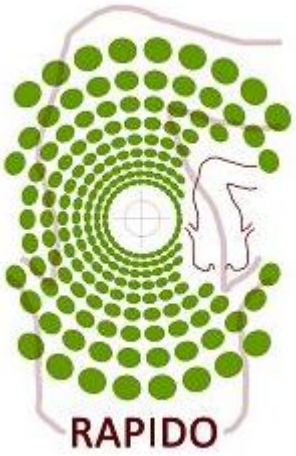
Version 3.1, 08 January 2016

Randomized Multicentre Phase III study of short course radiation therapy followed by prolonged pre-operative chemotherapy and surgery in primary high risk rectal cancer compared to standard chemoradiotherapy and surgery and optional adjuvant chemotherapy.

RAPIDO

Rectal cancer **A**nd **P**re-operative **I**nduction therapy followed by **D**edicated **O**peration



This research has been funded by DUTCH CANCER SOCIETY

NL36315.042.11

EudraCT number 2010-023957-12

CKS number 2011-4997

NCT01558921

NTR 3230

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23-09-2010	**Protocol version 1.0 submitted to CKS-KWF**
13-01-2011	**Protocol version 1.0 submitted to EC UMCG**
12-04-2011	**Protocol version 1.0 submitted to CKS-KWF**
23-06-2011	**Swedish Version**
26-09-2011	**EC comments included**
14-10-2011	**Central Ethical Approval EC UMCG**
07-11-2011	**CKS-KWF Approval**
01-12-2011	**Protocol Version 2.0 Amendment**
27-02-2012	**Central Ethical Approval EC UMCG version 2.0 amendment**
01-03-2012	**Initiation Date Netherlands**
26-03-2013	**Protocol Version 2.1.1 Amendment**
08-05-2013	**Central Ethical Approval EC UMCG version 2.1.1. amendment**
30-04-2014	**Protocol Version 2.2 Amendment**
20-06-2014	**Central Ethical Approval EC UMCG Substantial amendment 3.**
08-01-2016	**Protocol Version 3.1 Amendment**
07-03-2016	**Central Ethical Approval EC UMCG amendment version 3.1**

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Table of contents

Protocol Signature Sheet

I declare that I have read and familiarized myself with the following protocol **version 3.1:**

Randomized Multicenter Phase III study of short course radiation therapy followed by prolonged pre-operative chemotherapy and surgery in primary high risk rectal cancer compared to standard chemoradiotherapy and surgery and optional adjuvant chemotherapy.

RAPIDO

NL36315.042.11
EudraCT number 2010-023957-12
CKS number 2011-4997

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Synopsis of the protocol

Protocol title	Randomized multicentre phase III study of short course radiation therapy followed by prolonged pre-operative chemotherapy and surgery in patients with high risk primary rectal cancer compared to standard preoperative chemoradiotherapy and surgery and optional adjuvant chemotherapy.
Protocol Phase	Final
Indication	Primary rectal cancer with high risk of failing locally and/or systemically
Background	In patients with a newly diagnosed rectal cancer at high risk of failing locally and/or systemically, standard therapy is long-course preoperative radiotherapy with concomitant chemotherapy followed by surgery preferably after 8 weeks (±2 weeks). Despite lack of strong scientific evidence, postoperative adjuvant chemotherapy is added in many centres. To achieve higher compliance and better effect of chemotherapy, the aim is to deliver the systemic treatment pre-operatively. Most standard adjuvant chemotherapy schedules in colorectal cancer have a duration of 24 weeks. Modifications of current standard therapy could theoretically include increase of dose or number of chemotherapy agents for the concomitant therapy but this would increase toxicity and possibly decrease compliance. Long course radiotherapy takes 5-6 weeks to deliver but to omit this and start with systemic chemotherapy would not gain acceptance because of the risk of local progression. An alternative to modifications of the present long-course schedule is to explore the possibilities of using a short-course radiotherapy regimen in the locoregional therapy and combine this with pre-operative chemotherapy. A peri-operative chemotherapy regimen was successfully explored for liver metastases of colorectal cancer in the EORTC-EPOC trial. A trial with a similar schedule with an experimental arm consisting of 12 weeks of chemotherapy pre-operatively followed by short-course radiotherapy and immediate surgery and 12 weeks of post-operative chemotherapy could be considered [1]. This design would, however, have some drawbacks including no locoregional therapy initially and the risk of not being able to deliver half of the chemotherapy to a substantial proportion of the patients. Moreover, when surgery is performed immediately after radiotherapy, the desired down-staging on these locally advanced tumours may not occur, leading to a potential risk of decreased local control rates. Yet another alternative is to explore possibilities connected with using the short-course radiotherapy with delayed surgery as the locoregional therapy. Again there would be potential problems connected with starting with systemic therapy whereas putting the week of radiotherapy first is an option that offers part of the locoregional therapy first. 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. Data

	from retrospective trials [2, 3] and the "M1 trial" [4] support the notion that systemic chemotherapy also acts on the primary tumour, thus leading to improved locoregional therapy as compared to short-course and a "waiting period" without chemotherapy. However, in order to minimise interval between radiotherapy and surgery and still being able to deliver all systemic chemotherapy prior to surgery, adjustments of standard chemotherapy schedules for colorectal cancer may be necessary. The schedule explored in the "M1 trial" consisting of 18 weeks with oxaliplatin/capecitabine is 6 weeks shorter than commonly used in post-operative adjuvant schedules and offers an attractive alternative. Bevacizumab was included in the "M1 trial" but there is no data suggesting that bevacizumab [5] or cetuximab [6] improves the antitumour effects against subclinical disease.
Endpoints	**Primary endpoint:** • 3-year time to disease related treatment failure (TdrTF) **Secondary endpoint:** • Overall survival • CRM negative (margin > 1 mm) rate • Pathological complete response (pCR) rate • Short and long-term toxicity • Surgical complications • Quality of life
Study design	Patients will be randomized between an experimental group (arm B) in which short course 5 x 5 Gy radiation scheme is followed by six cycles of combination chemotherapy (capecitabine and oxaliplatin; *or alternatively nine cycles of folinic acid, fluorouracil and oxaliplatin (FOLFOX4)*) and surgery and a control group (arm A) with long course chemoradiotherapy followed by surgery. In arm A adjuvant chemotherapy is allowed according to the local protocol of the institution. In both groups the rectal tumour will be removed by TME surgery or more extensive surgery if required because of tumour extent.
Total number of centres	All hospitals in Sweden and The Netherlands treating rectal cancer patients can be involved. Centers in Norway, Slovenia, Denmark, Spain and US are also participating. Centers from Canada are interested in participating too.
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 not having a CRM negative resection or a recurrence, local or distant, within three years.
Main criteria for inclusion	**Primary tumour characteristics:** 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 (T4a, i.e. overgrowth to an adjacent organ or structure

	like the prostate, urinary bladder, uterus, sacrum, pelvic floor or side-wall (according to TNM version 5), cT4b, i.e. peritoneal involvement, extramural vascular invasion (EMVI+). N2, i.e. four or more lymph nodes in the mesorectum showing morphological signs on MRI indicating metastatic disease. Four or more nodes, whether enlarged or not, with a rounded, homogeneous appearance is thus not sufficient. Positive MRF (previously named CRM), i.e. tumour ≤ 1 mm from the mesorectal fascia [60]. Enlarged lateral nodes, > 1 cm (lat LN+). **General:** Staging done within 5 weeks before randomization. No contraindications to chemotherapy, 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, see appendix B. 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:** Time to disease related treatment failure (TdrTF) after 3 years **Secondary:** Overall survival, CRM negative resection rate and pCR rate
Main parameters of safety	• Adverse events, graded according to the NCI CTCAE (version 4.0). • CRM negative resection rate
Screening	Baseline screening includes: • CT (or MRI) of the abdomen and liver • MRI of the pelvis • CT of the thorax • Routine blood tests
Stratification parameters	• Institution • Performance score 0 versus 1 • Clinical T-stage cT2 or cT3 versus cT4 • Clinical lymph node status cN- versus cN+

Treatment	**Standard Arm A:** week 1-6 : Chemoradiotherapy (CRT): 28 x 1.8 Gy or 25x2 Gy at working days combined with capecitabine b.i.d. 825 mg/m^2 (twice daily) day 1-33-38. 8 weeks (±2 weeks) after CRT: Surgery (TME). Adjuvant chemotherapy (8 cycles of CAPOX (Capecitabine b.i.d.1000 mg/m^2 (twice daily) day 1-14 every 3 weeks, Oxaliplatin 130 mg/m^2 day 1 every 3 weeks or alternatively twelve cycles of folinic acid, fluorouracil and oxaliplatin (FOLFOX4) allowed according to the local protocol of the particular institute. **Experimental Arm B:** Week 1: 5 x 5 Gy Week 3-19: 6 courses of CAPOX (Capecitabine b.i.d.1000 mg/m^2 (twice daily) day 1-14 every 3 weeks, Oxaliplatin 130 mg/m^2 day 1 every 3 weeks or alternatively nine cycles of folinic acid, fluorouracil and oxaliplatin (FOLFOX4). Week 22-24: Surgery (TME)
Statistical considerations	This randomized phase III study compares an experimental treatment against the present standard treatment. Of relevance is also the immediate anti-tumour secondary endpoints, CRM negative and pCR rates. It is expected that 3-year TdrTF in the control group (arm A) is 50%. The hypothesis is that the experimental treatment will improve this figure to 60%.
Planned sample size	842 evaluable patients, with estimated drop-out of 5 % : 920 patients to be included, at least 421 evaluable patients in each arm.
Analysis plan	The primary endpoint will be analyzed two years after the last patient was included. At this timepoint median follow up is three years.
Duration of the study	Four year inclusion, two year follow up after inclusion of the last patient. Estimated duration of the study is six year.

Abbreviations

ANC	absolute neoutrophil 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
CTV	clinical target volume
DFS	disease free survival
DPD	dihydropyrimidine dehydrogenase
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EMVI	extramural vascular invasion
EORTC	European Organisation for Research and Treatment of Cancer
FOLFOX	folinic acid, fluorouracil and oxaliplatin
5FU	5fluorouracil
GTV	gross target volume
5HT3	5-hydroxytryptamine (serotonin) receptor 3A
LAR	low anterior resection
LV	leucovorin or folinic acid
IMRT	intensity-modulated radiotherapy
ICRU	international commission on radiation unit and measurements
MDT	multidisciplinairy 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
TdrTF	time to disease related treatment failure
TTF	time to treatment failure
TNM	tumour node metastasis classification
TME	total mesorectal excision
W&W	Wait & Watch policy or Watchful Waiting policy

1. Background and introduction

1.1 Epidemiology

Colorectal cancer is globally, and in the Western world, with about 1 million new cases annually, the third most common cancer. 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 2006, more than 11000 new colorectal cancer patients were registered in the Netherlands, and 5500 in Sweden [7, 8]. 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.

1.2 Treatment of rectal cancer

1.2.1 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) can not be achieved, the chances of cure are very low. A few small tumours in the rectum can be treated with external and local radiotherapy [9] and there are indications that some, likewise small rectal cancers that are very chemoradiosensitive can be successfully handled without (major) surgery [10].

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 [11] led to the understanding that the entire mesorectum must be completely removed in one package to obtain low local failure rates [12]. 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 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 10 of 15% in the group of patients where the intention is to do a radical procedure [13].

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 (T4a), 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.

1.2.2 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 [14-16]. 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 improves local control [17-19] and is thus standard treatment to patients who are suitable for this combined therapy. As an alternative to radiochemotherapy, the short-course schedule with a delay prior to surgery has been used in unfit patients, with results that appear promising [3, 20]. This approach is used in a now ongoing randomized trial in resectable patients (Stockholm III study) [21].

1.2.3 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 [62] [[63].This approach has been successful in many tumours, such as breast and colon cancer with meaningful reductions in relapse rates [22, 23] and post-operative adjuvant chemotherapy in colon cancer stage III and high-risk stage II is standard treatment. 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 [18, 24-26], although some recent trials show that gains are present in a low-risk group (chiefly stage II) of patients [27, 28]. At many centres post-operative adjuvant chemotherapy is standard in rectal cancer [25]. However, the results of the PROCTOR/SCRIPT trials did not show a benefit of adjuvant chemotherapy [61].

1.3 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 periphery of the tumour and its relations to the mesorectal fascia and surrounding structures better than other techniques [29-31]. Positron emission tomography (PET) is also sometimes used to detect tumour manifestations not otherwise detectable [32, 33]. 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 recently published criteria dividing rectal tumours into three groups (low, intermediate and high, or 'good', 'bad' and 'ugly') [34, 35]. There is presently no international consensus about the criteria, 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 a trial exploring the value of treating patients with neo-adjuvant chemotherapy.

1.4 Motivation for a trial of pre-operative chemotherapy in rectal cancer

Better staging, improved decision-making at multidisciplinary team (MDT) meetings, more refined surgery (TME/PME), appropriate use of preoperative radiotherapy, being superior to postoperative chemoradiation together with quality control (pathology and registries) have resulted in substantial lowering of local failure rates (from above 30% to below 10% in many populations). It can then be stated that 'the local problem in rectal cancer is in principal solved'. Although this may be true for rectal cancer patients in general, certain subgroups of patients still suffer a substantial risk of not having R0 surgery or a local failure. In addition, survival for rectal cancer patients has improved, but not nearly to the same extent as local failure rates have. Thus, it is important to study treatment approaches aimed at reducing the risk of systemic relapse without compromising local control. It is not reasonable to believe that further improvements in the loco-regional treatment of the primary will reduce the systemic relapses.

1.4.1 Systemic relapses

About 25-65% of patients with locally advanced rectal cancer (cT3c/d-4 and/or N1-2) develop distant metastases [36-38]. Systemic chemotherapy aim 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. Administration of chemotherapy concomitantly during radiotherapy improves local control in randomized trials [17-19]. In the Nordic trial cancer-specific survival was also improved [14]. However, when giving chemotherapy concomitantly toxicity increases and dosage of chemotherapy must be reduced which may influence the systemic efficacy. In many centres post-operative adjuvant chemotherapy is prescribed to these patients but since rectal cancer surgery is associated with relatively high complication rates (e.g. anastomotic leakage in 19% [39]) many patients cannot receive chemotherapy postoperatively. In a German randomized rectal cancer trial comparing pre-operative chemoradiation to post-operative chemoradiation only 50 % of patients in the post-operative arm received full-dose chemotherapy compared to 89 % in the pre-operative arm [40].

An alternative approach is to administer the systemic therapy before surgery, which is often termed "neo-adjuvant" therapy. Support of greater efficacy from neo-adjuvant (or combined neo-adjuvant and adjuvant, so called peri-operative treatment) comes from some other tumour types, but not universally. The strongest support likely comes from gastric cancer, where peri-operative platinum-based therapy resulted in better overall survival than surgery alone (by about 13 – 14%-units), MAGIC trial [41] and FFCD trial [42]. In colorectal cancer metastatic to the liver, a gain in event-free survival was seen in an EORTC trial [1] with peri-operative chemotherapy. The difference was seen during the first 10 weeks, indicating that the preoperative part of the chemotherapy was more important than the postoperative. Neo-adjuvant treatment with chemotherapy has also been explored in e.g. head- and neck cancer and oesophageal cancer (in the MAGIC and FFCD gastric cancer trials, patients with oesophageal adenocarcinoma were also included) and muscle invasive bladder cancer [43], with unequivocal results. In early breast cancer, it does not appear to be important to initiate the systemic therapy early [22], although up-front systemic chemotherapy is the treatment of choice in locally advanced breast cancer.

In the Dutch "M1 trial" short course radiation therapy, neoadjuvant chemotherapy with bevacizumab and radical resection of primary tumour and metastases in primary stage IV rectal cancer was evaluated [4]. The study included 50 patients (approximately 75 % with T3/T4/N+ tumours) who were treated with 5 x 5 Gy radiotherapy followed by 6 cycles of bevacizumab (7.5 mg/kg every 3 weeks), oxaliplatin (130 mg/m^2 every 3 weeks) and capecitabine (1000 mg twice daily day 1-14 mg/m^2). Eight weeks after last dose of bevacizumab surgery was performed. The

completion rate for all (six) cycles of chemotherapy was 85% and more than 90 % completed at least 4 cycles. No significant tumour progression of the primary rectal cancer was observed during chemotherapy. None of the patients could not be operated on their local rectal tumour due local tumour progression. Only 1 patient had significant morbidity of the primary tumour due to the pre-operative treatment, this was caused by a perforation and pelvic abscess due to a massive tumour response with tumour necrosis. In 91% of patients a R0 resection of the primary tumour was performed. Pathological evaluation of rectal specimens showed a complete response rate of 27%. This is higher than after standard chemoradiotherapy. No severe toxicity was observed upon radiotherapy and chemotherapy related toxicity was mostly mild.

Thus, it appears reasonable to assume that pre-operative chemotherapy is more likely to be administered in full doses (giving full systemic effect) compared to concomitant or post-operative chemotherapy.

1.4.2 Locoregional therapy

In many centres the current standard of treatment for rectal tumours at high-risk of failing locally or non-resectable tumours is pre-operative long-course chemoradiation (1.8-2 Gy x 25-28 with capecitabine) whereas low-risk patients with resectable tumours receive short-course hypofractionated radiotherapy (5 Gy x 5). The biological effective dose (BED) of a fractionated radiation scheme is calculated as LQ time = $n.d(1+d/\alpha/\beta) – (\gamma/\alpha)(T-T_k)$ in which n is the number of fractions, d is the dose (Gy) per fraction, α/β is the common linear-quadratic quotient (set to 10 Gy), γ/α is the repair rate (set to 0.6 Gy/day), T is the total treatment time (days), and T_k is the initial delay time (days, set to 7 days). Using this formula, the BED of 5 x 5 Gy equals to 37.5 Gy and the BED of 28 x 1.8 Gy equals to 40.9 Gy [44].

In patients with more advanced tumours (e.g. T4, MRF-positive, positive lateral nodes) the pre-operative therapy aims at down-staging or down-sizing the tumour whereby the chances of performing a R0-resection are increased. Long-course radiotherapy, in particular in combination with concomitant chemotherapy increases resectability and improves local control [45-47]. When long-course chemoradiation is delivered, surgery is post-poned for 4-8 weeks allowing for acute radiation-induced tissue reactions to settle prior to surgery and this “waiting period” also allows for down-sizing to occur. When short-course radiotherapy is used, surgery is generally performed the following week without a “waiting period” and it has been questioned whether any down-staging occurs following this regimen. A recent Polish trial demonstrated that significantly more down staging occurred when a conventional radiotherapy scheme (50.4 Gy, surgery after 4-6 weeks) combined with chemotherapy (5-FU/Leucovorin) was compared with short-term preoperative radiotherapy (5 x 5 Gy, surgery within 7 days), but with no difference in local recurrence rate and survival [45]. Similar results were reported (ASCO 2010) from an Australasian trial [48]. An ongoing trial (Stockholm III) is randomizing patients with resectable rectal cancer to either long-course radiotherapy (50 Gy), short-course radiotherapy with immediate surgery or short-course radiotherapy with delayed surgery (4-8 weeks “waiting period”) and recently data from an interim analysis including 300 patients demonstrated that short-course radiotherapy with delayed surgery is feasible [21]. Retrospective observational data have shown that short-course radiotherapy with delayed surgery can produce significant down-staging and also pathological complete response (pCR) in some patients .[2, 3, 49]

In the M1 trial where systemic chemotherapy was administered after short-course before surgery no significant local tumour progression during chemotherapy was seen [4]. As stated above in 11 of 41 (27%) resected rectal specimens a pCR was observed.

Thus, data to support that short-course pre-operative radiotherapy with delayed surgery is feasible and that down-staging or down-sizing may occur following this regimen are present in

the literature. Furthermore, the interval between radiotherapy and surgery can be prolonged and if chemotherapy is delivered in this interval, significant effects can be seen on the primary rectal tumour.

1.5 Design considerations of a trial of pre-operative chemotherapy in rectal cancer

In patients with a newly diagnosed rectal cancer at high risk of failing locally and/or systemically standard therapy is long-course preoperative radiotherapy with concomitant chemotherapy followed by surgery after 4-8 weeks. Despite lack of indisputable scientific evidence, postoperative adjuvant chemotherapy is added in many centres.

To achieve higher compliance and better effect of chemotherapy, the aim is to deliver the systemic treatment pre-operatively. Most standard adjuvant chemotherapy schedules in colorectal cancer have a duration of 24 weeks. Modifications of current standard therapy could theoretically include increase of dose or number of chemotherapy agents for the concomitant therapy but that would increase toxicity and possibly decrease compliance. To postpone all locoregional therapy in order to start with systemic chemotherapy would not gain acceptance because of the risk of local progression.

A peri-operative chemotherapy regimen was successfully explored for liver metastases of colorectal cancer in the EORTC-EPOC trial and with a similar schedule a trial with an experimental arm consisting of 12 weeks of chemotherapy pre-operatively followed by short-course radiotherapy and immediate surgery and 12 weeks of post-operative chemotherapy could be considered [1]. This design would, however, have some drawbacks including no locoregional therapy initially and the risk of not being able to deliver half of the chemotherapy to a substantial proportion of the patients. Moreover, when surgery is performed immediately after radiotherapy, the desired down-staging on these locally advanced tumours may not occur, leading to a potential risk of decreased local control rates.

Another alternative is to explore possibilities connected with using the short-course radiotherapy with delayed surgery as the locoregional 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. Data from the retrospective trials [2, 3] and the M1 trial [4] support the notion that systemic chemotherapy also acts on the primary tumour, thus leading to improved locoregional therapy as compared to short-course and a “waiting period”. However, in order to reduce the interval between radiotherapy and surgery and still being able to deliver all systemic chemotherapy prior to surgery, adjustments of standard chemotherapy schedules for colorectal cancer may be necessary. The schedule explored in the M1 trial consisting of 18 weeks with oxaliplatin/capecitabine is 6 weeks (2 cycles) shorter than commonly used in post-operative adjuvant schedules and offers an attractive alternative. Bevacizumab was included in the “M1 trial” but there is no data suggesting that bevacizumab [5] or cetuximab [6] improves the antitumour effects against subclinical disease.

1.6 Proposed trial design

This study protocol proposes a randomized multicentre Phase III trial in patients with non-metastatic primary rectal cancer with a high risk of failing locally and/or systemically. Standardised MRI criteria will be used to identify eligible patients. Patients will be randomized between a standard therapy arm (A) and an experimental arm (B).

A: Long-course radiotherapy (1.8-2 Gy x 25-28) with concomitant capecitabine. After a "waiting period" of 8 weeks (±2 weeks) during which response is evaluated, surgery according to TME/PME principles will be performed. In this arm it is allowed according to the local protocol of the participating institute to admit after recovery, optimally within 6-8 weeks, post-operative adjuvant chemotherapy consisting of 8 cycles oxaliplatin/capecitabine (or alternatively 24 weeks of FOLFOX4).

B: Short-course radiotherapy (5 Gy x 5). Within 11-18 days after the last day of radiotherapy pre-operative systemic chemotherapy with oxaliplatin/capecitabine will commence and is delivered in 6 cycles. Alternatively 18 weeks cycles of FOLFOX4 is an option. Response is evaluated after the systemic chemotherapy. Within 2-4 weeks after the final chemotherapy cycle surgery according to TME/PME principles will be performed. No postoperative therapy will be given.

2. Objectives of the trial

2.1 Primary objective

- To increase the time to disease related treatment failure (TdrTF). after 3 years follow-up.

2.2 Secondary Objectives

- To describe the toxicity profile of the combined modality treatment in schedule.
- To determine the completion rate of the neo-adjuvant treatment.
- To determine the fraction of patients with a radical resection (negative CRM)
- To determine the pathological complete response rate (pCR).
- To determine the postoperative complications
- To describe the local recurrence rate after 3 years follow-up.
- To evaluate quality of life.
- To evaluate functional outcome.
- To increase overall survival after 5 years of follow-up.

2.3 End-points

2.3.1 Primary endpoint

Time to disease related treatment failure (TdrTF). after 3 years follow-up is the primary endpoint.

2.3.2 Secondary endpoints

- Treatment associated toxicity, including surgical morbidity
- Completion rate of neo-adjuvant treatment
- Negative CRM (margin > 1 mm)
- pCR
- Postoperative complications
- Local recurrence at 3 years
- Overall survival
- Functional outcome
- Quality of life

For an exact definition of the parameters used as end-points, and the detailed method of assessment: see section 7.

3. Trial design

This trial is a multicentre, randomized, open-label, phase III trial organized by the Dutch Colorectal Cancer Group and the Nordic Gastrointestinal Tumour Therapy Group.

Patients will be randomized between a standard group (arm A) with long course chemoradiotherapy followed by surgery and optional postoperative chemotherapy (eight cycles of capecitabine and oxaliplatin; or alternatively twelve cycles of FOLFOX4) and an experimental group (arm B) in which short course 5 x 5 Gy radiation scheme is followed by six cycles of combination chemotherapy (capecitabine and oxaliplatin, or alternatively nine cycles of FOLFOX4 and surgery. In both groups the rectal tumour will be removed by TME/PME surgery or more extensive surgery if required because of tumour extent.

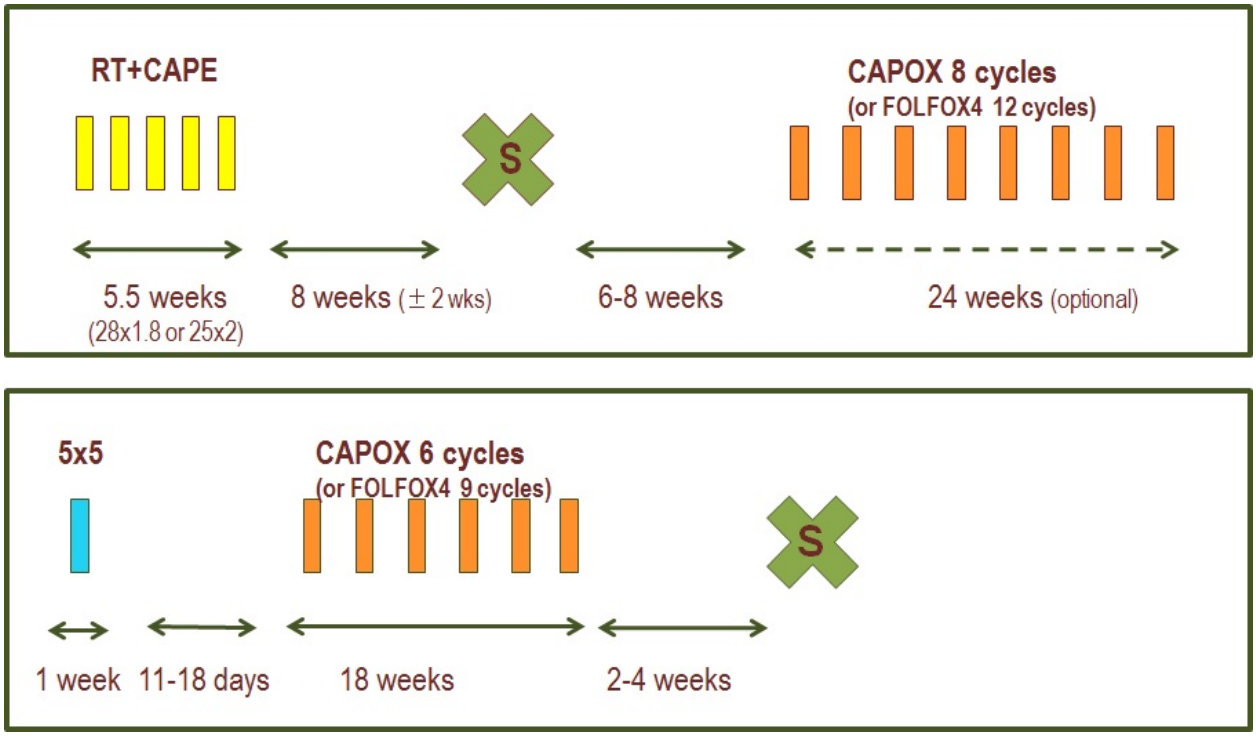
Randomization is performed to avoid bias by investigators and minimize bias in the assessment of the disease and follow-up of the patient. The following stratification factors will be used with the randomization:

Institution, performance score, clinical T-stage, clinical lymph node status

Time to disease related treatment failure (TdrTF) after 3 years of median follow-up is the primary endpoint. This definition of TdrTF is based on the consensus agreement for Time to Treatment Failure (TTF) as described for the adjuvant setting [67]. TdrTF is an adaptation for the neo-adjuvante setting.

Time to disease related treatment failure (TdrTF)	**Endpoints**		
Event	**TTF**	**TdrTF**	time from randomisation until*:
Locoregional recurrence	E	E	date locoregional recurrence
Distant metastases	E	E	date distant metastases
Second primary, same (colorectal) cancer	E	E	date second primary
Second primary, other cancer	E	I	
Death from same (colorectal) cancer	E	E	date of death
Death from other cancer	E	C	date of death
Non-cancer-related death	C	C	date of death
Treatment-related death	E	E	date of death
Lost to follow-up	C	C	date last fup
No resection/R2 resection		E	0
No surgery at all (PD, not fit)		E	0
M1 at restaging/during surgery		E	0
Local regrowth after WW and R0/R1 resection		I	
Local regrowth after WW and no resection/R2 resection		E	date of diagnosis local regrowth
Distant metastases only in FUP after WW		E	date distant metastases
TTF = time to treatment failure			
TdrTF = time to disease related treatment failure			
E = event; C = censor; I = ignore			
* whichever date comes first			

Study Flow Chart



4. Patient Selection Criteria

4.1 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 using a rigid rectoscope or flexible endoscope.
- Locally advanced tumour fulfilling at least one of the following criteria on pelvic MRI indicating high risk of failing locally and/or systemically:
    - Clinical stage (c) T4a, i.e. overgrowth to an adjacent organ or structure like the prostate, urinary bladder, uterus, sacrum, pelvic floor or side-wall (according to TNM version 5).
    - cT4b, i.e. peritoneal involvement.
    - Extramural vascular invasion (EMVI+).
    - N2, i.e. four or more lymph nodes in the mesorectum showing morphological signs on MRI indicating metastatic disease, see appendix **G**.
    - Positive MRF, i.e. tumour one mm or less from the mesorectal fascia.
    - Metastatic lateral nodes, > 1 cm (lat LN+)., see appendix **G**

4.2 General

- Staging done within 5 weeks before randomization.

- No contraindications to chemotherapy, including adequate blood counts, (within 5 weeks prior to randomsation):
  - 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, see appendix **B**.

- 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.

4.3 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 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.
- Previous radiotherapy in the pelvic region (e.g. prostate) or previous rectal surgery (e.g. TEM) or 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 or history of peripheral neuropathy.

4.4 Comments to the inclusion criteria with an assessment of risks

The presence of one or more of the risk factors indicates that the estimated risk of failing (no CRM negative resection, local pelvic or systemic recurrence) within 3 years is 60% or above if surgery is the primary treatment and 40% or above 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.*

The criteria mentioned all indicate that the risk of systemic relapse is high, whereas not all indicate that the risk of failing locally is high [34].

5. Therapeutic regimens, expected toxicity, dose modifications

5.1 Chemotherapy and radiotherapy (in Arm A and B)

5.1.1 Radiotherapy

Preoperative radiotherapy will be delivered on a linear accelerator in prone or supine position, preferably with full bladder. The use of a belly board is allowed. Isocentric 3 or 4 fields, as well as an IMRT technique is allowed, as long as all beams are treated on a daily basis.

The dose distribution and calculation should be performed on CT or MRI and specified according to the ICRU 50 guidelines.

5.1.1.1 Dose specification

Arm A = standard treatment:

All patients will receive 28 daily fractions of 1.8 Gy up to a total dose of 50.4 Gy or 25 fractions of 2.0 Gy up to a total dose of 50.0 Gy to the pelvic field including the tumour bed with a margin and the regional lymph nodes. A field reduction after 45 (1.8 Gy schedule) or 46 (2.0 Gy schedule) is recommended. The last fractions will then be given to the tumour bed with a margin. Institutions must indicate which schedule they will use and whether field reduction will routinely take place in their patients.

Capecitabine will be given during radiotherapy day 1-38 or day 1-33 in a dose of 825 mg/m^2 bid (twice daily) (see section 5.1.2).

Arm B = experimental treatment

All patients will receive 5 daily fractions of 5 Gy up to a total dose of 25 Gy. Overall treatment time should be maximum eight days.

A boost dose to the tumour bed is optional.

5.1.1.2 Target volume

Pelvic field (see Appendix **F** for further details)

Tumour bed with a margin, plus regional lymph nodes according to tumour location and growth. The mesorectal and pre-sacral lymph nodes are always included whereas the lateral obturator nodes and internal iliac nodes are only included if the tumour grows below the peritoneal reflection. The external iliac nodes should be included if the primary tumour invades the bladder, prostate, cervix or vagina to such an extent that the external nodes are at risk for metastases. Napping or minimal overgrowth dorsally is not sufficient.

If it is decided to give an additional boost, the boost will include the assessable (via MRI, CT, clinical examination) tumour with a 1 cm margin within the same anatomical compartment as the tumour is located in.

5.1.1.3 Toxicity and stopping rules

Toxicity will be assessed and recorded according to the CTCAE v4.0 acute radiation morbidity scoring criteria. Toxicity for the different treatment arms may be different. Stopping rules are therefore defined per treatment arm.

Arm A:

Adverse event	Definition	Action	Other
RADIOTHERAPY			
Diarrhoea	Grade 4	should be interrupted until the treatment-related symptoms have been reduced and parental support is no longer necessary	
Other gastro-intestinal toxicity	Grade 4	should be interrupted and restarted according to the patients' condition	

Table 1. *Dose modification schedule for radiotherapy during chemoradiation.*

Arm B:

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 help.

5.1.2 Chemotherapy

5.1.2.1 CAP(OX)

The concomitant chemotherapy in arm A consists of capecitabine only.

(Neo)adjuvant chemotherapy consists of a combination of capecitabine and oxaliplatin

Oxaliplatin

The standard dose of oxaliplatin is 130 mg/m^2 (5 mg/ml concentrate for solution for infusion) in 500 ml glucose 5% i.v. infusion in 2 hours and should *never* be dissolved in NaCl.

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 (Xeloda®) 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.

5.1.2.2 FOLFOX4

Alternatively FOLFOX4 can be given. [62] [68]

Then, oxaliplatin (85 mg/m^2) is administered as a 2-hour infusion on day 1; leucovorin (200 mg/m^2) administered as a 2-hour infusion on day 1 and day 2; followed by a loading dose of 5-FU (400 mg/m^2) IV bolus, then 5-FU (600 mg/m^2) administered for a period of 22 hours on day 1 and day 2 every 2 weeks. When prescribing 5-FU, the contra-indications, special warnings and interactions, as described in the latest version of the SmPC (1B text), should be observed. When prescribing leucovorin, 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.

5.1.2.1 Chemotherapy doses and timing

Arm A:

Concomitant chemotherapy:

Capecitabine will be given during radiotherapy day 1-33 or 38, also in weekends, in a dose of 825 mg/m^2 bid (twice daily).

Optional Adjuvant chemotherapy

Adjuvant chemotherapy with capecitabine and oxaliplatin is allowed to start after the recovery of surgery (scheme and dose see Table 2.). Optimal time for start of the adjuvant chemotherapy is 6-8 weeks after surgery with a maximum of 12 weeks. In total eight cycles will be administrated. An alternative option is twelve cycles of FOLFOX4 .

Arm B:

Neoadjuvant chemotherapy

Preferably, chemotherapy in the experimental arm 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 untill 4 weeks after the last day of radiotherapy. If this is not feasible for your patient then please discuss this with the principle investigator of your country. 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**	
Capecitabine	1000 mg/m^2	Twice daily, day 1-14	Every 3 week cycle, in total 6 cycles
Oxaliplatin	130 mg/m^2	Every 3 weeks	

Table 2 *Dose of (neo) adjuvant chemotherapy*

As alternative nine cycles of FOLFOX4 is allowed.

Oxaliplatin (85 mg/m^2) administered as a 2-hour infusion on day 1; leucovorin (200 mg/m^2) administered as a 2-hour infusion on day 1 and day 2; followed by a loading dose of 5-FU (400

mg/m^2) IV bolus, then 5-FU (600 mg/m^2) administered for a period of 22 hours on day 1 and day 2 every 2 weeks.

5.1.3 Dose modification schedules

These are the same for the concomitant and adjuvant chemotherapy in the standard arm (group A) and for the neoadjuvant chemotherapy in the experimental arm (group B).

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

5.1.3.1 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 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 3. Dose adaptions of **capecitabine** for non-haematological toxicity.*

5.1.3.2 5-FU/LV

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

Diarrhoea

Prophylactic treatment:

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

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 performance status > 2 should be hospitalised immediately for i.v. rehydration.

5-FU/LV 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 4 below).

	Grade 2	**Grade 3**	**Grade 4**
1st occurrence	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 100% of the 5FU/LV dose	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 75% of the 5FU/LV dose	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 50% of the 5FU/LV dose
2nd occurrence	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 75% of the 5FU/LV dose	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 50% of the 5FU/LV dose	Discontinue treatment
3rd occurrence	Interrupt treatment ♦ Until symptom recovery to grade 0-1 ♦ Continue with 50% of the 5FU/LV dose	Discontinue treatment	
4th occurrence	Discontinue treatment		

*Table 4. Dose adaptions of **5FU/LV** for non-haematological toxicity.*

5.1.4 Oxaliplatin

The most frequently occurring non-hematologic 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 a 50% dose reduction, neurotoxicity does recur, oxaliplatin will be discontinued permanently and patients will continue treatment with capecitabine. 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 5 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 5. Dose adaptions for **oxaliplatin** for sensory neuropathy (cycles 1 – 12)*

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 [49, 50]. In case such a reaction occurs, prophylaxis with steroids ± anti-histamines is indicated.

Dose adaptions for **oxaliplatin and capecitabine /5-FU&LV** for non-haematological toxicity: see Table 6 below.

Toxicity during previous cycle	**Grade**	**Next dose Oxaliplatin**	**Next dose Capecitabine/5-FU&LV**
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 6. Dose adjustment relative to the previous cycle for next cycle.

5.1.5 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.

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

Haematological toxicity may be induced by oxaliplatin, and less frequently by capecitabine or 5-FU.

Neutrophils (10^9/l)	**WBC (10^9/l)**	**Platelets (10^9/l)**	**Next dose oxaliplatin**	**Next dose Capecitabine/5-FU**
< 0.5 (grade 4) or febrile neutropenia	< 1.0 (grade 4)	< 25 (grade 4)	-25%	No adjustment

*Table 7. Dose adaptations for **oxaliplatin and capecitabine/5FU&LV** 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/5-FU&LV. 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.

5.1.7 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.

5.1.8 Permanent discontinuation of individual drugs due to toxicity

If patients experience severe toxicity despite dose reductions which necessitates the discontinuation of individual drugs, these patients will remain on study and should be followed for progression of disease according to the specified timelines. If neo-adjuvant treatment is preliminary discontinued proceed with staging to determine if surgery can be done

5.1.9 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 profylaxis

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

5.1.10 Other concomitant medication

All concomitant medication must be documented in the patients' file at time of randomization, and at the end of study treatment or death.

5.2 Surgery (in Arm A and B)

Patients are treated with tromboembolic prophylaxis, antibiotic prophylaxis and bowel preparation according to local protocols. An open or laparoscopic approach may be used.

After entering the abdomen, the liver, the peritoneum 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 or not the procedure is done open or laparoscopic. Care has to be taken to identify the hypogastric nerves to avoid damage. 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. 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. In mid or low rectal tumours (< 12 cm) a TME down to the pelvic floor has to be performed. When an anterior resection or a Hartmann's procedure is performed, rectum should be irrigated 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. In case of an abdominal perineal resection (APR) in low tumours a perineal resection with the extra-levator technique aiming at a cylindrical specimen without

“waisting” is mandatory. In patients with 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, 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.

6. Clinical evaluation, laboratory tests, follow-up

6.1 Before treatment start

6.1.1 Eligibility evaluation

The following studies are required upon entry into the study, maximum 5 weeks prior to randomisation:

- Physical examination, including blood pressure, ECOG performance score
- 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 of thorax, abdomen and pelvis
- Laboratory tests: haemoglobin, white blood cell count, platelets, bilirubin, ALP, ALAT, creatinine, and CEA.
- MRI of the pelvis (protocol see Appendix **G**)

6.1.2 Obstructing tumours

Patients who present with obstructing tumours may be candidates for a diverting colostomy which can be performed laparoscopically. Randomization will only be performed after treatment of clinically significant obstruction.

6.2 During treatment

6.2.1 Standard arm (chemoradiotherapy – surgery (group A)

6.2.1.1 Evaluation during chemoradiation

Toxicity, haematology and ECOG performance status is evaluated weekly.

6.2.1.2 Stopping rules due to chemoradiation toxicity.

See chapter **5.1.3.**

6.2.1.3 Restaging

In the standard treatment group (arm A) after finishing the chemoradiotherapy, 2 – 3 weeks prior to planned surgery re-staging is performed by CT of thorax, abdomen and pelvis and MRI of the pelvis.

6.2.1.4 Interval between long-course chemoradiation and surgery

Surgery should be performed between 8-10 weeks after the last radiation fraction.

6.2.1.5 Stopping rules due to chemotherapy toxicity.

See chapter **5.3**

6.2.1.6 Interval between surgery and adjuvant chemotherapy

The adjuvant chemotherapy is optional according to the local protocol of the participating institute. It should start as soon as the patient has recovered from surgery, in practise between 6 – 8 weeks after surgery, at maximum 12 weeks after surgery.

6.2.1.7 Evaluation during adjuvant chemotherapy

Prior to all cycles (1 to 12)

- ECOG performance status
- Haematology
- Physical examination
- Biochemistry (Na, K, bilirubin, ALP, ASAT, creatinine)

6.2.2 Experimental arm (5 x 5 Gy, neo-adjuvant chemotherapy, surgery (group B),

6.2.2.1 Interval between short course radiation and chemotherapy

In case of no or moderate toxicity chemotherapy starts the following week, 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 (see also Chapter 5.1.1.3)

6.2.2.2 Evaluation during neo-adjuvant chemotherapy

Prior to all cycles (1 to 6):

- ECOG performance status
- Haematology
- Physical examination
- Biochemistry (Na, K, bilirubin, ALP, ASAT, creatinine)

6.2.2.3 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 contrast-enhanced multi-detector CT of thorax, abdomen and pelvis, at the end of chemotherapy.

An MRI of the pelvis is recommended to be performed in the middle of the neo-adjuvant chemotherapy (week 12-14) particularly in case there are clinical signs or uncertainties about tumour progression.

6.2.2.4 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 or 5-FU in the last cycle of chemotherapy.

6.3 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 or 5-FU/LV and oxaliplatin for a maximum delay of two weeks:

- Absolute neutrophils count (ANC) < 1.0 and platelets <100 x 10^9/L, respectively
- If the chemotherapy-induced gastrointestinal toxicity does not normalize
- If any other toxicity ≥ grade 2 persists

Toxicity will be assessed and documented according the CTCAE version 4.0. Most common grade 3-4 toxicity are demonstrated in Tables 3, 4, 5, 6, 7 in Chapter **5**.

6.4 Resection and response evaluation

A multidisciplinary team with a panel of radiologist, rectal surgeons, medical-oncologist and radiation-oncologist will evaluate the imaging studies in both groups (A+B) to assess resectability and tumour response. 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)
- Carcinosis peritonei (=M1)

In order to have Quality Control before analysis of the primary and secondary endpoints MRI's have to be collected and evaluated after inclusion of all patients. Response of target lesions will be scored by a selected board of radiologists. These assessments will be done according the criteria in **Appendix G**):

Special notes on the assessment of target lesions regarding lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis should be given.

6.5 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 (see appendix **C**) 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 5th edition of TNM will be used in this study, again according to Dutch and European guidelines for rectal cancer [53, 54]. In addition, an evaluation of the involvement of circumferential resection margins (CRM) [55], quality of surgery by photo [56-58] and tumour regression must be done. A circumferential margin of 1 mm or less for tumour or lymph node 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).

6.5.1 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

6.5.2 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).

6.6 After the end of treatment: Follow-up

If pre-operatively no complete colonoscopy could be performed a total colonoscopy has to be performed within the first year after treatment. At 6, 12, 24 and 36 and 60 months after date surgery, physical examination, ECOG performance score, symptoms according to CTC (see case record forms) and CEA will be done. 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 also Table 8). Quality of Life assessment should be done at 3 years after surgery. A more intense follow-up is possible if this is routinely done. On indication other diagnostic or imaging techniques (MRI, FDG-PET, colonoscopy, endoluminal ultrasound) can be used to confirm or detect recurrent or metastatic disease. When recurrent or metastatic disease is detected this time

is marked as the time to progression starting from time of randomization. Hereby the time to disease related treatment failure (TdrTF). can be calculated (see also chapter **7**). After five years, routine follow-up will be ended in case of no evidence of disease after performing a final colonoscopy. More intense follow-up is allowed if this routinely done.

6.6.1 Requirements for Follow-Up

Months since date of surgery	**6**	**12**	**24**	**36**	**60**
History, incl. morbidity assessment	X	X	X	X	X
Physical Examination	X	X	X	X	X
QoL Assessments and LARS score				X	
CEA	X	X	X	X	X
X-thorax & US-liver or CT thorax-abdomen		X		X	
Colonoscopy					X

Table 8: follow-up scheme. More intense follow-up is allowed if this is routinely done.

6.6.2 Assessment of Recurrent Disease

Evidence of recurrent disease is accepted when one of the following criteria is present:

- Positive histology or cytology of adenocarcinoma, compatible with the primary tumour in any location.
- Liver metastases on Ultrasound and/or (PET)CT.
- Lung metastases on X-ray and/or (PET)CT or MRI.
- Bone metastases on X-ray and/or bone-scintigraphy and/or MRI
- Brain metastases on MRI
- Distant lymph node metastases

Pelvic pathology on PET/CT, PET/MRI or MRI of the pelvis combined with increased CEA levels together consistent with local recurrence

Parameters for Recurrent Disease:

The following parameters will be recorded and studied:

- Loco-regional recurrence site and date (local within the pelvis).
- 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.

6.7 Treatment Summary table

6.7.1 Standard arm (group A)

Standard arm (group A)	Baseline	Chemoradiation						Restaging	Surgery	Adjuvant chemotherapy (if policy)										
Required Investigations	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**12**	**14**	**20**	**22**	**23**	**24**	**26**	**28**	**29**	**30**	**32**	**34**	**35**	**36**	**38**	**38**	**40**	**41**	**42**
week																										
Physical examination	x								x	(x)								(x)								
ECOG performance score	x								x	(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)
Tumour related symptoms	x								x																	
Blood Pressure	x																									
Haematology[1]	x	x		x		x			x	(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)
Biochemistry[2]	x								x	(x)								(x)								
CEA[3]	x																									
CT thorax-abdomen-pelvis	x							x																		
MRI pelvis	x							x																		
Colonoscopy/rectoscopy[4]	x																									
QOL assessment																										
Toxicity Evaluation[5]		x		x		x		x	x	(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)		
Chemoradiotherapy		x	x	x	x	x	x																			
Surgery									x																	
CAPOX (optional)										(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)		
FOLFOX4 (optional as alternative for CAPOX)										(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)
Side study, blood samples	x								x																	

1)	Hb, WBC count, platelet count At baseline: < 72 hour prior to cycle of chemotherapy. Once per 2 weeks during the chemoradiotherapy Adjuvant: prior to start of each chemotherapy course
2)	Na, K,creatinin, ALP, ASAT At baseline: < 72 hour prior to cycle of chemotherapy
3)	Within 5 weeks prior to start of chemoradiotherapy
4)	Biopsy taken
5)	According to the criteria of NCI CTCAE version 4.0

Treatment/drug	**dose**	**frequency**
Chemoradiotherapy	Radiotherapy: 28 x 1,8 Gy combined with capecitabine b.i.d. 825 mg/m2 or 25 x 2,0 Gy combined with capecitabine b.i.d. 825 mg/m^2	week 1-6 at working days day 1-38 day 1-33
post-operative capecitabine (optional in certain centers) *)	1000 mg/m^2 b.i.d.	day 1-14 every 3 week cycle starting at 6-8 weeks after surgery 8 cycles
post-operative Oxaliplatin *) (optional in certain centers)	130 mg/m^2	day 1 every 3 week cycle starting at 6-8 weeks after surgery 8 cycles

6.7.2. Experimental arm (group B)

Experimental arm (group B)	Baseline	Radiotherapy		Chemotherapy																Restaging	Surgery
week:	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21-22	22-25
Required Investigations																							
Physical examination	x			x			x			x			x			x			x				x
ECOG performance score	x			x			x			x			x			x			x				x
Tumour related symptoms	x			x			x			x			x			x			x				x
Blood Pressure	x			x			x			x			x			x			x				
Haematology[1]	x	x		x			x			x			x			x			x				x
Biochemistry[2]	x			x			x			x			x			x			x				x
CEA[3]	x																						
CT thorax-abdomen-pelvis	x																					x	
MRI pelvis	x												(x)									x	
Colonoscopy/rectoscopy[4]	x																						
QOL assessment																							
Toxicity Evaluation[5]		x	x	x			x			x			x			x			x			x	x
Radiotherapy		x																					
CAPOX				x			x			x			x			x			x				
FOLFOX4 (alternative for CAPOX)				x		x		x		x		x		x		x		x		x			
Surgery																							x
Side study, blood samples	x																						x

1) Hb, WBC count, platelet count
At baseline: < 72 hour prior to start of chemotherapy

2) Na, K, creatinin, ALP, ASAT,
At baseline: < 72 hour prior to start of chemotherapy

3) Within 5 weeks prior to start of radiotherapy

4) Biopsy taken

5) According to the criteria of NCI CTCAE version 4.0

6) MRI is recommended to be performed in the middle of the neo-adjuvant chemotherapy particularly

Treatment/drug	dose	frequency
Radiotherapy	5x5Gy	week 1 day 1-5
Capecitabine	1000 mg/m^2 b.i.d.	day 1-14 every 3 week cycle starting at week 3 6 cycles
Oxaliplatin	130 mg/m^2	day 1 every 3 week cycle starting at week 3 6 cycles

*)
or alternatively 9 cycles of FOLFOX4

7. Criteria of evaluation

7.1 Definitions

Time to disease related treatment failure (TdrTF) Time to disease related treatment failure will be computed as the time between randomization 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. See also the table depicted in Chapter **3**. Patients lost to follow-up will be censored the last date of patient visit. Follow-up is described in Chapter **6**.

7.1.1 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 4.0 Adverse events and serious adverse events will be reported as described in section **6**. See also Appendix **D**.

7.1.2 Fraction of radical resection (CRM > 1 mm)

Negative CRM will be evaluated according the pathology protocol described by Quirke et al. (see also chapter **6** and appendix **C**)

7.1.3 Complete pathological response (pCR).

pCR evaluation is done by the method described in section **6**.

7.1.4 Local recurrence

Local recurrence is described as relapse of tumour in the pelvic region. This will be assessed by clinical investigation and imaging studies as described in chapter **6**.

7.1.5 Distant relapse

Distant relapse is described as relapse of tumour outside the pelvic region. This will be assessed by clinical investigation and imaging studies as described in chapter **6**. Special attention has to made on the liver and lung since these are the predominant side of metastases.

7.1.6 Local control

Local control will be computed as the time between randomization and local relapse. If the primary tumour can not be removed macroscopically radically, the time to local failure is zero months. Patients who died or are lost to follow-up without evidence of local relapse are censored at the date of death or the last date of patient visit.

7.1.7 Overall survival

Overall survival will be computed as the time between randomization and colorectal cancer or treatment related death. Patients lost to follow-up will be censored the last date of patient visit. In case of a second primary tumour patients will be censored at the date of diagnosis of the second primary tumour. See table depicted in Chapter **3**.Follow-up is described in Chapter **6**.

7.1.8 Quality of Life (QoL)

Quality of life including functional outcome will be studied as described in Chapter **8**.

7.2 Statistical considerations

7.2.1 Sample size

Fifty percent time to disease related treatment failure is described in several studies with locally advanced rectal cancer patients [36-38]. The hypothesis is that the new treatment (arm B) increases the time to disease related treatment failure after 3 years of follow-up from 50 to 60%. A difference of 10 % in TdrTF after 3 years corresponds to a hazard ratio of 0.737.

A two-sided logrank test with a total of 452 TdrTF events achieves 90% power at $\alpha = 0.05$ significance level to detect a hazard ratio of 0.737 when the proportion surviving in the control group is 50%. Based on four years of uniform accrual and two years of additional follow-up after the last patient has been included (six years total), a total of 842 evaluable patients will be required to achieve 452 TdrTF events. With a drop-out of 5% the total number of patients to be included is 885, or up to 920 if needed to have 421 evaluable patients per arm. Median follow-up will then be three years.

7.2.2 Randomization and stratification

Randomization will be performed stratifying by institution, performance score 0 or 1, clinical T stage (cT2-T3 or cT4), clinical N stage (cN- or cN+).

7.2.3 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 treatment received and will include only eligible patients.

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

All tests will be two-sided.

A table will present the completion rate of the neo-adjuvant treatment, pCR frequency and percentages, fraction of patients with a radical resection with 90 and 95% CI.

Frequency and percentages for toxicity will be presented according to the CTCAEv4.0 (see appendix **D**).

All proportions will be presented with 95% CI.

7.3 Interim Analyses

Two interim analyses are planned with 50% and 75% of the TdrTF information for efficacy.

Assessment (i.e. after 226 and 339 TdrTF events have been observed), based on O'Brien-Flemming boundary. At each interim analysis, the primary efficacy variable will be analyzed as described above. The nominal alpha levels at first, second interim and final analysis are 0.008, 0.021, 0.040, respectively.

All interim analyses will be conducted by a team external to the sponsor project team and the results will be reviewed by the external independent data monitoring committee (*DSMB*). Each interim analysis will include the primary efficacy endpoint as well as key safety parameters. Key safety parameters include radiotherapy and chemotherapy induced toxicity, negative CRM, mortality during treatment, recurrent disease after radical resection. The analysis may be expanded to key secondary endpoints if the outcome of the primary efficacy variable is positive.

7.4 Data safety monitoring committee (DSMB)

A data safety monitoring board (DSMB) will be appointed by the study coordinators and will be composed of experts in the field of medical oncology, surgery, radiotherapy, biostatistics, epidemiology and medical ethics. The DSMB will be established at the onset of the trial and will be independent of the trial organizers and participating investigators. A DSMB charter is available.

8. Quality of life assessment

8.1 Rationale

Rectal cancer negatively impacts patients' quality of life. In curative treatment, major surgery has to be performed. Consequently, post-operatively, physical and mental well-being are affected, in particular bowel function, sexual function and body image. Moreover, pre-operative chemotherapy has an impact due to toxic side-effects. Since patients in the experimental arm in the current study will receive chemotherapy preoperatively, insight is needed into the impact on quality of life as compared to patients in the standard arm that receive chemoradiotherapy only. In the experimental arm no adjuvant chemotherapy is given so quality of life may be different compared to the standard arm in which adjuvant chemotherapy is optionally given after recovery from surgery.

Several quality of life issues are considered relevant: late effects, psychological domains, colorectal cancer related items.

8.2 QL questionnaires

The following questionnaires developed by the European Organization for Research and Treatment of Cancer (EORTC) will be used (see also Appendix **H**):

QLQ-C30: to assess cancer specific but generic aspects of quality of life

QLQ-CR29: the colorectal module to assess the quality of life and the functional outcome. To optimally evaluate the sexual functioning, for male patients questions 56 and 57 from QLQ CR-29 have been replaced by questions 50 to 55 from QLQ PR-25, whereas for female patients questions 58 and 59 from QLQ CR-29 have been replaced by questions 49 to 54 from QLQ EN-24.

QLQ-CIPN20: the module to assess the chemotherapy induced peripheral neuropathy [64]

LARS score: a validated questionnaire consisting of 5 questions and evaluating the low anterior resection syndrome [65] [66]

8.3 Study design

Timing of assessments;

- 3 years after surgery

Questionnaires have to be given to the patient by the treating physician or staff member. The local center will call patients if questionnaires are not returned within two weeks. They will send the questionnaires to the Datacenter in Leiden.

8.4 Statistical considerations

All patients included still alive and disease free will be asked to complete the quality of life questionnaires 3,5 years after randomisation.

Descriptive analyses will be performed to describe the study population. Chi-square tests and unpaired t-tests will be computed to compare relevant sociodemographic and illness related variables of those who agree to participate with those who decline participation.. Effect sizes will be computed to examine clinical relevance of change and of between group differences.

Additionally, a difference of 5-10 points on an EORTC QoL functional subscale is considered to be a small clinically meaningful difference, a difference of 10-20 points is considered to be a moderate clinically meaningful difference and a difference of >20 points is considered to be a large clinically meaningful difference [59].

Univariate and multivariate analyses will be performed to examine relationships between QoL and the sociodemographic and illness related variables.

9. 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. A tissue block (or two-three cores for tissue microarray, TMA) will be collected from the preoperative biopsy (if sufficient material is available) and from the operative specimen (See appendix C). Optional collection of fresh tissue for freezing and blood samples include:

- Tumour biopsy (at time of colonoscopy), and directly after surgical resection of the rectum, stored at -80˚C. At the time of inclusion, the buffy coat will be collected and frozen separetely.

- Two blood samples at two time points, collected by venapunction in 10 ml EDTA tubes. One 10 ml EDTA tube with fresh whole blood should be aliquoted in four to five 2.0 ml Eppendorf tubes. If this is not feasible, whole blood can be stored in two 5 ml EDTA tubes. The second 10 ml EDTA tube should be centrifuged at 1500 x g for 10 minutes at 4˚ C within 10 minutes after collection. Blood plasma will be aliquoted in 2 Eppendorf tubes. All Eppendorf tubes should be marked with a waterproof pen (study number, center number, patients code, date of birth (day/month/year), sample date and sample description (t=0 before radiotherapy; t=1 before operation)) and stored at -20 or -80˚ C directly (see appendix K).

Control arm (group A):

- 2 Blood samples may be collected at the following moments during treatment:
  - at time of inclusion, before the start of chemoradiation therapy
  - before surgical resection

Experimental arm (group B):

- 2 Blood samples may be collected at the following moments during treatment:
  - at time of inclusion, before the start of radiation therapy
  - before surgical resection

- It is up to each participating center to decide if they will participate in the translational research side study, but this is highly recommended after the patient has given informed consent.

10. Investigator authorization procedure

This study is designed to be carried out in multiple centres in the Netherlands and Sweden. The study concept was conceived at the University Medical Center Groningen (UMCG) and the Leiden University Medical Centre from the Netherlands, the Uppsala University, Uppsala and the Karolinska Institutet in Stockholm from Sweden. Other centers, also from other countries, may enter the study based on consensus between investigators. Approval from the UMCG central medical ethical committee will serve as basis for medical ethical approval in other institutions, according to Dutch law and national laws is other countries.

11. Patient registration / randomization procedure

11.1 Randomization

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 can be performed by the LUMC Datacenter Surgery, the Central Datacenter or online through the ProMISe randomization programme.

11.1.1 Randomization by facsimile, email or phone

Randomization can be done by facsimile +31-71-526 6744 email datacenter@lumc.nl or telephone **+31 71 526 3500; Monday-Friday; 9:00-17:00**.

During the randomization procedure eligibility criteria will be checked. E-mails with the answered questions, the allocated treatment and the patient number will be automatically sent to the local team and the person responsible for CRF completion.

After randomization, a sequential identification number will be applied. This number has to be recorded on the randomization form, along with the randomization date. The randomization form must be signed by the investigator (in case of faxed and mailed randomization, the confirmation of the data manager also has to be signed by the investigator) and filed with the CRFs.

11.1.2 Online randomization

Randomization can also be performed online 24 hours per day through the ProMISe randomization programme. Go to:

www.clinicalresearch.nl/PROMISE/S/HEIT/S_O_LUMC_C_HEELK_RAPIDO_/LOGON/INDEX.HEI

Investigators or comprehensive cancer centers can apply to the Central Datacenter for a username and password. E-mails with the answered questions, the allocated treatment and the patient number will be automatically sent to the local team and the person responsible for CRF completion.

Datacenter details:

LUMC Datacenter

Ms Annet Roodvoets or Ms Elma Meershoek - Klein Kranenbarg

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phone +31-71-526 3500

fax: +31-71-526 6744

e-mail: datacenter@lumc.nl

12. Forms and procedures for collecting data

The case record forms (CRF's) for this study are available on paper and electronically. They are divided in different numbered sections. All CRF's are identified by the patients study number and month and year of birth. All CRF's have to be signed and dated by the person filling in the form.

All CRF's allow registration of optional collection of tissue or plasma for translational research. A logistical form will be kept up to date with all planned clinic appointments and admissions, scheduled studies and treatments.

12.1 Case report forms

- F01 Randomization Form
- F02 History and Staging Form
- F03 Baseline Radiology Form
- F04 Radiotherapy Form for both groups
- F05a Pre-operative Chemotherapy Form standard group (Arm A)
- F05b Pre-operative CAPOX Form experimental group (Arm B)
- F05c Post-operative CAPOX Form standard group (Arm A)
- F05d Pre-operative FOLFOX Form experimental group (Arm B)
- F05e Post-operative FOLFOX Form standard group (Arm A)
- F06 Restaging Radiology Form
- F07 Surgery Form
- F08 Post-surgery Form
- F09 Pathology Form
- F11 Follow-up Form
- F12a Locoregional Recurrence Form
- F12b Distant Recurrence Form
- F12c New Primary Tumour Form
- F13 End of Pre-operative Treatment Form
- F14 Off Study Form
- F20 Death Form
- F30 Adverse Events Form
- F40 Serious Adverse Event Form
- F50 Comment Form

The central data center will collect all CRFs and questionnaires and when applicable complete the form as much as possible.

12.2 Data flow

Paper CRFs may be filled in by treating physicians or data managers at all participating centers and departments. Data of completed and submitted paper CRFs will also be entered in the same database. The system will automatically generate queries, which will be sent to the person responsible for CRF completion. It is not possible to relate the data entered in the database to a specific patient. A copy of the paper CRFs will be kept in the patient file and a copy will be sent to the Datacenter. Missing or due forms will be identified using the database system. In this case, the responsible physician, investigator, nurse or data manager will be contacted by the study coordinators or data managers from the central datacenter.

13. Reporting adverse events

13.1 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.

13.2 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)
- recurrences. For recurrences, the CRF "new primary / recurrences" has to 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. All adverse events reported spontaneously by the subject or observed by the investigator or his staff 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.

The Datacenter will report SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

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 Datacenter by **fax: +31-71-5266744 or email: datacenter@lumc.nl** as soon as possible but no later than one working day. The datacenter will inform the international trial coordinators Prof Dr G.A.P. Hospers, Dr D.J.A. de Groot, Dr. W.H. Kapiteijn, Dr B. van Etten and the national trial coordinators. The datacenter will also inform the Medical Ethics Committee(s) and the Competent Authority as described in the previous section.

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 follow-up SAE form. SAEs occurring within 30 days after discontinuation of the study treatment should be reported.

13.3 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).
The Datacenter will report expedited the following SUSARs for Dutch participants through the web portal *ToetsingOnline* to the METC:
– SUSARs that have arisen in the clinical trial that was assessed by the METC;
– SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.
The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The Datacenter will report expedited all SUSARs to the national principal investigators in other Member States. The national principal investigators will report expedited all SUSARs to the competent authorities, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

13.4 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.

This safety report consists of:

– a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

13.5 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.

13.6 Data Safety Monitoring Board (DSMB)

A DSMB is established to perform ongoing safety surveillance and to evaluate interim analyses on the safety data. This committee is independent of the conducted trial. The DSMB is composed by a president, secretary and three independent members, of whom at least one is a statician. The members of the DSMB are independent and have no conflicts of interest with the conducted trial, principal investigator or sponsor of the study.

Interim analyses are performed according to chapter 7. Accumulating data is reviewed, including updated figures on recruitment, data quality, primary outcome and safety data. The interim-analysis will be performed by an independent statistician. The statistician will report to the independent DSMB. The DSMB will discuss the results of the interim-analysis and advice the steering committee. Discontinuation of the trial is advised by the DSMB according to the pre-defined stopping guidelines stated in paragraph 7.3.

14. Quality assurance

14.1 Control of data consistency

Data for this study will be recorded using Case Report Forms CRF. It will be transcribed by the site from the source documents onto the CRF. In no case is the CRF to be considered as source data for this trial. Accurate and reliable data collection will be assured by verification and cross–check of the CRFs against the investigator's records by the study monitor (source document verification).

Central data management will be performed by ***LUMC Datacenter***

The data managers will verify the data and discrepancy reports will be generated accordingly for resolution by the investigator / local data manager.

14.2 On-site quality control

A monitoring committee will be appointed which will perform onsite monitoring two months after the first patient in the experimental arm underwent surgery and when the first three patients who ended the study are two months post surgery. To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the "Sponsor" may conduct site visits to institutions participating to protocols.

When necessary regular visits by research nurses, data managers of the regional cancer center or monitoring committee members will be organized.

14.3 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 or company supplying the product under investigation, 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.

14.4 Central review of pathology

In order to optimize pathology quality, central review of pathology will be performed after inclusion of the last patient. A committee of experienced rectal cancer pathologists will be appointed. This board will review biopsies and resected rectal cancer specimens according to the pathology protocol described in section 6 and Appendix

14.5 Central review of radiology

In order to optimize pre-operative staging and restaging, central 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.

15. Ethical considerations

15.1 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 (ref: http://www.ifpma.org/pdfifpma/e6.pdf).

The protocol will be approved by the Local, Regional or National Ethics Committees.

15.2 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 center, 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 .

15.3 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, and the mechanism of treatment allocation. 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. An example of a patient informed consent statement is given as an appendix to this protocol.

It is the responsibility of the individual investigator to translate the enclosed informed consent document. The translated version should be dated and version controlled.

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 or randomized in the study. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient".

16. Trial sponsorship and financing

The trial is supported by the DCCG (Dutch Colorectal Cancer Group, www.dccg.nl) and by the NGTTG (*Nordic Gastrointestinal Tumour Trial Group)*. Data management is financed by the Dutch and Swedish cancer societies.

17. Trial insurance

In accordance with the Dutch W.M.O. insurance coverage for all participating patients from all centers, has to be arranged. A participating hospital has to arrange the insurance coverage for all patients participating at this center.

18. 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. Members of the writing committee and central datacenter and investigators from centers who have entered the top 8 of included patients qualify for co-authorship. The others qualify for acknowledgements.

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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Appendix A - TNM- Classification of Rectal Cancer

TNM 5th edition. Sobin and Wittekind, 1997 is used in the Netherlands and will be used in this study

TNM 7th edition 2011, is used in Sweden

TNM 5th edition:

Primary tumour (T)

T0: No evidence of primary tumour

Tis: Carcinoma in situ: intraepithelial or invasion of the lamina propria*

T1: Tumour invades submucosa

T2: Tumour invades muscularis propria

T3: Tumour invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues

T4: Tumour directly invades other organs or structures, and/or perforates visceral peritoneum**,***

* Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) orlamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

** Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa; for example, invasion of the sigmoid colon by a carcinoma of the cecum.

*** Tumour that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumour is present in the adhesion, microscopically, the classification should be pT3.

Regional Lymph Nodes (N)

N0: No regional lymph node metastasis

N1: Metastasis in 1 to 3 regional lymph nodes

N2: Metastasis in 4 or more regional lymph node

A tumour nodule greater than 3 mm in diameter in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of a residual node in the nodule is classified in the pN category as a regional lymph node metastasis.

Distant metastasis (M)

M0: No distant metastasis

M1: Distant metastasis

STAGE GROUPING

AJCC/UICC

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T3	N0	M0
	T4	N0	M0
Stage III	any T	N1	M0
	anyT	N2	M0
Stage IV	anyT	anyN	M1

Appendix B - ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Reference: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

Appendix C – Pathology protocol

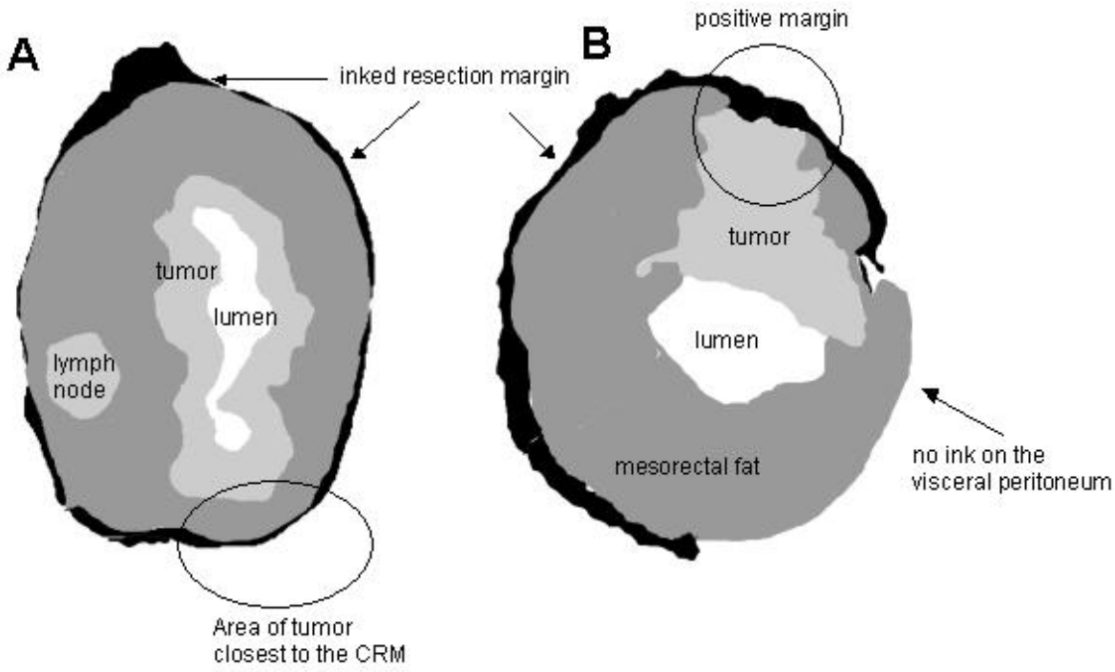
Guidelines for the Dissection Method: (based on Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer. J Clin Oncol 2008, 26(2): 303-312).

The unopened resected specimen is received fresh, carefully inspected for lacerations both of the peritoneal and the non-peritoneal covered surface. The plane of resection should be determined in order to grade the quality of the resection specimen and the specimen should be photographed before inking and opening the specimen. Subsequently, the specimen should be opened anteriorly *except in the area of the tumour where the full circumference of the bowel should be left intact.* This allows the adequate examination of the bowel wall for circumferential margin involvement as well as peritoneal involvement. The specimen should be pinned under gentle tension to a cork board and fixed by immersion in formalin for at least 48 hours. If possible, tissue should be inserted in the unopened bowel to improve fixation of the tumour. After fixation, the peritoneal reflection is identified and the relative position of the tumour noted i.e. below, partially covered by peritoneum or totally covered by peritoneum. Areas covered by peritoneum are inspected for serosal penetration and if apparent are sampled separately. Tumours completely covered by peritoneum are handled in the routine manner for colonic specimens, whereas those with a retroperitoneal component are subjected to close scrutiny for circumferential margin involvement by tumour. Before slicing the specimen, the CRM should be inked. The site of the tumour is sliced as thinly as possible (approximately 0.3 - 0.5 cm) including up to 2 cm above and below, and laid out on a flat surface for macroscopic inspection. Slides are photographed, with special emphasis on deepest levels of tumour invasion and the circumferential margin (CRM). Again the plane of resection should be evaluated and compared with the earlier score.

The extent of tumour involvement of the perirectal tissue is assessed with particular attention being paid to the circumferential resection margin. The maximum extent of tumour spread from the outer limit of the muscularis propria is measured using a ruler. This should be to the edge of tumour's greatest distance of penetration from the muscular wall, be it direct, discontinuous, vascular or lymph node involvement. Area(s) of involvement can usually be seen with the naked eye and any suspicious area or areas should be sampled for histology. One block should be sufficient, but up to six might need to be taken in cases with extensive spread before it is possible to be certain that all the margins are free of tumour. On average four blocks will suffice for the majority of tumours.

Whilst incising the mesentery and the mesorectum, lymph nodes and tumour deposits should be identified and sampled. Metastases and lymph nodes adjacent to the circumferential margin should be sampled "en-bloc" with the resection margin.

Lymph nodes further than 1 cm from the circumferential resection margin or present in the mesentery of the sigmoid colon may be sampled in a routine fashion. The distal resection margin should be sampled (and can be used as a background “normal mucosa” in most cases).Accurate measurement of the minimum distance between tumour or involved lymph node and circumferential resection margin should be performed by microscopy on the haematoxylin and eosin stained slide using a scale on the microscope stage. Shrinkage of tissue occurs during processing but this does not materially affect the accuracy of this measurement. Assessment by microscopy is preferred as a florid peri-tumoural inflammatory reaction or fibrosis will lead to an overestimate of macroscopic tumour spread.



Schematic representation of the circumferential margin. A. Circumferential growing tumour with lymph node metastasis, in one part of the figure the tumour approaches the inked resection margin. The positive lymph node is nearer to the inked margin, and should be mentioned separately. B. Tumour growing into the inked resection margin. Note that only the mesorectal surface is inked, not the visceral peritoneum. The tumour is apparently located in the rectosigmoid area.
When a positive lymph node is closer to the circumferential margin than the tumour itself, the margin between the positive node and the CRM should be registered in addition to the margin between the tumour and the CRM (see above figure).
If the circumferential margin is between 1 and 2 mm, deeper levels should be cut to exclude margin involvement.

Evaluation of quality of the resection and tumour response:

The quality of resection is evaluated at two different levels for APRs (mesorectum as well as anal canal) and at one level for LAR (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

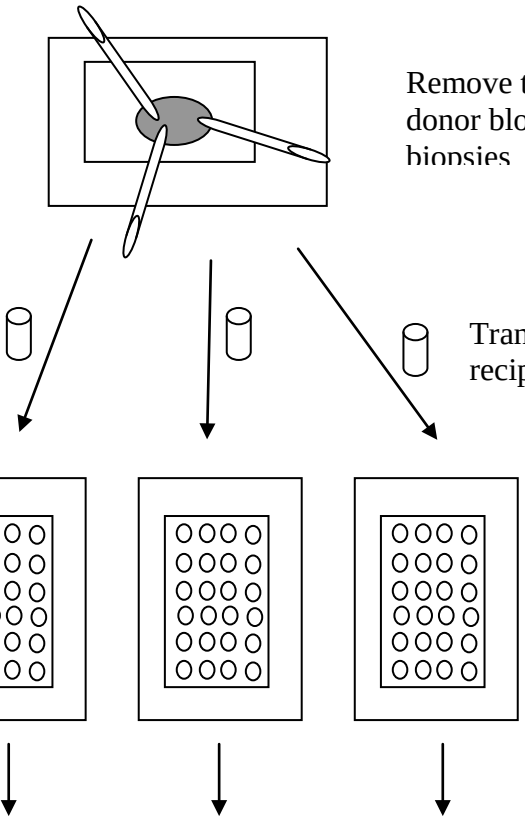
Tumour regression is scored using a three-tiered system: no regression, regression and complete response. Complete pathological response is only used after standardized workup of the specimen which includes blocking of the whole tumour area and cutting three levels of each block (at 250 μm).

TME procedure

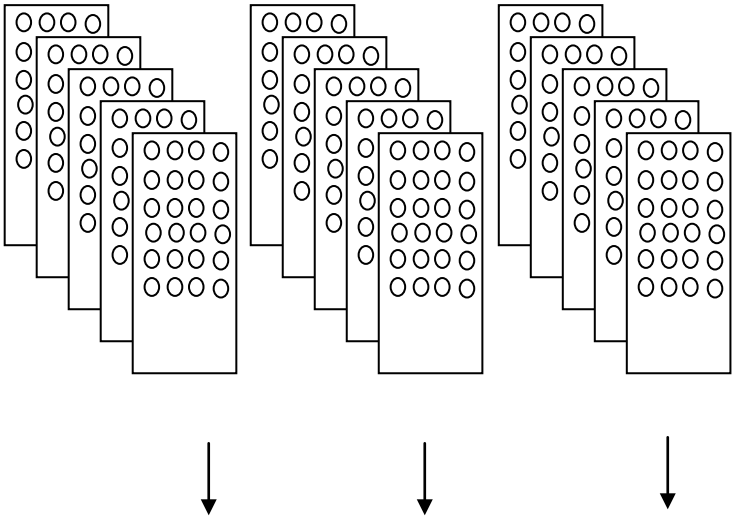
Paraffin embedded tissue block of the tumour will be collected from both the preoperative biopsy and the resection specimen by the datacenter in Leiden at certain time points during the trial. When sufficient material is available, two or three cores will be taken to make a Tissue Micro Array (TMA). The TMAs will be made by the pathology department in Nijmegen, the Netherlands.

Briefly, a section of tissue will be stained using haematoxylin & eosin (H&E) to identify areas of tumour. Three tumour areas will be selected and 0.6 or 2 mm^2 cores of tumour tissue will be removed in total from each block. These cores of tumour tissue will be transferred to recipient blocks (multiple cores per block) to form tissue TMAs. From each tissue array up to 100 4 μm sections will be taken for analysis of biomarkers.

In addition, up to 20 serial 4 μm tissue sections will be taken for evaluation of additional factors and DNA extraction.



Take multiple sections (100-300) from the tissue array block containing 100-500 tumours per section



Use for IHC, etc

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Appendix D – CTCAE V4

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

See website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Appendix E - English Patient Information and Informed Consent RAPIDO TRIAL (with CAPOX)

A study investigating the difference in effect of short term radiotherapy and chemotherapy followed by surgery compared to standard treatment of high risk rectal cancer.

Original title in English: Randomised Multicentre Phase III study of short course radiation therapy followed by prolonged pre-operative chemotherapy and surgery in primary high risk rectal cancer compared to standard chemoradiotherapy and surgery and optional adjuvant chemotherapy

You have been asked to participate in a medical research study on new treatment for high risk rectal cancer. The following written information is intended as an addition to the information you have already received from your doctor in attendance. If, however, this information is unclear or insufficient you can always request additional information. Discuss the information with your partner, family, friends, or doctor/general practitioner. There is also the possibility to consult an impartial person, the details of which will be provided in this document. This person is knowledgeable on the research matter though is not in any way involved in the research. You will be given at least 2 days and up to one week, to consider your participation.

This international study is initiated by University Medical Center Groningen (UMCG) in the Netherlands. The study will be performed according to national and international rules and laws.

Background of this study

Surgery is the most important type of treatment of cancer of the rectum. In some patients with high risk rectal cancer it is not possible to remove the whole tumour during surgery. Additional treatments both before and after the operation are applied as an attempt to reduce the chance of recurrence of the disease and thus increase the chance of cure. To this end, various kinds of chemotherapy (cell-killing drugs) and radiotherapy (radiation) have been applied in the past.

Current standard treatment consists of long term (5 to 6 weeks) radiotherapy combined with chemotherapy before surgery (also called neoadjuvant chemoradiotherapy). This neoadjuvant chemoradiotherapy is mainly aimed to prevent your cancer of the rectum from returning in the area around the tumour (this is called a local recurrence)., Neoadjuvant chemoradiotherapy does not adequately treat micro metastases that may be present at the time of surgery in places far from the rectum such as in the liver or lungs.. If cancer grows in places like the liver or lungs after surgery, this is known as a distant recurrence. Treatment with chemotherapy immediately *after* surgery may not adequately avoid or prevent distant recurrent disease. Possibly this is because many patients are not fit enough to start chemotherapy in time or not at all, after recovering from relatively tough surgery.

In this study we hope to test a new experimental treatment to see if it is more effective than standard treatment in decreasing the risk of local and distant recurrence. In the experimental arm of the study, prior to surgery, we will give short term radiotherapy (5 days), after which the size of the rectal tumour often decreases. During this waiting time before surgery we will give chemotherapy to treat possible micro metastases and to possibly decrease the risk of distant recurrence.. We will comparethis experimental treatment to the standard treatment of neoadjuvant chemotherapy (6 weeks) and then surgery. According to the opinion of the doctors in your local hospital post-operative chemotherapy can also be given. In your hospital post-operative chemotherapy <is / is not> standard treatment.

Object of this study

The aim of this study is to find out whether the experimental treatment can be tolerated better by the patients and has at least the same effect on survival as the standard treatment. To be able to judge the effect of the treatment, all patients will be followed up for three years to assess recurrence of disease. Results of patients with experimental and standard treatment will be compared. In order to avoid the investigators being influenced with regard to their choice in favour of one of the treatment types, the participants will be divided into two equal groups randomly. It is a matter of chance to which group you are assigned. This ensures that both patient and doctor are not able to influence the treatment choice.

Chemotherapy consists of two types of drugs; capecitabine tablets (Xeloda) and oxaliplatin (Eloxatin) which is given by infusion. Both drugs have been evaluated positively on efficacy and safety by International and National Health Authorities.

About 920 patients from Sweden, the Netherlands, Spain, Slovenia, Norway, Denmark, USA and Canada .

What does the research involve?

Standard treatment:

- Pre-operative chemoradiotherapy: 25 to 28 radiations will be given in a period of 5 to 6 weeks. Simultaneously twice daily tablets of capecitabine have to be ingested.
- 8±2 weeks after the last radiation the rectum tumour will be removed during surgery.

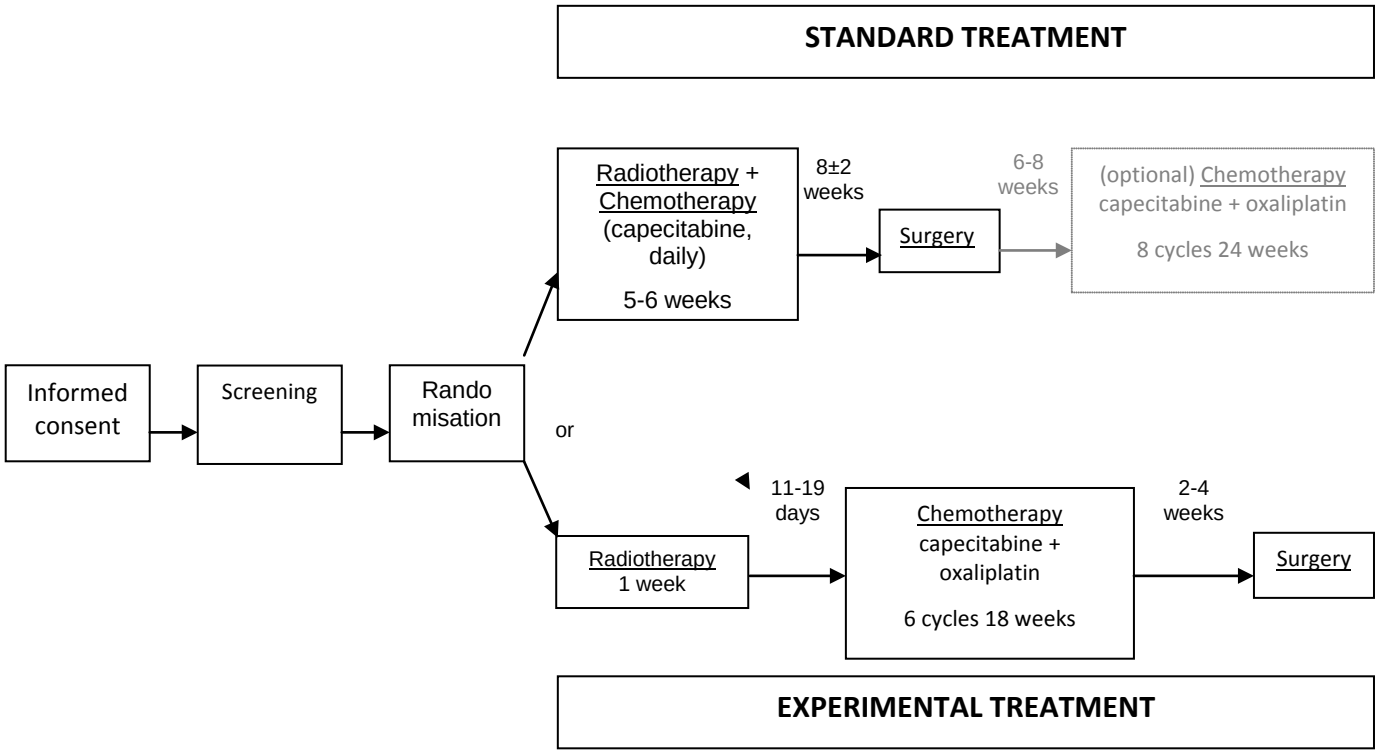
- (*depending on local policy)* 6-8 weeks after the operation 8 cycles of post-operative chemotherapy will be given. In each cycle of 3 weeks, a course consisting of infusion with oxaliplatin will be given on day 1. During the first two weeks of each course, you must take capecitabine tablets twice daily; but not during the third week ("free week").

Experimental treatment:

- Radiation will be given during 5 workings days of a week.
- 11 to 25 days after last radiation, 6 cycles of pre-operative chemotherapy will be given. In each cycle of 3 weeks, a course consisting of infusion with oxaliplatin will be given on day 1. During the first two weeks of each course, you must take capecitabine tablets twice daily; but not during the third week ("free week").
- 2-4 weeks after the last chemotherapy, the rectum tumour will be removed during surgery.

Content of the study

Prior to the start of the treatment you will be asked to sign for informed consent. During the screening several examinations will be carried out and visits to the involved specialists will take place to conclude whether you meet with all criteria to participate in this study. If not, participation in this study is not possible, your doctor will discuss other treatment options with you. The study looks like this:



Participating in a study often means extra tests and extra visits to the hospital. That is not the case in this study. Before surgery you will need to visit the hospital and /or radiotherapy center about 25 times in 14 weeks time (standard); in case of the experimental treatment this is about 12 times during a period of about 22 weeks. So the experimental treatment means that you will need to make fewer visits, but the time till surgery takes longer. Both study groups will be asked to fill out quality of life questionnaires three years after surgery, this will take you about fifteen minutes. If this is standard treatment in your hospital, patients in standard treatment group will receive 8 cycles of chemotherapy (8 visits in 24 weeks) after surgery.

Screening:

- Medical history, concomitant medication and medical complaints
- Physical examination
- Rectoscopy and / or colonoscopy. A biopsy of the tumour might be taken
- If significant for the study an X-ray of the colon will be taken
- CT of lungs, abdomen and pelvis and a MRI of the pelvis will be performed to examine size and spread of the tumour.

Each visit (screening, treatments and follow up)

- Discussion of complaints
- Blood samples for testing general health condition and effects of study treatment (about 10 ml per visit).

Periodically (during and after treatment)

- Physical examination (2-4 times)
- CT of lungs, abdomen and pelvis (twice) and a MRI of the pelvis (2-3 times) will be performed to examine size and spread of the tumour.

After surgery:

- After the operation you will be followed up for at least five years. Follow-up visits will take place at 6, 12, 24, 36 and 60 months after surgery. Periodically blood samples and examinations will be performed.
- 3 Years after the operation questionnaires to assess your quality of life.

What do we expect from you?

- Swallow the capecitabine tablets as prescribed. Do not take any drugs without consulting your doctor
- Inform your doctor or his study personnel of any health changes or if you consider quitting study participation.
- Report to your doctor or his personnel if you have a fever (temperature of 38,5 ^{o}C or more) or if you suffer from diarrhoea or vomiting.

Potential advantages and disadvantages of participation

All drugs can cause side-effects, this also counts for capecitabine and oxaliplatin.

Capecitabine: The side effects of capecitabine have been extensively described: nausea, (rarely) painful damage to the mucosa in the mouth (mucositis) or bowels, resulting in diarrhoea, and redness and pain in the skin of hands and feet (the hand-foot syndrome).

Oxaliplatin: Common side effects include bruises, bleedings, signs of infections like sore throat and raised temperature, diarrhoea and vomiting, mucositis, dry cough, numbness and “pins and needles” in fingers and toes.

Radiotherapy: The side effects of radiotherapy usually increase towards the end of the treatment. The complaints usually consist of fatigue, loss of appetite, nausea and pain behind the sternum if this area overlaps the field of irradiation. Pain during swallowing may also occur.

When you are assigned to standard treatment, there is no difference with the treatment that you would have received outside study participation. It can be expected that side effects of the experimental treatment will be tolerated better.

Contraception

Chemotherapy and radiation results in damage to the unborn child. Therefore, patients may not become pregnant or father children during the treatment. Reliable contraception is therefore essential. Please discuss this with your doctor.

Refusal to participate or withdrawal from participation

Participation in this treatment in a study setting will only occur if you provide your explicit consent. Naturally, your participation is entirely voluntary. Therefore, you are free to decide not to participate in this study. If you wish to stop during the treatment, your doctor in attendance will discuss the best options for your further care with you.

Privacy

All information that will be gathered during this study, will be kept in confidence and processed anonymously.

Insurance

Conformable to the requirements of the Wet Medisch Onderzoek bij mensen (Dutch Decree on Compulsory Insurance in Medical Research Involving Human Subjects), a compulsory insurance has been taken out for this scientific study. You can find information about this in the enclosure.

Approval

This study has been approved by the Ethical Review Board of the UMC Groningen (NL)

Questions

If you have any questions regarding the treatment in the context of this study, please contact your doctor in attendance: .....

Or the national coordinator of the RAPIDO Study in your country: .....

Questions concerning the study may be addressed to the independent doctor of this study Prof. dr. H.J.M. Groen

Patient information on extra blood and tissue collection (RAPIDO trial)

If you agreed to participate in the RAPIDO trial, we would also like to ask you to participate in a side study. This extra study will not be of direct benefit to you personally, but might provide information to improve treatment for future patients with rectal cancer.

We would like to save a fragment of the tumour tissue obtained during the operation for scientific research. This tissue will be analysed with a microscope by the pathologist, who will also provide a description of his/her findings. Moreover, an extra sample of the tissue will be stored, in order to be able to predict in the future, using tissue analysis which treatment is most suitable for each individual patient with rectal cancer. We would also like to take some extra blood samples to store for this scientific research. If you agree, three extra samples will be taken twice at a moment default blood samples are taken to test your general health (before radiotherapy and before surgery).

In principle, the result of this research will have no consequences for your treatment. You will therefore not be informed regarding the results of this research. The chance that the results of research into characteristics will be of importance for you personally is small. In this case, you can indicate on the consent form whether or not you would like to know the results after all. Your doctor is willing to help you to make a decision in this case.

Participation in this part of the study is not obligatory, and you are requested to sign a separate part of the consent form for this. If you decide not to participate in this part of the study, you are still able to participate in the rest of the study.

Your blood and tissue will be stored up to 15 years. It will be destructed after use.

INFORMED CONSENT FORM RAPIDO STUDY

Randomized Multicentre Phase III study of short course radiation therapy followed by prolonged pre-operative chemotherapy and surgery in primary high risk rectal cancer compared to standard chemoradiotherapy and surgery (and adjuvant chemotherapy).

I have read and understood the patient information concerning the RAPIDO study of which I got a copy and I have had the opportunity to ask questions. I have understood the answers and these answers were clear.

I confirm that I had time to think about it, and I know that I can ask for more information from my doctor and stop my participation in the study and that this will not influence the care given to me.

I allow that the study coordinator and his assigned personnel should be able to look at the medical file to check study-related data. They will not be used for any other purpose. My name will not appear in any report. I agree my data will be kept for 15 years.

I allow that my doctor may give information to my general practitioner concerning my participation in this study and other information which might be important. In addition, I allow that he might ask information about my current or past illnesses and treatment.

I agree to participate in the study	**YES** ☐	**NO** ☐
I allow that tumour tissues will be collected and will be used for future research	**YES** ☐	**NO** ☐
I allow that extra blood samples will be taken from me and will be collected for future research	**YES** ☐	**NO** ☐

Name patient …… Signature……

Date …… / …… / …….

The undersigned declares that the above person has been informed with regard to the above study.

Name doctor …… Signature……

Date …… / …… / …….

NB. The original informed consent document must be stored in the medical records of the patient; de patient will receive a copy.

Appendix F - Radiation therapy

Target dose

All patients will receive 28 daily fractions of 1.8 Gy up to a total dose of 50.4 Gy or 25 fractions of 2.0 Gy up to a total dose of 50.0 Gy to the pelvic field including the tumour bed with a margin and the regional lymph nodes. A field reduction after 45 (1.8 Gy schedule) or 46 (2.0 Gy schedule) is recommended. The last fractions will then be given to the tumour bed with a margin.

An extra boost is possible to deliver towards the primary tumour area with 1.8-2.0 Gy x 2 – 4. The treatment is given in combination with chemotherapy (capecitabine).

In group B, the experimental arm, the target dose to the pelvic PTV is 25 Gy with 5 Gy in 5 fractions during one week. The boost volume is included. An extra boost of 2 Gy x 2 – 3 is also possible to deliver in certain circumstances.

Target volumes

Boost GTV

Gross tumour volume (GTV) is the visible primary tumour and visible pathological lymph nodes.

CTV boost

GTV boost plus a margin of 2 cm within the same anatomical compartment as the tumour is in, for the dose from 45 to 50.4 Gy, also around radiologically engaged lymph nodes! If the tumour is entirely within mesorectum with no threatened MRF, the 2 cm extension for uncertainties in tumour spread does not need to go outside the fascia. The margin of 2 cm will thus chiefly be added cranially and caudally. If the tumour e.g. grows into the sacral bone or the urinary bladder, the 2 cm margin does apply within those organs.

GTV boost plus a margin of 1 cm within the same anatomical compartment if an additional boost is given above 50.4 (or 50.0) or 25 Gy.

Pelvic CTV

1. The primary tumour

2. Primary lymph nodes in the bowel wall and within mesorectum. Mesorectum is composed of the surrounding fat around the bowel and extends dorsally towards sacrum. Distally, only lymph nodes or tumour deposits up to 4 cm are included. For tumours in lower rectum this means that the entire mesorectum down to the pelvic floor is included whereas in tumours high up in rectum, the most distal part of mesorectum is not included. The reason for this is to diminish radiation towards the sphincters.

3. The closest secondary lymph node stations consisting of presacral nodes and nodes along the rectal superior artery. These lymph nodes are partly overlapping with the primary mesorectal

lymph nodes and they are important for all tumours within the rectum. Since local recurrences are very unusual above S1 – S2, lymph nodes above this level should not be included unless there are signs of pathological lymph nodes presacrally. If this is the case, the cranial limit of CTV should be at least 1 cm above the most cranial pathological lymph node.

4. The lateral lymph node stations along the medial rectal and obturator arteries until they reach the level of the obturator canal should be included if the primary tumour is below the peritoneal reflection or up to about 8 to 10 cm from the anal verge. In higher tumours, these nodes are rarely involved.

5. The lateral lymph node stations also include lymph nodes along the internal iliac artery up to the bifurcation from the external iliac artery. The cranial border for the CTV is in most cases just below the bifurcation of the internal and external iliac arteries. In most patients this is at the level of S1 – S2. In certain individuals, the bifurcation can be above L5 – S1. In these instances the cranial CTV border is at the level of S1-S2, unless lymph nodes along the internal iliac artery is seen. Then a margin of at least 1 cm above the most cranial lymph nodes must be drawn.

6. Inguinal lymph nodes are included in CTV only if the tumour grows into the anal canal and distal to the dentate line or if it grows into the distal part of vagina.

7. The entire ischio-rectal fossa, the anal canal and peritoneum is included in pelvic CTV only if the tumour grows into the levators or down into the anal canal. In these instances, rectal excision is always required.

8. Lymph nodes along the external iliac artery are included if the tumour grows into anterior organs like the prostate, urinary bladder, cervix, vagina or uterus to such an extent that the external nodes are at risk for metastases. Therefore, napping or minimal overgrowth dorsally is not sufficient.

PTV

The above description relates to the CTV. A PTV should normally be defined and includes CTV and internal target volume (ITV) and a margin necessary for the setup. These margins are depending upon several factors that are related to the equipment at each radiotherapy centre.

Treatment verification

Treatment verification should be performed at least twice during the first treatment week, preferably according to a NAL or SAL procedure, and weekly thereafter for the chemoradiotherapy. For the 5x5 Gy schedule online correction is strongly recommended. Acceptable deviations should be in line with the chosen CTV-PTV margin.

Appendix G - Magnetic resonance imaging

Requirements

1.5T or 3T equipments

Phased-array reciever coils for pelvic-/body imaging

No obligatory preparations.

(Four hours fasting) allowed

Antispasmodic agents allowed

No endoluminal or intravenous contrast agents

Image sequences

T2-weighted high resolution sequences in at least three different planes (Sagittal, transaxial and oblique planes) where one imaging sequence is perpendicular to the rectum at the level of the tumour interleaved with maximum 3 mm section thickness (1). If low tumours, additional oblique sequences including the tumour parallel and perpendicular to the anal canal are performed.

T1-weighted axial images of the pelvis and diffusion weighted images of the pelvis allowed but can only be performed if the quality of the T2-weighted images have been guaranteed.

MRI reporting

Level of the tumour

The distance of the tumour from the anorectal junction and/or from the anal verge is measured by electronic calipers on sagittal images. The length of the tumour is measured and reported. It is also stated whether the tumour is above, at or below the level of the peritoneal reflection. For low tumours it is stated whether the tumour is within a mm from the levator muscles or not, whether there is involvement of the intershpincteric plane and the external sphincter.

Morphology

of the tumour is described whether the tumour is polypoid, (semi)annular. If there is evidence of a mucinous tumour indicated by typical high signal intensity on T2-weighted images, this is also reported.

Depth of extramural spread

The maximum depth of extramural depth from the outer edge of the muscle layer to the outer edge of the tumour is measured on high resolution images perpendicular to the rectum at the level of the tumour (1)

Extramural vascular invasion

is recorded when there is tumour extension along a vessel as a serpintiguous extension of tumour signal within a vascular structure (2)

Mesorectal Fascia

Involvement of the potential circumferential margin is defined as tumour extending within 1 mm of the mesorectal fascia or closer.

Perforation of the peritoneal reflection by tumour

Is reported when nodular extension of tumour beyond the peritoneal reflection is found (3)

Mesorectal lymph node metastases

The total number of mesorectal lymph nodes is reported and the number of lymph nodes regarded as metastatic according to morphological criteria by G. Brown et al. A suspicion of mesorectal lymph node metastases is high if two or more of the following morphological criteria can be appreciated on high resolution T2-weighted sequences – round, irregular border and heterogeneous signal intensity (4).

In addition to the morphological criteria. The following criteria are also used

Mesorectal lymph nodes with a short axis diameter of more than 10 mm and round shape are regarded as metastatic. Mesorectal lymph nodes between 5-9 mm and at least two of the ciriteria round shape/irregular border/heterogeneous signal intensity are also regarded as metastatic.

Extramesorectal lymph node metastases

Presence of suspected metastatic inguinal, lateral pelvic lymph nodes should be reported. Metastatic extramesorectal lymph nodes or pelvic sidewall lymph nodes are defined by morphological criteria similar as for mesorectal lymph nodes: irregular border and/or heterogeneous signal intensity and/or round (not-oval) lymph nodes with short axis diameter of more than 10 mm.

Evaluation post chemoirradiation

When MRI is performed after neoadjuvant treatment, the post treatment MRI is compared with MRI at baseline. Viable tumour (high signal intensity) is separated from post treatment fibrosis (low signal intensity) on T2-weighted images. For mucinous tumours, remaining or increasing pure mucin pools may not necessary indicate progressive disease.

Length of tumour and tumour and fibrosis if these are not clearly separated is measured as in baseline on sagittal T2-weighted images.

The minima distance of tumour (and fibrosis) is measured and the transaxial direction noted 1-12 O´clock.

Regarding lymph nodes, the short axis diameter of mesorectal and extramesorectal lymph nodes is measured. Lymph nodes with malignant morphological features pre treatment and a short axis diameter post treatment of equal to or more than 5 mm are considered malignant.

A clinical complete response (CR) or near CR is defined as presence no visible tumour on T2-weighted images with normal bowel wall layers or presence of residual fibrosis that is confined to the bowel wall.

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Appendix H - EORTC Quality of Life Questionnaire, Colorectal Module and chemotherapy induced peripheral neuropathy

EORTC C30 instrument is a copyrighted instrument, which has been translated and validated into 81 languages and is used in more than 3,000 studies worldwide. Presently QLQ-C30 Version 3.0 is the most recent version and should be used for all new studies.

It is supplemented by disease specific modules for e.g. Breast, Lung, Head & Neck, Oesophageal, Ovarian, Gastric, Cervical cancer, Multiple Myeloma, Oesophago-Gastric, Prostate, Colorectal Liver Metastases, Colorectal and Brain cancer which are distributed from the EORTC Quality of Life Department. Other disease specific modules are under development but not yet validated

The C30 questionnaire will be provided by the LUMC Datacenter.

While the EORTC QLQ-C30 is an important tool to assess the generic aspects of QOL, it has limitations and therefore a modular approach was adopted for disease specific treatment measurements. An essential aspect of the "modular" approach to QOL assessment adopted by the EORTC QLG (Quality of Life Group) is the development of modules specific to tumour site, treatment modality, or a QOL dimension, to be administered in addition to the core questionnaire (EORTC QLQ-C30). The modules, like the core questionnaire, are designed for use in cancer clinical trials. The CR 29 module is developed for colorectal cancer patients.

QLQ-CR29: the colorectal module to assess the quality of life and the functional outcome. To optimally evaluate the sexual functioning, for male patients questions 56 and 57 from QLQ CR-29 have been replaced by questions 50 to 55 from QLQ PR-25, whereas for female patients questions 58 and 59 from QLQ CR-29 have been replaced by questions 49 to 54 from QLQ EN-24.

QLQ-CIPN20: the module to assess the chemotherapy induced periferal neuropathy

Appendix J - National coordinators

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Appendix K - Collection of blood samples
Investigator study laboratory manual

RAPIDO study

Randomised Multicentre Phase III study of short course radiation therapy followed by prolonged pre-operative chemotherapy and surgery in primary high risk rectal cancer compared to standard chemoradiotherapy and surgery (and adjuvant chemotherapy)

Protocol code: RAPIDO

EudraCT registration number:

2010-023957-12

1. CONTACT DETAILS

For this study, DNA, RNA and proteomics samples will be stored at the University Medical Center Groningen, the Netherlands.

Contact

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2. LABORATORY TESTING SCHEDULE

The schedule for sample collection is included below.

Sample collection time points

Before radiotherapy	14 till 0 days
Before operation	7 till 1 days

3. SAMPLE COLLECTION AND HANDLING

Blood samples will be collected on two time points: before start (chemo)radiotherapy and before operation. On each time point two 10 ml (or one 10 ml and two 5 ml) EDTA containing tubes will be filled with whole blood and afterwards directly processed according to this protocol. After processing there are four to five Eppendorf tubes with 2 ml full blood in EDTA and two Eppendorf tubes with 2 ml blood plasma per timepoint per patient. To minimize the patient's burden the blood sampling shall be combined with other laboratory tests.

Complete the patient details on the sample tubes. Adhere a completed tube label to each tube prior to collection. Ensure that these details are consistent with the patient details you have recorded on the Clinical Requisition Form. Each tube should be marked with a waterproof pen with the study number, center number, patients code, date of birth (day/month/year), sample date and sample description (t=0 before radiotherapy; t=1 before operation). Phlebotomy**:** perform a standard venipuncture and allow a tube to fill completely under vacuum.

Note: Blood collection may proceed according to local procedures.

3.1 Full blood sample collection and freezing procedure

Tube used

One standard 10 ml EDTA containing tube (preferred) OR two standard 5 ml EDTA containing tubes. The EDTA tube type can be chosen by the center.

Handling of sample for whole blood

- After whole blood is drawn, pipette the 10 ml of fresh whole blood into four or five 2.0 ml Eppendorf tubes.
- Discard the empty EDTA tube.
- Mark the Eppendorf tubes with a waterproof/cryoproof label and pen with the study number, center number, patient code, date of birth (day/month/year), sample date, sample description (t=0/t=1).

Storage

Store the Eppendorf tubes with full blood directly at -20 or -80 degrees Celsius.

Note: It is preferred to aliquot 10 ml of fresh whole blood into four to five 2.0 ml Eppendorf tubes before storing at -20 or -80 degrees. If this is not feasible, it is possible to draw whole blood into two 5 ml EDTA containing tubes, and store these at -20 or -80 degrees Celsius.

Purpose

DNA will be isolated from the blood for genotyping. RNA will be isolated from the blood to determine expression patterns.

3.2 Blood plasma sample collection and freezing procedure

Tube used

One standard 10 ml EDTA containing tube.

Handling of sample for plasma

- After whole blood is drawn, spin the tube in a balanced centrifuge at 1500 x g for 10 minutes at 4 degrees Celsius.
- Remove the tube from the centrifuge after spinning and pipette all the plasma (top layer) into two 2.0 ml Eppendorf tubes.
- Discard the EDTA tube with the remaining debris.

- Mark the Eppendorf tubes with a waterproof/cryoproof label and pen with the study number, center number, patient code, date of birth (day/month/year), sample date, sample description (t=0/t=1).

Storage

Store the Eppendorf tubes with the supernatant directly at -20 or -80 degrees Celsius until collection and analysis.

Purpose

The samples will be used for proteomics.

3.3 Sending samples

The samples will be collected twice a year (depending on accrual in the particular center) and transferred to the laboratory MOL, De Vitrine Z2.32, Medical Oncology, DA13 at the University Medical Center Groningen. First contact person is Ms.Lolkje Abma , +31 (0)50 3610030 orl.abma@umcg.nl. Second contact person is Ms. Gerry C.M. Sieling, +31 (0)50 3616161, pager 77045, 31 (0)50 3612053 or g.c.m.sieling@umcg.nl.

Appendix L - LARS score

Bowel function questionnaire

The aim of this questionnaire is to assess your bowel function.
Please tick only one box for each question. It may be difficult to select only one answer, as we know that for some patients symptoms vary from day to day. We would kindly ask you to choose one answer which best describes your daily life. If you have recently had an infection affecting your bowel function, please do not take this into account and focus on answering questions to reflect your usual daily bowel function.

The LARS Score - Scoring Instructions

Add the scores from each 5 questions to one final score.

Do you ever have occasions when you cannot control your flatus (wind)?

☐ No, never	**0**
☐ Yes, less than once per week	**4**
☐ Yes, at least once per week	**7**

Do you ever have any accidental leakage of liquid stool?

☐ No, never	**0**
☐ Yes, less than once per week	**3**
☐ Yes, at least once per week	**3**

How often do you open your bowels?

☐ More than 7 times per day (24 hours)	**4**
☐ 4-7 times per day (24 hours)	**2**
☐ 1-3 times per day (24 hours)	**0**
☐ Less than once per day (24 hours)	**5**

Do you ever have to open your bowels again within one hour of the last bowel opening?

☐ No, never	**0**
☐ Yes, less than once per week	**9**
☐ Yes, at least once per week	**11**

Do you ever have such a strong urge to open your bowels that you have to rush to the toilet?

☐ No, never	**0**
☐ Yes, less than once per week	**11**
☐ Yes, at least once per week	**16**

Total Score:
Interpretation:
0-20: No LARS
21-29: Minor LARS
30-42: Major LARS

Appendix M - English Patient Information and Informed Consent RAPIDO TRIAL (with FOLFOX4 treatment)

A study investigating the difference in effect of short term radiotherapy and chemotherapy followed by surgery compared to standard treatment of high risk rectal cancer.

Original title in English: Randomised Multicentre Phase III study of short course radiation therapy followed by prolonged pre-operative chemotherapy and surgery in primary high risk rectal cancer compared to standard chemoradiotherapy and surgery and optional adjuvant chemotherapy

You have been asked to participate in a medical research study on new treatment for high risk rectal cancer. The following written information is intended as an addition to the information you have already received from your doctor in attendance. If, however, this information is unclear or insufficient you can always request additional information. Discuss the information with your partner, family, friends, or doctor/general practitioner. There is also the possibility to consult an impartial person, the details of which will be provided in this document. This person is knowledgeable on the research matter though is not in any way involved in the research. You will be given at least 2 days, and up to one week, to consider your participation.

This international study is initiated by University Medical Center Groningen (UMCG) in the Netherlands. The study will be performed according to national and international rules and laws.

Background of this study

Surgery is the most important type of treatment of cancer of the rectum. In some patients with high risk rectal cancer it is not possible to remove the whole tumour during surgery. Additional treatments both before and after the operation are applied as an attempt to reduce the chance of recurrence of the disease and thus increase the chance of cure. To this end, various kinds of chemotherapy (cell-killing drugs) and radiotherapy (radiation) have been applied in the past.

Current standard treatment consists of long term (5 to 6 weeks) radiotherapy combined with chemotherapy before surgery (also called neoadjuvant chemoradiotherapy). This neoadjuvant chemoradiotherapy is mainly aimed to prevent your cancer of the rectum from returning in the area around the tumour (this is called a local recurrence). Neoadjuvant chemoradiotherapy does not adequately treat micro metastases that may be present at the time of surgery in places far from the rectum such as in the liver or lungs. If cancer grows in places like the liver or lungs after surgery, this is known as a distant recurrence. Treatment with chemotherapy immediately *after* surgery may not adequately avoid or prevent distant recurrent disease. Possibly this is because many patients are not fit enough to start chemotherapy in time or not at all, after recovering from relatively tough surgery.

In this study we hope to test a new experimental treatment to see if it is more effective than standard treatment in decreasing the risk of local and distant recurrence. In the experimental arm of the study, prior to surgery, we will give short term radiotherapy (5 days) after which the size of the rectal tumour often decreases.. During this waiting time we will then give chemotherapy to treat possible micro metastases and to possibly decrease the risk of distant recurrence. We will compare this experimental treatment to the standard treatment of neoadjuvant chemotherapy (6 weeks) and then surgery. According to the opinion of the doctors in your local hospital post-operative chemotherapy can also be given. In your hospital post-operative chemotherapy <is / is not> standard treatment.

Object of this study

The aim of this study is to find out whether the experimental treatment can be tolerated better by the patients and has at least the same effect on survival as the standard treatment. To be able to judge the effect of the treatment, all patients will be followed up for three years to assess recurrence of disease. Results of patients with experimental and standard treatment will be compared. In order to avoid the investigators being influenced with regard to their choice in favour of one of the treatment types, the participants will be divided into two equal groups randomly. It is a matter of chance to which group you are assigned. This ensures that both patient and doctor are not able to influence the treatment choice.

Chemotherapy in the experimental arm will consist of three types of drugs; folinic acid, fluorouracil, and oxaliplatin , which are all given by infusion. These drugs have been evaluated positively on safety by International and National Health Authorities.

About 920 patients from Sweden, the Netherlands, Spain, Slovenia, Norway, Denmark, USA and Canada will participate.

What does the research involve?

Standard treatment:

- Pre-operative chemoradiotherapy: 25 to 28 radiations will be given in a period of 5 to 6 weeks. Simultaneously twice daily tablets of capecitabine have to be ingested.
- About 8 weeks after the last radiation the rectum tumour will be removed during surgery.

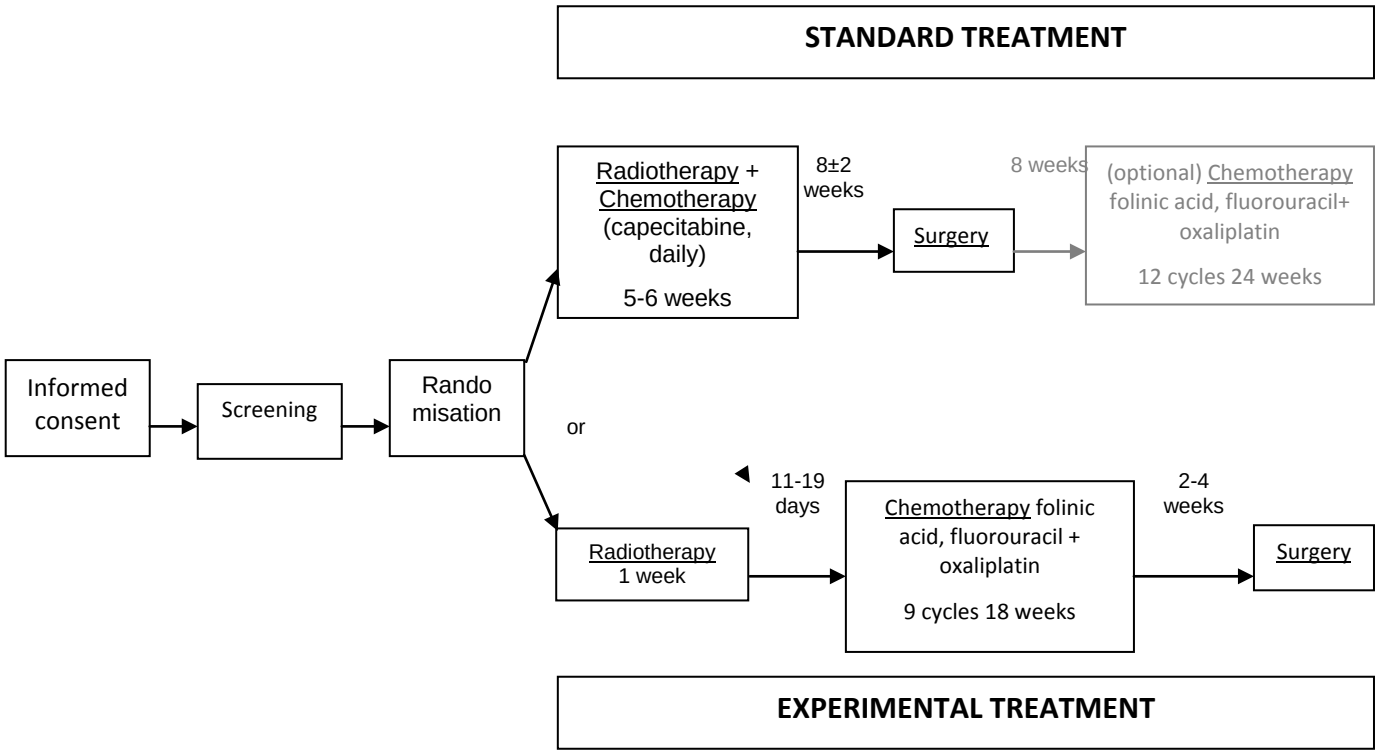
- (*depending on local policy)* 6-8 weeks after the operation 12 cycles of post-operative chemotherapy will be given. In each cycle of 2 weeks, a course consisting of infusion with folinic acid, fluorouracil, and oxaliplatin will be given on day 1. On day 2 there will be additional infusion with folinic acid and fluorouracil.

Experimental treatment:

- Radiation will be given during 5 workings days of a week.
- 11 to 25 days after last radiation, 9 cycles of pre-operative chemotherapy will be given. In each cycle of 2 weeks, a course consisting of infusion with folinic acid, fluorouracil, and oxaliplatin will be given on day 1. On day 2 there will be additional infusion with folinic acid and fluorouracil. 2-4 weeks after the last chemotherapy, the rectum tumour will be removed during surgery

Content of the study

Prior to the start of the treatment you will be asked to sign for informed consent. During the screening several examinations will be carried out and visits to the involved specialists will take place to conclude whether you meet with all criteria to participate in this study. If not, participation in this study is not possible, your doctor will discuss other treatment options with you. The study looks like this:



Participating in a study often means extra tests and extra visits to the hospital. That is not the case in this study. Before surgery you will need to visit the hospital and /or radiotherapy center about 25 times in 14 weeks time (standard); in case of the experimental treatment this is about 23 times during a period of about 22 weeks. So the experimental treatment means that you will need similar number of visits, but the time till surgery takes longer. Both study groups will be asked to fill out quality of life questionnaires, three years after surgery. If this is standard treatment in your hospital, patients in standard treatment group will receive 12 cycles of chemotherapy (24 visits in 24 weeks) after surgery.

Screening:

- Medical history, concomitant medication and medical complaints
- Physical examination
- Rectoscopy and / or colonoscopy. A biopsy of the tumour might be taken
- If significant for the study an X-ray of the colon will be taken
- CT of lungs, abdomen and pelvis and a MRI of the pelvis will be performed to examine size and spread of the tumour.

Each visit (screening, treatments and follow up)

- Discussion of complaints
- Blood samples for testing general health condition and effects of study treatment (about 10 ml per visit).

Periodically (during and after treatment)

- Physical examination (2-4 times)
- CT of lungs, abdomen and pelvis (twice) and a MRI of the pelvis (2-3 times) will be performed to examine size and spread of the tumour.

After surgery:

- After the operation you will be followed up for at least five years. Follow-up visits will take place at 6, 12, 24, 36 and 60 months after surgery. Periodically blood samples and examinations will be performed.
- 3 years after the operation questionnaires to assess your quality of life.

What do we expect from you?

- Swallow the capecitabine tablets as prescribed. Do not take any drugs without consulting your doctor
- Inform your doctor or his study personnel of any health changes or if you consider quitting study participation.
- Report to your doctor or his personnel if you have a fever (temperature of 38,5 ^{o}C or more) or if you suffer from diarrhoea or vomiting.

Potential advantages and disadvantages of participation

All drugs can cause side-effects, this also counts for capecitabine and oxaliplatin.

Capecitabine: The side effects of capecitabine have been extensively described: nausea, (rarely) painful damage to the mucosa in the mouth (mucositis) or bowels, resulting in diarrhoea, and redness and pain in the skin of hands and feet (the hand-foot syndrome).

Oxaliplatin: Common side effects include bruises, bleedings, signs of infections like sore throat and raised temperature, diarrhoea and vomiting, mucositis, dry cough, numbness and “pins and needles” in fingers and toes.

*Folinic Acid: S*ide effects are uncommon with the drug. Allergic reactions happen rarely and result in a fever, rash, itchiness or even swelling of the face or throat.

Fluorouracil: Common side effects include poor appetite, nausea and vomiting, diarrhea, and sometimes unusual bleeding or bruising, and fever or chills. You may also experience dry or red eyes, and your skin may be sensitive to sunlight.

Radiotherapy: The side effects of radiotherapy usually increase towards the end of the treatment. The complaints usually consist of fatigue, loss of appetite, nausea and pain behind the sternum if this area overlaps the field of irradiation. Pain during swallowing may also occur.

When you are assigned to standard treatment, there is no difference with the treatment that you would have received outside study participation. It can be expected that side effects of the experimental treatment will be tolerated better.

Contraception

Chemotherapy and radiation results in damage to the unborn child. Therefore, patients may not become pregnant or father children during the treatment. Reliable contraception is therefore essential. Please discuss this with your doctor.

Refusal to participate or withdrawal from participation

Participation in this treatment in a study setting will only occur if you provide your explicit consent. Naturally, your participation is entirely voluntary. Therefore, you are free to decide not to participate in this study. If you wish to stop during the treatment, your doctor in attendance will discuss the best options for your further care with you.

Privacy

All information that will be gathered during this study, will be kept in confidence and processed anonymously.

Insurance

Conformable to the requirements of the Wet Medisch Onderzoek bij mensen (Dutch Decree on Compulsory Insurance in Medical Research Involving Human Subjects), a compulsory insurance has been taken out for this scientific study. You can find information about this in the enclosure.

Approval

This study has been approved by the Ethical Review Board of the UMC Groningen (NL)

Questions

If you have any questions regarding the treatment in the context of this study, please contact your doctor in attendance: .....

Or the national coordinator of the RAPIDO Study in your country: .....

Questions concerning the study may be addressed to the independent doctor of this study Prof. dr. H.J.M. Groen.

Patient information on extra blood and tissue collection (RAPIDO trial)

If you agreed to participate in the RAPIDO trial, we would also like to ask you to participate in a side study. This extra study will not be of direct benefit to you personally, but might provide information to improve treatment for future patients with rectal cancer.

We would like to save a fragment of the tumour tissue obtained during the operation for scientific research. This tissue will be analysed with a microscope by the pathologist, who will also provide a description of his/her findings. Moreover, an extra sample of the tissue will be stored, in order to be able to predict in the future, using tissue analysis which treatment is most suitable for each individual patient with rectal cancer. We would also like to take some extra blood samples to store for this scientific research. If you agree, three extra samples will be taken twice at a moment default blood samples are taken to test your general health (before radiotherapy and before surgery).

In principle, the result of this research will have no consequences for your treatment. You will therefore not be informed regarding the results of this research. The chance that the results of research into characteristics will be of importance for you personally is small. In this case, you can indicate on the consent form whether or not you would like to know the results after all. Your doctor is willing to help you to make a decision in this case.

Participation in this part of the study is not obligatory, and you are requested to sign a separate part of the consent form for this. If you decide not to participate in this part of the study, you are still able to participate in the rest of the study.

Your blood and tissue will be stored up to 15 years. It will be destructed after use.

INFORMED CONSENT FORM RAPIDO STUDY

Randomized Multicentre Phase III study of short course radiation therapy followed by prolonged pre-operative chemotherapy and surgery in primary high risk rectal cancer compared to standard chemoradiotherapy and surgery (and adjuvant chemotherapy).

I have read and understood the patient information concerning the RAPIDO study of which I got a copy and I have had the opportunity to ask questions. I have understood the answers and these answers were clear.

I confirm that I had time to think about it, and I know that I can ask for more information from my doctor and stop my participation in the study and that this will not influence the care given to me.

I allow that the study coordinator and his assigned personnel should be able to look at the medical file to check study-related data. They will not be used for any other purpose. My name will not appear in any report. I agree my data will be kept for 15 years.

I allow that my doctor may give information to my general practitioner concerning my participation in this study and other information which might be important. In addition, I allow that he might ask information about my current or past illnesses and treatment.

I agree to participate in the study	**YES** ☐	**NO** ☐
I allow that tumour tissues will be collected and will be used for future research	**YES** ☐	**NO** ☐
I allow that extra blood samples will be taken from me and will be collected for future research	**YES** ☐	**NO** ☐

Name patient …… Signature……

Date …… / …… / …….

The undersigned declares that the above person has been informed with regard to the above study.

Name doctor …… Signature……

Date …… / …… / …….

NB. The original informed consent document must be stored in the medical records of the patient; de patient will receive a copy.