COLLISION RELAPSE trial - Recurrent colorectal liver metastases: repeat local treatment +/- neoadjuvant systemic therapy - a phase III prospective randomized controlled trial

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This study has been transitioned to CTIS with ID 2024-515341-41-01 check the CTIS register for the current data. The primary objective is to demonstrate superiority of neoadjuvant systemic therapy followed by repeat local treatment as compared to...

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

Summary

ID

NL-OMON54123

Source
ToetsingOnline

Brief title
COLLISION RELAPSE - Repeat local treatment +/- neoadjuvant systemic therapy

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Metastases
- Hepatobiliary therapeutic procedures

Synonym
Colorectal cancer liver metastases; Metastatic colorectal cancer

Research involving

Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: N.t.b.,N.t.b.

Intervention

Keyword: Colorectal liver metastases, Neoadjuvant systemic therapy, Recurrence, Repeat local treatment

Outcome measures

Primary outcome

Primary objective is to compare overall survival (OS) in both study arms,

counting from the date of randomization to the date of death of the patient or

to the last day of follow-up (censored).

Secondary outcome

Main secondary endpoints are overall distant progression-free survival (DPFS),

local tumor progression-free survival (LTPFS), systemic therapy related

toxicity, procedural morbidity and mortality, length of hospital stay,

assessment of pain and quality of life (QoL), cost-effectiveness ratio (ICER)

and quality-adjusted life years (QALY).

Study description

Background summary

Colorectal cancer (CRC) has a high incidence and mortality rate worldwide. The prognosis of CRC patients is largely dependent on the presence of distant metastases, most frequently involving the liver. Up to 50% of patients develop colorectal liver metastases (CRLM) at some time during the course of treatment. If left untreated five-year overall survival (OS) is <3% and when treated with palliative chemotherapy five-year OS improves to approximately 11%. One-fifth

of CRLM patients are eligible for local treatment with curative intent. This approach for upfront resectable and/or ablatable disease reaches 5-year OS of 44-58%. If CRLM are initially unresectable and unablatable, 5-year OS up to 33% is reached, when CRLM are successfully downstaged with induction chemotherapy. Two randomized controlled trials (EORTC 40983, Nordlinger et al. and JCOG 0603, Kanemitsu et al.) showed that routine use of (neo)adjuvant chemotherapy for resectable and/or ablatable disease does not lead to improved OS. Therefore perioperative and adjuvant treatment is no longer recommended for resectable and/or ablatable CRLM.
After initial treatment of CRLM, new intrahepatic recurrence develops in 64%-85% of patients. To treat recurrent CRLM partial hepatectomy or thermal ablation is considered standard of care. With upfront repeat local treatment 5-year reaches 51%. Given the poorer prognosis associated with patients with recurrent disease, attributed to presumed worse tumor biology and the presence of intrahepatic micrometastases, neoadjuvant chemotherapy prior to repeat local treatment has been suggested to prolong survival and to select responders who will benefit from local treatment.
Our recent pooled meta-analysis (Dijkstra et al.) reported no difference in OS between neoadjuvant chemotherapy followed by repeat local treatment and upfront repeat local treatment. However, the included retrospective comparative series showed a trend towards improved survival for the addition of neoadjuvant chemotherapy to repeat local treatment. Furthermore, the largest to date registry study (LiverMetSurvey) advocates neoadjuvant chemotherapy followed by repeat local treatment to adequately select good candidates and to control rapidly progressive disease based on an OS benefit favoring the use of neoadjuvant chemotherapy before repeat local treatment: 5-year OS: 61.5% vs. 43.7% (HR = 0.529; 95%CI 0.299-0.934).
Although the recommendation of neoadjuvant chemotherapy followed by repeat local treatment is frequently reported, the exact role of neoadjuvant chemotherapy prior to repeat local treatment in case of recurrent and locally treatable CRLM remains uncertain.
The negative results from the EORTC 40983 and JCOG 0603 trials for (neo)adjuvant chemotherapy prior to the initial local treatment and the absence of prospective randomized controlled studies for recurrent disease makes us question the benefit of adding neoadjuvant chemotherapy to repeat local treatment. Furthermore, the well-known risks associated with liver surgery following repeated cycles of oxaliplatinum (sinusoidal obstruction syndrome) and 5-fluorouracil or irinotecan (liver steatosis) and the systemic toxicity, side-effects, reduced quality of life (QoL) and added direct costs should be considered.
To assess the added value of neoadjuvant chemotherapy we have designed a phase III randomized controlled trial (RCT) directly comparing upfront repeat local treatment (control) with neoadjuvant systemic therapy followed by repeat local treatment (intervention).

Study objective

This study has been transitioned to CTIS with ID 2024-515341-41-01 check the CTIS register for the current data.

The primary objective is to demonstrate superiority of neoadjuvant systemic therapy followed by repeat local treatment as compared to upfront repeat local treatment in patients with at least one locally treatable recurrent CRLM in the absence of extrahepatic disease.

Study design

The COLLISION RELAPSE trial is a prospective multicenter phase III randomized controlled trial. The primary conducting center will be the Amsterdam UMC (Amsterdam, the Netherlands). We hypothesize that neoadjuvant systemic therapy followed by repeat local treatment is superior to upfront repeat local treatment for the selected patient groups in terms of the primary objective (OS). We hypothesize that neoadjuvant systemic therapy followed by repeat local treatment is superior to upfront repeat local treatment for the selected patient groups in terms of the primary objective (OS). The Cox proportional hazards model (1-sided; superiority) and the PASKWIL criteria for adjuvant treatment for the benefit of OS from the Dutch Society of Medical Oncology are used for the sample size calculations. A total number of 360 patients will be randomized (NR) into one of two arms: arm A (control group) upfront repeat local treatment (n=180) and arm B (intervention group) 4 cycles of CAPOX (capecitabine with oxaliplatin) +/- bevacizumab or 6 cycles of neoadjuvant FOLFOX/FOLFIRI (5-fluorouracil/leucovorin with oxaliplatin or irinotecan) +/- bevacizumab followed by repeat local treatment (n=180).

Intervention

Eligible patients will be randomized into one of two arms: arm A (control group) upfront repeat local treatment and arm B (intervention group) 12 weeks of neoadjuvant systemic therapy followed by repeat local treatment. Patients in arm B will receive maximum 4 cycles of CAPOX or 6 cycles of FOLFOX/FOLFIRI +/- bevacizumab regardless of the location of primary tumor or RAS/BRAF mutation. Choice of repeat local treatment is to the discretion of the local investigator, and may be selected on a per patient basis.

Eligible patients will be stratified into two groups depending on the interval between initial local treatment and first detection of recurrent CRLM: recurrence within 6 months and recurrence between 6 and 12 months, RAS/BRAF mutation vs RAS/BRAF wildtype, prognostic risk score (low vs high risk, clinical risk score Fong et al. and previous chemotherapy versus no previous chemotherapy.

Study burden and risks

When adhering to a maximum of 12 weeks of neoadjuvant systemic therapy, no negative effect on procedural morbidity was found. Despite the possible damage to the liver, there was no difference found in liver volume and function after neoadjuvant systemic therapy before repeat local treatment. By participating in the study, patients agree to either undergo neoadjuvant systemic therapy followed by repeat local treatment for CRLM (intervention) or to undergo upfront repeat local treatment (control). For each participant, the method of treatment will be decided upon by randomization. Pre-operative work-up screening will not be different from standard treatment and will not be an additional burden. If participants receive systemic therapy before repeat local treatment, we anticipate higher burden due to related systemic toxicity. Follow-up after the procedure will be identical to standard treatment. If our hypothesis will prove to be wrong, patients having undergone systemic therapy before repeat local treatment are at risk of having a comparable overall survival, comparable disease-free survival, and comparable local recurrence rate, while the use of systemic therapy could lead to side-effects causing a temporary or prolonged decrease in quality of life. If the addition of systemic therapy to repeat local treatment proves to be superior to upfront repeat local treatment, this patient group will have a prolonged life expectancy at the cost of these side-effects.

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 documentation of primary colorectal tumor
- Local treatment performed for initial CRLM
- >=1 locally treatable recurrent CRLM (partial hepatectomy and/or thermal ablation)
- Resection for resectable lesions considered possible obtaining negative resection margins (R0) and preserving adequate liver reserve
- Total number of new CRLM <= 5
- No microsatellite instability (MSI)
- Good performance status (ECOG 0-2) // ASA 1-3
- No extrahepatic disease
- Both chemo-naïve patients and patients who did not progress on either CAPOX, FOLFOX, or FOLFIRI chemotherapy prior to the initial local treatment

Exclusion criteria

- Pregnant or breast-feeding subjects. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment;
- Immunotherapy <= 6 weeks prior to the randomization;
- Chemotherapy <= 6 weeks prior to the randomization;
- Progression on both oxaliplatin and irinotecan;
- Severe allergy to contrast media not controlled with premedication.

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:	Recruiting
Start date (anticipated):	24-04-2023
Enrollment:	360
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fluorouracil
Generic name:	5-fluoro-uracil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Irinotecan
Generic name:	Irinotecan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Levoleucovorin
Generic name:	Folinic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Oxalisin/Oxaliplatin
Generic name:	Oxaliplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xeloda/Capecitabin
Generic name:	Capecitabin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-02-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC

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
EU-CTR	CTIS2024-515341-41-01
EudraCT	EUCTR2022-002214-17-NL
CCMO	NL78220.029.22