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Surgical treatment of breast cancer liver metastases - A nationwide registry-based case control study

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ABSTRACT

Introduction: The benefit of liver resection or ablation for breast cancer liver metastases (BCLM) remains unclear. The aim of the study was to determine survival after isolated BCLM in nationwide cohorts and compare surgical versus systemic treatment regimens.

Materials and methods: The Swedish register for cancer in the liver and the bile ducts (SweLiv) and the National register for breast cancer (NBCR) was studied to identify patients with 1–5 BCLM without extrahepatic spread diagnosed 2009–2016. Data from the registers were validated and completed by review of medical records. A Kaplan-Meier plot and log rank test were used to analyse survival. Prognostic and predictive factors were evaluated by Cox regression analysis.

Results: A surgical cohort (n = 29) was identified and compared to a control cohort (n = 33) receiving systemic treatment only. There was no 90-day mortality after surgery. Median survival from BCLM diagnosis was 77 months (95% CI 41–113) in the surgical cohort and 28 months (95% CI 13–43) in the control cohort, (p = 0.004). There was a longer disease-free interval and more oestrogen receptor positive tumours in the surgical cohort. Surgery was a significant positive predictive factor in univariate analysis while a multivariable analysis resulted in HR 0.478 (CI 0.193–1.181, p = 0.110) for surgical treatment.

Conclusion: Surgery for BCLM is safe and might provide a survival benefit in selected patients but prospective trials are warranted to avoid selection bias.

Introduction

Metastatic breast cancer (MBC) is the cause of death for 1400 patients every year in Sweden and 522 000 globally [1,2]. Isolated breast cancer liver metastases (BCLM) are found in 5% of all with MBC [3]. Despite advances overall in treatment of breast cancer, prognosis remains poor for patients with BCLM, with a median survival of 2–3 years [4].

The role for liver resection and ablation in modern treatment of BCLM remains unclear. Several case series [5–9] indicate a survival benefit if liver surgery or ablation is used for BCLM in conjunction with systemic therapy. Moreover, these studies and review articles have shown that liver surgery for BCLM is safe [10–14]. Prognostic factors useful for selecting patients eligible for surgery have been described [15–21], and include single metastases, metastases limited to the liver, oestrogen positive breast cancer, non-triple negative tumours and good response to systemic treatment.

Opponents to liver resection and ablation for BCLM argue that the published studies have a low level of evidence and that liver surgery could delay, or interrupt systemic treatment. There are no randomized clinical trials available, but this is warranted according to the latest European guidelines for treatment of advanced breast cancer [4]. This study explores available nationwide retrospective

Abbreviations: BCLM, breast cancer liver metastases; SweLiv, Swedish registry for cancer in the liver and the bile ducts; NBCR, National breast cancer register; MBC, Metastatic breast cancer.

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data to prepare for such prospective trial. In published case series, the numbers of included patients are small, usually treated at single institutions; thus there is an inherent risk for selection bias. There are only three reports that have a control group of patients receiving systemic treatment only, and these show conflicting results regarding the value of liver surgery [22–24].

This is a nationwide registry-based study where surgically treated patients are compared to a control group receiving systemic treatment alone. The primary aim was to investigate whether there is a survival benefit for patients undergoing liver resection or ablation for BCLM. Our hypothesis is that local treatment for BCLM improves survival for patients with BCLM. The secondary aims were to study safety and prognostic factors for survival in the surgically treated group.

Method

Two national cancer registries, the Swedish registry for cancer in the liver and bile ducts (SweLiv) and the National breast cancer register (NBCR) were used to identify patients with BCLM. SweLiv was founded in 2009 and includes all primary tumours in the liver as well as all liver resections and ablations for primary cancers and/or metastatic disease. The NBCR was founded in 2008. Both registries have a high coverage (>90%) for inclusion, but NBCR has a lower coverage in the follow-up form where metachronous metastases are registered.

Inclusion criteria were history of breast cancer and one to five BCLM. Patients with bilateral or recurrent breast cancer were excluded in the analysis, since it was unknown which cancer metastasized, disabling studies of survival and prognostic factors. Patients with extrahepatic metastases were excluded. All molecular subtypes of breast cancer were included.

Patients with BCLM were identified from the NBCR. In order to identify an accurate control group, imaging reports within three months prior to the date of liver metastasis diagnosis were studied and patients having more than five BCLM or extrahepatic disease were excluded. The following information was retrieved from NBCR and patients records; date of diagnosis of primary tumour and BCLM, age at diagnosis of BCLM, primary tumour size, axillary nodal status, oestrogen and progesterone hormonal receptor status, human epidermal growth factor-2 (HER2) amplification, vascular ingrowth, histological grade and adjuvant oncological treatment. The following parameters were collected from the SweLiv registry; number of metastases, size of the biggest metastasis, neoadjuvant treatment, age at time of surgery, complications and 90-day mortality.

All patients were followed until 2017-12-31 or death, whichever came first. Vital status and date of death was retrieved from the registries. Survival was calculated both from time of breast cancer diagnosis, and from the time of liver metastasis diagnosis.

Descriptive statistics was used to describe both cohorts concerning baseline data (Table 1). Comparisons were made using Chi square test or independent value T-test. To calculate and compare survival, a Kaplan-Meier plot and log rank test was used. Prognostic and predictive factors were evaluated by Cox regression analysis. All variables with a p-value ≤ 0.2 in the univariate analysis were used in the multivariable analysis. A p-value ≤ 0.05 was considered significant. Missing data were considered missing at random. No imputation was performed.

All statistical analysis was made using SPSS Statistics version 25.0, IBM. The study was approved by the Regional Ethical Review Board in Gothenburg (DNR 398–16).

Results

Surgical cohort

In SweLiv, a total of 101 patients had surgery for BCLM or metastases from an unknown primary tumour between 2009 and

Table 1
Characteristics of the study cohorts.

Characteristics	Surgical cohort n = 29	Control cohort n = 33	p-value
Female sex	29 (100%)	33 (100%)	
Age at diagnosis of metastases	54 (26–78)	58 (28–86)	0.329
Number of metastases			
Single	19 (65.5%)	23 (69.7%)	0.725
Multiple	10 (34.5%)	10 (30.3%)	
BC ER receptor status			
Neg	9 (40.9%)	24 (75.0%)	**0.012**
Pos	13 (59.1%)	8 (25.0%)	
BC PgR receptor status			
Neg	11 (55.0%)	16 (51.6%)	0.813
Pos	9 (45.0%)	15 (48.4%)	
BC HER 2			
Neg	11 (55.0%)	23 (71.9%)	0.213
Pos	9 (45.0%)	9 (28.1%)	
BC NHG			
I	0 (0.0%)	0 (0.0%)	0.102
II	6 (30.0%)	17 (53.1%)	
III	14 (70.0%)	15 (46.9%)	
BC Vascular invasion			
No	7 (53.8%)	18 (72.0%)	0.263
Yes	6 (46.2%)	7 (28.0%)	
Size of BC			
<20 mm	9 (50.0%)	10 (33.3%)	0.253
>20 mm	9 (50.0%)	20 (66.7%)	
Axillary met BC			
No	5 (31.3%)	12 (37.5%)	0.670
Yes	11 (68.8%)	20 (62.5%)	
Time from BC to metastases (months)*	48 (0–251)	20 (2–68)	**0.032**

BC, primary breast cancer; BC ER, oestrogen receptor status of primary breast cancer; BC PgR, progesterone receptor status of primary breast cancer; BC HER 2, HER 2 gene amplification of primary breast cancer; BC NHG, Nottingham grade of primary breast cancer.
*range.

2016. Twenty-six of those were registered as BCLM. By review of patient records and pathology reports from the metastases classified as being of unknown origin, six additional patients with BCLM were identified. In total, only 32 patients had undergone surgical treatment for BCLM in Sweden 2009–2016. One patient was excluded due to more than five metastases and two patients because of earlier radiation therapy against liver metastases. Thus, the final surgical cohort consisted of women with a history of breast cancer with liver metastases without any extrahepatic manifestations (n = 29), (Fig. 1). Twenty-one of the patients that underwent surgery were given neoadjuvant treatment, with nineteen responding to treatment. No information is available about the specific type of medical treatment regimen. Twenty-four resections and five ablations were performed. Eight patients had a hemihepatectomy and the remaining sixteen had a segmentectomy or an atypical resection. Mean diameter of the metastases was 34 mm. No portal embolization was performed. Seventeen resections were radical (R0) while six were uncertain (R1). The remaining six, including the ablations, had no data concerning radicality.

Control cohort

During the same time period (2009–2016) a total of 540 patients were registered in NBCR with BCLM. Out of these, 297 patients were registered as having synchronous extrahepatic metastases and were therefore excluded. Another six patients were excluded due to recurrent breast cancer. The remaining control cohort consisted of 237 patients. After review of reports from radiology performed within three months prior to the diagnosis of metastasis, the following exclusions were made; extrahepatic metastases not registered in NBCR (n = 82), more than five metastases (n = 129) or lack of adequate imaging reports (n = 53). The final control cohort thus consisted of 33 patients (Fig. 1).

Table 1 shows baseline characteristics for the two cohorts. Mean age at time of surgery was 54 years. Mean age in the control group at time of diagnosis of the liver metastases was 58 years. About two thirds in both groups had a single metastasis (19 of 29 in the operated group and 23 of 33 in the control group). There were significantly more oestrogen receptor positive tumours in the surgical cohort but there was no difference in percentage of triple-negative tumours; 23% and 26% in the surgical and control cohort respectively. Time from breast cancer diagnosis to diagnosis of liver metastases was significantly longer in the surgical cohort (48 months compared to 20 months). Both cohorts received systemic treatment but there is no information on oncological treatment regimens of BCLM in the registries. However, the medical treatment adjuvant to breast cancer surgery is specified for 28 patients (9 in the surgical cohort and 19 in the control cohort) and followed national guidelines in relation to TNM-status and molecular subtype.

Prognostic factors for survival

Cox regression analysis was used to analyse factors affecting survival after surgery for BCLM (Table 2). For the surgical cohort a univariate analysis identified HER2 gene amplification, oestrogen receptor positivity, progesterone receptor positivity, time from primary breast cancer to diagnosis of metastasis and complications as possible prognostic factors. Only HER2 gene amplification was

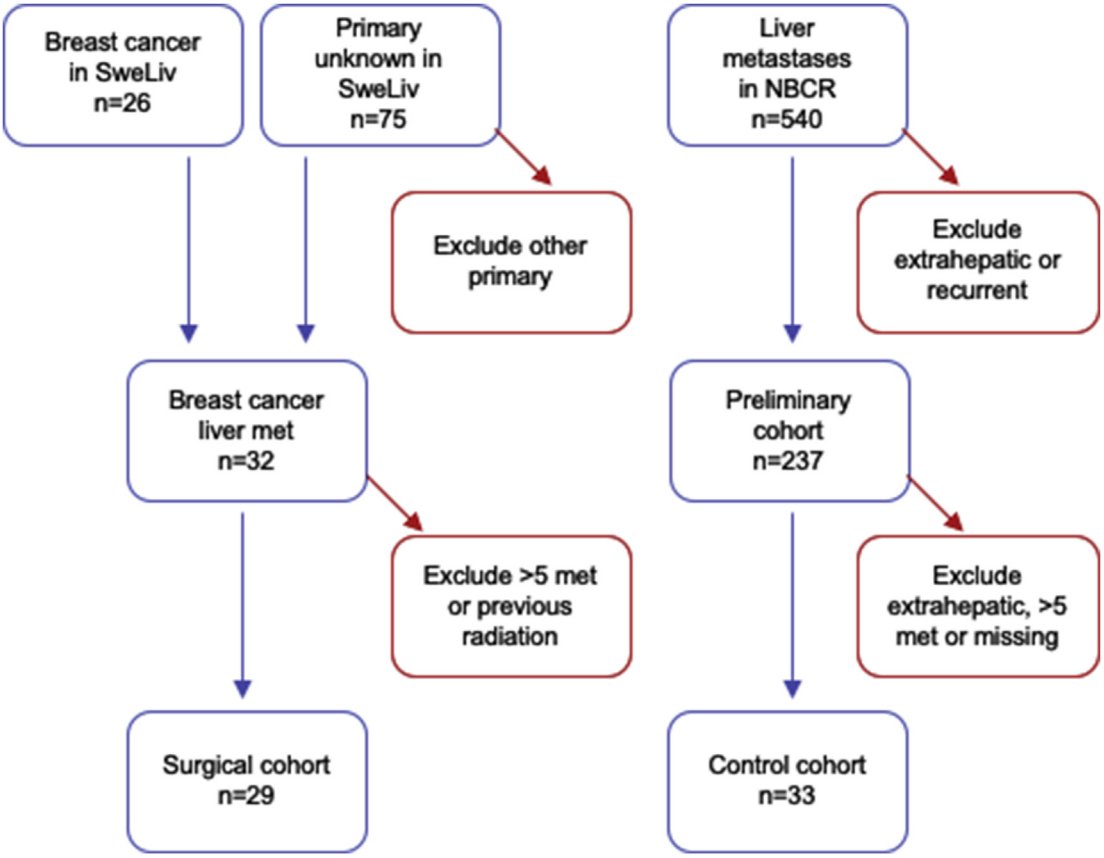

Fig. 1. Flowchart for selection of study cohorts. SweLiv, Swedish registry for cancer in the Liver and bile ducts. NBCR, national breast cancer registry.

Table 2
Prognostic factors for survival in the surgical cohort analysed with Cox regression analysis. Variables with p < 0.2 in the univariate analysis were used in the multivariable analysis.

Prognostic factors surgery group	Univariate analysis HR (95% CI); p-value	Multivariable analysis HR (95% CI); p-value
Age at time of breast cancer diagnosis (years)	0.989 (0.933–1.047); 0.694	
BC ER		
Negative	Ref 1.000	Ref 1.000
Positive	0.361 (0.095–1.374); **0.135**	1.846 (0.130–26.314; 0.651
BC PgR		
Negative	Ref 1.000	Ref 1.000
Positive	0.275 (0.054–1.386); **0.118**	0.051 (0.001–2.326); 0.127
BC HER 2		
Negative	Ref 1.00	Ref 1.000
Positive	0.124 (0.015–1.013); **0.051**	0.023 (0.001–0.777); **0.036**
BC NHG		
I	–	
II	Ref 1.000	
III	1.213 (0.250–5.893); 0.811	
BC vascular invasion		
No	Ref 1.00	
Yes	2.702 (0.477–15.317); 0.262	
Size of BC		
<20 mm	Ref 1.000	
>20 mm	1.256 (0.280–5.637); 0.766	
BC axillary metastases		
No	Ref 1.00	
Yes	1.015 (0.195–5.281); 0.986	
Number of metastases		
Single	Ref 1.000	
Multiple [2–5]	0.603 (0.166–2.197); 0.443	
Time BC to metastases (months)	1.005 (0.997–1.013); **0.190**	0.958 (0.093–14.703); 0.216
Complications		
No	Ref 1.000	Ref 1.000
Yes	3.921 (0.508–30.241); **0.190**	1.166 (0.093–14.703); 0.905

BC, primary breast cancer; BC ER, oestrogen receptor status of primary breast cancer; BC PgR, progesterone receptor status of primary breast cancer; BC HER 2, HER 2 gene amplification of primary breast cancer; BC NHG, Nottingham grade of primary breast cancer; HR, hazard ratio; CI, confidence interval.

significant for improved survival after surgery in a multivariable analysis.

Complications

There was no mortality within 90 days after surgery. Six (6 of 29) patients who underwent surgery were registered for a post-operative complication. The complications were bile leakage, intestinal obstruction, ascites, wound infection, other small bowel complication and one unspecified complication. No grading of the severity of the complications was available in the registry.

Survival

Survival was analysed in a Kaplan-Meier plot (Fig. 2) and by log rank test. There was a significantly better survival in the surgical cohort, both from date of breast cancer and date of liver metastases. Median survival from time of breast cancer diagnosis in the surgical and control cohorts was 136 months (95% CI 58–214) and 41 months (95% CI 27–55), respectively (p = 0.002). Median survival from time of diagnosis of liver metastases in the surgical and control cohorts was 77 months (95% CI 41–113) and 28 months (95% CI 13–43), respectively (p = 0.004). To adjust for differences between the cohorts, all patients from both cohorts were studied in a cox regression analysis (Table 3). Surgery was a positive predictive factor for survival in univariate analysis (HR 0.39 (C.I. 0.19–0.79)) but its significance was lost in the multivariable analysis (HR 0.478 (C.I. = 0.193–1.181).

Discussion

This study of a nation-wide cohort shows that surgical treatment of isolated oligometastatic BCLM is rare but safe and may prolong survival in selected patients although a prospective trial is warranted to avoid selection bias.

The strength of the present study is that the patients were recruited from national registries with good coverage. Both surgical and systemic treatment of breast cancer was given in several centres, while liver surgery in Sweden is centralized to six centres. Previous studies on surgery for BCLM are mainly single centre case series without a control group. Published case control studies have only included surgical cohorts from single centres and they have included patients over long periods with shifting systemic treatment regimens [22–24]. Systemic breast cancer treatment in Sweden is given according to national guidelines [3] and thus is relatively uniform. The patients were treated during the last 10 years with modern systemic treatment regimens, including anti-Her2 therapy when indicated.

The complication rate in this nationwide material was equal to other studies concerning liver surgery [25–27] and there was no 90-day mortality. A reasonable conclusion is that liver surgery for BCLM is safe when performed at experienced liver surgery centres.

In spite of the national coverage, a weakness of this retrospective study is the small number of patients. The liver registry SweLiv has a coverage >90% and we conclude that surgical treatment for BCLM is rare. In addition, despite a large initial source of patients for the control cohort, no more than 33 representative controls could be identified. Most excluded patients had either extrahepatic disease, multiple liver metastases or lack of valid imaging. The real incidence of oligometastatic BCLM in Sweden is higher, since distant metastases are registered on a follow-up form in NBCR with a low coverage in some regions.

Based on the incidence of advanced breast cancer in Sweden and the proportion developing isolated liver metastases [3], it can be

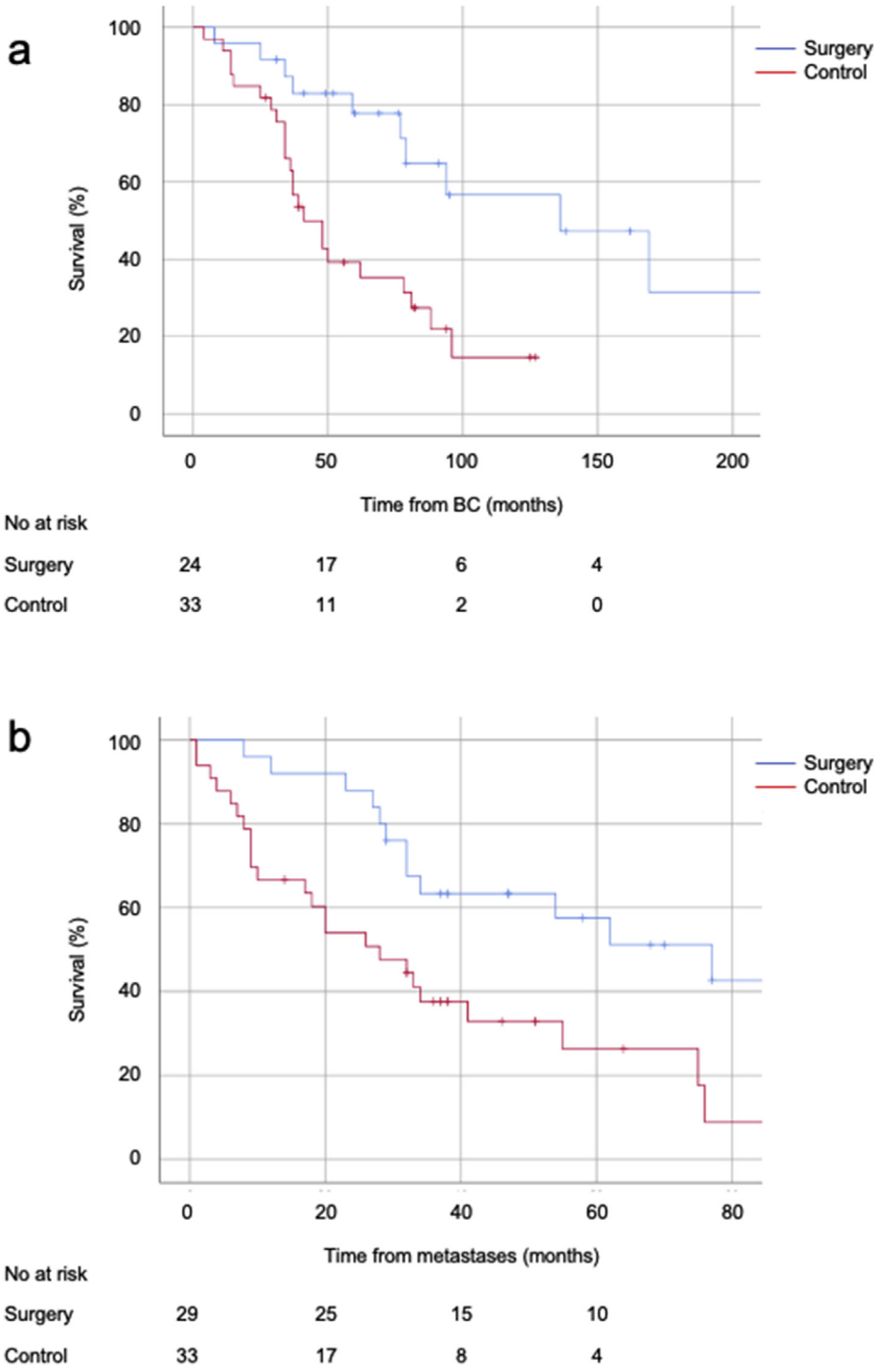

Fig. 2. Survival from primary breast cancer (BC) diagnosis (A). Survival from diagnosis of liver metastases (B).

estimated that 70 patients could be eligible for liver surgery for BCLM each year. Only five patients underwent surgery per year as shown here, meaning that an increased number of patients could potentially be offered surgical treatment if proven effective. During the study period, there was no tendency towards increasing number of operations for BCLM, despite the rise of liver surgery on other indications. Patients with BCLM and bone metastases could be considered for surgery since bone metastases can be stable for a long time [10]. This could further increase the number of patients with a possible benefit from surgery. The low number of patients undergoing liver surgery for BCLM might be explained by lack of evidence of improved survival. Due to this knowledge gap, there is currently no active surveillance of breast cancer patients to find potentially operable liver metastases.

In the present cohort, HER2 gene amplification was a positive prognostic factor for survival after surgery for BCLM. In previous studies, other prognostic factors were identified such as oestrogen receptor positivity, single metastasis and lack of vascular invasion [15–21]. The small number of patients included in this study might explain the discrepancy in these findings. HER2 gene overexpression

Table 3
Prognostic and predictive factors for survival in both groups analysed with Cox regression analysis. Variables with p < 0.2 in the univariate analysis were used in the multivariable analysis.

Prognostic factors both groups	Univariate analysis HR (95% CI); p-value	Multivariable analysis HR (95% CI); p-value
Age at time of breast cancer diagnosis (years)	1.012 (0.984–1.040); 0.418	
BC ER		
No	Ref 1.00	Ref 1.00
Yes	0.389 (0.177–0.854); **0.019**	0.781 (0.253–2.414); 0.668
BC PgR		
No	Ref 1.00	
Yes	0.70 (0.33–1.48); 0.355	
BC HER 2		
No	Ref 1.00	Ref 1.00
Yes	0.320 (0.131–0.784); **0.013**	0.414 (0.133–1.286); 0.127
BC NHG		
I	–	
II	Ref 1.00	
III	0.651 (0.324–1.307); 0.227	
BC vascular invasion		
No	Ref 1.00	
Yes	0.627 (0.245–1.604); 0.330	
Size of BC		
<20 mm	Ref 1.00	
>20 mm	1.505 (0.693–3.270); 0.302	
BC axillary metastases		
No	Ref 1.00	
Yes	0.912 (0.439–1.897); 0.806	
Number of metastases		
Single	Ref 1.00	
Multiple [2–5]	0.746 (0.361–1.543); 0.429	
Time BC to metastases (months)	1.001 (0.994–1.008); 0.775	
Surgery for metastases		
No	Ref 1.00	Ref 1.00
Yes	0.385 (0.194–0.765); **0.006**	0.478 (0.193–1.181); 0.110

BC, primary breast cancer; BC ER, oestrogen receptor status of primary breast cancer; BC PgR, progesterone receptor status of primary breast cancer; BC HER 2, HER 2 gene amplification of primary breast cancer; BC NHG, Nottingham grade of primary breast cancer; HR, hazard ratio; CI, confidence interval.

is generally correlated with worse prognosis, but an efficient anti-Her2 targeted treatment for this subgroup, might explain why HER2 falls out as a positive prognostic factor in this study.

A weakness of this study is the obvious risk of selection bias. The longer disease free interval from breast cancer diagnosis to BCLM and the larger number of oestrogen receptor positive tumours in the surgical group can be interpreted as a proof of selection bias. The registries lack information about comorbidity, which likely has influenced patient selection to surgery.

Surgical treatment is a positive predictive factor in a univariate analysis but the significance was lost in a multivariable analysis including hormonal receptor status and HER2 amplification (Table 3). This might be due to the small size of the cohorts, and more oestrogen positive primary tumours in the surgical cohort (Table 1). Thus, in spite of nationwide data in this study, it is too early to recommend surgical treatment of BCLM outside of prospective studies and the possible survival benefit in the surgical cohort should be interpreted with caution.

In conclusion, this is the first multicentre case control study on liver resection for BCLM. The results show that surgical treatment of a single or up to five liver metastases is safe and might prolong survival in selected patients, compared to systemic treatment only. The present results strongly support a prospective trial to minimize selection bias. Based on these results, a randomized clinical trial, the BRECLIM-trial, will be initiated (Clinical trials, NCT04079049).

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Role of the funding sources

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Declaration of competing interest

The authors have no conflict of interest to declare.

CRediT authorship contribution statement

Marcus Sundén: Investigation, Validation, Visualization, Writing - review & editing. **Cecilia Hermansson:** Investigation, Writing - original draft. **Helena Taflin:** Validation, Writing - review & editing. **Anne Andersson:** Validation, Writing - review & editing. **Malin Sund:** Methodology, Supervision, Writing - review & editing. **Oskar Hemmingsson:** Methodology, Supervision, Project administration, Funding acquisition, Writing - review & editing.

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