Outcome and Factors Related to Isolated Liver Metastasis due to Breast Cancer

Ebru Sen[1], Tolga Canbak[2], Ozgur Bostanci[3] and Muharrem Battal[4]

[1]*Department of General Surgery, Faculty of Health Sciences, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkiye*
[2]*Department of General Surgery, Faculty of Health Sciences, Umraniye Education and Research Hospital, Istanbul, Turkiye*
[3]*Department of General Surgery, Faculty of Health Sciences, Hamidiye Sisli Etfal Education and Research Hospital, Istanbul, Turkiye*
[4]*Department of General Surgery, Yeni Yuzyil University, Gaziosmanpasa Hospital, Istanbul, Turkiye*

ABSTRACT

Objective: To determine the associated risk factors for isolated liver metastasis in breast cancer patients and to detect the prognostic factors related to survival.

Study Design: Analytical study.

Place and Duration of the Study: Department of General Surgery, The University of Health Sciences, Istanbul, Turkiye, from January 2011 to November 2020.

Methodology: Patients with breast cancer liver metastasis who experienced surgery were retrospectively analysed for breast cancer and metastases-related characteristics. Descriptive statistical methods were used in the evaluation of data. Survival analyses were estimated by the Kaplan-Meier method. Log-rank and univariable Cox regression tests were utilised to search for prognostic factors' impact on survival.

Results: Out of 12 patients, 11 had recurrent disease after a median of 36 months of disease-free survival (DFS) and one patient had *de novo* metastasis. Grade 3 tumours and increased expression of Ki-67 had a negative effect on DFS. The median follow-up period was 66 months. Survival analysis showed 2- and 3-year progression-free survival (PFS); overall survival rates were 82%, 69%, 92%, and 82%, respectively. Development of liver metastasis in 3 years following breast cancer treatment was linked to worse PFS ($p = 0.040$).

Conclusion: Long-term survival is possible for breast cancer survivors with liver metastasis. Disease-free interval is an important determinant. Longer progression-free survival was detected in patients who had developed metastasis after three years of breast cancer treatment.

Key Words: *Breast cancer, Liver metastasis, Hepatic surgery.*

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INTRODUCTION

Breast cancer (BC) is the most common type of female cancer. Although breast cancer mortality has dropped by nearly 40% in high-income countries during the last 20-30 years, it is still the second leading cause of all cancer-related deaths among women.[1] In the course of breast cancer, metastases may develop either at the diagnosis of the disease called *'de novo'* metastasis, which occurs in 6% of BC patients, or following primary tumour treatment as a recurrence, affecting 20-30% of breast cancer survivors.[2] Isolated liver metastasis (LM) develops in nearly 5% of the patients, usually occurring as a recurrent disease. Whether metastatic BC could be a curable disease remains a dilemma, but it is essential to increase both survival and quality of life for metastatic patients. Therefore, searching for the optimal treatment of LM is an important issue.

Correspondence to: Dr. Ebru Sen, Department of General Surgery, Faculty of Health Sciences, Basaksehir Cam and Sakura City Hospital, Istanbul, Turkiye
E-mail: ebrusenoran@windowslive.com

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Surgery plays an essential role in the management of liver metastases due to colorectal and neuroendocrine tumours. In contrast, the surgical approach is more equivocal in patients with breast cancer liver metastases (BCLM).[3] Secondary to improvement in hepatic surgery with low mortality and morbidity rates, whether hepatic resections is a convenient therapeutic option for patients with BCLM has become questionable.[1,4] Recent studies delineating the survival advantages of patients who underwent hepatic surgery for liver metastasis compared to nonsurgical patients encourage surgeons to consider more aggressive strategies.[5,6] Moreover, promising evidence to repeat hepatectomy for second liver metastases of breast cancer is available in the literature.[7]

The aim of this study was to explore the associated risk factors for isolated LM in BC patients and to detect prognostic factors related to survival after treatment of hepatic metastasis.

METHODOLOGY

Before conducting the study, approval was taken from the ethical review committee of the Basaksehir Cam and Sakura City Hospital, Istanbul, Turikye. In this retrospective analytical study, inclusion criteria were patients who had undergone hepatic surgery between January 2011 and November 2020 for LM due to BC by one of the three surgeons who were specialised in liver

surgery at the University of Health Sciences. Except for one patient with *de novo* metastasis, all patients had a history of BC surgery. All of them had isolated LM and had undergone hepatic surgery by curative intent. Patients in whom extrahepatic metastasis (EHM) was intraoperatively detected were excluded from the study. Before hepatic surgery, cytotoxic chemotherapy or hormonotherapy was administered to all the patients according to molecular type. Targeted therapy was applied to all HER2+ patients along with chemotherapy. Surgery was performed after two to three months of the systemic treatment.

BC and metastases-related features were analysed. Age at BC and LM were recorded separately. Disease-free survival (DFS) was defined between the treatment of BC and the detection of the first LM. Primary tumour's histopathological features, TNM stage, and the patient's surgical and other oncological therapies were collected. The diagnosis of liver metastasis was based on the radiologic scans, the biopsy of metastatic lesions, and the final pathologic results. Location and number of metastases, size of the biggest metastasis, type of liver resection, utilisation of ablative treatment, and final resection margin were documented.

A multidisciplinary tumour board individually decided the treatment modality at the surgeon's hospital. Liver resection was the preferential treatment approach. For patients with a high likelihood of morbidity related to surgical resection, ablative therapy was chosen. A thorough surgical exploration was performed on all patients at the beginning of the operation. Any suspicious lesion was evaluated by intraoperative pathologic examination. Intraoperative ultrasound (IUSG) was used to search the liver for any additional lesions if no extrahepatic disease had been found. The targeted surgical clearance margin was at least 1cm. Radiofrequency ablation (RFA) was performed *via* open technique, using the RF 2000 or 3000 generator system and a 15-gauge insulated monopolar needle electrode with IUSG guidance.

After hepatic surgery, all patients were followed at the outpatient clinic every three months for two years and every six months for up to 5 years. Outcome data included median follow-up time, progression-free survival (PFS), and overall survival (OS). Factors statistically affecting DFS, PFS, and OS were calculated.

All analyses were performed using SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as count and percentage (%), and continuous variables were represented as median and range. Descriptive statistical methods were used in the evaluation of data. PFS and OS were estimated as the interval from liver surgery to the first progression and as the time from liver surgery to the date of the last follow-up visit or death, respectively. Survival analyses were estimated by the Kaplan-Meier method. Log-rank and univariable Cox regression tests were utilised in searching the impact of prognostic factors, including patients' characteristics, breast cancer, and metastasis-related features on disease-free, progression-free, and overall survival. All p-values lower than 0.05 were considered statistically significant, and results were calculated using 95% confidence interval (CI).

RESULTS

Twelve female patients were operated because of BCLM. The median age of patients at the diagnosis of hepatic metastasis was 51 (31-59) years. The median DFS was 36 months, ranging from 18 to 72 months. The median age of patients at the diagnosis of primary BC was 46 (29-57) years. There was no regular follow-up for two BC survivors.

Metachronous metastasis was detected in 11 (91.7%) patients and synchronous in one patient. Metastasis had developed during 24 months following BC treatment in 2 patients. In seven patients, metastasis was detected between 36 and 60 months. Metastasis was seen 60 months later in 2 patients. Liver resection was performed in 11 patients who had R0 resection. RFA was applied in one patient who had four liver metastases. The patient's characteristics related to BC and LM are summarised in Table I.

Table I: Patient's characteristics.

Variables (n = 12)	Category	Statistics
Diagnostic age#	All	46 (29-57)
Metastatic age#	All	51 (31-59)
pT stage, n (%)	$I_{(n=3)}$/$II_{(n=4)}$	7 (58.3)
	III	5 (41.7)
pN stage, n (%)	$0_{(n=1)}$/$I_{(n=5)}$	6 (50)
	$II_{(n=5)}$/$III_{(n=1)}$	6 (50)
Breast cancer	Unilateral	11 (91.7)
	Bilateral	1 (8.3)
Histological tumour type, n (%)	Ductal	11 (91.7)
	Lobular	1 (8.3)
Tumour size-breast (mm) #	All	40 (10-70)
Tumour size-liver (mm) #	All	20 (15-60)
Breast involvement, n (%)	Unifocal	10 (83.3)
	Multifocal	2 (16.7)
Neoadjuvant chemotherapy n (%)	Yes	7 (58.3)
	No	5 (41.7)
Surgical type (breast), n (%)	BCS	4 (33.3)
	Mastectomy	8 (66.7)
Surgical type (axilla)	Axillary dissection	12 (100)
	SLNB (contralateral BC)	1 (8.3)
Histological grade, n (%)	I/II	4 (33.3)
	III	8 (66.7)
Lymphovascular invasion, n (%)	Positive	8 (66.7)
	Negative	4 (33.7)
Estrogen receptor, n (%)	Positive	9 (75)
	Negative	3 (25)
Progesterone receptor, n (%)	Positive	9 (75)
	Negative	3 (25)
HER 2, n (%)	Positive	5 (41.7)
	Negative	7 (58.3)
Ki-67 (%)#	All	37.5 (10-80)
Subgroup, n (%)	Luminal	9 (75)
	Non-luminal	3 (25)
Other treatment following BC surgery	Adjuvant chemotherapy	5 (41.7)
	Radiotherapy	12 (100)
	Hormonotherapy	9 (75)
Hepatic segment involvement, n (%)	Single	7 (58.3)
	Multiple	5 (41.7)
Liver resection type (n=11), n (%)	Anatomical	2 (18.2)
	Non-anatomical	9 (81.8)
Number of metastatic liver lesion#	All	1 (1-4)
Post-relapse chemotherapy response	Regression	3 (25)
	Stable	9 (75)
Follow-up time	All	66 (32-130)
Progression, n (%)	Yes	3 (25)
Mortality, n (%)	Yes	3 (25)
Disease-free survival time (month) #	All	36 (18-72)
Progression-free survival time (month) #	All	27 (10-58)
Overall survival time (month) #	All	30 (14-58)

#: Median (range).

Table II: The impact of patients' characteristics on disease-free survival.

Variables (n = 12)	Category	Univariate HR (95% CI)	p-value
Age	All	1.00 (0.92-1.08)	0.995
pT stage	I/II	1	
	III	1.92 (0.48-7.75)	0.357
pN stage	0/I	1	
	II/III	1.44 (0.41-5.04)	0.568
Tumour size-breast (mm)	All	1.01 (0.98-1.05)	0.486
Surgical type (breast)	BCS	1	
	Mastectomy	2.96 (0.66-13.39)	0.159
Grade	I/II	1	
	III	7.47 (1.01-55.49)	0.049*
Lymphovascular invasion	Negative	1	
	Positive	1.14 (0.29-4.52)	0.854
HER 2	Negative	1	
	Positive	2.44 (0.57-10.35)	0.227
Ki-67 (%)	All	1.04 (1.002-1.07)	0.038*
Subgroup	Luminal	1	
	Non-luminal	1.75 (0.39-7.92)	0.465

** p <0.05, (Cox Regression analysis), HR: Hazard ratio, CI: Confidence interval, 1: Reference value.*

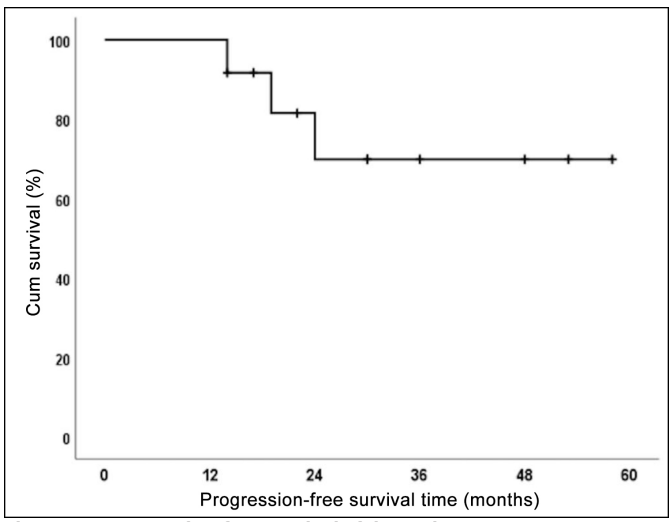

Figure 1a: Progression-free survival of the patients.

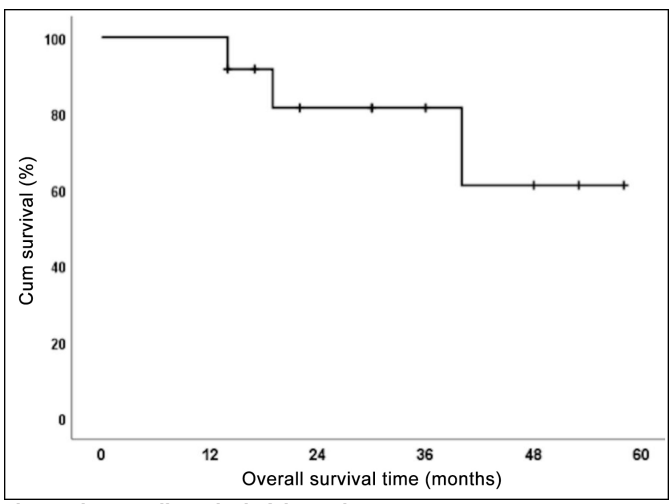

Figure 1b: Overall survival of the patients.

The median PFS and OS were 27 (10-58) months and 30 (14-58) months, respectively. The median follow-up period was 66 (32-130) months for the whole series. At the time of data analysis, 9 patients were alive without evidence of disease. Three patients died from liver insufficiency due to progression to multiple metastases.

Grade and Ki 67 index were significantly associated with DFS. Grade 3 tumours and increased expression of Ki-67 had a negative effect on DFS (Table II).

According to Kaplan-Meier survival analysis, 2- and 3-year PFS and OS rates were 82%, 69%, 92%, and 82%, respectively (Figure 1 a-b).

Development of LM in 3 years following BC treatment was linked to worse PFS ($p = 0.040$). No other characteristics were statistically associated with PFS and OS ($p > 0.05$).

DISCUSSION

Some authors regard metastatic BC as a chronic disease, given the long-term survival. For BC patients with liver metastases, the median survival time is 4-8 months without any treatment.[4] Chemotherapy prolongs the survival, but the 5-year survival rate is approximately 10%.[8-10] In the context of metastatic breast cancer, the first series of liver surgery belonged to Stehlin *et al.* in 1988.[11] In the following years, surgical resection was suggested in selected patients with isolated or oligometastatic disease to extend survival.

Many trials have demonstrated a survival benefit in favour of surgery.[1,5,6] Vertriest reported a 5-year OS even as high as 78% for patients of isolated metachronous liver metastases due to early Stage 1 or 2 breast carcinoma.[5] Ruiz *et al.* determined 5-year OS as 69% and 24% in a group of liver resections following chemotherapy and in a group of systemic therapy alone, respectively.[10] According to a Swedish nationwide registry-based trial, the median survival time of patients with isolated liver metastases in the surgical and systemic treatment groups was 77 and 28 months, successively.[12] Mariani *et al.* reported three 3-fold increased risk of death in patients without surgery.[13] They found a 3 year survival rate of 80%. Similarly, it was 82% in this study.

A multi-institutional registry study from Turkiye evaluated 200 BC patients with metachronous metastasis in the lung and liver.[14] Eighty-one patients of the systemic treatment group were compared to 119 patients of the interventional group, including those who underwent either surgery, RFA, or various local treatments. The trial has shown that intervention for metastases reduced the risk of death by 56%. Because of the low number of patients, subgroup analyses could not be performed among different interventional methods. MSKCC (Memorial Sloan Kettering Cancer Center) conducted a case control study of 167 patients with isolated BCLM to compare the outcomes of patients who underwent surgery and/or ablation to those with medical treatment.[15] Although no survival benefit was found between both groups, the recurrence-free interval was 28.5 months in the surgical cohort, along with the median

chemotherapy-free interval of 25 months. Therefore, the authors suggested surgical intervention in highly selected patients to attain a treatment-free holiday, which provides a probable enhancement in quality of life and decreased costs.

There is a tendency for different molecular types of BC to metastasise to various organs, which is explained by metastatic heterogeneity.[9] Luminal tumours usually develop bone metastasis, while TN and HER2+ tumours are prone to involve the brain. As for liver metastasis, HER2-enriched tumours are more prone to involve the liver. According to SEER data, HR+/HER2+ tumours are more likely to develop metastases to the liver than HR+/HER2– tumours.[4] In some studies, no association was shown between the BC subtype and hepatic metastasis.[2] In this study, luminal A was the most common type of BC, whereas HER2+ and HER2+/HR+ patients constituted 41% of the whole group.

In a systematic review of BCLM, the median time between BC surgery and the diagnosis of LM was reported as 35 months, ranging from 11 to 71 months.[9] In accordance with the literature, 11 patients in this study experienced liver metastasis with a median DFS of 36 months. A prolonged interval between BC treatment and diagnosis of metastasis is a favourable indicator for survival. Similarly, this trial observed better PFS in patients who had developed metastasis after three years of BC treatment. In many trials, a 2-year interval was reported as a cut-off time in identifying patients with better prognoses.[9,14] On the other hand, Hoffmann *et al*. noted over one year as a favourable prognostic factor associated with OS.[16]

Low tumour burden is the most relevant prognostic factor. Although there is no exact definition of low tumour burden, in most studies, solitary metastasis less than 4-5 cm in diameter was a better survival.[4,6] Vertiest *et al.* detected 47 months of DFS in patients with single lesions compared to 15 months in those with multiple lesions.[5] On the other hand, many studies, including patients with less than five liver metastases that had undergone metastasectomy or major hepatectomy, have demonstrated survival advantages.[3,8] Another important factor for prognosis is the presence of EHM. There is no consensus on whether EHM is a contraindication of liver surgery. According to a systematic review, evaluating 1,686 patients undergoing liver resection due to BCLM, EHM was identified in 18% of patients.[9] The presence of EM was accepted as an exclusion criterion for liver resection in 150 patients of this review. There are a few studies demonstrating no correlation between EHM and survival.[17] Conversely, in the review by Tasleem *et al.* BC patients who underwent liver surgery between 2005 and 2017 were evaluated.[8] Eight thousand two hundred eighty patients with isolated LM were compared to 800 patients with extrahepatic disease. The 5-year survival was found to be ranging from 24.6 to 78% and from 21 to 57% in those with LM only and with oligometastasis, respectively. Although median survival time was better in the first group, the authors highlighted liver surgery in both groups.

Except for surgical resection, there are few options in managing BCLM. A recent meta-analysis shows the survival advantages of hepatic surgery over RFA.[18] Therefore, treatment by local ablations is available for patients with poor health conditions, limited hepatic reserve, and those whose tumours are not larger than a few centimetres or not in conjunction with major vascular structures. Hepatic transarterial chemoembolisation or radioembolisation might be another management option, but literature is scarce. These are not usually recommended as first-line therapy and are generally thought to be a choice for patients who are amenable to resection.

Many authors offer to see the chemotherapy response before hepatic surgery since either stabilisation or diminishment of the disease is associated with a better prognosis.[3,7] Commencing with chemotherapy provides early systemic control and reduces the risk of recurrence. However, Adam *et al*. did not apply strict inclusion criteria to resect LM.[7] They described 5-year survival rates as 42% and 12% in patients with partial response and no response to preoperative chemotherapy, respectively. The authors suggested pre-metastasectomy chemotherapy response as a determinant factor in selecting surgical candidates. The study by Ellis *et al.* shed light on the timing of metastasectomy, which analysed the outcome of BC patients diagnosed with *de novo* metastases isolated to the liver in the national cancer database of the period from 2004 to 2015.[19] Compared to those without metastasectomy, 90 patients with hepatic metastasectomy were found to be associated with a 37% reduction in the risk of death. They demonstrated the loss of survival advantage if metastasectomy was performed after 12 months following the chemotherapy response. The authors have suggested early surgical referrals during this potential therapeutic window to gain improved survival. Similarly, in this study surgery was performed within 2-3 months after the systemic therapy. According to the literature, no long-term survival has been reported following surgery *per se*. The best results were achieved by combined treatment modality.

Proper patient selection for surgery is of utmost relevance in managing LM to achieve survival benefits. There is no established algorithm for patients with organ-specific metastasis for BC survival. The 5th ESO-ESMO International Consensus Guidelines advocate local therapy for only very selected cases with limited liver involvement, good performance scores, and no extrahepatic lesions following disease control after adequate systemic therapy.[20] In the literature, the studies are heterogeneous. There is no level 1 evidence yet. Most of the series are small, have single-centre data, and consist of highly selected and retrospective single-arm patients. Therefore, all data should be interpreted conscientiously. Moreover, a prospective multicentre randomised trial is required to elucidate the ideal candidates for liver surgery.

This study has several limitations. It is a retrospective study with the possibility of selection bias. Secondary to the rarity of single BCLM, it included only 12 patients. This low sample size limits the accuracy of statistical analysis.

CONCLUSION

A considerable portion of patients is at risk of metastasis due to BC. In patients with BCLM, thorough patient selection for surgical candidates is a relevant issue to gain survival advantage. In addition, to postpone the disease progression and to supply cancer survivors with a time interval of chemotherapy-free, surgical options should be individually evaluated. This study showed that higher histological grade and increased Ki-67 proliferation index of BC were significantly associated with worse DFS. Longer progression-free survival was observed in patients who had developed metastasis after three years of BC treatment.

ETHICAL APPROVAL:

Before conducting the study, approval was taken from the Ethical Review Committee of Basaksehir Cam and Sakura City Hospital at the University of Health Sciences, Istanbul, Turkiye (Approval number: 2023.03.127).

PATIENTS' CONSENT:

Informed consent were obtained from all patients who were alive.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

ES: Conception, design, supervision, data collection and processing, analysis and interpretation, literature review, writing and critical review.
TC: Conception, design, and critical review.
OB: Conception, design, supervision, and critical review.
MB: Conception, design, supervision, analysis and interpretation, and critical review.
All authors approved the final version of the manuscript to be published.

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