

Long-term Survivors After Liver Resection for Breast Cancer Liver Metastases

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Abstract. *Although breast cancer liver metastases are considered a sign of systemic recurrence and are considered a poor prognostic factor that transforms the patient into a candidate for palliative chemotherapy, surgery might be performed with good results. Success reported after liver resection for colorectal hepatic metastases encouraged the oncological surgeon to apply similar protocols in breast cancer liver metastases. Patients and Methods: Data of patients submitted to hepatectomies for breast cancer liver metastases in the “Dan Setlacec” Center of Gastrointestinal Disease and Liver Transplantation, Fundeni Clinical Institute, Bucharest were retrospectively reviewed. Results: Among five cases survival after liver surgery surpassed 5 years and was considered long-term survival. One of the five cases was submitted to a second liver resection. Most often long-term survivors were reported among patients with single, metachronous and smaller than 5-cm lesions. Conclusion: In selected cases liver resection for breast cancer liver metastases can be associated with a significant increase in survival.*

Distant metastases are expected in almost half of patients diagnosed with breast cancer, this fact being responsible for the high number of breast cancer-related deaths in women diagnosed with this malignancy worldwide (1, 2, 3). The presence of distant metastases is usually a sign of systemic

disease that is associated with the presence of malignant cells in the blood stream, with an extremely poor prognosis, the reported survival of untreated patients ranging between 3 and 6 months (4, 5); in all these cases the traditional therapeutic approach consists of systemic therapy including intravenous chemotherapy, anti-hormonal therapy or monoclonal antibodies; however the reported survival after the apparition of liver metastases remains very poor, ranging from 3 to 15 months (4, 6). Once the benefits of liver resection were widely demonstrated in cases with hepatic metastases from colorectal primaries (7-9), attention has been focused on a possible benefit of hepatic resection for breast cancer liver metastases (4, 10-13). The reported results after breast cancer liver metastases remain heterogeneous with 5-year overall survival rates ranging between 21% and 61% (4, 10, 14-16). Few prognostic factors such as tumor dimensions, number of lesions and disease-free survival between breast cancer surgery and apparition of liver lesions have been incriminated as predictors of long-term survival after liver resection; however the results vary widely between different studies (4-6, 10-16). The aim of the present study was to analyze the characteristics of long-term survivors after resection for breast cancer liver metastases and to determine the factors that could be associated with an improved outcome.

Patients and Methods

After obtaining the approval of the Ethics Committee (no 147/2015), data of patients submitted to liver resection for breast cancer liver metastases in the “Dan Setlacec” Center of Gastrointestinal Disease and Liver Transplantation, Fundeni Clinical Institute, Bucharest were retrospectively reviewed. Among the women submitted to liver resection we identified five cases in which a longer than 5-year survival after hepatic resections was reported. Patients’ characteristics regarding the characteristics of primary tumor as well as the characteristics of the liver metastases, type of hepatectomy, early postoperative outcomes, long term outcomes,

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necessity of performing a hepatic re-resection were also collected. Major liver resection was defined as the ablation of at least two hepatic segments according to Couinaud's classification, R0 resection was considered if the specimen had negative resection margins, while the postoperative complications were classified according to Clavien scale (17).

Results

The mean age at the time of diagnosis of the primary breast tumor was 57.2 years (range 31-78 years), all patients being initially submitted to surgery for primary breast malignancy. One patient was diagnosed with stage IV disease, with synchronous liver metastases and was submitted to radical mastectomy and left lobectomy during the same surgical time, while in the other four cases metachronous lesions developed. In all cases the liver was the first site of recurrence. The main demographic and histopathological characteristics are summarized in Table I.

Postoperatively, all patients were submitted to adjuvant chemotherapy; taxane-based regimens were applied in a single patient (case 5) while in all other cases non-taxane-based chemotherapeutic protocols were applied. In the meantime adjuvant radiation therapy was administrated in three cases (cases 1, 4 and 5) while hormone-therapy was also initiated in two patients (cases 1 and 2). The mean disease-free survival to the moment of diagnosis of liver metastases was 33.25 months (range=16-71 months), none of the cases reporting a disease-free survival under 12 months. Neo-adjuvant chemotherapy was performed in all patients. The main intraoperative and postoperative outcomes after liver resection are summarized in Table II.

Histopathological examination confirmed the presence of breast cancer liver metastases in all cases. There was no case of modification of the positivity of hormone-receptor or HER2 status. The postoperative course was uneventful in all cases except one case who reported a febrile syndrome of unknown origin which was successfully managed in a conservative manner, the complication being classified as Clavien-Dindo grade II. The 30 days postoperative mortality was null.

Postoperatively all cases were submitted to adjuvant chemotherapy. Liver recurrence necessitating re-resection was diagnosed in a single patient (case 1) and occurred six years after the first liver resection. The second liver metastasis was successfully resected at the end of the study the patient being alive with no signs of recurrent disease. The long-term outcomes after breast and liver surgery are summarized in Table III.

When studying the characteristics of liver lesions it can be observed that in all cases the maximal diameter of the lesion did not exceed 5 cm while in three of the five cases a single lesion was found. The patient diagnosed with multiple liver metastases (four lesions) had a stage IV breast cancer and was submitted to synchronous resection: radical mastectomy

Table I. Demographic and histopathological characteristics of the patients submitted to surgery for breast cancer.

	Age at breast cancer diagnosis	Neo-adjvant CHT	Neo-adjvant RT	TNM stage	Tumor grade	ER/PR status	HER status	DFS (months)
Case 1	31	No	No	IIA	G3	++	NA	71
Case 2	54	Yes	Yes	IIIA	G2	++	-	20
Case 3	71	Yes	Yes	IV	G1	NA	NA	0
Case 4	78	No	No	IIB	G2	++	-	26
Case 5	52	Yes	Yes	IIB	G2	NA	NA	16

CHT: Chemotherapy; RT: radiotherapy; TNM: tumor, nodes, metastases classification; ER/PR: estrogen receptor / progesterone receptor; HER: human epidermal growth factor; DFS: disease-free survival.

and liver resection. Although a good control of the disease was achieved, the patient remained alive for 84 months and finally died of disease until the end of the study. All the other four cases submitted to liver resection for metachronous lesions experienced a longer than 100 months survival and were still alive at the end of the study. When it comes to disease-free survival between breast cancer diagnosis and breast cancer liver metastases diagnosis, all four cases reported a longer than 12 months interval.

Discussion

The main sites of recurrence after breast cancer surgery are the bone (85% of cases), liver (40-50% of cases), pleura (20% of cases), lung (15-25% of cases) and brain (6-16% of cases) (18). A limited number of patients (up to 5% of cases) will develop isolated liver metastases, in the absence of extrahepatic disease; in these cases if standard chemotherapeutic regimens are introduced, a median overall survival between 19-26 months has been reported (19). Due to this fact and correlated to the benefits reported after liver resection for colorectal hepatic metastases (8, 9) attention has been focused on determining which are the patients who could benefit most after liver resection for breast cancer liver metastases. The most important prognostic factors influencing the overall survival were a longer disease-free interval, the presence of hormone-receptors, the absence of extrahepatic tumoral burden, a good response to chemotherapy and a complete R0 resection (18). In the meantime liver resection for breast cancer liver metastases proved to be a safe method, with low rates of postoperative morbidity and almost null postoperative mortality (18). Few authors went even further and studied the benefits of re-resection for liver recurrent metastases: while Sakamoto *et al.* reported a rate of re-operation for liver recurrence of 5%,

Table II. *Intraoperative outcomes after liver resection for breast cancer liver metastases.*

	Neoadjuvant CHT	Type of liver resection	Extension of liver resection	Maximum diameter of liver lesion (cm)	No. of lesions	Type of resection	Hepatic hylum adenopathy	Adjuvant CHT
Case 1	Taxotere, gemcitabine	Atypical hepatectomy	Minor	3	1	R0	Yes	Paclitaxel, carboplatin
Case 2	Epirubicin, cyclophosphamide, 5-fluorouracil	Atypical hepatectomy	Minor	3.5	2	R0	No	Epirubicin, cyclophosphamide, 5-fluorouracil
Case 3	Epirubicin, cyclophosphamide, 5-fluorouracil	Left segmentectomy	Major	5	4	R0	No	Epirubicin, cyclophosphamide, 5-fluorouracil
Case 4	Taxotere	Atypical hepatectomy	Minor	3.5	1	R0	No	Not available
Case 5	Taxotere	Atypical hepatectomy	Minor	4.5	1	R0	No	Taxotere

CHT: Chemotherapy.

Table III. *Long-term outcomes after breast and liver surgery and current status of patients.*

	Survival after breast cancer surgery (months)	Survival after breast cancer liver metastases surgery (months)	Current status
Case 1	185	115.1	Alive
Case 2	116	95.4	Alive
Case 3	84.3	84.3	Dead
Case 4	149.5	123.7	Alive
Case 5	123.4	107.7	Alive

Adam *et al.* reported one liver re-resection in half of the patients with liver recurrent disease (4, 20).

The largest studies regarding the early postoperative outcomes, the benefits in terms of survival and the most important prognostic factors are summarized in Table IV.

Based on these findings, the main recommendations for breast cancer liver metastases resections were proposed: longer disease-free interval, positive hormone receptor status, the absence of extrahepatic disease, resection with curative intent and good response to systemic therapy (18).

In order to evaluate the long-term survival benefits after breast cancer liver metastases, Jee Kim *et al.* introduced in their study 13 patients submitted to hepatectomy with curative intent. The median time between breast cancer surgery and liver metastasis diagnosis was 62.5 months. According to the recurrence type the patients were divided

in two groups: the first group included seven patients with isolated liver lesions while the second group included six patients with multi-organ metastases. Among patients with extra-hepatic disease, the main sites of recurrence included bone metastases (in two cases), cervical lymph nodes (in two cases), brain metastases (in one case) and respectively ovarian metastases (in one case). Liver resection was performed by open surgery in nine cases and by laparoscopy in four cases. Major resection was performed in a single case while in the other 12 cases minor resections were performed. All patients with extrahepatic tumor burden were submitted to surgery with curative intent for all lesions; postoperatively adjuvant chemotherapy was performed in all cases. When studying the long-term outcomes, the 1-year and 3-year overall survival rate was 83.3% and 66.7% respectively in patients with no extrahepatic disease and only 80% and 0 respectively in cases with extrahepatic burden. The study came to demonstrate the efficacy of liver resection for breast cancer liver metastases especially in selected cases with good general condition and isolated liver lesions. However, long-term survivors after liver resection were reported only among cases with no extrahepatic disease (22).

In the study conducted by Rene Adam *et al.* 85 patients submitted to hepatectomy for breast cancer liver metastases were included. At univariate analysis, an improved outcome was correlated with positive response to prehepatectomy chemotherapy ($p=0.004$), the absence of extrahepatic disease ($p=0.004$) and R0 resection ($p=0.00001$). An interesting aspect was the correlation between overall survival and the necessity of repeat hepatectomy ($p=0.01$). Among the 85 cases initially included in the study 59 patients developed

Table IV. Short and long term outcomes and prognostic factors after liver resections for breast cancer liver metastases.

Author of the study and year	No of cases	Postoperative morbidity rate	Postoperative mortality rate	Median overall survival after liver resection (months)	Prognostic factors (univariate analysis)	Prognostic factors (multivariate analysis)
Adam <i>et al.</i> , 2006 (4)	85	26%	0	46	Response to prehepatectomy chemotherapy Overall metastasis status Completeness of liver resection (R0) Repeated hepatectomy	Response to prehepatectomy chemotherapy Completeness of liver resection (R0) Repeated hepatectomy
Weinrich <i>et al.</i> , 2014 (21)	29	3,44%	0	53	TNM status Completeness of liver resection (R0)	TNM status
Walsum <i>et al.</i> , 2012 (10)	32	34%	0	55	Hormone receptor status No. of metastases Distribution of metastases	No. of metastases
Kim <i>et al.</i> , 2014 (22)	13	NR	NR	NR, 3 year overall survival rate of 49,2%	Extrahepatic metastases	Extrahepatic metastases
Abbott <i>et al.</i> , 2012 (23)	86	21%	0	57	Hormone receptor status Disease-free interval>2 years Radiographic response	-hormone receptor status -disease free interval>2 years
Belda <i>et al.</i> , 2010 (24)	21	0	0	17	Disease-free interval >2 years	NR
Bacalbasa <i>et al.</i> , 2014 (11)	43	16,27%	0	32,2	Hormone receptor status Size of liver lesion Number of liver lesion Node involvement of the primary tumor	Hormone receptor status

TNM: Tumor, nodes, metastases classification.

additional metastatic disease after a median time to recurrence of 10 months (range 1-132 months). Limited to liver recurrences were reported in 28 cases, the median time between liver resection and intrahepatic recurrence being 10 months (range 1-47 months). Twelve patients were submitted to hepatic re-resection, while four of these 12 patients experienced another hepatic relapse and underwent a third hepatectomy. The reported disease-free survival after the first hepatectomy ranged between 14 and 166 months. The authors concluded that the necessity of liver re-resection is a good prognostic factor associated with long-term survival (4).

In our case, one of the five cases was submitted to a second hepatectomy for second liver isolated relapse. The patient was submitted to the second liver resection at six years after the first hepatectomy and experienced a 43 months survival after the second liver resection.

Conclusion

Once the benefits of liver resection for breast cancer liver metastases were widely accepted, attention has shifted to determining the characteristics of patients who could benefit most from this surgical approach. According to existing results, long-term survivors after breast cancer liver metastases resection are found among cases with isolated liver recurrence, in the absence of extrahepatic tumor burden. In the meantime a longer disease-free survival and repeated hepatic resections also seem to be positively correlated with an improved outcome. In cases presenting synchronous liver metastases a slightly decreased survival can be expected when compared to those with metachronous lesions; however even in these cases a significant benefit in terms of survival can be achieved when compared to cases submitted solely to systemic chemotherapy.

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