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 study)

Published: 26-04-2011
Last updated: 28-04-2024

Primary Objective: disease related treatment failure.Secondary Objectives: Overall survival, CRM negative (margin > 1 mm) rate, Pathological complete response (pCR) rate, Short and long-term toxicity, Surgical complications, Quality of life....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON47895

Source
ToetsingOnline

Brief title
RAPIDO

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
rectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: KWF (centraal en lokaal datamanagement;goedkeuring binnenkort verwacht)

Intervention

Keyword: chemotherapy, radiotherapy, rectal cancer, surgery

Outcome measures

Primary outcome

disease related treatment failure.

Secondary outcome

Overall survival, CRM negative (margin > 1 mm) rate, Pathological complete

response (pCR) rate, Short and long-term toxicity, Surgical complications,

Quality of life. Pharmacogenomics.

Study description

Background summary

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 6-10 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 and to postpone all locoregional therapy in order to 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 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. 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 and the *M1 trial* 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 or cetuximab improves the antitumour effects against subclinical disease.

Study objective

Primary Objective: disease related treatment failure.
Secondary Objectives: Overall survival, CRM negative (margin > 1 mm) rate, Pathological complete response (pCR) rate, Short and long-term toxicity, Surgical complications, Quality of life. Pharmacogenomics.

Study design

Multicenter randomized open phase III parallel group study.
Patient will be randomly allocated to either:
• Standard treatment: week 1-6 : Chemoradiotherapy (CRT): 28 x 1.8 Gy at working days combined with capecitabine b.i.d. 825 mg/m2 day 1-38. 6-8 weeks after CRT: Surgery (TME). Adjuvant chemotherapy 8 cycles of CAPOX (Capecitabine b.i.d.1000 mg/m2 day 1-14 every 3 weeks, Oxaliplatin 130 mg/m2 day 1 every 3 weeks) is allowed according to the local protocol of the particular institute, starting preferably 6-8 and max. 12 weeks after surgery.
• Experimental treatment: Week 1: 5 x 5 Gy. Week 3-18: 6 courses of Capecitabine b.i.d.1000 mg/m2 day 1-14 every 3 weeks, Oxaliplatin 130 mg/m2 day 1 every 3 weeks. Week 22-24: Surgery(TME).
Follow-up until 2 years after inclusion of last patient. Total study duration estimated 6 years.
885 patients to be included.
Independent DSMB.

Intervention

Standard or experimental treatment.

Study burden and risks

Risk: adverse events and less effective experimental treatment.
Burden:
Quality of Life questionnaires (3 after OK). Optional farmacogenomics substudy: in total 120-180 ml blood.
In hospitals with standard treatment without adjuvant chemotherapy: 6 infusions of Oxaliplatin in the experimental arm.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ

NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Biopsy-proven, newly diagnosed primary rectal adenocarcinoma.
• Locally advanced tumour fulfilling at least one of the following criteria on pelvic MRI indicating high risk of failing locally and/or systemically:
o Clinical stage (c) T4a
o cT4b
o EMVI+
o N2
o Positive MRF, i.e. tumour <= 1 mm from the mesorectal fascia
• Staging done within 5 weeks before randomization.
• Age >= 18 years.
• ECOG Performance Status of 0 - 1.

Exclusion criteria

• Extensive growth into cranial part of the sacrum (above S3) or the lumbosacral nerve roots.
• 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.
• Pregnancy or lactation.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-03-2012
Enrollment:	361
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Eloxatin
Generic name:	oxaliplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Xeloda
Generic name:	capecitabine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	26-04-2011
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-10-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-02-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-02-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-05-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-01-2014
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-08-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-09-2019
Application type:	Amendment

Review commission: METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-023957-12-NL
Other	NL3082 (NTR3230)
CCMO	NL36315.042.11