

Role of Surgical Treatment in Breast Cancer Liver Metastases: A Single Center Experience

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Abstract. *Background/Aim:* The aim of the present study was to review a single hepatobiliary center experience, the benefit of hepatic metastasectomy in breast cancer liver metastases (BCLM) patients and to identify predictors of survival. *Patients and Methods:* Fifty-two female patients underwent surgery for BCLM between 2002 and 2013. Only patients with liver resections (n=43) were included in the analysis. *Results:* The median survival of the 43 patients with liver resection was 32.2 months. The factors significantly associated with overall post-hepatectomy survival were estrogen/progesteron receptor (ER/PR) status (p=0.002), node involvement of the primary tumor (p=0.049), size (p=0.005) and number (p=0.006) of the metastatic lesions. The 1-, 3- and 5-year survival rates after curative liver resection were 93.02%, 74.42%, 58.14%, respectively. *Conclusion:* BCLM resection is a safe procedure and offers survival benefit, especially in patients with reduced liver metastatic burden (solitary metastases, diameter of the metastases <5 cm) and positive ER/PR status.

Approximately 5% to 10% of breast cancers are metastatic at diagnosis (1). The presence of metastatic disease confined to the liver occurs in only 4% to 5% of the cases (2) liver metastases are associated with a negative impact on survival of patients with breast cancer. In such patients, metastases

seed the liver via systemic circulation, and thus a microscopic dissemination may be present in multiple sites. For this reason, a current modern multimodal approach is based on systemic chemotherapy, hormonal and targeted therapy. Although resection of colorectal cancer metastases is a widely-accepted therapeutical option (3), a similar indication for non-colorectal hepatic metastases, including breast cancer liver metastases (BCLM) is still an ongoing debate. There is increasing evidence that liver metastasectomy associated with systemic treatment may provide survival benefit in a subset of patients with BCLM (4). Moreover, the 5-year survival rate is comparable to that after colorectal cancer liver metastases resection (5). Large disease-free intervals between primary breast cancer surgery and liver metastases diagnosis (6, 7), positive hormone receptor status (8), response to chemotherapy and R0 resection (9) are all favorable prognostic factors in patients with BCLM (10, 11). The variables associated with poor outcome after liver resection for BCLM include the presence of the extrahepatic disease at the resection time (12), multiple liver metastases, estrogen receptor (E)-negative status (13, 14). The aim of the present study was to review a single hepatobiliary center experience regarding the benefit of hepatic metastasectomy in BCLM patients and to identify predictors of survival that could be assessed preoperatively.

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Key Words: Breast cancer liver metastases, liver resection, estrogen/progesteron receptor status.

Patients and Methods

Patients and classification. Between January 2002 and December 2013, 52 female patients underwent surgery for BCLM at the Center of General Surgery and Liver Transplantation of the Fundeni Clinical Institute, Bucharest, Romania. Informed consent was obtained from each patient before surgery and the study was approved by the Ethics Committee of the Fundeni Clinical Institute. Patients demographics, characteristics of primary breast and metastatic liver tumor, type of liver resection, postoperative

morbidity and mortality, chemotherapy and radiotherapy regimens, were collected retrospectively from medical records. Synchronous hepatic metastases are defined as liver metastases occurring at the time of the primary breast tumor (13); metachronous BCLM are defined as metastases diagnosed after therapy for the primary tumor, that were not present at initial diagnosis. Disease stage at the time of surgery was defined using the tumor-node-metastasis (TNM) staging System (UICC). Neoadjuvant or adjuvant therapy for primary breast cancer were administered according to their hormone receptor status and stage, according to evidence-based protocols available at the time. Surgical techniques for liver resection were selected according to the disease extent and tumor location. Major hepatectomy was defined as resection of three or more anatomical Couinaud liver segments, while minor hepatectomy as less than three. A R0 resection was defined as curative resection if in presence of a negative microscopic resection margin. Postoperative mortality was defined as death within 30 days of hepatectomy and postoperative morbidity was classified according to the Clavien scheme.

Statistical analysis. Descriptive statistical measures, including the mean±standard deviation (SD), median and range, were calculated. Survival was calculated from the time of the first breast cancer surgery to death and from the moment of liver surgery to death. The patients were followed-up closely until March 01, 2014. Univariate analyses of survival were performed using the log-rank test. Multivariate analyses were performed using a Cox proportional hazards model and forward stepwise procedures. The data were censored from the analysis of the surviving patients at the date of last follow-up. The overall and 1-, 3- and 5-year survival rates were calculated since the breast surgery and since hepatectomy for BCLM, respectively. All differences and associations were considered statistically significant if the 2-sided *p*-value was below 0.05 (95% Confidence Intervals (CI)). All statistical analyses were performed with The SPSS software, version 17.0 - (SPSS, Chicago, IL, USA).

Results

Clinical and histopathological data. Fifty-two female patients underwent liver surgery for metastatic breast cancer but curative resection was tempted in 43 patients with a median age of 52 years (range=31-79); seven patients in which initial abdominal exploration revealed unresectable hepatic and/ or intra-abdominal disease not identified on preoperative imaging, as well as two cases of radiofrequency ablation (RFA) were excluded from the analysis. All patients underwent surgery for primary breast cancer. The demographic, primary and metastatic tumor data are listed in Tables I and II. Thirty-five patients (81.4%) received systemic chemotherapy and/or hormone therapy before liver resection. There was no postoperative mortality and complications occurred in 7 (16.27%) patients including biliary leakage in 3 cases, intra-abdominal abscess in 2, urinary infection in 1 and wound infection in 1 case. During the follow-up period, recurrence occurred in 17 patients (40%); out of these, 10 patients had recurrence in the liver. Six of these patients underwent a second hepatectomy for liver recurrence and 2 patients third hepatectomy.

Table I. Demographic and pathological characteristics of the primary breast tumor (n=43).

Variable	Number of patients	%
Age at breast cancer surgery (years)		
Mean (±SD)	53.47 (±11.09)	
Median (range)	52 (31-79)	
T stage of the primary tumor		
T1-2	23	54
T3-4	10	23
NA*	10	23
N stage lymph node status		
N0	12	28
N1-N2	21	49
NA	10	23
M-Metastasis status		
M0	29	67
M1	4	10
NA	10	23
Tumor grade		
G1	5	11
G2	14	33
G3	9	21
NA	15	35
Stage of disease		
IA	5	11
IIA-IIIB	16	37
IIIA-IIIB	8	19
IV	4	10
NA	10	23
Histology		
Invasive ductal adenocarcinoma	5	63
Invasive lobular carcinoma	28	12
NA	10	23
Hormone receptor status (HR)		
ER positive /negative (N=27)	22/5	82/18
PR positive/negative (N=29)	22/7	82/18
HER2 (n=27)		
Overexpressed	10	37
Not expressed	17	63
Postoperative systemic therapy		
Yes (Taxane-based, n=17; Non-taxane, n=24)	41	96
No	2	4

Estrogen receptor (ER), Progesteron receptor (PR), human epidermal growth factor receptor 2 (HER2); *NA= not available data.

Survival and relationship with clinicopathological characteristics. The median time between surgical treatment of primary breast cancer and diagnosis of the subsequent liver metastases was 20.29 months (range=0-228.03). The median survival of the 43 patients with liver resection was 32.2 months (range=3-123.7). The factors significantly associated with overall post-hepatectomy survival were estrogen/progesteron receptor status (*p*=0.002), size (*p*=0.005) and number (*p*=0.006) of the liver metastatic lesions. Node involvement of the primary

Table II. Clinicopathological data of hepatic metastases (n=43).

Variable	No. of patients	%
No. of liver metastases		
Solitary	24	56
Multiple	19	44
Maximal liver metastasis size		
≤5 cm	29	67
>5 cm	10	23
NA	4	10
Tumor grade		
G1-G2	14	33
G2-G3	25	58
NA	4	9
Chronology of metastases		
Synchronous	4	9
Metachronous	39	91
Hepatic resection		
Minor (<3)	29	67
Major (>3)	14	33
Resection margin status		
R0	39	91
R1	4	9
Mortality rate	0	0
Morbidity rate	7	16

*NA= Not available data.

tumor was associated with a reduced survival ($p=0.049$) (Table III). Based on univariate analysis results, a cox regression analysis was performed to identify independent factors associated with survival. Multivariate analysis showed that only estrogen/progesterone receptor status affected overall survival ($p=0.032$). The 1-, 3- and 5-year survival rates after curative liver resection were 93.02%, 74.42%, 58.14%, respectively. Patients with ER-positive, PR-positive primary breast cancer had median survival 36 months (range, 5.2-123.7), while in patients with primary breast cancer ER-negative, PR-negative median survival was 23.9 months (range=10.8-33.6). Patients with tumor size ≤5 cm had a significantly higher overall survival than those with tumor >5 cm ($p=0.005$) (Figure 1), with median survival of 32.2 months (range=3-123.7) and 22.5 months (range=7.1-56.6), respectively. The patients with multiple hepatic metastatic lesions had a significant shorter survival compared with patients with single metastatic lesion ($p=0.006$) (Figure 1), with median survival 25.3 months (range=4.9-95.4) and 33.2 months (range=3-123.7), respectively. The mean survival time after re-resection of the BCLM was 46.45 months (range=32.8-115.1). For 9 patients the survival after liver resection was longer than 48 months (range, 48-123.7). Median survival for this group of patients was 83.6 months and disease-free survival of 25.3 months (Table IV).

Table III. Univariate analysis for prognostic factors of overall survival.

Characteristics	Survival after liver resection - median (range-months)	Log-rank test p -Value
Age (years)		
≤50	23.9 (3-115.1)	0.787
>50	33.4 (4.9-123.7)	
Lymph node status - primary breast tumor		
N0	34.75 (5.2-123.7)	0.049*
N1+N2	32.45 (3-95.4)	
Tumor grade- primary breast tumor		
G1	27.7 (10.8-83.6)	0.795
G2	41.35 (5.2-123.7)	
G3	32.2 (13.2-115.1)	
Stage of disease - primary breast tumor		
I (n=5)	27.7 (5.2-56.6)	0.488
IIA si IIB (n=16)	28.9 (10.8-123.7)	
IIIA si IIIB (n=8)	25.45 (3-95.4)	
IV (n=4)	44.85 (10.95-83.6)	
ER status- primary breast tumor		
Positive (n=22)	36 (5.2-123.7)	0.002*
Negative (n=5)	23.9 (10.8-33.6)	
PR status - primary breast tumor		
Positive (n=22)	36 (5.2-123.7)	0.002*
Negative (n=7)	23.9 (10.8-33.6)	
HER2 status- primary breast tumor		
Overexpressed (n=22)	21.25 (7.7-48)	0.335
Negative (n=5)	27.7 (5.2-123.7)	
Adjuvant therapy for breast cancer		
Yes	39.8 (4.9-123.7)	0.436
No	25.8 (3-95.4)	
Taxane-/non taxane-based drugs		
Taxane	16.9 (3-107.7)	0.605
Non-taxane	40.4 (11.1-115.1)	
Tumor grade- liver metastases		
G1-G2	22.9 (10.95-48)	0.587
G2-G3	25.6 (4.9-123.7)	
Maximal size of liver metastases (cm)		
≤5	32.2 (3-123.7)	0.005*
>5	22.5 (7.1- 56.6)	
Number of liver metastases		
Solitary	33.2 (3-123.7)	0.006*
Multiple	25.3 (4.9-95.4)	
Hepatic resection		
Minor (<3)	39.8 (3-123.7)	0.086
Major (>3)	23.3 (4.9-83.6)	
The first site of recurrence		
Liver	33.2 (3-123.7)	0.616
Bone, lung, breast (N=5)	16.9 (4.9-51.4)	

*Statistically significant, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2).

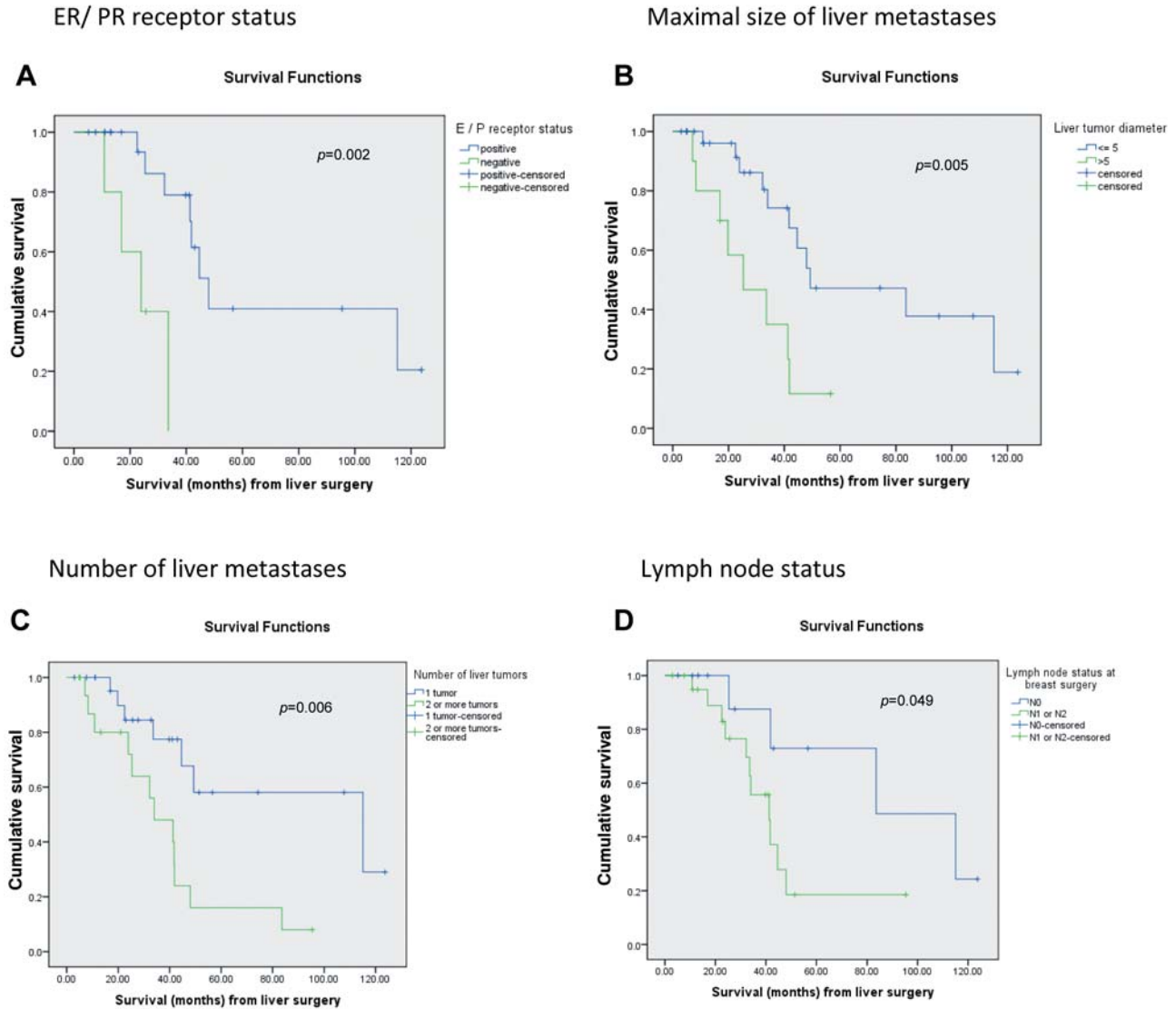


Figure 1. Kaplan-Meier survival curves for overall survival after liver resection for BCLM based on A) ER/ PR receptor status; B) maximal size of liver metastases; C) number of liver metastases; D) lymph node status.

Discussion

The success of liver resection in colorectal cancer liver metastases has raised questions about possible benefit of liver resection in other primaries. There is an important difference in the way liver is involved in colorectal cancer as compared to breast; while in colorectal cancer liver is involved through portal flow (thus, in principle a colorectal primary with liver metastases could be confined solely to the abdominal compartment, without systemic spread) and in a breast primary liver is involved through systemic circulation, which makes systemic spread a certainty. The rationale for liver resection in a systemic disease is based on an important

survival difference between different locations of stage IV breast cancer; while median overall survival for bone metastases is 24 to 48 months (15), medically managed liver metastases allows a median overall survival of 16.5 to 26 months (16), being surpassed as worse prognosis only by brain metastases, having an overall survival of, 3-6 months. Since BCLM progression leads, eventually, to liver failure the aim of liver resection is to increase the liver disease-free interval, thus shifting survival for this category of patients towards survival of patient groups with more favorable survival. Several studies (4, 6-14, 17-22) have been published in the last 20 years; however, the number of patients included has been rather small (range=9-86), reflecting surgeons and

Table IV. Long-term survivors of resected BCLM patients.

Case	Age (years)	ER/PR	Interval to liver metastases (months)	Neoadjuvant therapy before liver resection	Type of liver surgery	Adjuvant therapy after liver resection	Number of liver metastases	Maximal size of liver metastases (cm)	Second liver metastases resection (Yes/no)	Survival from breast surgery (months)	Survival from first liver resection (months)
1	78	+/+	25.3	T	Minor	NA	1	3.5	No	149.5	Alive, 123.7
2	31	+/+	69.4	T+G	Minor	P+C	1	3	Yes	185	Alive, 115.1
3	52	NA	15.7	T	Minor	T	1	4.5	No	123.4	Alive, 107.7
4	54	+/+	19.7	FEC+H	Minor	FEC	2	3.5	No	116.1	Alive, 95.4
5	71	NA	Synchronous	CMF	Major	CMF	4	5	No	84.3	Dead, 84.3
6	69	+/+	39	T+HT	Major	Ca	1	6	Yes	95.6	Alive, 56.6
7	60	NA	51.4	CMF	Minor	No	1	4	No	106.2	Alive, 51.4
8	66	+/+	12	T+HT	Minor	T+HT	1	3	No	61	Dead, 49.3
9	40	+/+	Synchronous	FEC	Minor	V+ CI +TR	2	3	Yes	48	Alive, 48

FEC= Epirubicin/ cyclophosphamide/ 5-fluorouracil, CMF= cyclophosphamide/ cyclophosphamide/5-fluorouracil, HT= hormonotherapy, T= taxotere, G= gemcitabine, P= paclitaxel, C= carboplatin, CI= cisplatin, V= vinorelbine, CA= capecitabine, Tr= trastuzumab.

oncologists' reluctance towards the procedure. In the absence of the prospective data, the role and effectiveness of hepatic metastasectomy in BCLM has not been defined. As safety is concerned, mortality was 0 in the large majority of studies (4, 6, 8, 9, 14, 17-20, 22, 25) and morbidity ranged between 0% (24) and 35.9% (27). Regarding survival, median survival after hepatectomy ranged between 24 and 63 months (27). Our study comprised of 43 liver resections performed in a single center between 2002-2013. Median survival was 32.2 months (range=3-123.7) with a 5-year survival rate of 58.14% which, in principle surpassed survival of patients treated solely with systemic chemo-hormonotherapy (29), indicating survival benefit of liver resection. Regarding the risk associated to the procedure, liver resection is becoming increasingly safe. In our series mortality was 0%, while morbidity (16.27%) comprised of biliary leakage, intra-abdominal abscess, urinary infection and wound infection, all managed in a conservative manner. Surgical management proved safe regardless of age, being performed also to older patients (5 patients >70 years old at the time of liver surgery). While there appears to be a survival benefit in general, it is important to identify who benefits most, thus tracing future indications of the procedure.

Characteristics of the primary breast tumor do not impact on survival after liver resection, except axillary lymph node status at the time of breast surgery ($p=0.049$); this is in accordance with results presented in previous studies (6, 23). The hepatic metastases burden impacts survival in terms of number ($p=0.006$) and size ($p=0.005$) of lesions. However, in multivariate analysis the only factor independently associated with survival after liver resection was estrogen/progesterone receptor status, in accordance to several other studies (8,13). Other parameters analyzed in already published studies such as R0 vs. R1 liver resection and the

presence of extrahepatic metastases could not be assessed in our study since the large majority of patients underwent R0 resection and had liver as unique metastatic site. We found that the mean survival time for patients with repeated hepatectomy was 46.45 months. Other authors have also noted that repeat hepatectomy for BCLM is associated with improved survival (17).

Conclusion

Liver resection in BCLM is a safe procedure and brings survival benefit, especially in patients with reduced liver metastatic burden (solitary metastases, diameter of the largest metastases <5 cm) and positive ER/PR receptor status.

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