Extended criteria treatment for liver metastases and heavy tumour burden (Excalibur III trial)

A multicenter, randomized, controlled trial for patients with heavy tumour burden and resectable disease.

Protocol Title:

A randomized, clinical control trial for patients above 18 years of age with colorectal liver metastasis, heavy tumor burden and resectable disease comparing 2nd line chemotherapy to 2nd line chemotherapy and surgical resection to study whether there is any survival benefit to surgical resections compared to chemotherapy alone.

Protocol Number: 1.0

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Medical Monitor Name and Contact Information [will be provided separately OR can be found in XX]

Protocol Amendment Summary of Changes Table

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Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A randomized, clinical control trial for patients above 18 years of age with colorectal liver metastasis, heavy tumor burden and resectable disease comparing 2nd line chemotherapy to 2nd line chemotherapy and surgical resection to study whether there is any survival benefit to surgical resections compared to chemotherapy alone.

Brief Title: Extended criteria treatment for liver metastases and heavy tumour burden (Excalibur III trial)

Rationale:

Patients with multiple colorectal liver metastases that progress on 1st line chemotherapy have a very dismal prognosis, and their options are few. Resections are regularly performed although this is only supported by anecdotal evidence for this patient group. We want to assess whether resections actually confer benefit as compared to 2nd line chemotherapy alone, in a randomized controlled trial.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To optimize treatment for patients with a large tumour burden and borderline resectability who have progressive disease on 1st line chemotherapy	• Median survival
Secondary	
•	• Overall survival at 2, 5 and 10 years after randomization • Progression-free survival (PFS) • Response rate • Resection rate • Quality-of-life (EORTC QoL C30 + EQ5D) • Adverse events and major surgical complications • Molecular analyses related to disease-free and overall survival

Overall Design:

Excalibur 3 is a two-armed RCT comparing 2nd line systemic chemotherapy alone (standard care) to systemic chemotherapy combined with liver resections with or without adjuvant local destructive techniques (radiation/thermo-ablation)

Brief Summary:

Patients with multiple colorectal liver metastases that progress on 1st line chemotherapy have a very dismal prognosis, and their options are few. Resections are regularly performed although this is only supported by anecdotal evidence for this patient group. We want to assess whether resections actually confer benefit as compared to 2nd line chemotherapy alone, in a randomized controlled trial.

44 patients, totally, will be randomized leaving 22 in each group. Patients found at hospital MDT meeting to have CRLM with progression on 1st line chemotherapy, extensive, but resectable in liver, tumour burden, although considered biological unresectable, will be considered as candidates for the study. If eligible by inclusion/exclusion criteria they will be informed, and if they accept, randomized to either 2nd line chemotherapy and surgery or just standard treatment/2nd line chemotherapy. There are no crossovers. Further controls according to local and national guidelines.

Number of Participants:

Adding 15 % to allow for drop-outs, we aim to randomise a total of 44 patients in a 1:1 ratio, i.e. 22 patients per group.

Intervention Groups and Duration:

A one-sided parallel-group test of proportions to answer this with a power of 0.80 and an alpha of 0.15, will require 19 completed patients per group to show superiority for the group where resections are added to chemotherapy. This is based on a three-year accrual time, and a total of five-year follow-up from the first patient, ensuring at least two years follow-up for all patients. Adding 15 % to allow for drop-outs, we aim to randomise a total of 44 patients in a 1:1 ratio, i.e. 22 patients per group.

Data Monitoring/Other Committee: [Yes/No]

1.2. Schema

1.3. Schedule of Activities (SoA)

Procedure	Visits	Visits												E/D		
		1	2 Surgery/ chemo start*	3	4	5	6	7	8	9	10	11	12	13			
Timeline	**Weeks**	**0**	**2**	4	6	8	10	12	14	16	18	20	22	24			
Informed consent		X															
Inclusion and exclusion criteria		X															
Demography		X															
Full physical examination including height and weight		X															
Medical history (includes substance usage		X															
Past and current medical conditions		X															
pregnancy test (WOCBP only)		X															
Laboratory tests (include liver chemistries)		X	X	X	X	X	X	X	X	X	X	X	X	X			
12-lead ECG		X															
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X			
Randomization		X															
Genetic sample – MAYBE??		X	X														

Procedure	Visits	Visits												E/D		
		1	2 Surgery/ chemo start*	3	4	5	6	7	8	9	10	11	12	13			
Study intervention - surgery		X	X														
AE review		X		X													
Chemotherapy			X	X	X	X	X	X	X	X	X	X	X	X			
Questionnaires EQ-5D + QLQ-C30		X			X			X			X			X			
SAE review		X	←==========											→|		
[Device deficiencies] if applicable		X	←==========											→|		
Concomitant medication review		X	←==========											→|		
Survival assesment																	

*surgery group will start chemo 4-6 weeks after surgery

2. Introduction

Patients with multiple colorectal liver metastases that progress on 1st line chemotherapy have a very dismal prognosis, and their options are few. Resections are regularly performed although this is only supported by anecdotal evidence for this patient group. We want to assess whether resections actually confer benefit as compared to 2nd line chemotherapy alone, in a randomized controlled trial.

2.1. Study Rationale

This trial targets a group of patients that are not eligible for the Excalibur 1 and 2 trials but still have as dismal or even worse prognosis. They will – according to the inclusion criteria – have a large tumour burden and have shown progression on 1st line systemic chemotherapy treatment. Based on previous trials, only 30 % of this patient group are estimated to be alive after two years. These patients have today only one treatment modality available: 2nd line systemic chemotherapy. Response can, however, only be expected in a small minority.

With such a dismal outcome for these patients, almost any attempt to improve survival would be warranted and anecdotal evidence shows that some appear to benefit substantially. This may, however, be a result of biased selection and the benefit of surgery in this *grey zone* is unproven.

We will secure ethical approval (REK).

2.2. Background

Colorectal cancer (CRC) is the second most frequent malignant disease in Norway (Cancer in Norway 2017). About 50% of the patients will have metastatic disease at the time of diagnosis or develop metastatic disease later on. Liver metastases are the most frequent presentation of metastatic disease. Liver resection is considered the only curative treatment option in CRC patients with liver metastases, however only about 20% of the patients are candidates for liver resection. The treatment option for the majority of the patients is palliative chemotherapy with a median overall survival from start of chemotherapy of about 2 years, and only 10-12 months from starting 2nd line chemotherapy.

While high-quality data (randomized trials) is wanting, it is generally accepted that the only curative treatment for colorectal liver metastases (CRLM) is surgery. Liver resections are generally well tolerated and safe [1], but some patients recur early and probably have no benefit from surgery, or even a net loss of quality-of-life (QoL). These are hard to identify beforehand, but patients with multiple tumours that progress on 1st line chemotherapy are at high risk of early recurrence following resection[2, 3]. These patients are in a *grey zone*: their metastases may be technically resectable, but the aggressive biology of their disease makes overall outcome of surgery highly uncertain. The decision to offer resection to some of these patients primarily results from want of better alternatives and from lack of sufficiently precise prognostication.

As resections are generally well tolerated and adequate prognostication is wanting, there is a tendency to offer resections to patients who have borderline resectable CRLM or who exhibit other non-favourable

traits like large or multiple metastases, or progression on 1st line chemotherapy. Resections followed by early recurrence represent a net loss of quality-of-life and an unwanted expenditure for society. Exploring the optimal treatment modality for patients in this *grey zone*, i.e. with uncertain benefit from surgery, is important to provide optimal treatment for patients in a critical situation.

Palliative chemotherapy is in general the only treatment option for the vast majority of non-resectable patients. The expected median overall survival (OS) from start of *first* line chemotherapy is about 2 years and the 5 years OS is about 10%, although longer median OS has been obtained in selected patients with good performance status (ECOG 0-1), no (K)RAS or BRAF mutations and left-sided tumours [4-8]. The OS from start of *second* line chemotherapy however is only 10-12 months [9]. This places the prognosis for this group of cancer patients on par with those having pancreatic cancer.

3. Project objective

To optimize treatment for patients with a large tumour burden and borderline resectability who have progressive disease on 1st line chemotherapy, we will randomise patients to either have liver resections of marginally resectable disease added to the use of 2nd line chemotherapy (intervention) or continue with 2nd line chemotherapy alone (control).

3.1. Research hypothesis

In patients with large tumour burden and/or borderline resectability of colorectal liver metastases and progression on 1st line systemic chemotherapy, overall survival following systemic therapy combined with liver resection is better than following conventional systemic chemotherapy alone.

4. Project plan

4.1. Outline of methodology

Excalibur 3 is a two-armed RCT comparing 2nd line systemic chemotherapy alone (standard care) to systemic chemotherapy combined with liver resections with or without adjuvant local destructive techniques (radiation/thermo-ablation).

4.2. Primary endpoint

Median survival

4.3. Secondary endpoints

- Overall survival at 2, 5 and 10 years after randomization
- Progression-free survival (PFS)
- Response rate
- Resection rate
- Quality-of-life (EORTC QoL C30 + EQ5D)
- Adverse events and major surgical complications
- Molecular analyses related to disease-free and overall survival

5. Inclusion/Exclusion criteria

5.1. Inclusion criteria

The trial seeks to include patients in whom liver resection is not considered standard of care.

All the following criteria must be present

1. Verified adenocarcinoma in colon or rectum

2. Liver metastases that are technically resectable (ablation can be used as an adjunct) without PVE, HVE or ALPPS, but judged in need of further (next line) chemotherapy based on insufficient response to at least one line of chemotherapy.

And either

a. Six or more liver metastases, with extra-hepatic disease *that exceeds*
i. 3 pulmonary metastases and/or
ii. radiologically positive liver hilar lymph nodes.

Or
b. Ten or more liver metastases with at least one of the following negative prognostic signs:
i. At least one lesion > 7 cm in diameter before chemotherapy
ii. CEA > 100 following chemotherapy
iii. KRAS and/or BRAF mutant primary tumour.
iv. Node positive primary tumour.

Or
c. Fifteen or more liver metastases

3. ECOG 0/1
4. Informed consent

5.2. Exclusion criteria

Any of the following criteria will exclude participation in the trial:
1. Previous or current bone or CNS metastatic disease
2. Peritoneal deposits/metastases that are not amenable to resection
3. Any other reason why, in the opinion of the investigators, the patient should not participate.

6. Location

We will invite the other university centres in Norway to suggest and refer eligible patients. Assessment for eligibility, inclusion and surgical interventions will take place at OUH.

6.1. Determination of sample size

We estimate an overall survival of 12 months in the standard care group. We aim to decide whether resections added to chemotherapy can increase this to 24 months in a phase-II trial. A one-sided parallel-group test of proportions to answer this with a power of 0.80 and an alpha of 0.15, will require 19 completed patients per group to show superiority for the group where resections are added to chemotherapy. This is based on a three-year accrual time, and a total of five-year follow-up from the first patient, ensuring at least two years follow-up for all patients. Adding 15 % to allow for drop-outs, we aim to randomise a total of 44 patients in a 1:1 ratio, i.e. 22 patients per group.

6.2. Ethical considerations

With the treatment offered today, the prognosis is dismal for the patients eligible for this trial. In addition, second line systemic chemotherapy has a low response-rate and is associated with side-effects. While resections are offered to selected patients in this group, we have very limited data to support the benefits of such a strategy. Approval from regional ethics committee (REK) will be secured.

7. Impact

7.1. The knowledge gap and potential impact

The patients eligible for this trial have a prognosis with today's treatment on par with the most aggressive tumours i.e. an estimated survival of about 10-12 months. As such, almost any improvement will be of high value to a large group of patients where there are few survivors to announce their predicament and advocate their needs. Modern treatment of CRLM has indeed resulted in improved outcomes but benefits primarily those who respond to 1st line chemotherapy and undergo surgical resection. Patients with no or very poor response to chemotherapy frequently undergo attempts at resections for want of better alternatives. Rapid recurrences mean the patients have a net loss of quality-of-life (QoL) and testify to the futility of this approach. It is also a poor use of society's resources.

7.2. Dissemination, communication and exploitation strategy

All results will be published in peer-reviewed international papers.

The implications of our findings will primarily answer to whether alternative treatment strategies may significantly improve overall survival for the patients in the *grey zone*, i.e. patients with heavy tumour burden and unfavourable biological traits.

8. Implementation

8.1. Project manager and project group

The study group is listed below. It comprises top level expertise in liver resectional surgery (open and minimally invasive), CRLM oncology, health economics, RCT-methodology and outcomes research.

The study PI and lead researchers (KL and SD) head the surgical and oncological interventions at the OUH program (HPB) that currently perform about 450 interventions for liver malignancies (300 resections and 150 non-resectional interventions for liver malignancies) per year. This collaboration, combined with the Norwegian one-payer system, ensures that Norway is one of the very few countries in the western hemisphere where a trial like this can be done.

Kristoffer Lassen	MD, PhD. Project manager/PI.	Chief consultant surgeon HPB-surgery, OUH/Rikshospitalet and professor at the University of Tromsø. Has experience in running large surgical RCTs and chairs the Norwegian Gastrointestinal Cancer Group for liver- and pancreatic surgery (NGICG-HPB) and the Norwegian Quality Register for Gastrointestinal Surgery (NoRGast). Supervisor PhD-candidate
Svein Dueland	MD, PhD, lead researcher	Consultant oncologist at OUH/Rikshospitalet. He has led several studies on liver transplants for CRLM and published expensively on the subject. Will oversee use of chemotherapy in the trial. Co-supervisor PhD-candidate. Main liaison with the oncology group at MSKCC.
Bård Røsok	MD, PhD, researcher	Consultant surgeon at OUH/Rikshospitalet. Has experience in running large surgical RCTs.
Åsmund A.Fretland	MD, PhD, researcher	Consultant surgeon at OUH/Rikshospitalet and the Intervention Centre (IVS). Has experience in running large surgical RCTs.
Kristoffer W. Brudvik	MD, PhD, researcher	Consultant surgeon at OUH/Rikshospitalet. He will oversee inclusion, allocation and follow-up (with KL) and supervise cancer specialist study nurses (with SD). Co-supervisor PhD-candidate
Eline Aas	Msc., PhD	Health economist. Will perform health economy and QoL analyses to calculate cost for society and quality adjusted life years (QALYs).
John Christian F. Glent	MD, PhD-candidate	Fellow surgeon at OUH/Rikshospitalet. He will be responsible for patient recruitment and allocation, and the day-to-day running of the trial. Will perform analyses and write the scientific publications as 1st or 2nd author.

8.2. Project organization and management

Milestone	**Contributions/expertise**
2018: Study group formation	Surgery, oncology, RCT-methodology, health economy (KL/SD/BR/ÅAF/KWB/EAA)
2018-2020: WP1 Preparations	Protocol preparation (KL/SD) REK approval (SD/KL)
2020: Management group formation	Surgery, oncology (KL/SD/BR/ÅAF/KWB) + study nurses and PhD-candidate (TBA)
2021-2023: WP2 Trial inclusion, treatment and follow-up	PhD-candidate (and supervisors/management group) + study nurses
2021-2024: WP3 Data accrual and analyses	PhD-candidate (and supervisors/study group) + study nurses
2022-2024: WP4 Manuscript preparation and dissemination	PhD-candidate (and supervisors/study group)

8.3. User involvement

The patient group targeted by this project has few long-term survivors. CRLM patients have no dedicated organization that will speak for them in the competition for grants, time, efforts and new knowledge. We base our efforts on the daily encounters with these patients as surgeons and oncologists. This project is the latest of a series of studies on unresectable or marginally resectable patients. User involvement has been established for several years in these projects. Patients and family members have reviewed protocols, consent form and questionnaires and offered views on details and perspective and will do so also for this trial.

It is our view that this should be further expanded. Efforts to increase survival must achieve this without compromising social independence and QoL. While studying feasibility of a new treatment strategy will be supported by the patients and their next of kin, the interpretation of results and post-trial implementation will need a careful assessment of preferences. As illustrated by the inclusion/exclusion criteria, the targeted group in this trial is not unequivocally described. The boundaries of the *grey zone* are blurred and if resection proves beneficial within the trial, the generalizability (external validity) may not be obvious. Extrapolating results to other groups of patients with different combinations of metastases (numbers, size, mutations) or other liver cancers (cholangiocarcinoma) must be balanced against patient experiences from the trial and patient preferences. We believe this assessment of preferences is well suited for user involvement. As the patients will have many repeated contacts with our department, we will discuss this with recruited patients both during and after the trial itself and attempt to establish an advisory user board.

8.4. Project infrastructure

The participating departments/sections will provide the definitive treatments (resection, systemic chemotherapy within existing budgets/reimbursements. All patients will be admitted and treated at OUH/Rikshospitalet.

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