I arbete 2 studeras olika röntgenmetoder som används inför strålbehandling. När patienter planeras för strålbehandling måste man ha tillgång till röntgenundersökningar som visar tumörens aktuella läge och utbredning. Dessa används till att rita in det område som skall strålbehandlas och det är naturligtvis av yttersta vikt att all tumör kommer med i strålfältet. I arbete 2

jämförs MRT; magnetisk resonans tomografi med en modern form av isotopröntgen som kallas för PET; positron emissions tomografi. MRT är det som rutinmässigt används inför strålbehandling idag. Jämförelsen visar att PET kunde tillföra ny kunskap i ett antal fall – 15% av de 77 patienter som ingick i studien fick sitt tumörstadium ändrat efter att ha gjort en PET-undersökning. Man kan sammanfatta arbete 2 genom att säga att patienter med avancerade ändtarmstumörer kan i vissa fall få en bättre anpassad strålbehandling genom att göra både en MRT och en PET-undersökning inför behandlingsstart.

Ur samma patientgrupp som i arbete 2 valdes sju patienter ut som hade de allra största tumörerna. Dessa patienter var inte möjliga att operera från början eftersom tumörerna växte in i korsbenet eller sidorna av lilla bäckenet. Dessa patienters röntgenbilder användes för att göra en hypotetisk studie om vilken typ av strålbehandling som hade kunnat ge bästa resultat. Med modern utrustning för planering av strålbehandling kan man testa olika typer av strålbehandling och med hjälp av dataprogram räkna ut risk för biverkningar i förhållande till effekt. Arbete 3 syftar till att se huruvida det vore möjligt att öka dosen i områden där tumören vuxit in i omgivande strukturer samt till att jämföra protonstrålning med konventionell extern fotonstrålning. Det verkar vara möjligt att öka dosen i de områden där tumören vuxit in i t.ex. ben, vilket är viktigt om man ska ha chans att operera bort all tumör efter strålbehandling eller att ha chans till lokal kontroll av sjukdomen utan operation. Det hade varit möjligt att behandla fem av sju patienter med både proton- och fotonstrålning, medan återstående två hade fått alltför hög stråldos i tunntarm och löpt hög risk att få svåra biverkningar.

Arbete 4 utgörs av en ”halvtidsanalys” av de patienter som inkluderats i en stor strålbehandlingsstudie för ändtarmscancer kallad ”Stockholm III Trial”. Studien pågår alltjämt och planerar att inkludera totalt 840 patienter. I arbete 4 granskas de första 303 patienterna som inkluderats. I Stockholm III-studien jämförs fem dagars strålbehandling (där patienterna opereras antingen direkt efteråt eller efter några veckors väntan) med fem veckors strålbehandling, med operation efter några veckors väntan. Studien förväntas svara på om det finns fördelar med något av de tre behandlingsuppläggen. Denna analys, gjord när knappt hälften av patienterna inkluderats, visade att alla tre behandlingsupplägg verkar fungera och att inga signifikanta skillnader finns mellan dem avseende biverkningar eller komplikationer efter kirurgi. En grupp patienter som oavsiktligt opererats för sent, dvs. de som fått fem dagars strålbehandling och skulle opererats veckan därpå men fått vänta litet längre, hade mer komplikationer än andra. Detta talar för att man bör hålla sig till ett så kort tidsintervall som möjligt mellan avslutad strålbehandling och operation för dessa patienter och nya vårdrutiner för detta har använts sedan dess.

Arbete 5 studerar livskvalitet, dvs. hur behandlingen upplevts av patienterna i arbete 4. Genom självskattningsformulär har patienterna i arbete 4 fått

svara på hur deras olika kroppsfunktioner samt deras sinnesstämning påverkats av given behandling. Man har använt standardiserade frågeformulär som är vanliga i forskningssammanhang kring cancerpatienter. Resultaten visar att den grupp som verkar ha störst påverkan på livskvaliteten är de patienter som får fem dagars strålbehandling och operation veckan efter. Själva operationen påverka patienternas livskvalité mer än strålbehandlingen, i alla tre grupper. På sikt sker en läkning, med återgång till bättre livskvalitet för alla tre grupper, även om en del problem (bl. a. sexuella biverkningar) kvarstår lång tid efter strålbehandlingen och kirurgin.

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