BRECLIM

Breast Cancer Liver Metastasis

A multicentre randomized clinical trial investigating local treatment for breast cancer liver metastasis

Protocol Version	2020-09-14
Trial registration	ClinicalTrials.gov Identifier: NCT04079049 Cancer studies in Sweden (cancercentrum.se) #88154
Trial funding	Swedish Breast Cancer Association Swedish Research Council
Methodology:	Multiple Center Randomized Clinical Trial
Study Duration:	The planned duration of study participation for an individual subject from inclusion to follow-up are at least 3 years
Study Centers:	Norrlands University Hospital Umeå Sahlgrenska University Hospital Gothenburg Skane University Hospital Lund Akademiska University hospital Uppsala University Hospital of Linkoping Karolinska University Hospital Huddinge
Primary Investigator:	Oskar Hemmingsson (Umeå)
Study coordinating group	Oskar Hemmingsson (Umeå) Malin Sund (Umeå) Anne Andersson (Umeå) Helena Taflin (Göteborg) Marcus Sundén (Sunderbyn)
Statistician	Per Liv (Umeå)
Data Management	Mats Hellström (Stockholm)
Project coordinator	Lisette Marjavaara and Emma Wede (Umeå)
Study nurse coordinator	Agneta Karhu (Umeå)
Local Investigators surgery:	Oskar Hemmingsson (Umeå) Helena Taflin (Gothenburg) Per Sandström (Linköping) Bengt Isaksson (Uppsala) Christina Villard (Stockholm) Bodil Andersson (Lund)
Local Investigators oncology:	Anne Andersson (Umeå) Cecilia Remling (Gothenburg) Ahmed Albu-Kareem (Linköping) Henrik Lindman (Uppsala) Theodoros Foukakis (Stockholm) Farnaz Lindqvist (Lund)
Safety committee	*Representative for surgery* *Representative for oncology* *Representative for statistics*
Study monitor	Clinical trial unit Umeå

Objective(s)/ Outcome(s):	Primary endpoint: 1. Time to death from any cause Secondary endpoints: 1. Three years survival 2. Progression free survival 3. Median overall survival 4. Breast cancer specific survival 5. Overall complications 6. Quality of life 7. Prognostic factors
Number of Subjects:	200 patients, 100 in each arm
Inclusion Criteria:	§ 1-4 liver metastasis amendable to surgery with functional liver remnant volume >30%. § Signed informed consent § >18 years old § ECOG 0-1 § Breast cancer history § Breast cancer liver metastasis verified by biopsy § Patient amendable for liver surgery and pre- and postoperative oncological treatment
Exclusion Criteria:	§ Previous or present non-skeletal extrahepatic disease § Pregnancy § > 4 liver metastases on preoperative or previous examination § Progression of disease upon oncological treatment
Study Schedule:	First-Subject-In is planned in 2020 Last-Subject-In is planned for 2026 Last-Subject out is planned for 2029
Ethics approval	Sweden. Dnr 2018-116-31M and 2019-05717
Web	https://www.umu.se/en/research/projects/the-breclim-trial/

Purpose and aims

Breast cancer is the second most common cancer in Sweden with an incidence of 8000 per year. Even though the majority is cured from the disease it is the cause of death for 1400 patients in Sweden each year (1). Breast cancer is treated by a combination of surgery, radiotherapy, and (neo-) adjuvant treatment including chemotherapy, endocrine and targeted therapies. The role of surgery for distant breast cancer metastasis beyond local lymph nodes remains controversial even though some reports suggest there might be a survival benefit from resection of oligometastases in the liver.

The purpose of this multicentre randomized clinical trial is to evaluate local treatment for breast cancer liver metastases, compared to systemic oncological treatment only. The primary endpoint is time to death from any cause, which will be compared using cox proportional hazard regression. The secondary endpoints are three years survival, progression-free survival, median overall survival, breast cancer specific survival and quality of life. The aim is also to evaluate overall safety and predictive factors for survival during oncological and surgical treatment. The overall purpose is to ameliorate treatment for advanced breast cancer.

Survey of the field

Most patients with breast cancer liver metastasis (BCLM) receive only medical treatment today. Isolated BCLM are found in at least 5% of patients with advanced breast cancer (3). This equals to about 70 patients per year in Sweden. Only 5 patients were operated for BCLM per year in Sweden 2009-2016, according to the national registry for liver surgery.

A systemic review on liver resection for BCLM summarizes 43 studies with 1686 patients and reports a median overall survival of 36 months and a 3-year survival of 56% (2). Both Swedish and European guidelines conclude that the value of surgical or other local treatment for BCLM is unknown and that a randomized trial is needed (3, 4). Opponents to surgery argue that the published material has a low level of evidence and surgery could interrupt oncological treatment.

Most previous studies are based on results from a single centre. There are only four studies with a control cohort of patients receiving oncological treatment only. In a retrospective case-control trial including 102 patients with a maximum of four BCLM who were stable or responded on oncological treatment (5), a multivariate analysis showed 3.04-fold increased risk of death in the oncological group. In contrast, Sadot et al, compared 67 operated patients to 98 patients only receiving medical treatment (6). Despite more positive prognostic factors in the surgical cohort, there was no survival advantage.

We recently conducted a retrospective study on nationwide cohorts from Swedish quality registers (*7*). We concluded that liver surgery for BCLM in Sweden is safe but rare. The study showed a significantly longer survival among operated patients compared to those who received medical treatment. When adjusting for prognostic factors, there was still a tendency towards a better prognosis after surgery but the result was no longer significant. A randomized trial without selection bias is needed to evaluate if there is a true difference in survival.

Study design

This is a randomized trial comparing local treatment of liver metastases in addition to oncological treatment versus medical oncological treatment only. A prospective randomized trial is chosen to avoid selection bias. A flowchart describes the schedule (figure 1).

Oncological treatment
Participants in both arms receive oncological treatment. Oncological breast cancer treatment is based on the molecular subtype of the tumour and follows established principles according to the national guideline (3). All participants are discussed at multidisciplinary conferences as in general clinical practice to optimize treatment. Chemotherapy is given for two months while hormonal therapy is given for three months. Those who are stable or respond to treatment are randomized to either surgery followed by oncological treatment or oncological treatment only.

Local treatment
Liver surgery or ablation is performed at one of the six study centres, in accordance with the routine at the centre. Radiofrequency ablation or microwave ablation are alternative treatment options to resection for metastases of a maximum size of 2 and 3 cm respectively. Stereotactic body radiotherapy (SBRT) for the liver metastasis can be considered when surgery or radiofrequency-/microwave ablation is not possible. The SBRT should be performed at a radiotherapy department with experience of this treatment. It should be guided by fiducial markers and the dose should be ablative (e.g. 45Gy in 3 fractions).

Participants will be followed by CT every 3 months the first year and every 6 month the following 2 years.

Population:	200 patients with 1-4 BCLM and no extrahepatic disease (except bone metastases) who are stable or respond to oncological treatment.
Intervention:	Local treatment of BCLM by surgical resection, ablation or stereotactic radiotherapy, followed by oncological treatment.
Comparison:	Oncological treatment.
Outcome:	Participants will be followed for at least three years. The primary endpoint is time to death from any cause, which will be compared using cox proportional hazard regression.
Hypothesis:	Local treatment for breast cancer liver metastases improves overall survival, compared to standard medical treatment only.

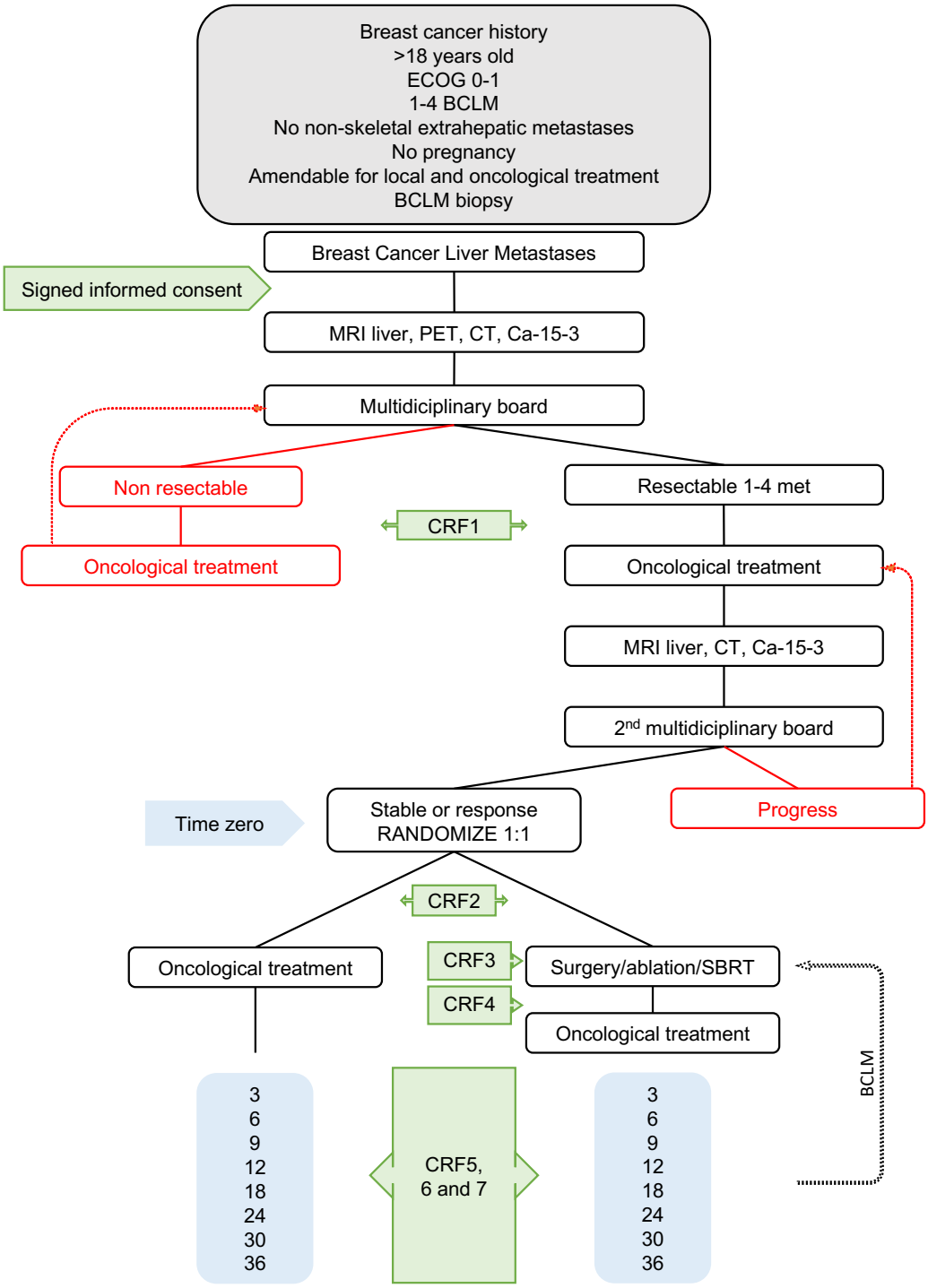
Breast cancer history
>18 years old
ECOG 0-1
1-4 BCLM
No non-skeletal extrahepatic metastases
No pregnancy
Amendable for local and oncological treatment
BCLM biopsy
Breast Cancer Liver Metastases
Signed informed consent
MRI liver, PET, CT, Ca-15-3
Multidiciplinary board
Non resectable
Resectable 1-4 met
CRF1
Oncological treatment
Oncological treatment
MRI liver, CT, Ca-15-3
2nd multidiciplinary board
Time zero
Stable or response
RANDOMIZE 1:1
Progress
CRF2
Oncological treatment
CRF3
CRF4
Surgery/ablation/SBRT
Oncological treatment
BCLM
3
6
9
12
18
24
30
36
CRF5,
6 and 7
3
6
9
12
18
24
30
36

Figure 1.

Research questions

1. Is there a survival benefit of local treatment of BCLM by liver resection, ablation or stereotactic radiotherapy, compared to oncological treatment only? We will primarily compare time to death from any cause and calculate the hazard ratio in each arm, adjusted for known predictive factors. Secondary endpoints are three years overall survival after randomization, median overall survival, progression free survival and breast cancer specific survival.
2. What is the complication rate for each treatment and what kind of complications arise? 30-days and 90-days mortality after surgery will be determined and complications will be described and graded by the Clavien-Dindo score. Chemotherapy toxicity will be graded by the CTC 4.03 scale.
3. What are the predictive factors for survival after surgical and/or oncological treatment of BCLM? Predictive factors for survival (described on page 4) will be analyzed in a cox proportional hazards model.
4. How is quality of life influenced in BCLM patients after surgical treatment compared to oncological treatment? EORTC QLQ-C30 and QLQ-LM21 will be followed at inclusion, and follow up 3, 12 and 24 months after randomization. Quality of life will be analyzed using an ordinal proportional odds regression model.

Variables and measures

Variables are collected in electronic case report forms (CRFs) as in figure 1 and table 1. CRF 1 and 2 are divided into section A and B with variables in A related to liver surgery and in B to breast oncology. CRF 3 and 4 is only for those randomized to local treatment.

CRF1	Registration. Ca 15-3. Performance status. Somatic comorbidities.
	1a BCLM characteristics
	1b Breast cancer characteristics and. Oncological and surgical breast cancer treatment of prior to inclusion.
CRF2	2a Liver metastases after oncological treatment. Evaluations of response according to RECIST 1.1 (9).
	2b Oncological treatment after inclusion.
	2c. Result of randomization.
Only for those randomized to local treatment	
CRF3	*Local treatment.*
CRF4	*Complications (30-day) according to Clavien-Dindo and the CTC 4.03 scale. Pathological anatomical diagnosis of liver metastases including ER, PgR, Her2. Total number of days at hospital.*
CRF5	Follow up 3, 6, 9, 12, 18, 24, 30, 36 months (5a-h). Oncological treatment and grading of complications by the CTC 4.03 scale. Secondary intervention against metastases. Performance score. Quality of life 3, 12 and 24 months.
CRF6	Recurrence. Progression.
CRF7	End of study. Vital status.

For survival analyses, the primary endpoint is time from randomization to death from any cause. Secondary endpoints are three years overall survival, progression free survival, breast cancer specific survival and median overall survival. Disease progression will be evaluated at each radiology control. This analysis cannot be blinded since radiologists can see signs of previous liver resections. Survival will primarily be evaluated in an intention to treat manner and secondary in a per protocol analysis.

To study safety and complications, 30-days and 90-days mortality after surgery will be determined and complications will be described and graded by the Clavien-Dindo score. Chemotherapy toxicity will be graded by the CTC 4.03 scale.

To study predictive factors, patient related factors (age and comorbidity), primary tumour related factors (size, histology, molecular subtype) and factors related to the metastatic disease (number, size, locations, molecular subtype, response to treatment, disease free interval) will be related to survival. Hormonal receptor status will enable characterization of the molecular subtype of the primary tumour. To predict outcome, they will be classified according to the St Gallen classification; Luminal A, Luminal B (HER2- positive), Luminal B (HER2-negative), HER2- enriched (non- luminal) and triple-negative breast cancer.

Quality of life will be registered by EORTC QLQ-C30 and QLQ-LMC21 at inclusion, and follow up 3, 12 and 24 months after randomization. QLQ-LMC21 will be added to the study when available in Swedish.

STUDY PLAN	**Breast Cancer MDT**	**1st visit info**	**1st Liver Surgery MDT**	**Oncol. treatm.**	**2nd Liver Surgery MDT**	**Local treatm. or oncol. treatm.**	**Postop visit**	**Follow up 3 months**	**Follow up 6, 9, 12 months**	**Follow up 18, 24, 30, 36 months**
Time					0			3	6, 9, 12	18, 24, 30, 36
Admission		X		X		X	X	X	X (12m)	X (24m, 36m)
Randomization					X					
CRF		1			2	3	4	5 (6, 7)	5 (6, 7)	5 (6, 7)
Informed consent and inclusion		X								
Randomization					X					
MRI liver, liver contrast		X			X					
CT thx-abdomen		X			X	X (only liver and only post ablation)		X	X	X
PET-CT		X								
RECIST 1.1					X					
CA 15/3 (recom-mended)	X					X		X	X (12M)	X (24M)
Biopsy of metastasis	X									
Histology	X					X (surgery)				
QoL EORTC QLQ C30		X						X	X (12M)	X (24 M)

Table 1.

Material: Patient selection

Inclusion will start in all six regional cancer centres in Sweden.

Inclusion criteria	§ Signed informed consent § >18 years old § ECOG 0-1 § Breast cancer history § Breast cancer liver metastasis verified by biopsy § Patient amendable for liver surgery and pre- and postoperative oncological treatment § 1-4 liver metastasis amendable to surgery with functional liver remnant volume >30%
Exclusion criteria	§ Previous or present non-skeletal extrahepatic disease § > 4 liver metastases on preoperative or previous examination § Pregnancy § Progression of disease upon oncological treatment

Participants will be randomized by an oncologist at a study centre. Participants will be stratified on study centre. Randomization and stratification will be computer-based and administered upon the study website. The 1:1 allocation of participants into groups will be performed in random blocks, with random block sizes of 2 to 6. The study website will apply the Pheedit system and provide electronic CRFs. Each site coordinator will have access to the website and will be able to include and randomize participants. Non-participants who fulfill inclusion criteria will be registered by date, initials, clinic and date of birth.

Estimated sample size and power

Based on preliminary results from a nationwide retrospective study (7) and the most recent case series, we assume that the overall 3-year survival to be approximate 40% averaged across both groups. Mariani et al (5) conducted a case control study of a population similar to the inclusion criteria in this study and detected RR 3.04 (CI: 1.87-4.92) in a multivariate cox regression analysis in favour of liver surgery. A smaller reduction of risk is clinically relevant but the challenge of this study is to recruit participants. In order to reach a power of 80 % to detect a hazard ratio of 1.9 with a significance level of 0.05, 190 study participants are required. Under the assumption of a drop-out rate of 5%, we therefore intend to include 200 participants in total. The sample size calculation is made assuming an unadjusted analysis. In the analysis of the primary outcome, model adjustments for baseline covariates will be made (age, molecular subtype of primary tumour, TNM-stage of primary tumour, disease free interval, single or multiple BCLM and presence of bone metastases yes/no). As these covariates are well known prognostic factors, we expect this to give additional gain in power or equivalent opportunity to detect smaller hazard ratios (8). Based on results from a nationwide retrospective study (7) and the most recent case series we assume that the secondary endpoint 3-years survival will be 30% in the control arm (oncological treatment only) and 50% in the treatment arm (surgery and oncological treatment). To reach 80% power with a 5% drop out rate and a level of significance $p<0.05$, the total study population is calculated to 200 participants also in this analysis.

Isolated oligometastases in the liver affect about 5% of those with advanced breast cancer. This corresponds to 70 patients per year in Sweden. We assume that we can include 50% of these, thus 35 per year. The study will be open for recruitment from centres outside of Sweden with a further specified protocol for surgical and oncological treatment and additional ethical review.

The study will be open for recruitment during 8 years and participants will be followed for at least 3 years. Interim analyses will be performed by the safety committee after inclusion of 100 participants. If the primary endpoint is reached at the interim analysis, the study will be

stopped and participants in the control arm will be allowed to cross over. If the study reaches a non-significant result in the end of the study it may be prolonged according to a new power calculation and a second ethical review.

Statistical methods

The primary outcome, time to death for any cause, will be visualized in a Kaplan-Meier plot and analyzed using Cox proportional hazard regression. The null hypothesis to be tested is that the hazard for the intervention group is equal to the hazard of the control group, in a two-sided test. A random effects model will be applied with study centre as random effect. Adjustments will be made for age, molecular subtype of primary tumour, TNM-stage of primary tumour, disease free interval, single or multiple BCLM and presence of bone metastases (yes/no) for the purpose of increasing precision and statistical power in analysis. Age will be modelled as a continuous variable using natural cubic splines with three nodes distributed at the 10th, 50th and 90th percentile of the age distribution to account for non-linear effect. The significance level will be set at 0.05.

Three years survival will be analyzed using logistic regression, adjusted for the same covariates as above,
Progression free survival and breast cancer specific survival will be analyzed using cox regression, as described for the primary outcome.
Predictive factors for survival will be analyzed in a cox proportional hazards model.
Quality of life will be analyzed using a ordinal proportional odds regression model.

Per Liv, PhD and statistician at Registercentrum Norr, will be responsible for the statistical analysis plan.

Ethics

Approval was granted from the ethics committee Dnr 2018-116-31M.
An amendment included

- § stereotactic body radiation therapy
- § earlier inclusion for intention to treat analysis
- § updated primary endpoint time to death instead of three years survival
- § updated statistical analysis and stratification
- § updated information to participants

The amendment was approved 2020-03-10 Dnr 2019-05717

Time plan

The study will be open for recruitment up to 8 years and participants will be followed for 3 years. The study will start January 2020.

Project organisation

A study coordinating group has written the protocol and organized the trial (Oskar Hemmingsson, Malin Sund, Anne Andersson, Helena Taflin and Marcus Sundén). There is one liver surgeon in each of the six regional cancer centres in Sweden responsible for the study;

- Oskar Hemmingsson (Umeå)
- Helena Taflin (Gothenburg)
- Per Sandström (Linköping)
- Bengt Isaksson (Uppsala)
- Christina Villard (Stockholm)
- Bodil Andersson (Lund).

There is one oncologist in each of the six regional cancer centres in Sweden responsible for the study;
Anne Andersson (Umeå)
Cecilia Remling (Gothenburg)
Ahmed Albu-Kareem (Linköping)
Henrik Lindman (Uppsala)
Theodoros Foukakis (Stockholm)
Farnaz Lindqvist (Lund)

The clinical trial unit at Umeå University Hospital will monitor the study in collaboration with clinical trial units at participating hospitals. An external data monitoring committee and safety committee will be appointed. Per Liv, PhD and statistician at Registercentrum Norr, will be responsible for the statistical analysis plan. Mats Hellström, Centrum för kliniska cancerstudier, Karolinska University Hospital, provide support to build a pheedit database for the study. A safety committee consisting of a surgeon, an oncologist and a statistician will follow the study. They will perform an interims analyses after inclusion of 100 participants.

Specific intermediate objectives

After 18 months (June 2021), the following parameters will be reported to funding agencies;
° Publication of study protocol.
° Number of screened patients who fulfill inclusion criteria (estimated 100).
° Number of recruited participants (estimated 50).
° Number of recruited participants with complete CRF1 (estimated 50).
° Number of sites with included participants (estimated 6).
All additional information on request.

Papers and authorships

Paper 1. Study description. The study coordinating group (OH, MS, HT, MS, AA) will publish paper 1.

Paper 2. RCT survival.
For paper 2, in addition to the study coordinating group (OH, MS, HT, MS, AA), each participating study site will have two co-authors.

Paper 3. QoL

Paper 4. Prognostic factors.

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