The role of surgery of the primary tumour with few or -absent symptoms in patients with synchronous unresectable metastases of colorectal cancer, a randomized phase III study

Published: 16-05-2012
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The primary objective is overall survival (OS).Secondary objectives are progression free survival (PFS), grade 3 and 4 chemotherapy related toxicity, surgery related morbidity and mortality (30 day and 90 day), quality of life (QoL), number of...

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

Summary

ID

NL-OMON50614

Source
ToetsingOnline

Brief title
CAIRO4

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
bowel cancer, colorectal cancer, rectum cancer

Research involving
Human

Sponsors and support

Primary sponsor: Dutch Colorectal Cancer Group
Source(s) of monetary or material Support: Farmaceutische industrie,Hoffmann-La Roche

Intervention

Keyword: Colorectal cancer stage IV, surgery of the primary tumor, synchronous unresectable distant metastases, systemic therapy

Outcome measures

Primary outcome

The primary endpoint of the study is overall survival in the intent-to-treat population.

Secondary outcome

Secondary endpoints are progression-free survival, response to chemotherapy of the primary tumour compared to the response of metastases, systemic therapy related toxicity, surgery related morbidity and mortality (30 and 90 days), quality of life (QoL), interval between randomization and initiation of systemic treatment, cost-benefit analysis, patients requiring resection of the primary tumour in the non-resection arm, and overall survival in patients in whom treatment according to protocol was initiated (i.e. having received at least one cycle of systemic treatment in arm A, and surgery in arm B). Patients without recurrence and alive at the time of the analysis will be included as censored data. PFS curves will be constructed by means of the Kaplan Meier method. Comparisons of PFS curves will performed by mean of the Logrank test. Similar methods will be used to analyse the duration of survival.

Analyses will be done in eligible patients according to the intention-to-treat

principle.

Study description

Background summary

The clinical benefit of resection of the primary tumour in patients with synchronous unresectable metastases is not known. In the literature studies usually describe retrospective selected patients with synchronous metastases treated with or without resection of the primary tumour. All these studies are biased in patient selection and there are no prospective randomized studies on this topic. In patients with few or absent symptoms of the primary tumour, arguments both in favor and against initial resection have been presented, and therefore a randomized trial is warranted.

Study objective

The primary objective is overall survival (OS).
Secondary objectives are progression free survival (PFS), grade 3 and 4 chemotherapy related toxicity, surgery related morbidity and mortality (30 day and 90 day), quality of life (QoL), number of patients who undergo secondary surgery of initially irresectable metastases, number of patients who never receive systemic therapy after resection of the primary tumour, interval between randomization and initiation of systemic treatment, cost-benefit analysis, patients requiring resection of the primary tumour in the non-resection arm, patients requiring stenting or radiotherapy for symptom palliation, overall survival in patients in whom treatment according to protocol was initiated (i.e. having received at least one cycle of systemic treatment in arm A, and surgery in arm B).
Translational research will be performed on prognostic/predictive markers (resected tumour tissue, and in blood samples, i.e. angiogenic factors, and sCD95L levels).

Study design

Patients with synchronous metastatic colon cancer or rectum cancer with few or absent symptoms of their primary tumour are randomized 1:1 between systemic treatment without resection of the primary tumour and resection of the primary tumour followed by systemic treatment

Intervention

resection of the primary tumour

Study burden and risks

Both study arms are used in daily practice and therefore there are no additional risks. Until this study has taken place, it is not clear which strategy is best.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Histological proof of colorectal cancer
Resectable primary tumour in situ with unresectable distant metastases
No indication for neo-adjuvant (chemo)radiation.
No severe signs or symptoms related to the primary tumour (i.e. severe

bleeding, obstruction, severe abdominal pain) that require immediate surgery or other symptomatic treatment (e.g. stenting) (see 6.4 for exceptions)
No prior systemic treatment for advanced disease
Age >= 18 years
WHO performance status 0-2
Laboratory values obtained <= 4 weeks prior to randomization: Adequate bone marrow function (Hb * 6.0 mmol/L, absolute neutrophil count * 1.5 x 109/L, platelets * 100 x 109/L), renal function (serum creatinine <= 1.5x ULN and creatinine clearance, Cockroft formula, * 30 ml/min), liver function (serum bilirubin <= 2 x ULN, serum transaminases <= 3 x ULN without presence of liver metastases or <= 5x ULN with presence of liver metastases)
Expected adequacy of follow-up
Written informed consent
Unidimensionally measurable disease (* 1 cm on CT scan or * 2 cm on chest X-ray; liver ultrasound is not allowed, according to RECIST 1.1)
CT abdomen performed <= 4 weeks prior to randomization

Exclusion criteria

Pregnancy, lactation
Unresectable primary tumour (i.e. neurovascular encasement, substantial ingrowth in pancreatic head), or any condition preventing the safety or feasibility of resection of the primary tumour, i.e. massive ascites or extensive peritoneal disease
Second primary malignancy within the past 5 years with the exception of adequately treated in situ carcinoma of any organ or basal cell carcinoma of the skin
Any medical condition that prevents the safe administration of systemic treatment
Previous intolerance of fluoropyrimidines, known complete dihydropyrimidine dehydrogenase (DPD) deficiency
(Planned) radical resection of all metastatic disease
Uncontrolled hypertension, i.e. values consistently > 150/100 mmHg
Use of * 3 antihypertensive drugs
Significant cardiovascular disease < 1 yr before randomization (symptomatic congestive heart failure, myocardial infarction, unstable angina pectoris, serious uncontrolled cardiac arrhythmia, cerebrovascular event)
Chronic active infection
Concurrent treatment with any other anti-cancer therapy as described per protocol

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):	26-07-2012
Enrollment:	176
Type:	Actual

Ethics review

Approved WMO Date:	16-05-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-07-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-08-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	09-08-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-08-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-08-2012
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-10-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	31-03-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-07-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-09-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-01-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-03-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	05-10-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-06-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-10-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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
CCMO	NL38155.091.11