Surgery for Breast Cancer Liver Metastases – Factors Determining Results

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Abstract. Background/Aim: The results of the surgical treatment of liver metastases from breast cancer (BCLMs) may be determined by various factors. The aim of the present study was to specify the risk factors for surgical treatment of BCLM. Patients and Methods: Twenty-four female patients with BCLMs were treated with liver resection or radiofrequency ablation (RFA). We evaluated the effects of patient age, time interval between the breast cancer and BCLM surgery, the type of surgical procedure, histopathological findings of the primary tumor, the number and overall diameter of BCLMs, the presence of resectable extra-hepatic metastases, and local tumor recurrence after breast cancer surgery on patients' overall (OS) and progression-free survival (PFS). Results: Age <50 years and shorter interval between breast and liver surgery were risk factors for poorer OS (p<0.02 and p<0.01, respectively) and for PFS (p<0.01 and p<0.01, respectively). The presence of extra-hepatic metastases was a risk factor for OS (p<0.005). An overall diameter of BCLM ≥3.5 cm and a negative status of both estrogen (ER) and progesterone receptors (PR) in the primary tumor were risk factors for poorer PFS (p<0.009 and p<0.0003, respectively). Conclusion: The risk factors for surgery for BCLMs are age <50 years, the presence of extra-hepatic metastases, hormone receptor negativity of the primary tumor and an overall BCLM diameter ≥3.5 cm.

Breast cancer is the most frequent malignant disease affecting women and is the third most frequent malignant disease worldwide. In 2011, approximately 40,000 deaths from this disease were registered in the USA (1). In the Czech Republic, the incidence of breast cancer in 2011 was 67/100,000 women and the mortality was 15/100,000 persons. The incidence of breast cancer in the Czech Republic has continuously increased, although mortality from this disease has significantly decreased (2).

Distant metastases develop in approximately 50% of women with breast cancer at various times from the diagnosis of the primary tumor. Liver metastases usually occur together with other distant metastases, primarily involving the lungs and bones. Liver metastases from breast cancer (BCLMs) represent the primary site of tumor dissemination in approximately 12-15% of patients and are usually considered to indicate generalization of the malignant tumor. If untreated, the median survival of such patients is only 4-8 months. Despite significant progress in the systemic treatment of breast cancer metastases by chemotherapy, hormonal therapy and biological therapy, the prognoses of these patients remains poor, with a median survival of 22-27 months (3, 4). Therefore, the surgical treatment of BCLMs in these patients is undoubtedly sensible and prolongs both overall (OS) and progression-free survival (PFS). However, it remains unclear which patients with BCLMs will benefit the most from surgical treatment involving liver resection or radiofrequency ablation (RFA).

The aim of our prospective, non-randomized study was to evaluate risk factors for poor outcomes from the surgical treatment of BCLMs using multi-factorial analysis, and thus to supplement the current data in the literature dealing with the long-term results of surgical treatment in patients with BCLMs.

Patients and Methods

From 2000-2013, we operated on a total of 809 patients with both primary and secondary liver tumors. These consisted of 118 patients with non-colorectal liver metastases, including 24 women with BCLMs. The average age of this group of patients was 50.9±8.9 years. The average interval between initial breast surgery and the liver surgery for BCLMs was 4.0±2.8 years. Local recurrence was observed in six patients (28.6%), at various intervals from primary breast cancer

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surgery. Histopathologically, the primary tumor involved a ductal carcinoma in most cases (15/24, 62.5%). The primary tumor was estrogen receptor (ER)-positive in 15 cases (62.5%), and progesterone receptor (PR)-positive in 10 cases (41.7%). Both receptor types were positive in 19 patients (79.2%) and both were negative in three (12.5%). Sixteen patients had a solitary liver metastasis, and eight patients had two or more liver metastases (with a maximum of seven). The average sum of the liver metastasis diameters was 5.2±3.8 cm. Extra-hepatic metastases were present in six patients (25%). These involved a solitary bone metastasis in two patients. In three patients, the lymph nodes of the hepato-duodenal (HD) ligament were disease-positive. One patient had both a bone metastasis and positive HD lymph nodes, as shown in Table I.

Table I. *Patients' chracteristics*.

Variable	N=24	%	*p*-Value OS	*p*-Value PFS
Age (mean±SD=50.9±8.9 years)			0.02	0.01
<50 years	10	41.7		
≥50 years	14	58.3		
Time interval between breast cancer surgery and breast cancer liver metastases - BCLMs (mean±SD=4.0±2.9 years)			0.01	0.005
<4 years	11	45.8		
≥4 years	13	54.2		
Type of surgery			0.45	0.67
Liver resection	13	54.2		
Radiofrequency ablation -RFA	11	45.8		
Surgery for extrahepatic -EH metastases	5	20.8		
Primary tumor histology			0.81	0.42
Ductal carcinoma	15	62.5		
Lobular carcinoma	6	25.0		
Other	3	12.5		
Hormone receptor status (primary tumor)				
receptor ER				
Positive	15	62.5	0.30	0.77
Negative	9	37.5		
PR receptor				
Positive	10	41.7	0.39	0.17
Negative	14	58.3		
ER and PR				
Positive	19	79.2	0.24	0.0003
Negative	3	12.5		
Number of metastases			0.76	0.06
One	16	66.6		
Two	6	25.0		
Five	1	4.2		
Seven	1	4.2		
Extrahepatic metastases	6	25.0	0.005	0.06
Bone	2	8.3		
Hepatoduodenal (HD) ligamentum	3	12.5		
Bone + HD ligamentum	1	4.2		
Cumulative diameter (mean±SD=5.2±3.8 cm)			0.06	0.009
<3.5 cm	8	33.3		
≥3.5 cm	16	66.7		
Local tumor recurrence after breast cancer surgery			0.66	0.77
Yes	7	29.2		
No	17	70.8		

Treatment consisted of liver resection or RFA *via* laparotomy. The treatment strategy was always determined by a multi-disciplinary team consisting of a surgeon, an oncologist, and a radiologist. In patients with HD ligament lymph node involvement, we always performed a complete lymphadenectomy. The treatment of bone metastases was determined by an oncologist in cooperation with an orthopedic surgeon. The treatment involved either radical surgery or oncological treatment based on bone-modifying agents (BMAs). Contraindications for surgery included generalization of the underlying disease without the possibility of radical surgical treatment, technically impossible R0 radical resection, and the involvement of both liver lobes without the possibility of downsizing using neoadjuvant oncological treatment or two-stage liver resection. Poor overall patient condition (American Society of Anesthesiologists score - ASA IV) also represented a contraindication for surgical treatment. All patients were examined before surgery by ultrasound or contrast enhanced ultrasound, by multi-detector computed tomography and positron-emission tomography, to exclude other distant metastases. Magnetic resonance imaging was also used in unclear cases. If metastases were found in the HD ligament and were amenable to radical removal, radical lymphadenectomy of the HD ligament was performed at the same time as liver resection or RFA. Bone metastases in regression or those stationary over a long period of time were resolved either surgically, depending on their location, or by using adjuvant oncological treatment following the surgical procedure for BCLMs.

Liver resection was performed under the standard guidelines, with the aim of achieving R0 resection using a liver-sparing technique involving an ultrasonic dissector, a harmonic scalpel, bipolar and argon coagulation, with a maximum reduction of central venous pressure during the resection of the liver parenchyma to values of 0-4 mmHg. In patients indicated for RFA because of other comorbidities or unfavorable findings on the liver tissue (steatosis, steatohepatitis), we either used a simple or clustered RFA probe to thermally ablate the liver foci. RFA was limited to tumor diameters ≤5 cm. We also used RFA in two patients indicated to undergo a secondary liver procedure for BCLM recurrence.

We studied the effects of patient age, time interval between breast cancer and BCLM surgeries, the type of surgical procedure, histopathological findings of the primary tumor, the number and overall diameter of BCLMs, the presence of resectable extrahepatic metastases, and local tumor recurrence after primary breast cancer surgery on patients' OS and PFS.

Statistical analysis was performed using SW SAS (SAS Institute Inc., Cary, NC, USA). Basic statistical data were calculated for each parameter, such as the average, standard deviation, dispersion, median, minimum, and maximum, and were calculated for the sample as a whole and for individual groups and sub-groups. Selected statistical data were processed graphically in box and whisker plot diagrams and histograms. Spearman correlation coefficient was used to determine the correlation of the parameters, given their non-Gaussian distribution. Kaplan–Meier analysis and the Cox regression model were used to determine OS and PFS.

Differences in survival between groups were tested using the log-rank test. Multivariate analysis was performed with a stepwise regression using the Cox regression model.

Results

Our results are expressed in Table I. Overall, we performed 13 liver resections (54.2%) and 11 RFA (45.8%) for BCLMs. We performed four major resections (≥3 liver segments) and nine minor resections (<3 segments). In three patients, we concurrently performed a lymphadenectomy of the HD ligament because of the presence of positive lymph nodes. Three patients had isolated bone metastases at the time of liver resection, which in two cases were resolved radically after the liver procedure by an orthopedic procedure. In the other case, the patient received oncological treatment based on BMAs. Of the 13 liver resections, the histopathological BCLM diagnosis concurred with the primary tumor findings in 10 cases, while three cases involved a histopathologically-different tumor. All patients received adjuvant oncological treatment depending on the histopathological type and hormone receptor status of the BCLM.

No statistically significant differences were observed in OS between patients treated with RFA and those treated with liver resection. The 1-, 3- and 5-year OS for patients treated with RFA and those treated with resection were 89.6%, 85.7% and 14.3%, and 79.6%, 45.5% and 11.4%, respectively (Figure 1). Median survival following liver resection and RFA was 2.2 and 4.1 years, respectively.

In terms of the parameters studied here, the age of the patient at the time of liver surgery was important for both OS and PFS. Compared to the group of patients ≥50 years, the group of younger patients (<50 years) was shown to be at greater risk in terms of both OS (HR=4.163, 95% CI=1.146-15.118, $p<0.02$; Figure 2) and PFS (HR=4.303, 95% CI=1.056-17.531, $p<0.01$; Figure 3). A shorter interval (<4 years) between the primary procedure and surgery for BCLMs was a risk factor in terms of OS (HR=4.738, 95% CI=1.287-17.441, $p<0.01$; Figure 4) and PFS (HR=5.088, 95% CI=1.496=17.303, $p<0.005$; Figure 5). Negative status for both ER and PR in the primary tumor was a negative factor for PFS (HR=21.475, 95% CI=1.907-241.843, $p<0.0003$; Figure 6). The presence of extrahepatic surgically resectable metastases had a negative impact on OS (HR=5.078, 95% CI=1.437-17.949, $p<0.005$; Figure 7). If the overall diameter of the BCLM was ≥3.5 cm, then PFS was significantly worse (HR=9.999, 95% CI=1.257-79.513, $p<0.009$; Figure 8). The other factors studied here did not have any impact on OS or PFS (Table I).

Discussion

Metastatic breast cancer is considered a generalized disease with a poor long-term prognosis. Despite modern systemic oncological treatment (chemotherapy, hormonal therapy, biological therapy), patient survival remains between 6 to 14 months (5, 6).

The liver is the third most frequent site of such metastases after the lungs and bones. BCLMs are diagnosed together with the primary tumor in 5-10% of patients, and in more than 50% of patients, BCLMs develop together with other metastases at various intervals from primary breast surgery. The presence of an isolated BCLM is more of an exception than a rule (7). According to the available literature, patient survival depends on the location of the metastatic process, with bone metastases for example correlating with a longer patient survival (8). Nonetheless, patients with multiple sites of metastasis have a truly generalised disease with poor prognosis. When we divided our patient sample into a group with BCLMs but without demonstrable extra-hepatic metastases and a group with both BCLMs, and extra-hepatic metastases, the 3- and 5-year OS in the former group were 70.8% and 18.3%, respectively, and 20.8% and 0% in the latter. Thus, in contrast to liver metastases of colorectal cancer (9), for example, with the presence of surgically-removable extrahepatic metastases, where surgical treatment represents a significant benefit for the patient, it is clear that patients with BCLMs with extrahepatic, surgically-removable metastases do not experience significant benefit from surgery. Based on our results, as well as the experience of others (10, 11), oncological treatment appears to be more appropriate than surgical treatment for this group of patients. This statement applies also for patients with greater overall diameters of the tumor mass within the liver parenchyma. Here, patients with an overall diameter of BCLM <3.5 cm had a 5-year survival of 26.7% following surgery, while no patient with an overall BCLM diameter ≥3.5 cm survived five years after surgery.

In the literature, results relating to the 5-year survival of patients following surgery for BCLM vary considerably. While some report higher 5-year survival in patients following liver resection or RFA for BCLMs of approximately 21-66%, others report that more than 50% of patients who underwent surgery for BCLMs had very poor OS, despite radical surgery. These authors report that given the poor long-term results, liver resection in patients with BCLMs is controversial, to say the least. They recommend RFA as a palliative procedure that improves OS, especially by achieving tumor mass reduction, thus improving the efficacy of adjuvant chemotherapy and hormonal treatment. Another aspect of RFA (especially transcutaneous RFA) is its lower morbidity and mortality compared to liver resection (12-15).

Another important factor affecting the results of surgical treatment of BCLMs is the time elapsed between the development of the metastases and the primary breast cancer surgery (16). In general, a longer period between BCLM development and the primary surgery is associated with a greater chance of longer disease-free survival following liver

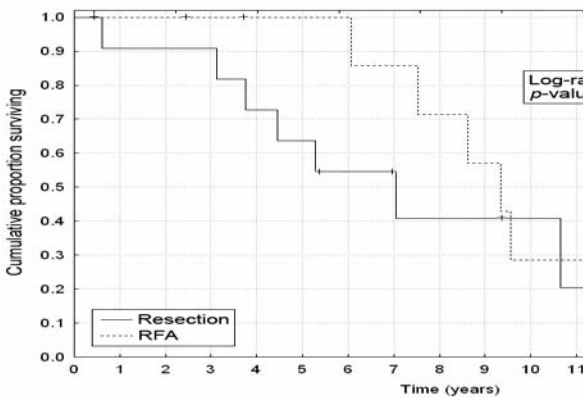

Figure 1. *Overall survival – resection versus RFA.*

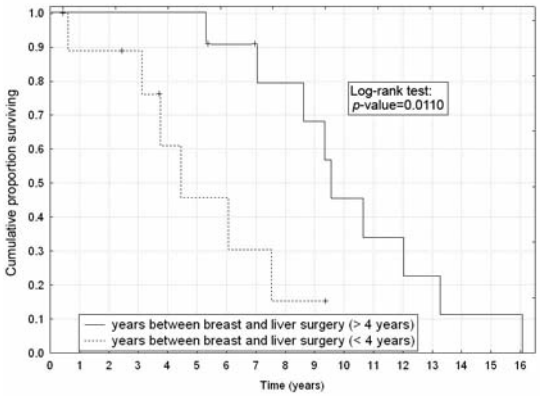

Figure 4. *Time interval between primary breast cancer surgery and liver surgery.*

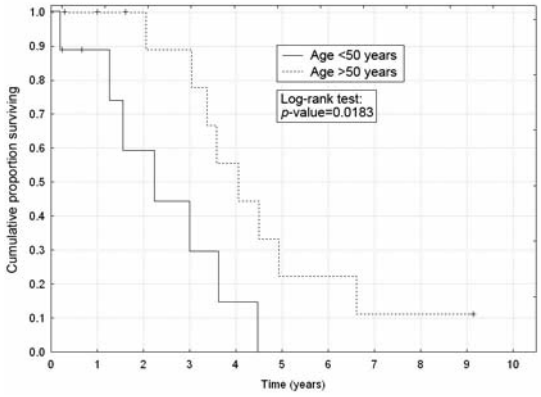

Figure 2. *Overall survival based on patients age in the time of liver surgery.*

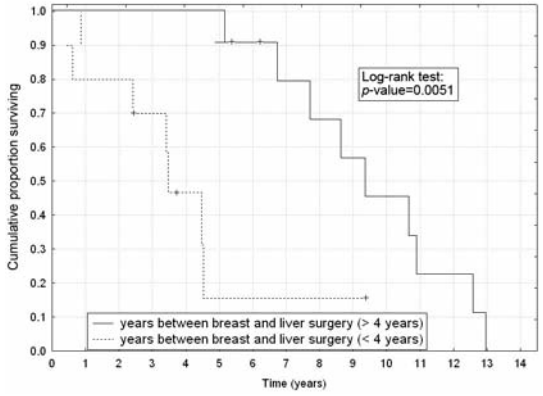

Figure 5. *Influence of time interval between primary breast and secondary liver surgery on progression free survival.*

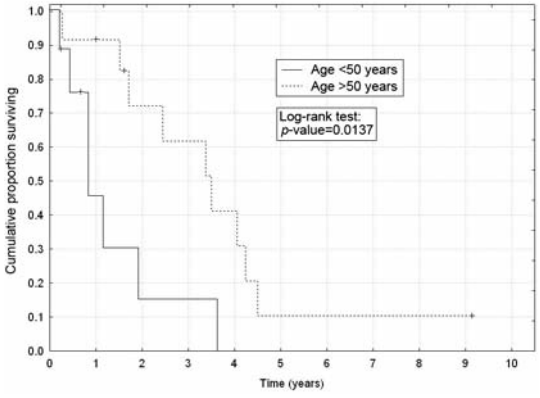

Figure 3. *Patients age and progression-free survival.*

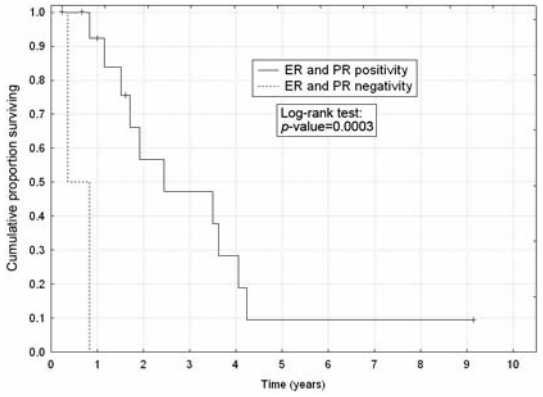

Figure 6. *Protective influence of estrogen and progesteron receptors' positivity on progression-free suvival.*

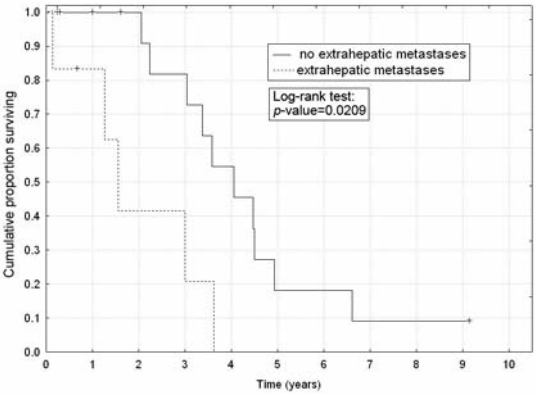

Figure 7. *Overall survival based on extrahepatic metastases.*

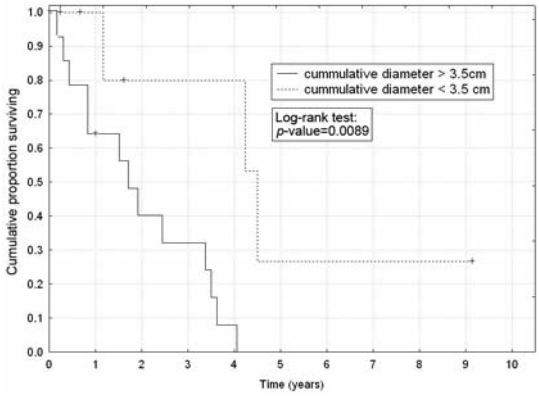

Figure 8. *Influence of cummulative metastases diameter on progression-free survival.*

surgery. Our results support this statement, showing that the long-term survival of patients who developed BCLMs more than four years following primary breast surgery, was significantly superior to that of patients with BCLMs diagnosed within four years following primary breast surgery.

In our sample group, patients younger than 50 had a worse long-term outcome compared older patients, a finding that has been previously documented in the literature (17, 18). This result is most likely related to the more aggressive biological activity of these tumors in younger patients. Some authors report that the combination of younger age and hormonal status (especially ER negativity) is a negative prognostic factor for surgical treatment of BCLMs (19).

Patients with ER-negative status had a worse prognosis. In our sample, we recorded poorer results in patients whose tumors were ER- and PR-negative; however, the data in the literature differs regarding the role of hormone receptor status (20).

Extra-hepatic metastases are a significant risk factor for long-term patient survival. In contrast to other types of liver metastases (especially of colorectal cancer), where the method of choice is removal of all resectable extrahepatic foci, these approaches will have to be carefully weighed in treating BCLMs. As our results show, the issue of resectable extra-hepatic metastases in BCLM is more complicated in terms of surgical intervention, and further studies with more patients will be required to determine the optimal therapeutic approach (21-23).

The response to neoadjuvant oncological treatment is one of the criteria indicating BCLM resectability according to some authors who report better long-term results of liver resection in responding patients compared to patients who fail to respond to neoadjuvant oncological treatment in primarily resectable BCLMs. One advantage reported is the subsequent effect of neoadjuvant oncological treatment in these patients (24). However, these results have not been confirmed by other studies, with one study showing that disease progression occurred 12-24 months following surgical treatment, even after a good response rate to neoadjuvant treatment (25). In general, the current literature does not enable equivocal recommendations regarding the treatment strategy of perioperative oncological treatment in patients with primarily-resectable BCLMs (26, 27). Nonetheless, neoadjuvant treatment could be beneficial in patients with a higher cumulative diameter of BCLMs. In our sample, this group of patients had a shorter PFS. It would thus be interesting to perform neoadjuvant treatment in high-risk patients with a cumulative BCLM diameter greater than 3.5 cm, with the aim of reducing tumor mass and tumor activity, and thus prolonging PFS following surgery.

Surgical treatment of BCLMs undoubtedly remains the method of choice in a selected, strictly indicated group of patients with BCLMs. The presence of extra-hepatic metastases, an overall large BCLM diameter, especially in patients who are younger than 50 years, and negative for status both hormone receptors represent significant risk factors, and in such cases, the decision to proceed with surgical treatment of BCLMs should be weighed on an individual basis by a multi-disciplinary team.

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