Preoperative Short-Course Radiation Therapy With PROtons Compared to Photons In High-Risk RECTal Cancer (PRORECT): A Prospective Randomized Swedish Phase II Trial

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Protocol Signature Sheet

We declare that we have read and familiarized ourselves with the following protocol:

Preoperative Short Course Radiation Therapy With Protons Compared to Photons in High-Risk Rectal Cancer (PRORECT): A Prospective Randomized Swedish Phase II Trial

Name	Site	Signature	Date
Study Coordinators			

Synopsis of the protocol

Protocol title	Preoperative Short-Course Radiation Therapy With Protons Compared to Photons in High-Risk Rectal Cancer (PRORECT): A Prospective Randomized Swedish Phase II Study
Protocol Phase	Phase II
Indication	Primary rectal cancer with high risk of failing locally and/or systemically
Background	In patients with a newly diagnosed locally advanced rectal cancer at high risk of local or systemic relapse, long-course preoperative radiotherapy with concomitant chemotherapy followed by surgery after 6-8 weeks has been standard therapy. In the randomized RAPIDO trial, this chemoradiotherapy (CRT) has been compared with an experimental treatment starting with short-course radiotherapy (RT) followed by 6 courses of neo-adjuvant chemotherapy with capecitabine and oxaliplatin (CAPOX). The trial closed patient entry early June 2016 after having randomized the planned number of 920 patients. Almost half of the patients were included in Sweden. The immediate experience with the experimental treatment (short-course photon radiotherapy with 5Gyx5) is that it is well tolerated by most patients. This treatment is considered the emerging standard of care. Neoadjuvant radiotherapy with protons has advantages over photon therapy in dosimetric treatment planning studies. When compared to photon plans, radiotherapy with proton reduced small bowel and femur dose in clinical re-irradiation studies suggesting the presence of clinical benefit in terms of reduced toxicity. There are also some suggestions that proton dosimetry may be particularly better for larger tumors. The aim of this study is to find out whether **proton therapy** in locally advanced rectal cancer can offer meaningful reductions in acute gastrointestinal toxicity compared to **standard treatment with photons** which may improve patient's tolerability of neoadjuvant chemotherapy. There are currently no published clinical reports evaluating the use of proton therapy in the upfront treatment of locally advanced rectal cancer. There are further no published randomized trials comparing radiotherapy with photon vs proton in locally advanced rectal cancer.

Endpoints	**Primary endpoint:** • The incidence of acute preoperative grade 2-5 gastrointestinal toxicity according to CTCAE v5.0 (Appendix 3 and Appendix 4) associated with proton vs. photon radiotherapy (Time Frame: from start of radiotherapy to planned start of the third (3) CAPOX cycle (week 9-10 of the trial). **Secondary endpoints:** • To estimate the incidence of all toxicity (hematologic and non-hematologic) associated with protocol treatment in the preoperative period, the postoperative period, and overall. • To determine differences in patient reported outcomes (PRO) between treatment arms in the preoperative period, the postoperative period, and overall • To determine differences between treatment arms in proportion of patients being able to undergo full dose neoadjuvant chemotherapy i.e. at least 4 cycles of CAPOX or 6 cycles of FOLFOX • To radiologically assess and compare tumour regression grading (mrTRG) between treatment arms • Health economic comparison between proton and photon treatment. Cost effectiveness analysis measured by QALY **Safety endpoints:** • Disease free survival after proton vs. photon treatment • Overall survival after proton vs. photon treatment • Quality of life after proton vs. photon treatment (QLQ-C30) • Difference in late postoperative complications between study arms according to LARS score (1) • Proportion of patients who reach a clinical complete remission (cCR) after chemoradiotherapy, enter a watch-and-wait period and remain free of regrowth at least one year • To determine differences in acute neurogenic pain during proton vs. photon treatment (Time Frame: from start of radiotherapy to end of radiotherapy) **Exploratory endpoints:** • To determine differences between treatment arms in concentrations of CD8+ and FOXP3 + tumor-infiltrating T cells after given radiotherapy

Study design	Patients will be treated with the short course 5 x 5 Gy radiation scheme (photons or protons) followed by planned at least four cycles of combination chemotherapy (capecitabine and oxaliplatin) and TME surgery. The planned number of chemotherapy courses may vary from four to six. An alternative is to give a comparable number of cycles giving FOLFOX.

Total number of centres	All seven Swedish University Hospitals participating in the Skandion clinical network
Selection criteria	Patients with a primary rectal cancer without detectable distant metastasis who after locoregional therapy only, meaning preoperative radio(chemo) therapy plus surgery have at least a 40% risk of having a CRM positive resection or a recurrence, local or distant, within three years.
Main criteria for inclusion	**Primary tumour characteristics (identical to those of the RAPIDO and LARCT-US trials):** • Histological proof of newly diagnosed primary adenocarcinoma of the rectum. • Locally advanced tumour fulfilling at least one of the following criteria on pelvic MRI indicating high risk of failing locally and/or systemically: T4b, i.e. infiltration of an adjacent organ or structure like the prostate, urinary bladder, uterus, sacrum, pelvic floor or side-wall (according to TNM version 8), cT4a, i.e. peritoneal involvement, extramural vascular invasion (EMVI+), N2-status regarded as metastatic according to ESGAR consensus criteria (2) (see Radiology Appendix), positive MRF, i.e. tumour or lymph node $\leq$ 1 mm from the mesorectal fascia, enlarged lateral nodes (lat LN+ according to ESGAR consensus criteria (2), see Radiology Appendix) **General:** • Staging done within 6 weeks before start of radiotherapy. • No contraindications to chemotherapy with CAPOX or FOLFOX, including adequate blood counts: - white blood count ≥4.0 x 10^9/L - platelet count ≥100 x 10^9/L - clinically acceptable haemoglobin levels - creatinine levels indicating renal clearance of ≥50 ml/min - bilirubin <35 µmol/l. • ECOG performance score ≤ 1. • Patient is considered to be mentally and physically fit for chemotherapy as judged by the oncologist. • Age ≥ 18 years • Written informed consent. • Adequate potential for follow-up.
Exclusion criteria	• See detailed description in the protocol
Main parameters of efficacy	**Primary:** Acute preoperative gastrointestinal toxicity at week 9-10 of the trial
	Secondary: Acute and late side effects; Adverse events and side effects graded according to CTCAE v5.0 (Appendix 3 and Appendix 4). Proportion of patients starting chemotherapy within 14 weeks after the first radiation fraction and able to undergo the full treatment schedule (at least 4 CAPOX/6 FOLFOX)
Screening	Baseline screening includes:

	• CT (or MRI) of the abdomen and liver • MRI of the pelvis • CT of the thorax • Routine blood tests
Treatment	**Standard Treatment (Arm A):** Week 1: 5 x 5 Gy External Radiation Therapy with Photons Week 3-14 4 courses of CAPOX (Capecitabine b.i.d.1000 mg/m^2 day 1-14 every 3 weeks, Oxaliplatin 130 mg/m^2 day 1 every 3 weeks) Week 17-20: Surgery (TME) **Experimental Treatment (Arm B):** Week 1: 5 x 5 Gy (Cobalt-Grey equivalent (CBE), RBE=1.1) External Radiation Therapy with Protons Week 3-14: 4 courses of CAPOX (Capecitabine b.i.d.1000 mg/m^2 day 1-14 every 3 weeks, Oxaliplatin 130 mg/m^2 day 1 every 3 weeks) Week 17-20: Surgery (TME)
Statistical considerations	Two independent study groups Primary endpoint: dichotomous Power: 80%, 5% type 1 error Rate of anticipated grade 2-5 GI-toxicity in standard group: 30% Rate of anticipated all-grade GI-toxicity in experimental group: 15% Dropout rate: 5 % Sample size: 127 patients in each group Total number of patients: 254 Incidence of adverse events as assessed by Common Terminology Criteria for Adverse Events version 5 [Time Frame: From baseline up to 5 years] A Chi-square test will be used to compare the number of patients with at least 1 grade 3 or higher adverse events between the treatment arms. Fatigue as measured by MFI. Anxiety and depression measured by HAD (Forms Attached) [Time Frame: From baseline to week 3, the assessment at the start of CAPOX or 1 month, months 3, 6, 9, 12, 24, 36, 60) Change in fatigue will be compared between treatment arms using a t-test. If the data do not satisfy the normality assumption, a Wilcoxon test may be used instead. P-values <=0.05 will be assumed to indicate statistical significance.

	DFS, PFS and overall survival will be analyzed using the Kaplan-Meier approach, comparing the arms by log-rank test. In a subsequent step, Cox regression will be used to address the relative risk of clinical factors on overall survival **Efficacy**: Stratified Cox regression analysis **Safety**: Mann-Whitney U-test
Planned sample size	The number of patients to be included has not been fixed, but it is estimated to be at least 254
Analysis plan	The primary endpoint will be analysed when the last patient has completed treatment including the surgery. For patients who are not operated because of a cCR, minimal follow-up for safety should be 12 months.
Duration of the study	Inclusion during two to three years, five years follow-up after inclusion of the last patient

Abbreviations

ANC	absolute neutrophil count
APR	abdominoperineal resection
BED	biological effective dose
CAPOX	capecitabine and oxaliplatin
CEA	carcinoembryonic antigen
CRM	circumferential resection margin
CRF	case record form or case report form
CT	computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
DPD	dihydropyrimidine dehydrogenase
DFS	disease free survival
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EMVI	extramural vascular invasion
EORTC	European Organisation for Research and Treatment of Cancer
5HT3	5-hydroxytryptamine (serotonin) receptor 3A
LAR	low anterior resection
IMRT	intensity-modulated radiotherapy
ICRU	international commission on radiation unit and measurements
MDT	multidisciplinary team
MRF	mesorectal fascia
MRI	magnetic resonance imaging
NCI	national cancer institute
RT	radiotherapy
OS	overall survival
pCR	pathological complete response
PET	positron emission tomography
PME	partial mesorectal excision
QoL	quality of life
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse event
TNM	tumour node metastasis classification
TME	total mesorectal excision

Background and introduction

Epidemiology

Colorectal cancer is globally the third most common cancer, with about 1 million new cases annually. Its incidence is relatively stable in the western world but increases in many developing countries. It is estimated that about 600 000 individuals every year die from colorectal cancer. In many western countries, it is the second cancer killer. In 2017, about 6400 new colorectal cancer patients were registered in Sweden (3). About every third colorectal cancer starts in the rectum, or the most distal 15 cm of the large bowel. The rest starts in the colon, most frequently in the sigmoid part or in caecum. Rectal cancers are more common in males.

Treatment of rectal cancer

Surgery

Surgery was for long the only curative treatment and is still the most important treatment. If a macro- and microscopically radical resection (R0 resection) cannot be achieved, the chances of cure are very low. A few small tumours in the rectum can be treated with external and local radiotherapy (4) and there are indications that some, frequently small rectal cancers that are very chemo radiosensitive can be successfully handled without (major) surgery (5).

Although some early, mostly polypoid tumours without unfavourable characteristics can be operated with a local, i.e. transanal procedure, most patients with a rectal cancer are operated with an abdominal procedure with a resection of the affected bowel segment and adjacent fatty tissues with its vessels and lymph nodes. Depending upon location, standardized procedures are done, at least if the aim is cure.

Recognition of the importance of the circumferential resection margin led to the understanding that the entire mesorectum must be completely removed in one package to obtain low local failure rates (6). The presently only accepted surgical method is to do a sharp dissection and a total mesorectal excision (TME) in all rectal cancers except in those in the upper third of rectum where at least a 5 cm distal margin within the mesorectum should be aimed at. The procedure in which the mesorectum and bowel are transected 5 cm distally of tumour is commonly termed partial mesorectal excision (PME). Most centres applying standardised TME/PME techniques can today report local failure rates of 5 to 10% in the group of patients where the intention is to do a radical procedure (7).

If the tumour involves the mesorectal fascia (MRF i.e. if a standard TME is done, there is a high risk that the circumferential resection margin will be positive, CRM+) or extends to adjacent structures or organs (T4b), a more extended procedure is required in order to reach an CRM negative resection. In certain patients, this may mean a full or partial pelvic exenteration or resection of parts of sacrum.

Radiotherapy

Radiotherapy has been extensively used in rectal cancer during the past decades. The purpose of adding radiotherapy to surgery has been mainly two-fold, firstly to reduce the risk of a local failure, even if an R0 surgery is considered likely and accomplished, or, secondly, to increase the chances of an R0-resection in a locally advanced tumour considered 'non-resectable'. In the first situation, a short-course schedule, like 5 x 5 Gy, with immediate surgery, is one option, since no down-sizing or down-staging is required. Data from randomized trials strongly support this approach in resectable rectal cancer (8-10). In the second situation, long-course, conventionally fractionated (1.8 – 2 Gy/fraction) to a dose of 45 – 50.4 Gy is used with a delay prior to surgery to allow for down-sizing/staging. Concomitant chemotherapy to the long-course radiotherapy (RT) improves local control (11-13) and is thus standard treatment to patients who are suitable for this combined therapy. As an alternative to chemoradiotherapy (CRT), the short-course schedule with a delay prior to surgery has been used in unfit patients, with results that appear promising (14, 15). This approach was used in the completed randomized trial in resectable patients (Stockholm III study) (16, 17). The results show that downsizing and downstaging is seen after 5x5 Gy with delayed surgery that is at least as large as that seen after long-course RT to 50 Gy without chemotherapy. There are no differences in local recurrence rates, disease-free and overall survival between the groups. The surgical morbidity after 5x5 Gy with immediate surgery is higher than after delayed surgery; however, radiation induced adverse effects requiring hospitalization is seen in 5-7% of the patients in the delay groups.

Rationale for using proton radiotherapy in CRC

Proton therapy

The proton is a positively charged particle given energy via acceleration in a cyclotron (or synchrotron). It possesses densely ionizing radiation qualities, which have low initial dose absorption upon tissue entry and a maximum radiation deposition at a given depth, so the dose absorbed by the body increases as the proton slows down at greater depth until the absorbed dose rises to an abrupt peak called Bragg peak. After the Bragg peak, there is a steep dose fall-off, which eliminates unnecessary dose distal to the intended tumor target (18). The proton radiation track structure thereby differs from that of photon, which also leads to the proton generating different biological effects. In particular, the biological effectiveness of protons is estimated to be on average 10% larger than that of photons, which is mirrored by a relative biological effectiveness (RBE) above 1.0. Around the Bragg peak, however, the RBE may be significantly higher. In the clinic, proton dose is typically prescribed and reported in Cobalt-equivalent Gy (CEG) for a RBE=1.1 (19). The proton's energy deposition pattern can be used to achieve improved tumor targeting and normal tissue sparing compared to photon-based radiotherapy. If the Bragg peak is placed within the tumour target, unnecessary radiation dose to nearby normal structures can be reduced, which offers potential acute and late toxicity advantages. In the treatment of localized rectal cancer this can translate into improved sparing of the small bowel, femoral heads, bladder, genitalia, and other abdominal and pelvic structures.

Treatment planning studies have nicely illustrated the ability of proton beam therapy (PBT) to reduce unnecessary dose to normal tissues adjacent to the tumor targets, and these dosimetric benefits are expected to translate to acute and late toxicity reduction. For localized rectal cancer, several dosimetric studies have compared PBT to photon beam therapy for pelvic treatments. In these studies, PBT was significantly superior to photons in reducing volumes irradiated to certain dose levels: V5Gy, V10Gy, V15Gy, and V20Gy to bone marrow; V10Gy and V20Gy to small bowel; and V40Gy to the bladder (20-23). Others have found better conformality indices with

protons and sparing of male genitalia with proton compared to photon therapy (21). There is also some suggestion that proton dosimetry may be particularly better for larger tumors (24).

This evidence suggests that toxicity risk may be significantly reduced for patients undergoing pelvic radiation for locally advanced rectal cancer. In particular, bone marrow sparing can be highly advantageous for patients who later undergo myelosuppressive chemotherapy. Being able to preserve marrow progenitors enables better tolerance to treatments with curative intent, and the bone marrow is one organ where low doses matter. Lower V_{10Gy} to the pelvic bone marrow has been associated with lower rates of significant cytopenia for patients being treated with pelvic radiation for anal cancer (25). Preserving bone marrow function is particularly important for patients with locally advanced or metastatic rectal cancer who inevitably require long courses of cytotoxic systemic therapy.

The clinical data regarding proton therapy in rectal cancer is limited. There is some evidence from re-irradiation studies suggesting that when compared to photon plans, proton therapy offers a reduction in small bowel and femur dose (26). In general, proton therapy in re-irradiation setting is considered feasible. However, there are no randomized trials directly comparing photon therapy to proton therapy in neoadjuvant setting for localized rectal cancer.

Overall, proton therapy in localized rectal cancer may offer a toxicity benefit over photon therapy with retained tumor control. The aim of this study is to find out whether proton therapy in localized rectal cancer can offer meaningful reductions in acute gastrointestinal and hematologic toxicity compared to standard treatment with photons which may allow patients to better tolerate neoadjuvant chemotherapy.

Chemotherapy

Systemic relapses constitute a major problem in colorectal cancer. The most widely used method to decrease systemic relapse rates is to give postoperative adjuvant systemic therapy, presently chemotherapy. This approach has been successful in many tumours, such as breast and colon cancer with meaningful reductions in relapse rates and post-operative adjuvant chemotherapy in colon cancer stage III and high-risk stage II is standard treatment. Presently six months of treatment is used, but several large groups have reported about five large trials comparing three and six months of oxaliplatin-containing therapy. These comparisons show that three months of CAPOX is non-inferior to six months, at least in tumours that are not a high risk of recurrence [IDEA data]. In rectal cancer, as opposed to colon cancer, the scientific support for sufficient activity from adjuvant chemotherapy is less strong, and its use is controversial. At many centres post-operative adjuvant chemotherapy is standard in rectal cancer, but recent randomized trials have not been able to detect any significant gains if RT or CRT were given prior to surgery (27-29).

Rectal cancer staging and risk evaluation

Appropriate ‘up-to-date’ staging of rectal cancer includes Magnetic Resonance Imaging (MRI) of the pelvis together with imaging of the lungs, liver and abdomen to exclude distant metastases. Pelvic MRI has evolved as the method of choice since it evaluates the the tumour and its relation to the mesorectal envelope including the mesorectal fascia and surrounding structures. 18F-FDG Positron emission tomography/Computed Tomography (18F-FDG PET/CT) is also sometimes used to detect tumour manifestations unclear or not detectable by conventional imaging modalities (30). Using MRI, rectal tumours can be grouped into categories having different risks of failing locally and, more recently, also systemically. A European project, The Magnetic Resonance Imaging and Rectal Cancer European Equivalence study (MERCURY) prospectively evaluated the risk of failing locally, and has published criteria dividing rectal tumours into three groups (low, intermediate and high, or ‘good’, ‘bad’ and ‘ugly’) (31, 32). There is presently no international

consensus about the criteria for these risk groups, but there is sufficient evidence to allow for identification of patients with a sufficiently high risk to fail either locally and/or systemically to be included in trials exploring the value of new treatment concepts.

Systemic relapses

About 40-60% of patients with locally advanced rectal cancer (cT3c/d-4 and/or N2) develop distant metastases. Systemic chemotherapy aims at treating occult or micro-metastatic sub-clinical disease that later can appear as distant metastases. Current standard treatment for patients at high risk of failing locally and/or systemically includes pre-operative chemoradiation.

Design considerations of a trial

In patients with a newly diagnosed rectal cancer at high risk of failing locally and/or systemically short-course radiotherapy with delayed surgery is an emerging standard therapy. One of the advantages of the short-course schedule is the low toxicity (in particular acute toxicity) which implies that a vast majority of patients would be able to start full-dose systemic chemotherapy a week or two after radiotherapy.

RAPIDO trial and the follow-up trial LARCT-US evaluated the short-course schedule and concluded that it can be considered equivalent to the previous standard therapy (long-course preoperative radiotherapy with concomitant chemotherapy followed by surgery after 6-8 weeks) and with better compliance. The results of the RAPIDO trial will be official in May 2020 but are already known for the coordinators of the proposed study. It is likely that either the experimental schedule in RAPIDO or the slightly abbreviated schedule in LARCT-US will become a new reference treatment.

The aim of this study is to find out whether proton therapy in localized rectal cancer can offer meaningful reductions in acute gastrointestinal toxicity compared to standard treatment with photons which may allow patients to better tolerate neoadjuvant chemotherapy.

There are currently no published reports evaluating the use of proton therapy in the upfront treatment of locally advanced rectal cancer. The are no published randomized trials comparing radiotherapy with photon vs proton in locally advanced rectal cancer.

Primary objective

To determine differences in acute grade 2-5 gastrointestinal toxicity of proton vs. photon radiotherapy prior to surgery (Time Frame: from start of radiotherapy to planned start of the third (3) CAPOX cycle (week 9-10 of the trial).

Endpoints

Primary endpoint:

- The incidence of acute preoperative grade 2-5 gastrointestinal toxicity according to CTCAE v5.0 (Appendix 3 and Appendix 4) associated with proton vs. photon radiotherapy

(Time Frame: from start of radiotherapy to planned start of the third (3) CAPOX cycle (week 9-10 of the trial).

Secondary endpoints:

- To estimate the incidence of all toxicity (hematologic and non-hematologic) associated with protocol treatment in the preoperative period, the postoperative period, and overall.
- To detect differences in patient reported outcomes (PRO) between treatment arms in the preoperative period, the postoperative period, and overall
- To radiologically assess and compare tumour regression grading (mrTRG) between treatment arms
- To detect differences between treatment arms in proportion of patients being able to undergo full dose neoadjuvant chemotherapy, i.e. at least 4 cycles of CAPOX or 6 cycles of FOLFOX
- Health economic comparison between proton and photon treatment

Safety endpoint:

- Disease free survival after proton vs. photon treatment
- Overall survival after proton vs. photon treatment
- Quality of life after proton vs. photon treatment (QLQ-C30)
- Difference in postoperative complications between study arms measured by LARS score
- Proportion of patients who reach a clinical complete remission (cCR), enter a watch-and-wait period and remain free of regrowth at least one year
- To determine differences in acute neurogenic pain during proton vs. photon treatment

(Time Frame: from start of radiotherapy to end of radiotherapy)

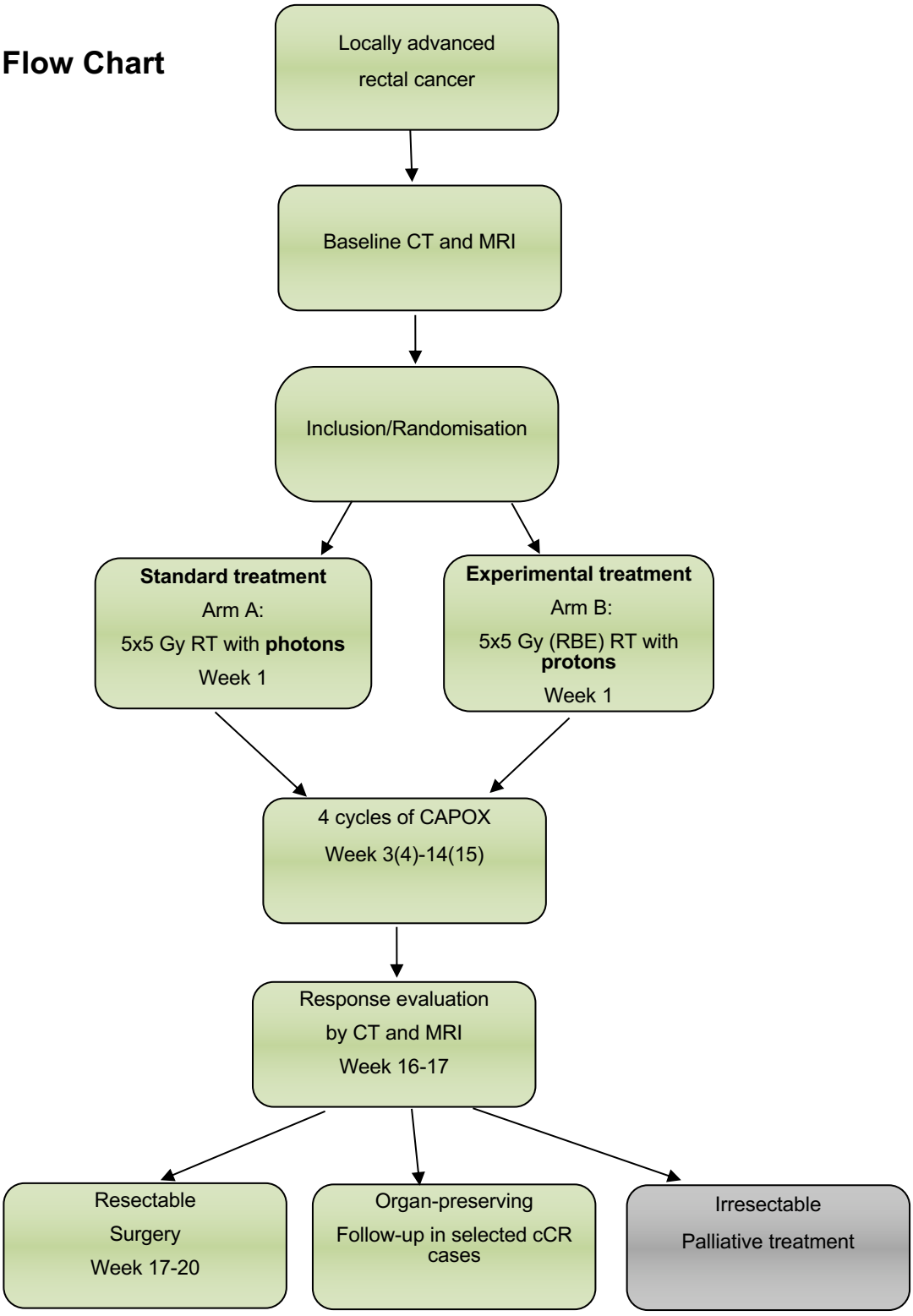
Exploratory endpoint:

- To determine differences between treatment arms in concentrations of CD8+ and FOXP3 + tumour-infiltrating T cells after given radiotherapy
- To determine difference in CEA dynamics between groups

Trial design

This trial is a prospective phase II trial, initially run at the limited number of centres but later expanded to other centres participating in the Skandion network. Patients will be treated with short course 5 x 5 Gy radiation scheme with either photons (standard arm) or protons (Skandion clinic) followed by four to six cycles of combination chemotherapy (capecitabine and oxaliplatin) and surgery. The rectal tumour will be removed by TME/PME surgery or more extensive surgery if required because of tumour extent. Patients with a clinical complete response after neoadjuvant treatment may be included in a Watch&Wait-programme.

Study Flow Chart



Patient selection criteria

Inclusion Criteria - Primary tumour characteristics

- Biopsy-proven, newly diagnosed primary rectal adenocarcinoma, i.e. with the lowest part of the tumour less than 16 cm from the anal verge detected using a rigid rectoscope.
- Locally advanced tumour fulfilling <u>at least one of the following criteria</u> on pelvic MRI indicating high risk of failing locally and/or systemically:
    - Clinical stage (c) T4b, i.e. infiltration of an adjacent organ or structure like the prostate, urinary bladder, uterus, sacrum, pelvic floor or side-wall (according to TNM version 8).
    - cT4a, i.e. peritoneal involvement.
    - Extramural vascular invasion (EMVI+).
    - N2-status regarded as metastatic according to ESGAR consensus criteria (2) (see Radiology Appendix)
    - Positive MRF, i.e. tumor or lymph node one mm or less from the mesorectal fascia.
    - Metastatic lateral nodes (lat LN+ according to ESGAR consensus criteria (2), see Radiology Appendix)

Inclusion Criteria - General

- Staging done within 6 weeks before start of radiotherapy. No contraindications to chemotherapy with CAPOX including adequate blood counts, (within 5 weeks prior to randomisation):

    - white blood count ≥4.0 x 10^9/L
    - platelet count ≥100 x 10^9/L
    - clinically acceptable haemoglobin levels
    - creatinine levels indicating renal clearance of ≥50 ml/min
    - bilirubin <35 µmol/l.

- ECOG performance score ≤ 1

- Patient is considered to be mentally and physically fit for chemotherapy with CAPOX as judged by the oncologist.

- Age ≥ 18 years

- Written informed consent.

- Adequate potential for follow-up.

Exclusion criteria

- Extensive growth into cranial part of the sacrum (above S3) or the lumbosacral nerve roots indicating that surgery will never be possible even if substantial tumour down-sizing is seen.
- Presence of metastatic disease or recurrent rectal tumour. Familial Adenomatosis Polyposis coli (FAP), Hereditary Non-Polyposis Colorectal Cancer (HNPCC), active Crohn's disease or active ulcerative Colitis.
- Concomitant malignancies, except for adequately treated basocellular carcinoma of the skin or in situ carcinoma of the cervix uteri. Subjects with prior malignancies must be disease-free for at least 5 years.
- Known complete DPD deficiency.
- Any contraindications to MRI (e.g. patients with pacemakers).
- Medical or psychiatric conditions that compromise the patient's ability to give informed consent.
- Concurrent uncontrolled medical conditions.
- Any investigational treatment for rectal cancer within the past month.
- Pregnancy or breast feeding.
- Patients with known malabsorption syndromes or a lack of physical integrity of the upper gastrointestinal tract.
- Clinically significant (i.e. active) cardiac disease (e.g. congestive heart failure, symptomatic coronary artery disease and cardiac dysrhythmia, e.g. atrial fibrillation, even if controlled with medication) or myocardial infarction within the past 12 months.
- Patients with symptoms of peripheral neuropathy.
- Patients with pacemaker or ICD
- Patients with bilateral hip protheses

Comments to the inclusion criteria with an assessment of risks

The presence of one or more of the risk factors (see Inclusion criteria-primary tumor characteristics) indicates that the estimated risk of failing (no CRM negative resection, local pelvic or systemic recurrence) within 3 years is => 60% if surgery is the primary treatment and => 40% if radiotherapy with 5FU chemotherapy followed by surgery (and adjuvant chemotherapy) is the primary treatment. It is assumed that at least a TME/PME is performed. In patients with overgrowth to adjacent organs or structures, these are removed *en bloc.*

All of the abovementioned criteria indicate that the risk of systemic relapse is high, whereas not all indicate that the risk of failing locally is high.

Radiotherapy and Chemotherapy

Radiotherapy

All patients eligible for radiotherapy according to inclusion criteria will be randomized to receive either a standard radiotherapy with photons or experimental treatment with protons. Inclusion can be done at any of the seven university hospitals in Sweden. Before treatment all proton plans will be discussed at national proton boards.

Treatment volumes and OARs will be contoured using Radiation Therapy Oncology Group (RTOG) guidelines as well as national Swedish guidelines (Appendix 2 Target volumes). The clinical target volume (CTV) consist of the gross tumor volume (GTV) plus margin. GTV is determined by a combination of physical examination, colonoscopy, and diagnostic CT and/or magnetic resonance imaging (MRI) scan plus the entire mesorectum, including the perirectal fat and presacral space along with the iliac lymph nodes. Tumour with a margin, plus regional lymph nodes according to tumour location and growth. The mesorectal, pre-sacral lymph and internal iliac nodes are always included whereas the lateral obturator nodes are only included if the tumour grows below the peritoneal reflection. The external iliac nodes should be included if the primary tumour invades anterior organs (e.g., bladder, prostate, cervix, vagina, uterus or seminal vesicles) to such an extent that the external nodes are at risk for metastases. Napping or minimal overgrowth dorsally is not sufficient.

Organs at risk (OARs) will be outlined in accordance with the national Swedish guidelines (STRÅNG-project) (33, 34). Bladder, bowel bag, femoral heads, sacral nerves, pelvic bones will be defined. Pelvic bone will be contoured for the full extent of the PTV

Rationale for using IMRT

Modern highly conformal radiation therapy planning and delivery techniques could potentially reduce the radiation dose to the bowel and, consequently, reduce gastrointestinal side effects. The small bowel has been estimated to have a 5% risk of late toxicity at 5 years with doses of between 45 and 50 Gy (35) (36). The risk of grade 3 or greater bowel toxicity has been shown to increase with both total dose and with the volume of bowel irradiated to higher doses and intensity modulated radiation therapy (IMRT) has previously been demonstrated to be effective in reducing small bowel dose and resultant gastrointestinal toxicity in patients with other pelvic malignancies (cervical, endometrial, prostate) (37) (38, 39)
(40). In one study, Urbano et al (40) conducted a dosimetric analysis comparing three dimensional conformal radiation therapy (3D-CRT) and IMRT. They found that IMRT improved small bowel sparing when compared with 3D-CRT as much as by a 64% reduction in the amount of small bowel receiving 45 Gy. The authors therefore concluded that the IMRT plan appeared to be clinically promising.

Inverse planning is required for the IMRT portion of treatment and planning constraints are provided in this section for both the planning target volume (PTV) as well as OARs. Acceptable treatment plans will be established from a DVH-based analysis of the volumetric dose to both the PTV and critical normal structures to ensure that minimally acceptable constraints for each volume of interest have been met.

Localization and Immobilization

All preparation with fixation, dose-planning CT, target definition and dose-planning will be done at one of the university hospitals participating in the Skandion network. A custom lower limb immobilization device (ProSTEP) for supine patients is required to minimize setup uncertainty. For details see Appendix 1.

Pre-treatment imaging

For details see Radiology Appendix.

Target Volumes

For details see Radiotherapy protocol. Appendix 1. The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

The Gross Tumor Volume (GTV) is defined as all known gross disease as determined from a combination of physical exam, colonoscopy, ultrasound, CT, MRI and PET-CT if performed.

The Clinical Target Volume (CTV) is defined as the GTV plus areas considered at significant risk of harboring microscopic disease.

The Planning Target Volume (PTV) will provide a margin around the CTV to compensate for the inter- and intra-fraction uncertainty consequent to daily setup uncertainty and to potential internal organ motion. By definition, the PTV will consist of a symmetrical 7-8 mm expansion around the CTV. In the event that PTVs extend outside of the skin surface, the clinician should manually trim the PTV contours to be 3-5 mm inside the outer skin (unless there is direct skin involvement).

OARs

Organs at risk (OARs) will be outlined in accordance with the national Swedish guidelines (STRÅNG-project) (33, 41). Bladder, bowel bag, femoral heads, sacral nerves, pelvic bones will be defined. Pelvic bone will be contoured for the full extent of the PTV.

Planning Constraints

For details see Radiotherapy protocol. Appendix 1.

Dose specification

Standard treatment with photons. Arm A:

Patients will receive daily preoperative radiotherapy with photons 5 Gy five days a week to a total dose of 25 Gy.

Overall treatment time should be maximum eight days.

Doses that have been reduced due to toxicity must never be re-escalated.

Experimental treatment with protons. Arm B:

Preoperative radiotherapy with protons will be delivered at the Skandion clinic, Uppsala, Sweden.

Skandionkliniken is the name of Sweden's only proton therapy facility. It is an Ion Beam Applications (IBA) powered facility, exclusively using the pencil beam scanning technique. An isochronous cyclotron is used for accelerating the protons up to 230 MeV

Patients will receive daily preoperative radiotherapy with photons 5 Gy (RBE) five days a week to a total dose of 25 Gy (RBE).

For proton therapy, the dose prescriptions should be in both physical dose and RBE-weighted absorbed doses. The RBE value of 1.1 should be used for protons and the prescribed dose is the corresponding dose for photons (Gy(RBE)).

Treatment planning and delivery

For details see Radiotherapy protocol. Appendix 1.

Treatment plan evaluation

For details see Radiotherapy protocol. Appendix 1.

Toxicity and stopping rules

Toxicity will be assessed and recorded according to the CTCAE v5.0 acute and late radiation morbidity scoring criteria (Appendix 3 and Appendix 4)

There is a risk of acute neuropathic pain. If this occurs, the upper border of the beams can be lowered by a few cm or, alternatively attempts to block the sacral nerve roots should be done if possible considering the tumour extent. This usually results in that the pain disappears. If not, treatment should be interrupted. A short period of corticosteroid treatment may be prescribed.

Chemotherapy

Neo-adjuvant chemotherapy consists of a combination of capecitabine and oxaliplatin.

Oxaliplatin

The standard dose of oxaliplatin in the CAPOX regimen is 130 mg/m^2 (5 mg/ml concentrate for solution for infusion) in 500 ml glucose 5% i.v. infusion in 30-120 minutes and should *never* be dissolved in NaCl. If FOLFOX used instead, the oxaliplatin dose is 85 mg/m$^{2.}$

When prescribing oxaliplatin, the contra-indications, special warnings and interactions, as described in the latest version of the Summary Product Characteristics (SMP) (1B text), should be observed.

Capecitabine

For practical reasons dosing of capecitabine should be rounded to the nearest dose that can be administered using the 150 and 500 mg tablets. When prescribing capecitabine, the contra-indications, special warnings and interactions, as described in the latest version of the SmPC (1B text), should be observed.

Other medication

Anti-emetic prophylaxis with a 5HT3 antagonist and a glucocorticosteroid is required for all patients prior to each oxaliplatin dose.

Other standard supportive therapies should be administered as clinically indicated.

Chemotherapy doses and timing

Neoadjuvant chemotherapy

Preferably, chemotherapy will start within 11-18 days after the last day of radiotherapy. However, in case of treatment related diarrhoea or other toxicity, further delay until the toxicity is resolved is allowed till 4 weeks after the last day of radiotherapy. If there are signs of tumour progression during the neo-adjuvant chemotherapy, this treatment should be stopped, and the patient should be evaluated as soon as possible for surgery.

drug	**dose**	**frequency**	Every 3 weeks cycle, in total 4 cycles
Capecitabine	1000 mg/m^2	Twice daily, day 1-14	
Oxaliplatin	130 mg/m^2	Every 3 weeks	

Table 1. *Dose of (neo) adjuvant chemotherapy*

As an alternative to CAPOX, particularly if capecitabine is not well tolerated, FOLFOX-6 can be used.

Dose modification schedules

Capecitabine

The most frequently occurring non-haematologic toxicities are: hand-foot syndrome, asymptomatic hyperbilirubinaemia, diarrhoea, nausea/vomiting (not requiring anti-emetic prophylaxis), abdominal pain, stomatitis, and anorexia.

In case of grade 2-3 hand-foot syndrome, capecitabine dosing should be interrupted until recovery until ≤ grade 1. The omitted doses should not be administered after resuming of treatment, i.e. the total length of each capecitabine treatment period should not exceed 14 days (during induction or reintroduction of MTD chemotherapy).

If painful swelling or erythema of hands or feet occur, emollients are beneficial. Pyridoxin, vitamin B6 50 – 150 mg/day has been reported to be of possible benefit to the patients. Pyridoxin is not licensed for that indication.

Diarrhoea

Prophylactic treatment:

No prophylaxis must be given, especially no loperamide should be administered prophylactically.

In case of diarrhoea grade 2-4, capecitabine intake should be interrupted immediately. Capecitabine can only be restarted when diarrhoea is resolved to grade ≤ 1.

In case of interruption of capecitabine therapy, the omitted doses should not be administered after resuming of treatment, i.e. the total length of each capecitabine treatment period should not exceed 14 days.

Patients experiencing severe diarrhoea should be followed cautiously. In case of risk of dehydration, fluids and electrolytes should be administered. Standard treatment for diarrhoea should be prescribed (i.e. loperamide).

If diarrhoea persists for more than 48 hours despite the recommended loperamide treatment, the patient should be hospitalised for parenteral support. Loperamide may be replaced by other anti-diarrhoeal treatment (e.g. octreotide etc.).

Patients who experience concomitant vomiting or fever or have a ECOG performance status > 2 should be hospitalised immediately for i.v. rehydration.

Capecitabine treatment interruption during the cycle

Capecitabine intake must be interrupted in case of ≥ grade 2 non-haematologic toxicity and can be resumed after improvement to ≤ grade 1. During induction treatment the omitted doses should not be administered after resuming of treatment, i.e. the total length of each capecitabine treatment period should not exceed 14 days. In case recovery to ≤ grade 1 does not occur within 2 weeks, the treatment should be discontinued.

Capecitabine dose adaptations for non-haematological toxicity

No dose reduction for the 1st occurrence of grade 2 toxicity, but treatment should be interrupted until recovery of symptoms to grade 0-1. The dose should be reduced 25% relative to the previous cycle at the 2nd occurrence of grade 2 or the occurrence of any grade 3 toxicity. The dose should be reduced 50% relative to the previous cycle at the 3rd occurrence of any grade 2 toxicity or a 2nd occurrence of any grade 3 toxicity or the occurrence of any grade 4 toxicity. Treatment should be discontinued if despite these dose reductions, a given toxicity occurs for a 4th time at grade 2, a 3rd time at grade 3, or a 2nd time at grade 4 (see table 3 below).

	Grade 2	Grade 3	Grade 4
1st occurrence	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 100% of the capecitabine dose	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 75% of the capecitabine dose	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 50% of the capecitabine dose
2nd occurrence	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 75% of the capecitabine dose	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 50% of the capecitabine dose	Discontinue treatment
3rd occurrence	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 50% of the capecitabine dose	Discontinue treatment	
4th occurrence	Discontinue treatment		

*Table 2. Dose adaptions of **capecitabine** for non-haematological toxicity.*

In the case of cardiac symptoms (angina, arrhythmia) considered possibly related to capecitabine, CAPOX can be replaced with Nordic FLOX (5-FU 500 mg/m^2 iv and calcium folinate 100 mg iv days 1 and 2 with oxaliplatin 85 mg/m^2 iv day 1 q 2 weeks) for the remaining time of neoadjuvant treatment.

Oxaliplatin

The most frequently occurring non-haematologic toxicities are: sensory neuropathy, nausea/vomiting (requiring anti-emetic prophylaxis), diarrhoea, mucositis/stomatitis.

Sensory neuropathy

A 25% dose reduction of oxaliplatin in case of persistent (≥ 14 days) paresthesia or temporary (7-14 days) painful paresthesia or functional impairment. In case of persistent (≥ 14 days) painful paresthesia or functional impairment, oxaliplatin should be omitted until recovery and may be restarted at 50% of the dose. If despite of a 50% dose reduction, neurotoxicity does recur, and oxaliplatin will be discontinued permanently and patients will continue treatment with capecitabine (or 5-FU, see above). In case oxaliplatin infusion is not possible according to this schedule on day 1 of the next cycle, this cycle should not be delayed, and oxaliplatin should be withheld until the following cycle. Acute neurosensory effects (acute laryngeopharyngeal dysesthesia with subjective feelings of dyspnea and dysphagia without signs of bronchospasms or pulmonary abnormalities) have been observed. See also table 4 below.

Sensory neuropathy	Oxaliplatin dose
Non-painful paresthesia ≥ 14 days or temporary (7-14 days) painful paresthesia/functional impairment	25% reduction
Persistent (pain≥ 14 days) painful paresthesia/functional impairment	Omit until recovery, then restart at 50%
Recurrent neurotoxicity after 50% dose reduction	Permanently discontinued

*Table 3. Dose adaptions for **oxaliplatin** for sensory neuropathy (cycles 1 – 6)*

Extravasation of oxaliplatin

No severe extravasation reactions have been observed so far with oxaliplatin.

As a general recommendation in the event of extravasation, the following measures are advised (like for any other cytotoxic drug):

1. Stop the infusion immediately.
2. Do not remove the needle or cannula.
3. Aspirate with the same needle as much infiltrated drug as possible from the subcutaneous site.
4. Apply ice to area for 15 to 20 minutes every 4 to 6 hours for the first 72 hours.
5. Watch the area closely during the following days in order to determine whether any further treatment is necessary.

Allergic/ideosyncratic reactions to oxaliplatin

These reactions have been described occurring shortly after oxaliplatin infusion, and a massive cytokine release has been suggested as its cause. In case such a reaction occurs, prophylaxis with steroids ± anti-histamines is indicated.

Dose adaptions for **oxaliplatin and capecitabine** for non-haematological toxicity: see Table 5 below.

Toxicity during previous cycle	Grade	Next dose Oxaliplatin	Next dose Capecitabine
Diarrhoea	3/4	75%	75%/50%
Mucositis	3/4	Full dose	75%/50%
Skin	3/4	Full dose	75%/50%
Hand-foot-syndrome	2-3	Full dose	See Table 3.
Neurotoxicity	See Table 4	See Table 4	Full dose
Other non haematologic toxicities	3/4	75%	75%/50%

Table 4. Dose adjustment relative to the previous cycle for next cycle.

Status of non-haematological toxicity at the start of each treatment cycle.

Non-haematological toxicity should be ≤ grade 1 before start of the next treatment cycle. If these conditions are not met dosing of all drugs should be delayed for a maximum of two weeks until recovery to ≤ grade 1. In case recovery to ≤ grade 1 does not occur within 2 weeks, the treatment will be discontinued. The only exception will be the occurrence of sensory neuropathy induced by oxaliplatin: in case oxaliplatin infusion is not possible after a 2 week delay, the next cycle should not be further delayed, but oxaliplatin should be withheld until the following cycle.

Status of haematological toxicity at the start of each treatment cycle.

Haematological toxicity may be induced by oxaliplatin, and less frequently by capecitabine.

Neutrophils (10^9/l)	**White blood cells (10^9/l)**	**Platelets (10^9/l)**	**Next dose oxaliplatin**	**Next dose capecitabine**
< 0.5 (grade 4) or febrile neutropenia	< 1.0 (grade 4)	< 25 (grade 4)	-25%	No adjustment

*Table 5. Dose adaptations for o**xaliplatin and capecitabine** for haematological toxicity relative to the previous cycle for the next cycle.*

If these toxicities recur after dose reduction for previous toxicity, the next cycle should be given with a 25% dose reduction of capecitabine. If these toxicities occur again, a 50% dose reduction of oxaliplatin should be given. Treatment should be discontinued if these toxicities recur despite these dose reductions.

At the start of each treatment cycle.

WBC and platelet counts should have been recovered to ≥ 3.0 and ≥ 75 x 10^9/L, respectively, before the start of the next treatment cycle. If these conditions are not met dosing should be delayed for a maximum of 2 weeks. If haematological toxicity has not recovered to the above-mentioned values after 2 weeks delay patients will discontinue treatment with chemotherapy.

Permanent discontinuation of individual drugs due to toxicity

If patients experience severe toxicity despite dose reductions which necessitate the discontinuation of individual or all drugs, these patients will remain on study and should be followed for progression of disease according to the specified timelines.

Prophylactic treatments

Anti-emetic prophylaxis

The prophylactic use of a 5HT3 antagonist i.v. is indicated prior to administration of oxaliplatin. Corticosteroids may be added as prophylaxis. All patients should be provided with a prescription for anti-emetics (metoclopramide or 5-HT3 antagonists) and should receive instructions on how to use this medication in case nausea/vomiting occurs at home.

Trombo-embolic prophylaxis

Trombo-embolic prophylaxis can be used according to local protocols during pre-operative treatment, peri-operatively and during adjuvant treatment.

Surgery

Patients are treated with tromboembolic prophylaxis, antibiotic prophylaxis and bowel preparation according to local protocols. An open or minimally invasive (MIS) approach may be used.

After entering the abdomen, the entire abdominal cavity and retroperitoneum are screened for metastatic disease. The operation starts with mobilization of the sigmoid from the lateral or medial approach, dependent upon experience of the surgeon, and whether the procedure is done open or with MIS. The vascular supply is ligated. Ligation of the inferior mesenteric artery at its origin from aorta ("high tie") is not mandatory and ligation the superior rectal artery is considered oncologically adequate. The inferior mesenteric vein is divided at the level of convenience. After the vessels are divided the sigmoid colon is transected. The dissection continues in the avascular plane between the mesentery and the parietal structures leaving the ureter covered by its fascia. Care has to be taken to identify the hypogastric nerves to avoid damage. The pelvic nerves and the inferior pelvic autonomic nerve plexus are identified and preserved if it is oncologically possible. The anterior dissection should always be carried out anteriorly to the Denonvilliers'fascia. The dissection is carried out keeping the mesorectal fascia intact, ending up with a total mesorectal excision (TME). The resection of the primary tumour is carried out using sharp dissection to encompass the circumference of the mesorectum. In high rectal tumours (>12 cm from the anal verge) a partial mesorectal excision (PME) may be used granted that the distal margin in both the bowel and the mesorectum is at least 5 cm. Transsection of the mesorectum should be perpendicular to the rectum. In mid or low rectal tumours (< 12 cm) a TME has to be performed. When an anterior resection or a Hartmann's procedure is performed, rectum should be irrigated transanally prior to division of the bowel. If a colo-anal anastomosis is planned for a very low rectal cancer, at least a 1 cm distal margin from the tumour is required. Care should be taken that adequate bowel length and blood supply is present in the bowel used to anastomise with the anal canal. In case of an abdominal perineal resection (APR) in low tumours a perineal resection with the extra-levator technique, when appropriate with a tailored approach, aiming at a cylindrical specimen without "waisting" is mandatory. In patients with pre-therapeutically poor bowel function, a Hartmann´s procedure or an inter-sphincteric APR may be used if oncologically safe.

Potentially invaded adjacent structures are resected en bloc with the rectum. This may include small bowel, ureter(s), bladder, seminal vesicles, vaginal wall and/or uterus and also the sacrum below the level of S3. Thus, patients may require a partial or full pelvic exenteration. Following APR, closure of the perineal wound is up to discretion to each surgeon, but musculocutaneous flaps are advisable. Omental flaps and drains can be used according to surgeon preference. Following an anterior resection, a covering stoma and drains can be used according to surgeon preference.

Lateral lymph nodes with a short-axis exceeding 7 mm pretherapeutically and 4 mm post neoadjuvant therapy should be cleared (42).

Clinical evaluation, laboratory tests, follow-up

Before treatment start

Eligibility evaluation

The following examinations are required upon entry into the study, maximum 6 weeks prior to planned start of radiotherapy:

- Physical examination, including blood pressure, ECOG performance score, patient's weight. Baseline evaluation according to CTCAE 5.0 (Appendix 3 and Appendix 4)

- Rigid sigmoidoscopy (rectoscopy) or colonoscopy with biopsy of the tumour and a "clean colon" investigation with CT-colonography, barium enema or colonoscopy.

- Contrast enhanced multi-detector CT scan of thorax, abdomen and pelvis

- Laboratory tests: haemoglobin, white blood cell count, platelets, bilirubin, ALP, ASAT, ALAT, creatinine, and CEA.

- MRI scan of the pelvis

Obstructing tumors Patients who present with obstructing tumours may be candidates for a diverting colostomy which can be performed laparoscopically.

- Baseline rearing Patient reported outcome (PRO) questionnaires (see Table

During treatment

Interval between short course radiation and chemotherapy

In case of no or moderate RT-induced toxicity, chemotherapy starts the week following completion of RT, ideally 11 – 18 days after the last radiation fraction. In case of more than moderate toxicity chemotherapy will be postponed with one week, or longer if necessary. Dose reduction of chemotherapy may be varying (see Table 4).

Evaluation during neo-adjuvant chemotherapy

See treatment summary table

Re-staging

After the end of chemotherapy (1 – 2 weeks after the last dose) resectability of the primary tumour is evaluated by MRI of the pelvis. Appearance of metastatic disease is evaluated with CT of thorax, abdomen and pelvis, at the end of chemotherapy.

Interval between chemotherapy and surgery

After completing the neo-adjuvant chemotherapy, time must be allowed for the patient to recover. Surgery (rectal resection) should be planned within 2 to 4 weeks after the last dose of capecitabine in the last cycle of chemotherapy.

Stopping rules due to chemotherapy toxicity

This may be the case if severe adverse events are persistent.

A patient should be withdrawn from treatment in any case due to toxicity, if one of the following toxicities persists despite withholding the capecitabine and oxaliplatin for a maximum delay of two weeks:

- Absolute neutrophils count (ANC) < 1.0 and platelets $<100 \times 10^9$/L, respectively
- If the chemotherapy-induced gastrointestinal toxicity does not normalize
- If any other toxicity ≥ grade 3 persists

Toxicity will be assessed and documented according the CTCAE version 5.0 (Appendix 3 and Appendix 4)

Resection and response evaluation

A multidisciplinary team with a panel of radiologist, rectal surgeons, medical-oncologist and radiation-oncologist will evaluate the imaging studies to assess resectability and tumour response. For the purpose of this trial, tumours will be considered resectable unless on imaging:

- T4 tumour with invasion of the sacrum above the level of S3.
- Encasement of lumbosacral nerve root(s)
- Para-aortic pathological nodes (=M1)
- Inguinal lymph nodes (=M1)

Pathologic evaluation of the rectal cancer resection specimen

Pathological evaluation of the resection specimen will be conducted according to national guidelines and will include standardized workup as well as standardized reporting. Key features in the reporting of rectal carcinoma include investigation of depth of tumour invasion and the presence of lymph node involvement. Using these parameters, TNM classification can be assessed. The 8th edition of TNM will be used in this study. A circumferential margin of 1 mm or less is considered positive. The exact measurements of the CRM should be given, and, in cases of lymph nodes or tumour deposits being closer to the CRM than the mass of the primary tumour, two separate CRMs should be measured (one of the closest margin and the other one from the primary

tumour mass). It should be noted that CRM can only be evaluated postoperatively; preoperatively the evaluation should relate to anatomical structures, like the mesorectal fascia (43).

Quality of resection evaluation

The quality of resection is evaluated at two different levels for APRs (mesorectum as well as anal canal) and at one level for anterior resections or Hartmann's (mesorectum).

The mesorectal score is based on the surgical plane which is achieved:

- Mesorectal plane (Complete): intact mesorectum with only minor irregularities of smooth mesorectal surface. No defect is deeper than 5 mm, and there is no coning toward the distal margin of the specimen. There is a smooth circumferential resection margin on slicing.

- Intramesorectal plane (Nearly complete): moderate bulk to the mesorectum, but irregularities of the mesorectal surface. Moderate coning of the specimen is allowed. At no site is the muscularis propria visible, with the exception of the insertion of the levator muscles.

- Muscularis propria plane (Incomplete): little bulk to mesorectum with defects down onto muscularis propria and/or very irregular circumferential resection margin.

In analogy, the score of the anal canal is:

- Outside levator plane: This plane has a cylindrical specimen with the levators removed *en bloc*
- Sphincteric plane: This plane has CRM on the surface of the sphincteric muscular tube, but this is intact.
- Intramuscular/submucosal plane: This plane has perforation or missing areas of muscularis propria indicating entry into the muscular tube at this level

Tumour regression score

Tumour regression is scored using a three-tiered system: no regression, regression and complete response. Complete pathological response is only used after standardized workup of the specimen which includes blocking of the whole tumour area and cutting three levels of each block (at 250 um).

After the end of treatment: Follow-up

If complete colonoscopy could not be performed pre-operatively a total colonoscopy has to be performed within the first year after treatment. Follow-up at, 12, 36 and 60 months after date of surgery will be done by taking history, physical examination, ECOG performance score, symptoms according to CTC 5.0 (see Appendix 3 and Appendix 4) and CEA. Follow-up visits with CEA and pulmonary x-ray and ultrasound of the liver or CT of thorax and abdomen should be done after 12, and 36 months (see Treatment summary). On indication other diagnostic or imaging modalitites (MRI, 18F-FDG-PET/CT, colonoscopy) can be used to confirm or detect recurrent or metastatic disease. If recurrent or metastatic disease is detected this point in time is marked as the time to progression starting from start of radiotherapy. Routine follow-up will be ended after five years in case of no evidence of disease after performing a final colonoscopy.

Patient-Reported Outcome Measures (PROM)

PROM data will be collected according to logistics established by the Proton Care group.

Data collection

Patient reported data (PROs) will be collected at the start of RT, one week after the end of RT-course and at 1, 3, 6, 9, 12, 24, 36 and 60 months after the termination of RT. The timing for data collecting is chosen to capture the expected maximum increase in symptom burden after treatment. All PROs will be collected by paper questionnaires.

Questionnaire	Baseline	Day 1-5	w2	w3	w 9-10	3m	6m	9m	12m	24m	36m	60m
EORTC QLQ-C30	X			X		X		X	X	X	X	X
EORTC QLQ-CR29	X			X		X		X	X	X	X	X
MFI	X			X		X		X	X	X	X	X
HAD	X			X		X		X	X	X	X	X
EQ5D	X			X		X		X	X	X	X	X
RSAS	X	X	X	X	X	X		X	X	X	X	X

Table 6. Overview over PRO questionnaires

Health related quality of life

HRQoL will be investigated with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, the QLQ-C30, version 3 (44). This is a generic cancer-specific questionnaire covering physical, social and psychological functioning, as well as cancer-specific symptoms. The instrument consists of 30 items covering five functioning scales (*physical, role, emotional, cognitive* and *social function*), three symptom scales (*fatigue, pain and nausea/vomiting*) and two *global health/QoL* items. Six single items address additional symptoms commonly reported by cancer patients (*loss of appetite, insomnia, dyspnea, diarrhea* and *constipation*) and *financial difficulties* are also included. The QLQ-C30 will be supplemented with the disease specific module (rectal-cancer) QLQ-CR29.

Symptoms experiences

Anxiety and depression will be evaluated with the Hospital Anxiety and Depression Scale (45) and fatigue with the Multidimensional Fatigue Inventory (MFI-20) (46). During radiotherapy, daily reported symptoms will be investigated by a newly developed symptom scale, Radiotherapy related symptom assessment scale (RSAS). The questionnaire includes 14 items. The RSAS is a validated instrument for assessing symptom intensity and distress in cancer patients undergoing radiotherapy, with psychometric properties within the expected range. Answering categories ranges from not at all to a great deal.

Requirements for Follow-Up **Months since last date of surgery**	**12**	**36**	**60**
CEA	X	X	X
CT thorax-abdomen	X	X	
Colonoscopy		X	
Rectoscopy if anastomosis	X	X	X

Table 7: Minimum follow-up scheme. More frequent follow-up is allowed if this is routinely done.

Assessment of Recurrent Disease

Recurrent disease is defined by the presence of at least one of the following criteria:

- Positive histology or cytology of adenocarcinoma, compatible with the primary tumour in any location.
- Liver metastases on Ultrasound and/or CT, PET/CT.
- Lung metastases on X-ray and/or CT, PET/CT or MRI scan.
- Bone metastases on X-ray and/or bone-scintigraphy and/or MRI
- Brain metastases on MRI
- Distant lymph node metastases
- Changes in soft tissue outlines on CT, PET/CT or MRI– pelvis in combination with an increased CEA to differentiate from fibrosis.

Parameters for Recurrent Disease

The following parameters will be recorded and studied:

- Loco-regional recurrence site and date (local within the pelvis) as well as tumour recurrence relation to radiotherapy volumes (in-field, marginal, out-of-field)

- Distant recurrence site and date (outside the pelvis).

- Cause of death: local failure, local failure and metastases, metastases only, complications due to treatment, intercurrent disease and unknown cause.

Treatment Summary table

	Baseline	WEEK									
Required Investigations		**1**	**2**	**3-4**	**6-7**	**9-10**	**12-13**			**16-17**	**17-20**
Physical examination	x			x	x	x					x
ECOG performance score	x			x	x	x					x
Tumour related symptoms	x			x	x	x					x
Blood Pressure	x			x							x
Haematology[1]	x			x	x	x	x				x
Biochemistry[2]	x			x							x
CEA[3]	x			x	x	x	x				
CT thorax-abdomen-pelvis	x									x	
MRI pelvis	x									x	
Colonoscopy/rectoscopy[4]	x										
Toxicity evaluation		x	x	x	x	x					x
Radiotherapy		x									
Oxaliplatin				x	x	x	x				
Capecitabine				x	x	x	x				
Surgery											x
1) Hb, WBC count, platelet count At baseline: < 72 hour prior to start of chemotherapy											
2) Na, K, creatinin, ALP, ALAT, ASAT, , bilirubin At baseline: < 72 hour prior to start of chemotherapy											
3) Within 5 weeks prior to start of radiotherapy											
4) Biopsy taken											
Treatment/drug	**dose**	**frequency**									
Radiotherapy	5x5Gy (RBE)	week 1 day 1-5									
Capecitabine	1000 mg/m^2	b.i.d. day 1-14 every 3 week cycle starting at week 3									
Oxaliplatin	130 mg/m^2	day 1 every 3 week cycle starting at week 3									

Table 8. Treatment summary

Criteria of evaluation

Definitions

Toxicity

All patients will be evaluable for toxicity from the time of their first treatment. Toxicity (acute and late) will be assessed and documented according the CTCAE version 5.0 (Appendix 3 and Appendix 4). Adverse events and serious adverse events will be reported as described in section 8.4.

Disease-free survival

Disease-free survival will be computed as the time between start of radiotherapy and either local or distant relapse or death caused by the rectal carcinoma whichever comes first. In case of non-rectal cancer related death patients will be censored at date of death. In case of a second primary tumour patients will be censored at the date of diagnosis of the second primary tumour. Patients lost to follow-up will be censored the last date of patient visit.

Fraction of radical resection (CRM > 1 mm)

Negative CRM will be evaluated according the pathology protocol described by Quirke (47).

Local recurrence

Local recurrence is described as relapse of tumour in the pelvic region.

Distant relapse

Distant relapse is described as relapse of tumour outside the pelvic region. This will be assessed by clinical investigation and imaging studies. Special attention must be made on the liver and lung since these are the predominant side of metastases.

Overall survival

Overall survival will be computed as the time between randomization and all causes of death. Patients lost to follow-up will be censored the last date of patient visit.

Statistical considerations

Sample size:

The number of newly diagnosed rectal cancers in Sweden is about 1850 per year (Onkologirapporten 2017). Of these, about 750 in Stockholm, Uppsala/Örebro regions. Historically, about 60-65% of all recal cancer patients receive neoadjuvant radiotherapy. About 35% of the patients receiving radiotherapy are also treated with chemotherapy. Totally, about 20% of newly diagnosed nonmetastatic rectal cancers are treated with both neoadjuvant radiotherapy and chemotherapy. The maximum inclusion capacity in this study for Stockholm and Uppsala/Örebro regions combined is about 150 patients/year and this figure for the whole country is approximately 370 patients. Less than two years should be enough to include the required number of patients to reach the primary endpoint.

Cost-utility analysis

The results of the health-economic part of the study will be expressed as cost per quality adjusted life years (QALYs) saved by one intervention as compared to the other. According the Swidish guidelines for health-economic studies, the analysis should be performed from a societal perspective, i.e. all relevant costs irrespectively of where they occur should be identified, qualified and valued. A societal perspective includes indirect costs, i.e. cost related to loss of production as a result of treatment-related disability. Specifically, not only the costs of interventions will be assessed but all type of resources associated with the two treatment arms during the total follow-up period. That includes costs for treatment of side-effects, costs of surgery, traveling costs. For evaluation and analysis of the study results, a relatively simple health-economic model will be developed that will be used for evaluation of the two treatment arms from inclusion until 5 years of follow-up period.

Randomization and stratification:

Patient randomization will only be allowed from authorized investigators, their authorized staff members or data manager. A patient can be randomized only after verification of eligibility. Randomization will be stratified by institution, ECOG performance score (0 or 1), clinical T-stage (cT2-T3 or T4), clinical N-stage (cN- or cN+).

Statistical analyses:

All efficacy analyses will be based on intention-to-treat. Per-protocol analyses will be performed as secondary analyses.

Safety analyses will be based on treatments received and will include only eligible patients.

Survival curves for disease-free survival and overall survival will be constructed using the method of Kaplan-Meier. Cumulative incidence of local recurrence will be computed accounting for death as competing risk. Differences in survival between subgroups will be tested with the log-rank test. Hazard ratios and 95% confidence intervals (CI) will be computed using Fine-Gray model.

Frequency and percentages for toxicity will be presented according to the CTCAEv5.0 grades.

All proportions will be presented with 95% CI.

Logistic regression will be used to compare rates of hematologic AEs for patients with a volume of bone marrow irradiated between 10 to 40 Gy (V_{10} to V_{40}) dichotomized at the median.

Univariate logistic regression models will be used to determine if there is any relationship between volume of bone marrow irradiation, cancer site, age and hematologic AEs.

Interim Analyses

No interim analysis is planned

Translational research

Proteomics, genomics, and circulating tumour cell analyses of plasma and tumour tissue along the treatment schedule may provide insight in biomarkers associated with response and prognosis. In the beginning of the trial no additional blood or tissue specimens are planned to be collected. This, however, may be relevant later during the trial.

Patient registration

Forms and procedures for collecting data

All patients included in the study will be identified by the patient identification number. Identification code lists that link patients' names to patients' identification number must be stored in the Investigation file. Study data will be recorded via Electronic Case Report Forms (eCRF). Study data may be recorded directly into the eCRF or be transcribed by the site from the paper source documents onto the eCRF according to the local source-data list. Prior to study start, the Investigator and the Monitor must identify and document the expected source location of CRF data. Accurate and reliable data collection will be assured by verification of the eCRF against the investigator's records and medical records by a study monitor.

Case report forms

Electronic Case Report Forms

Data flow

Electronic CRFs will be filled in by treating physicians or data managers at all participating centers and departments.

Reporting adverse events

Section 10 WHO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

Adverse events and serious adverse events

NOTE In this study, the following events are not reported as an AE or SAE:

- planned surgery (e.g. stoma removal)
- planned hospitalisation (e.g. for administering chemotherapy) or recurrences.
- For recurrences, the CRF "new primary / recurrences" must be filled in;
- death due to progression of disease;

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product / the experimental treatment. Only adverse events reported spontaneously by the subject or observed by the investigator or his staff of grade 2-5 will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose:
- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life-threatening disease, major safety finding from a newly completed animal study, etc.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

All SAEs, irrespective of relationship to the study treatment must be reported to the Coordinating centre. The SAE report should include the investigator's assessment of causality. If follow-up information changes the investigator's assessment of causality, this should be noted on the SAEs occurring within 30 days after discontinuation of the study treatment should be reported.

Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).

Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

Quality assurance

Control of data consistency

Data for this study will be recorded via using Case Report Forms (CRF). On-site quality control will be performed by a person not directly involved in the study. This monitor will either be a local monitor at the participating center nor a central monitor.

A monitoring committee will be appointed which will perform monitoring every 6 months after start of this trial.

Audits

The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the "Sponsor", national and/or foreign regulatory authorities, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorized individuals.

Review of pathology

In order to optimize pathology quality, review of pathology will be performed after inclusion of the last patient. A committee of experienced rectal cancer pathologists will be appointed.

Other review procedures

In order to optimize pre-operative staging, radiology review will be performed after the inclusion of the last patient. A committee of experienced rectal cancer radiologists will be appointed to review all pre-operative CT and MRI scans.

Ethical considerations

Patient protection

The responsible investigator will ensure that this study is conducted in agreement with most recent version of the Declaration of Helsinki and with the laws and regulations of the country.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice.

The protocol will be approved by the Local Ethics Committee.

All patients are covered by standard patient insurance.

Subject identification

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the data centre, patients should only be identified by the identification code and month and year of birth. The investigator and each investigator in each participating hospital should keep a patient enrolment log showing codes, names and addresses.

Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This must be done in accordance with the national and local regulatory requirements.

Trial sponsorship and financing

The trial will be sponsored separately by each participating site. Central cost including ethical applications, CRF and coordination will be covered by the sponsor.

Publication policy

The trial will be published after completion of the inclusion and completion of follow-up of patients with respect to results regarding the primary and secondary endpoints. The main results regarding the primary and secondary endpoints have to be published first, compared to publication of results of side-studies. The principal investigators will be first author and/or last authors of main papers based on this study. In case of papers of side results authors have to be appointed by the writing committee based on the topic studied and investigators involved.

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