Disappearing colorectal liver metastases DisCoRMet; a prospective multicentre trial

Summary

Rationale: Colorectal cancer is one of the most common cancers, and many patients will develop liver metastases. During preoperative systemic oncological therapy, some colorectal liver metastases (CRLM) may disappear. Currently, there is no evidence-based consensus on how to manage these lesions, resulting in a lack of standardized treatment protocols based on the best scientific evidence.

Objective: To investigate whether disappearing liver metastases (DLM) can safely be left in situ with a low risk of recurrence.

Study design: The DisCoRMet trial is a prospective, multicentre, international study including patients with at least one CRLM, synchronous or metachronous, visible on baseline hepatobiliary contrast magnetic resonance imaging (MRI), which is no longer detectable on follow-up hepatobiliary contrast MRI after systemic oncological therapy.

Study population: Eligible patients have at least one CRLM, synchronous or metachronous, visible on baseline hepatobiliary contrast MRI which is no longer detectable on follow-up hepatobiliary contrast MRI after systemic oncological therapy.

Intervention: If all metastases have disappeared and the patient is not a candidate for surgery, they will be followed with hepatobiliary contrast MRI every three months during the first year.
If surgery is indicated, contrast-enhanced intraoperative ultrasound (CEIOUS) is suggested perioperatively. If the lesion is identified, resection or ablation is recommended. If the lesion is not identified, the site of the tumour may be resected if easily accessible or left in situ at the attending surgeon's discretion. All resections will undergo histopathological examination. If the lesion is not identified, but the tumour site is resected together with another visible metastasis, the site will be marked. If the site of the lesion is left in situ, the patient will be followed with hepatobiliary contrast MRI every three months during the first year.

Main study endpoints: To determine time to progression and overall survival in patients with DLM left in situ.

Risks associated with participation: The study does not involve any intervention other than the best available treatment, as determined by regional multidisciplinary conference decisions, but advocates for registration and scheduled follow-up.

1. Introduction and rationale

1.1 Background

Colorectal cancer (CRC) is the third leading cause of cancer-related death worldwide, affecting both males and females (1). At the time of diagnosis, over 15% of patients present with liver metastases (CRLM), and up to 50% of the patient population will develop CRLM within three years (2). The five-year survival rate for patients with CRLM remains low, at approximately 20% (3).

Currently, surgical resection or ablation of CRLM are the most common options for curative treatment. In a curative setting, systemic oncological treatment is administered as neoadjuvant therapy to achieve systemic disease control, or as conversion therapy to make resection possible by reducing the extent of the metastases. Up to 56% of patients with synchronous CRLM who receive neoadjuvant systemic treatment show a response according to RECIST 1.1 criteria, which is an indicator of favourable prognosis (4).

However, in cases where preoperative systemic treatment is highly successful, a complete radiological response can occur. This phenomenon is referred to as disappearing liver metastases (DLM). The proportion of DLM in patients with CRLM is highly variable, up to 37%, depending on the accuracy of the imaging modality used for restaging after oncological treatment (5). Recently, a European pan-societal collaboration defined DLM as lesions visible on baseline hepatobiliary contrast magnetic resonance imaging (MRI) that are no longer detectable on follow-up hepatobiliary contrast MRI after systemic chemotherapy (6).

Several predictive factors for complete radiological response after chemotherapy have been identified, such as low carcinoembryonic antigen (CEA) levels at diagnosis and their normalisation after chemotherapy, age under 60 years, synchronous disease, and the size and number of CRLM at diagnosis, as well as the number of chemotherapy cycles (7). However, studies have shown a wide range of residual tumour cells, from 0% up to 80%, when DLM lesions are surgically resected (7). This results in a surgical dilemma regarding whether to resect the sites of the missing lesions or not. The situation has been described as “an oncological dream and a surgical nightmare”. The likelihood of achieving a true pathological complete response after chemotherapy is higher in patients with a combination of the above-mentioned factors, which is associated with prolonged survival and a decreased risk of recurrence (8).

The optimal management of DLM remains controversial due to uncertainty regarding residual microscopic disease and the long-term outcomes of resected versus unresected patients (9, 10). If left untreated, DLM may harbour viable tumour cells and be associated with a high rate of early recurrence (5). Furthermore, surgical trauma to the liver could theoretically induce an inflammatory response that might promote the growth of residual tumour cells. Previous consensus guidelines for hepatic resections of CRLM therefore recommended that surgery should include all sites of liver metastases identified before chemotherapy (11).

In the past decade, the number of patients with CRLM eligible for hepatic resection has significantly increased due to modern chemotherapeutic regimens, targeted therapies, and a broader acceptance of surgery for advanced tumour burden. However, complete eradication of the original metastatic sites can be very complex, particularly when the metastases are located deep in the liver parenchyma or when the extent of the CRLM is wide. Resection of all

original metastatic sites may also result in an insufficient future liver remnant or inadequate liver volume for the removal of future metastases. Downstaging or conversion chemotherapy is therefore necessary to offer curative resection to patients with widespread liver metastases.

DLMs require further understanding, as they may allow conversion from an unresectable to a resectable state. Oba et al. demonstrated that it might be safe to leave true DLM in situ (12). When DLM is not detected on hepatobiliary contrast MRI and contrast-enhanced intraoperative ultrasound (CEIOUS), the risk of viable disease is very low (4%) and the rate of recurrence is 14% (12).

Circulating tumour DNA (ctDNA) is a prognostic and predictive biomarker that enables the detection of molecular residual disease following surgical resection. ctDNA analysis may help identify patients at risk of early recurrence and has emerged as a promising assessment tool (13, 14).

DLM is a significant clinical challenge, and there is no consensus on how to balance the risk of recurrence with the risk of resecting too much healthy liver parenchyma (6). Therefore, a prospective study is urgently needed to address this issue in this patient cohort.

1.2 Rationale

Colorectal cancer is one of the most common cancers, and many patients will develop liver metastases. Despite surgery or ablation, around 50% of patients will experience recurrence. During preoperative systemic oncological therapy, some CRLM may disappear. Currently, there is no evidence-based consensus on how to manage these lesions, resulting in a lack of standardised treatment protocols based on the best scientific evidence. The DisCoRMet Trial will be important to both the medical community and patients, as it aims to provide crucial insight into the management of DLM.

2. Objectives

2.1 Hypothesis

Liver metastases from colorectal cancer, visible on baseline hepatobiliary contrast MRI but not detectable after chemotherapy on follow-up hepatobiliary contrast MRI with diffusion-weighted sequences or CEIOUS, can be safely left in situ with a low risk of recurrence.

2.2 Primary objective

- To determine time to progression and overall survival in patients with DLM left in situ.

2.3 Secondary objectives

- To assess the incidence of DLM in patients receiving curative-intent neoadjuvant chemotherapy.
- To evaluate the proportion of residual tumour cells in resected sites of DLM based on histological examination.

- To compare disease-free survival in patients where DLM is resected versus left in situ.
- To compare overall survival at 1 and 3 years in patients where DLM is resected or left in situ.
- To correlate the presence of ctDNA with radiological recurrence, evaluating the clinical utility of ctDNA in patients with DLM.

Overall purpose: To establish an evidence-based treatment algorithm for patients with disappearing liver metastases.

3. Study design

The DisCoRMet trial is a prospective, multicentre, international study including patients with at least one CRLM, synchronous or metachronous, visible on baseline hepatobiliary contrast MRI which is no longer detectable on follow-up hepatobiliary contrast MRI after systemic oncological therapy.

The primary endpoint is to determine time to progression and overall survival in patients with DLM left in situ.

Appendix 1- Flow Chart.

4. Study population

4.1 Population

Eligible patients have at least one CRLM, synchronous or metachronous, visible on baseline hepatobiliary contrast MRI which is no longer detectable on follow-up hepatobiliary contrast MRI after systemic oncological therapy.

For metachronous disease, patients may also be included if at least one CRLM, initially visible on CT scan at recurrence, is no longer visible on hepatobiliary contrast MRI after systemic chemotherapy. Although hepatobiliary contrast MRI is the preferred imaging modality, patients without a baseline MRI prior to chemotherapy will not be excluded.

4.2 Inclusion criteria

- Patients ≥18 years old with at least one synchronous liver metastasis from colorectal cancer, visible on baseline hepatobiliary contrast MRI and no longer detectable on follow-up MRI after systemic oncological therapy.
- Patients ≥18 years old with at least one metachronous liver metastasis from colorectal cancer, initially visible on CT scan at recurrence, but no longer detectable on hepatobiliary contrast MRI after systemic chemotherapy.

4.3 Exclusion criteria

- Patients <18 years old.
- Patients unable to understand verbal and written information.

4.4 Sample size calculation

Due to the unknown prevalence of DLM, a reliable power calculation to evaluate differences in recurrence and disease-free survival cannot be performed. Approximately half of patients treated for synchronous or metachronous CRLM with resection or ablation will experience recurrent metastases (15). The median time to recurrence of CRLM is 20 months (16), and overall survival is 45%, according to the Swedish National Registry for Cancer in Liver, Gallbladder and Bile Ducts (SweLiv) (17). This study will include patients over a three-year period, with a subsequent three-year follow-up to capture a large cohort of DLM cases and identify most recurrences.

5. Methods

5.1 Study parameters

5.1.1 Main study parameter/endpoint

- To determine time to progression and overall survival in patients with DLM left in situ.

5.1.2 Secondary study parameters/endpoints

- To assess the incidence of DLM in patients receiving curative-intent neoadjuvant chemotherapy.
- To evaluate the proportion of residual tumour cells in resected sites of DLM based on histological examination.
- To compare disease-free survival in patients where DLM is resected versus left in situ.
- To compare overall survival at 1 and 3 years in patients where DLM is resected or left in situ.
- To correlate the presence of ctDNA with radiological recurrence, evaluating the clinical utility of ctDNA in patients with DLM.

Overall purpose: To establish an evidence-based treatment algorithm for patients with disappearing liver metastases.

5.2 Study procedures

The study does not involve any intervention other than the best available treatment, as determined by regional multidisciplinary conference decisions, but advocates for registration and scheduled follow-up.

All patients with CRLM discussed at a multidisciplinary conference and offered curative-intent neoadjuvant chemotherapy will be registered at the participating site to analyse the incidence of DLMs in this specific cohort.

Patients with at least one DLM will be included at the time of evaluation following chemotherapy.

If all metastases have disappeared and the patient is not a candidate for surgery, they will be followed with hepatobiliary contrast MRI every three months during the first year. The follow-up interval may be extended according to regional guidelines after the first year.

If surgery is indicated, CEIOUS is suggested perioperatively. If the lesion is identified, resection or ablation is recommended. If the lesion is not identified, the site of the tumour may be resected if easily accessible, or left in situ, according to the attending surgeon's discretion. All resections will undergo histopathological examination. If the lesion is not identified, but the tumour site is resected together with another visible metastasis, the site will be marked. If CEIOUS is not performed, or if a visible lesion is not treated, the reason will be documented (see flow chart, Appendix 1).

Patient-, tumour-, and surgery-related data will be entered into a pseudonymised database, RedCap. Information on time to local recurrence, new liver metastases, and extrahepatic disease progression will be recorded. Cancer-specific treatments and survival outcomes will be collected. Plasma samples for ctDNA analysis will be obtained concurrently with radiological examinations. A list of variables is provided in Appendix 2.

5.3 Withdrawal of individual subjects

Subjects may leave the study at any time for any reason, if they wish to do so, without any consequences.

5.4 Follow-up of subjects withdrawn from treatment

Patients who withdraw from the study will be offered standard of care according to the institution's guidelines, without being registered for anything other than overall survival, unless they specifically indicate that this is not permitted.

5.5 Statistical analysis

Continuous data will be expressed as medians and interquartile ranges, while categorical variables will be reported as numbers and percentages, as appropriate. To compare groups, non-parametric tests such as the Chi-square test, Mann–Whitney U test, or Kruskal–Wallis test will be used. A significance level of 5% will be applied.

Disease-free survival and overall survival will be analysed using Kaplan–Meier curves and Cox regression models.

6. Ethical considerations

6.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki as well as all applicable national regulations regarding the conduct of clinical trials.

Ethical approval is received form the Swedish Ethical Review Authority and corresponding ethics committees in participating countries. The study will adhere to established ethical guidelines, and approval will be obtained prior to commencement. Participating countries will seek ethical approval as required by local regulations. No patient will be identifiable when data are presented.

6.2 Recruitment and consent

Prior to enrolment, all potential participants will be provided with comprehensive verbal and written information regarding the study, and informed consent will be obtained before any study-related procedures are initiated.

6.3 Compensation for injury

No financial compensation will be provided by the sponsor for any potential harm or injury related to participation in the study. However, participants are covered by the national patient injury insurance in accordance with applicable legislation.

7. Administrative aspects and publication

7.1 Handling and storage of data and documents

The sponsor and the trial management team will oversee the conduct of the trial according to Good Clinical Practice (GCP). The local investigators will be responsible for conduct at their respective sites.

Data will be handled confidentially. Each patient will receive an anonymous identification code. To trace data, a subject identification code list will be used. Each participating site will keep the key to this code secure. The handling of data will comply with the EU General Data Protection Regulation (GDPR).

Data will be kept for a minimum of ten years according to current regulations.

Data will be entered into the eCRF using the electronic online database RedCap. Data to be collected are derived from the protocol.
The CRF and instructions for completing it will be provided by the Clinical Trial Centre/Västra Götaland, Sweden.

7.2 Public disclosure and publication policy

Upon completion of the trial, the two principal investigators will be responsible for the public dissemination of the study outcomes. Results will be reported at symposia, and at national and international professional meetings. The final trial results will be submitted to a peer-reviewed medical journal regardless of study outcome.

Authorship credit will be based on the Recommendations of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). The criteria for authorship are defined as:

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data.
2. Drafting the article or revising it critically for important intellectual content; and
3. Final approval of the version to be published.

Authors must meet all three conditions.

For the final trial results manuscript, there is a minimum requirement of:

- 5 included patients per site for 1 co-authorship,
- 15 randomised patients per site for 2 co-authorships, and
- 30 randomised patients per site for 3 co-authorships.

Each site will internally determine which local investigator(s) will be co-author(s). The primary contact for this process will be the local principal investigator.

First and last authorships are reserved for the principal investigators. Principal investigators will be mentioned as such in the manuscript. All other authors will be listed in alphabetical order. Clinicians who are involved in this study but do not fulfil the above-mentioned criteria will be acknowledged as ‘collaborators’ in the final manuscript, and the medical journal will be requested to list all collaborators in PubMed accordingly.

The trial will be registered at ClinicalTrials.gov [registration number to be added].

8 References

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Appendix 1.
Flow chart
To be added

Appendix 2.
List of variables for eCRF.

Patient characteristics	Patient ID Gender (m/f) Age at diagnosis of CRLM
Tumour characteristics baseline	Primary tumour (Colon/rectal) Synchronous/metachronous Number of liver lesions Size of largest lesion (mm) Extrahepatic disease (y/n) CT scan baseline (date) MRI hepatobiliary contrast agent at baseline (date)
Chemotherapy details	Intention (neoadjuvant/conversion) Chemo agent (SingleAgent/DoubleAgent/TripleAgent) Antibody (y/n) Numbers of cycles Completed intended treatment (y/n) Interrupted intended treatment (y/n)
Tumour characteristics at evaluation	MRI hepatobiliary contrast agent with diffusion weight sequences at evaluation (y/n) Number of liver lesions Extrahepatic disease (y/n) Size of largest lesion (mm) CRLM response/stable/progression (Recist 1.1) Response primary tumour (y/n) DLM (y/n) Number of DLM
Operative variables	open/laparoscopic/robotic the DLM identified during surgery without CEIOUS (y/n) the DLM palpable? (y/n) CEIOUS used (y/n) CEIOUS identified DLM (y/n)

	Management of DLM (resection/ablation/leave in situ)
	site of DLM resected togehter with another metastases /y/n)
	Site of DLM sent to histopathology (y/n)
	reason for CEIOUS not used
	reason for identified DLM left in situ
	operation performed in total (segment 1-8 anatomical/non anatomical)
	extrahepatic metastatic disease found (y/n)
	Except DLM, other metastases left in the liver? (y/n)
	planned for second liver surgery (y/n)
	tumour still present extrahepatic (y/n)
Follow-up DLM left in situ	MRI hepatobiliary contrast agent 3 months (y/n)
	recurrent disease at site of DLM (y/n)
	recurrent disease elsewhere in liver (y/n)
	recurrent disease extrahepatic (y/n)
	blood sample ctDNA (y/n)
	MRI hepatobiliary contrast agent 6 months (y/n)
	recurrent disease at site of DLM (y/n)
	recurrent disease elsewhere in liver (y/n)
	recurrent disease extrahepatic (y/n)
	blood sample ctDNA (y/n)
	MRI hepatobiliary contrast agent 9 months (y/n)
	recurrent disease at site of DLM (y/n)
	recurrent disease elsewhere in liver (y/n)
	recurrent disease extrahepatic (y/n)
	blood sample ctDNA (y/n)
	MRI hepatobiliary contrast agent 12 months (y/n)
	recurrent disease at site of DLM (y/n)
	recurrent disease elsewhere in liver (y/n)
	recurrent disease extrahepatic (y/n)
	blood sample ctDNA (y/n)
	recurrence found (months from evaluation with DLM)
	recurrent disease at site of DLM (y/n)
	recurrent disease elsewhere in liver (y/n)

	recurrent disease extrahepatic (y/n)
	recurrence possible to resect/ablate (y/n)
Follow-up DLM resected	DLM identified at operation (y/n) site of DLM resected without DLM identified (y/n)
	histopathology finding (viable cells/fibrosis/no signs of tumour)
	recurrence found (months from evaluation with DLM) recurrent disease at site of DLM (y/n) recurrent disease elsewhere in liver (y/n) recurrent disease extrahepatic (y/n)
	recurrence possible to resect/ablate (y/n)
Follow-up DLM ablation	biopsy before ablation (y/n)
	histopathology finding (viable cells/fibrosis/no signs of tumour)
	recurrence found (months from evaluation with DLM) recurrent disease at site of DLM (y/n) recurrent disease elsewhere in liver (y/n) recurrent disease extrahepatic (y/n)
	recurrence possible to resect/ablate (y/n)
Long-term follow up	CT scan shows progression (date) patient deceased (date)