Determination of new biomarkers in patients with resectable colorectal liver metastases, the MIRACLE study

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To establish (i) whether or not pre-operative determination of cell-free DNA (cfDNA) and circulating tumor cells (CTC), alone or in combination with each other, in peripheral blood of CRC patients with isolated colorectal liver metastases (CRLM)...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metastases
Study type	Observational invasive

Summary

ID

NL-OMON50622

Source
ToetsingOnline

Brief title
MIRACLE

Condition

- Metastases

Synonym
colorectal liver metastases

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: KWF kankerbestrijding

Intervention

Keyword: biomarkers, chemotherapy, colorectal liver metastases, surgery

Outcome measures

Primary outcome

Our primary endpoint is recurrence of disease after hepatic resection for colorectal liver metastases within one year after resection.

Secondary outcome

- Improve the selection of patients who respond to neoadjuvant chemotherapy.

- Improve the selection of patients who will have a complete response after neoadjuvant chemotherapy.

- To identify tumor-specific characteristics of CTC and cfDNA at the molecular level, and to correlate these parameters with the response on chemotherapy and the recurrence rate within 1 year.

- To objectify whether serial measurements of cfDNA and CTCs will provide more adequate information than single point measurement prior to therapy.

- To address whether or not (serial) assessments of tumor-specific characteristics of CTC and DNA at the molecular level add to the current known prognostic factors in overall survival.

- To determine if cfDNA in patients who are recurrence free after >1 year can be used to discriminate between patients who will still develop recurrence during at least 2 remaining years of follow-up.

- To determine reference values and the incidence of elevated cfDNA upon diagnosis of recurrence (within 12 months) and prior to start of treatment.

Study description

Background summary

For colorectal cancer (CRC) patients presenting with isolated liver metastases, a treatment comprising a liver metastasectomy is the only potentially curative option. However, a substantial number of patients shows a relapse following this procedure underlining the need for prognostic factors. Such prognostic factors allow a more personalized treatment strategy; more intensified treatments for those with a high risk for relapse and maybe less intensified approaches for those with a low risk. In recent years, several pre-operative prognostic factors in patients with isolated colorectal liver metastases have been revealed for the risk of relapse after a metastasectomy including the number and size of metastases, synchronicity and CEA serum levels. Although this type of clinical risk scoring is well-validated and able to distinguish between high-risk and low-risk patients, further fine-tuning is desperately needed. Clinically low-risk patients may experience relapse rates of 40% at 1 year, whereas clinically high-risk patients may show a 5-year survival rate of 20-40%. This underlines the importance of novel pre-clinical and biological prognostic factors. Relevant prognostic and predictive factors are required to determine the most effective combination of treatments for each individual patient with metastatic CRC.

Study objective

To establish (i) whether or not pre-operative determination of cell-free DNA (cfDNA) and circulating tumor cells (CTC), alone or in combination with each other, in peripheral blood of CRC patients with isolated colorectal liver metastases (CRLM) undergoing hepatic resection determined before and/or after resection with or without pre-operative chemotherapy, can discriminate between patients showing a recurrence within 1 year from those who do not, and (ii) whether or not these novel factors significantly add to the current known prognostic factors. Furthermore, to evaluate (iii) if cfDNA can be used in patients who are recurrence free after >1 year to discriminate between patients who will still develop recurrence during at least 2 remaining years of scheduled follow-up. Lastly, to determine (iv) reference values and the incidence of elevated cfDNA upon diagnosis of recurrence and prior to start of treatment.

Study design

1.In total, 240 colorectal cancer patients with isolated liver metastases undergoing a potentially curative hepatic resection will be studied.
2.Known pre-operative prognostic factors nowadays used in the prognostic clinical scoring systems (including number and size of liver metastases, the

time interval from primary tumor to metastases, CEA levels, free resection margins) will be established.
3.Peripheral blood samples for quantitative determination of cfDNA levels and enumeration of CTCs will be drawn from all participating patients: before and after the start of neoadjuvant chemotherapy, and before and after hepatic resection.
4.Peripheral blood samples for quantitative determination of cfDNA levels will be collected in 40 participants who are recurrence-free at >=12 months of follow-up, on condition that the remaining regular follow-up duration is at least 2 years at the moment of sample collection.
5.Peripheral blood samples for quantitative determination of cfDNA levels will be collected from 10 participants upon diagnosis of recurrence within 12 months of follow-up. These samples will be collected before treatment for recurrent disease is initiated.
6.Patients will be monitored for recurrence of disease with traditional imaging techniques such as ultrasound, CT-, MRI- and PET-scans, according to the National guidelines.
7.Assessment whether or not determination of cfDNA, CTC, alone or in combination with each other, improves the prognostic value of currently known prognostic models to predict early recurrence in colorectal cancer patients with isolated liver metastases undergoing a potentially curative hepatic resection.
8.Assessment whether or not determination of cfDNA, CTC, alone or in combination with each other, have predictive value with respect to the outcome of neoadjuvant chemotherapy.
9.Exploratory analyses will be done using targeted next-generation sequencing of a panel of genes thought to be involved in the outcome of colorectal cancer to establish whether or not the genomic constitution of cfDNA taken at different time points relative to treatment is associated with outcome.

Study burden and risks

Not applicable

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

Age >= 18 years.
Histologically confirmed primary colorectal carcinoma.
Radiological confirmed and resectable liver metastasis of colorectal cancer, planned to undergo resection with or without neo-adjuvant chemotherapy.
Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations.

Exclusion criteria

Prior adjuvant chemotherapy for the primary colorectal carcinoma given <6 months prior to detection of the liver metastases.
Prior non colorectal malignancies, except for patients with basal or squamous cell carcinoma of the skin, or patients with carcinoma in situ of the cervix.
Presence of extrahepatic disease. Patients with small (<=1 cm) extrahepatic lesions that are not clearly suspicious of metastases are eligible.
Females with a positive pregnancy test (within 14 days before treatment start).
History of psychiatric disability judged by the investigator to be clinically significant, precluding informed consent.
Current or recent treatment with another investigational drug or participation in another investigational study.
Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those

conditions should be discussed with the patient before registration in study.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-10-2015
Enrollment:	240
Type:	Actual

Ethics review

Approved WMO Date:	05-06-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL53086.078.15