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ORIGINAL ARTICLE

Prognostic factors for longer disease free survival and overall survival after surgical resection of isolated liver metastasis from breast cancer

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Summary

Purpose: *Isolated liver metastases (LMs) from breast cancer (BC) occur in only 1-3% of the cases. Resection of isolated LMs improves survival. We examined the prognostic factors for time to LM development, disease free survival (DFS) and overall survival (OS) after BCLM resection.*

Methods: *From 2006 to 2009, 32 patients underwent LM resection. All of them had breast cancer surgery for their primary tumor and developed resectable LMs as the first and only site of disease progression.*

Results: *LMs developed after a median of 25 months. With a median follow up of 37 months (range 7-66) after metastases resection, median DFS and OS (with 95% CI) were 22.5 (12-40) and 37 (≥23) months, respectively. Tumor size ≥3 vs <3 cm and adjuvant chemotherapy vs no adjuvant chemotherapy correlated with shorter time to LM development ($p<0.01$ for both parameters). These parameters and BC negative estrogen (ER)/ progesterone receptors (PR) (ER^-/PR^- vs other) were related with shorter DFS. Positive (vs negative) axillary lymph nodes and BC negative ER/PR (ER^-/PR^- vs other) status correlated with shorter OS ($p<0.01$ for both parameters). A period to metastases development > 24 months (vs ≤24) and single (vs multiple) metastases were related with longer DFS and OS ($p<0.01$ for both conditions).*

Conclusion: *Despite the relatively small number of patients in this study, we believe that positive ER/PR status for both BC and LMs, negative axillary lymph nodes, time to liver metastases development >24 months and single liver metastases predict longer DFS and OS after LM resection.*

Key words: *breast cancer, disease free survival, liver metastasis, overall survival, prognostic factor*

Introduction

Distant metastases develop in approximately half of women with BC, indicating advanced disease and poor prognosis [1-9]. Isolated LMs appear in approximately 1-3% of BC patients [2,3]. According to literature data, the median OS of patients with LMs is 15 months for those who respond to chemotherapy and only 3 months for patients failing to respond [4,5,7].

Resection of LMs of BC can be performed in specialized centers with a trained team of hepatobiliary surgeons, anesthesiologists and other supporting personnel [1-6]. Several studies showed that resection improves the 5-year OS of BC patients by 20-37% (median 20-32 months), compared to patients not undergoing surgery [2,5,7].

The aim of this study was to examine the prognostic significance of the BC patient characteristics, characteristics of the primary BC and its treatment, time to LM development, and DFS and OS after liver metastasectomy. Analyzed were also the prognostic significance of LMs characteristics and their relation with DFS and OS.

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Methods

Patient selection

From February 2006 to December 2009, 32 patients had surgical removal of isolated LM at the Institute of Oncology and Radiology of Serbia (IORS). All patients were female with primary BC surgery. No local recurrence existed when LMs developed. Good general condition of patients and LMs as the first and only site of disease progression enabled LMs resection or ablation, while preserving sufficient functional liver volume.

Treatment of primary disease

Depending on the size of the primary BC, breast-conserving surgery or radical mastectomy were performed. Radiotherapy was delivered to patients who had breast-conserving surgery (quadrantectomy) or radical mastectomy with ≥4 positive lymph nodes, or tumor size >5 cm.

Adjuvant chemotherapy was administered based on tumor histological features, following current BC treatment protocols, combined with hormonotherapy (for patients with ER/PR positive tumors) or trastuzumab-targeted therapy (for patients with HER2 positive tumors).

Depending on the time period from BC to LMs development, two subgroups of patients were created and analysed:

1) ≤24 months – patients with LM appearance within the first 24 months or LM synchronous with BC.

2) >24 months – patients with LM appearance after 24 months.

Surgical treatment of liver metastases

The liver resection plan was made according to angio-CT scan and liver volumetry. The surgical approach included unilateral or bilateral subcostal laparotomy. Intraoperative ultrasound was performed for precise determination of localization, size and number of LMs, as well as their relationship to blood vessels and bile ducts, later to be followed by definite resection plan.

All patients underwent anatomical liver resection (resection of segments or lobes), metastasectomies (non anatomical liver resection) or radiofrequency ablation of LMs.

Postoperative treatment of liver metastases

After LMs resection, treatment was continued with postoperative chemotherapy, hormonal or targeted therapy, according to the histological characteristics of the LMs and/or the primary BC.

Statistics

For normal distribution data testing, the Kolmogorov–Smirnov and Shapiro-Wilk tests were used. Descriptive methods of statistical analysis (frequencies, percents, mean, median, standard deviation [SD], and range) were used to summarize the data. The statistical significance level was set at $p<0.05$. Curves of probabilities for time to LM, DFS and OS after LM resection, and OS from primary BC were constructed using the Kaplan-Meier product-limit method; the median of survival analysis with corresponding 95% CI were used for description, and the log-rank test was used for testing differences between curves for time to LM, DFS and OS after LM resection. Univariate and multivariate Cox proportional hazard regression models were used; the hazard ratio (HR) with the corresponding 95% CI were used for description; the Wald and Likelihood ratio test were used for statistical testing. The statistical analysis was done with the program R (version 2.15.1 (2012-06-22) - "Roasted Marshmallows"; Copyright (C) 2012, The R Foundation for Statistical Computing; ISBN 3-900051-07-0; downloaded: June 27, 2012).

Results

All patients were female (median age 49 years, range 29-73). From the primary BC treatment (1997-2011) until the end of this research (December 2012), the mean patient follow up time was 61.97 months (median 64, range 12-181) and the median OS from the primary BC was 70 months (95% CI ≥40) (Figure 1).

Only 3/32 (9.4%) patients had synchronous BC and LM. The remaining 29/32 patients (90.6%) developed LM in a period of 8-120 months (median time to LM 25 months; 95% CI 16-36).

The mean patient follow up time after LM surgery was 34.09 months (median 37, range 7-66). Median DFS and OS after LM resection were 22.5 (95% CI 12-40) and 37 (95% CI ≥23) months, respectively (Figure 1).

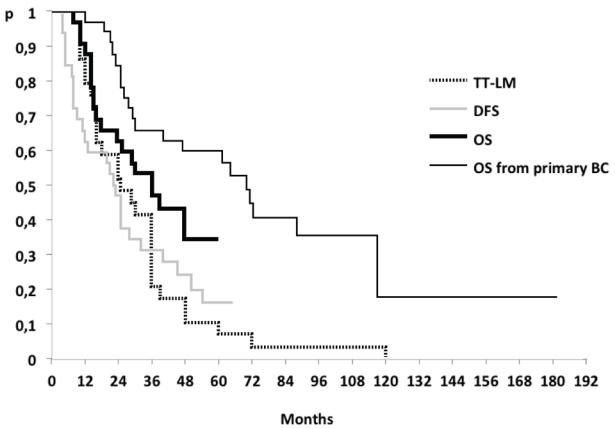

Figure 1. TT-LM, DFS OS and OS from primary BC for the whole group of patients. TT-LM: time to liver metastasis development, LM: liver metastasis, DFS: disease free survival, OS: overall survival, BC: breast cancer.

Table 1. Patient general characteristics, primary breast cancer, breast cancer treatment and their relationship with TT-LM, DFS and OS

Characteristics	*N (%)*	*Log-rank test* *TT-LM*	*N (%)*	*Log-rank test* *DFS*	*OS*
Age (years)					
Mean (SD)	51.10 (11.05)	-	51.66 (11.22)	-	-
Median (range)	48 (29-71)		49 (29-73)		
Age (years)					
<50	15 (51.7)		16 (50)		
≥50	14 (48.3)	ns	16 (50)	ns	ns
BC histology					
Ductal	16 (55.2)		19 (59.4)		
Lobular	13 (44.8)	ns	13 (40.6)	ns	ns
T in TNM staging					
T1	5 (17.2)		5 (15.6)		
T2	21 (72.4)	ns	23 (71.9)	ns	ns
T4	3 (10.4)		4 (12.5)		
ER/PR BC status					
ER/PR negative	12 (41.4)	p<0.05	12 (37.5)	p<0.01	p<0.01
Other	17 (58.6)		20 (62.5)		
HER2 BC status					
Negative	20 (69.0)	ns	23 (71.9)	ns	ns
Positive	9 (31.0)		9 (28.1)		
Lymph nodes					
Positive	19 (65.5)	p<0.05	22 (68.8)	ns	p<0.01
Negative	10 (34.5)		10 (31.2)		
Breast surgery for					
T≥3cm (radical)	14 (48.3)	p<0.01	15 (46.9)	p<0.01	p<0.01
T<3cm (sparing)	15 (51.7)		17 (53.1)		
Postoperative (adjuvant) chemotherapy					
No	8 (27.6)	p<0.05	23 (71.9)	p<0.01	p<0.01
Yes	21 (72.4)		9 (28.1)		
Postoperative (adjuvant) hormonotherapy					
No	13 (44.8)	p<0.05	14 (43.8)	ns	p<0.05
Yes	16 (55.2)		18 (56.2)		
Postoperative (adjuvant) radiotherapy					
No	11 (37.9)	ns	11 (34.4)	ns	ns
Yes	18 (62.1)		21 (65.6)		
Total	29* (100)	-	32 (100%)	-	-

*Patients with metachronous breast cancer and liver metastasis. ns: not statistically significant, LM: liver metastases, TT-LM: time to LM development, DFS: disease free survival, OS: overall survival, BC: breast cancer, ER: estrogen receptor, PR: progesterone receptor

Primary BC and its treatment, time to LM, DFS and OS after LM resection

The characteristics of the patients, the primary BC and its treatment are shown in Table 1.

Ductal carcinoma was slightly more frequent than lobular carcinoma (55 vs 45%). No other histological types were diagnosed. Almost 90% of the patients had T1 or T2

BC size, but radical mastectomy (patients with BC size ≥ 3cm) vs breast-conserving surgery (patients with BC size < 3cm) was nearly 50% : 50% (Table 1). Twenty-eight out of 32 (87.5%) patients had breast surgery as primary treatment, while 4/32 (12.5%) patients with T4 stage received neoadjuvant chemotherapy before radical mastectomy.

Negative ER/PR status was found in 41% of the patients. HER2 positive tumors were diagnosed in 31% of the patients. Two thirds of the patients (65%) had positive axillary lymph nodes found on breast surgery.

The association of the patient general characteristics, their primary BC and its treatment with time to LM, DFS and OS after LM resection are shown in Table 1.

All parameters identified as statistically sig-

Table 2. Results of univariate and multivariate Cox regression analyses for TT-LM, DFS and OS in relation to the characteristics of the patients, the primary BC and BC treatment

Characteristics	*Univariate Cox regression* HR (95%CI)			*Multivariate Cox regression* HR (95%CI)		
	TT-LM	*DFS*	*OS*	*TT-LM*	*DFS*	*OS*
Total patients: N (%)	29 (90.6)*	32 (100)	32 (100)	29* (90.6)	32 (100)	32 (100)
ER/PR BC status ER/PR neg vs other	2.36 (1.1-5.2) p<0.05**	4.8 (1.9-12.2) p<0.01**	5.71 (2.1-15.7) p<0.01**	-	2.87 (1.0-8.0) p<0.05#	3.40 (1.1-10.9) p<0.05#
Lymph nodes LN+ vs LN -	2.22 (1.0-5.0) p<0.05**	2.4 (1.0-6.1) p<0.05**	3.95 (1.2-13.6) p<0.05**	-	-	4.12 (1.1-14.9) p<0.05#
Breast surgery T≥3cm (radical) vs T<3cm (sparing)	2.8 (1.3-6.1) p<0.01**	2.9 (1.3-6.4) p<0.01**	4.02 (1.6-10.3) p<0.01**	3.42 (1.5-7.7) p<0.01#	2.54 (1.0-6.3) p<0.05#	3.14 (1.0-9.8) p<0.05#
Postop (adjuvant) chemotherapy Yes vs No	2.44 (1.0-5.8) p<0.05**	4.7 (1.6-13.8) p<0.01**	5.91 (1.4-25.8) p<0.01**	3.02 (1.2-7.6) p<0.05#	4.30 (1.3-13.7) p<0.01#	-
Postop.(adjuvant) hormootherapy No vs Yes	2.17 (1.0-4.7) ns**	2.2 (1.0-4.8) ns**	2.82 (1.1-7.0) p<0.05**	-	-	-
Likelihood ratio test for the multivariate Cox regression model				p<0.01	p<0.01	p<0.01

* Patients with metachronous BC and LM, ** Likelihood ratio test for univariate Cox regression analysis, # Wald test for multivariate Cox regression analysis. LN: lymph nodes. For other abbreviations see footnote of Table 1

nificant (log-rank test) (Table 1) were included in the univariate and multivariate Cox regression analysis (Table 2).

The factors assosiated with shorter time to LM, DFS and OS identified by the univariate Cox regression analysis were negative ER/PR status (ER^-/PR^- vs other), positive vs negative axillary lymph nodes, BC size ≥ 3cm (radical mastectomy) and administration of adjuvant chemotherapy after breast surgery. Patients who were not under hormonotherapy had shorter OS, which was directly related to the negative ER/PR BC status.

In the multivariate Cox regression analysis, the factors associated with time to LM development were BC size ≥ 3cm (radical surgery) and administration of adjuvant chemotherapy. Besides these treatment modalities, DFS after LM resection was also affected by ER/PR BC status (ER^-/PR^- vs other), whereas patients with positive axillary lymph nodes had a shorter OS post metastasectomy. Adjuvant chemotherapy administration had no statistically significant impact on OS.

Treatment of liver metastases and DFS, OS

After the development of LM, all patients underwent liver surgery. Characteristics of LM, and their treatment, as well as their correlation with DFS and OS are shown in Table 3.

Patients with a solitary LM were compared with the group bearing more than one LM. Liver resection was performed in 30/32 (93.8%) patients: anatomic liver resection was performed in 17/30 (56.7%) patients and metastasectomy in 13/30 (43.3%). Radiofrequency ablation as complementary treatment to surgery was carried out in 2/32 (6.2%) patients. Statistical analysis concerning the type of LM surgery was not done because of the small number of patients in the subgroups.

There was no evidence of disease in patients when post-liver surgery chemotherapy started. Statistical analysis regarding the type of the applied chemotherapy was not done because of the small number of patients in the observed subgroups (Table 3).

All parameters identified as statistically significant (log-rank test) for the observed times (DFS and OS after liver surgery in Table 3) were included in the univariate and multivariate Cox regression analysis (Table 4).

Patients with time to LM development ≤24 months, those with more than one liver metastasis or negative ER/PR LM status, and patients without hormonotherapy after the LM surgery had shorter DFS and OS (univariate Cox regression analysis).

The multivariate Cox regression analysis showed the that the time to LM (≤24 vs >24 months) and the number of LM (single vs ≥2) had statistically significant impact on DFS and OS, whereas ER/PR LM status was near to the statistical significance level (p=0.05). Hormonotherapy

Table 3. The influence of the LM characteristics and LM treatment for DFS and OS (N=32)

Characteristics	*N (%)*	*Log-rank test*	
		DFS	*OS*
Period from BC to LM			
Synchronous LM	3 (8.4)	ns	ns
Metachronous LM	29 (90.6)		
Period from BC to LM (months)*			
Mean (SD)	30.76 (23.4)	-	-
Median (range)	25 (8-120)		
Period from BC to LM (categories)			
≤24 months	17 (53.1)	p<0.01	p<0.01
>24 months	15 (46.9)		
Number of LM			
1	16 (50)	p<0.01	p<0.01
≥2	16 (50)		
Size LM (cm)			
Mean (SD)	2.81 (1.18)	-	-
Median (range)	2.6 (1-6)		
Type of LM surgery			
Resection	30 (93.8)		
Hepatectomy	1 (3.1)		
Lobectomy	1 (3.1)		
Two segments	3 (9.4)	-	-
One segment	12 (37.5)		
Metastasectomies	13 (40.6)		
Ablation	2 (6.2)		
ER/PR LM status			
ER/PR negative	25 (78.1)	p<0.05	p<0.05
Other	7 (21.9)		
HER2 LM status			
Negative	25 (78.1)	ns	ns
Positive	7 (21.9)		
Postoperative LM hormonotherapy			
Yes	25 (78.1)	p<0.05	p<0.05
No	7 (21.9)		
Postoperative LM chemotherapy			
FAC	9 (28.1)		
CMF	4 (12.5)	-	-
Taxol	17 (53.1)		
Xeloda	2 (6.2)		

*Period from BC to LM for patients with metachronous LM. SD: standard deviation. For other abbreviations see footnote of Table 1.

Table 4. Results of univariate and multivariate Cox regression analyses for DFS and OS in relation to the LM characteristics and treatment (N=32)

Characteristics	*Univariate Cox regression HR (95%CI)*		*Multivariate Cox regression HR (95%CI)*	
	DFS	*OS*	*DFS*	*OS*
Period from BC to LM (categories)	3.6	4.7	3.3	2.9
≤24 vs >24 months	p<0.01*	p<0.01*	p<0.05#	p<0.05#
Number of LM	3.8	3.8	6.5	5.3
≥2 vs 1	p<0.01*	p<0.01*	p<0.01#	p<0.01#
ER/PR LM status	4.4	8.2	3.9	7.2
ER/PR neg vs other	p<0.01*	p<0.01*	p=0.054#	p=0.076#
Postoperative LM hormonotherapy	4.4	8.2	-	-
No vs Yes	p<0.01*	p<0.01*		
Likelihood ratio test for the multivariate Cox regression model			p<0.01	p<0.01

*Likelihood ratio test, #Wald test. For other abbreviations see footnote of Table 1

was directly related to ER/PR LM status, and was not an independent prognostic factor.

Six out of 32 patients (18.8%) showed no disease progression, at a median follow up time of 61 months after LM resection (range 38-65). Disease progression was observed in 26/32 (81.2%) patients; progression took place in the liver and other organs in 8/26 patients (30.8%), in the liver alone in 2/26 (7.7%), while was extrahepatic in 16/26 (61.5%) patients.

Discussion

Visceral metastases of BC are a sign of advanced disease associated with poor prognosis [2,3]. Five-year survival of patients with LM in our study was 34.4%, while in the published series this figure ranges from 22 to 44% [1,2,6,8]. Adam et al. found OS 34% in 84 patients [5]. Indications for LM resection have been extended, because of reduced mortality and morbidity due to better surgical techniques and anesthesia [1-6].

In our study, we examined the effects of the general patient characteristics, primary BC and LM on the course and outcome of disease. Patients with adjuvant chemotherapy (positive axillary lymph nodes or BC size ≥ 3 cm subjected to radical mastectomy) had higher initial risk and a less favorable disease course ($p<0.01$).

Patients with T4 primary BC who had received neoadjuvant chemotherapy before BC surgery also had higher initial risk, but due to their small number, no statistical significance was shown.

Several authors have reported that ER and PR status (in primary BC and LM) strongly affect the disease outcome [1-3,11,13]. The best prognosis has been observed in patients with ER/PR positive status in both primary BC and LM. Elias et al. reported that positive hormone receptor status was the most significant positive prognostic factor in both univariate and multivariate analysis in a series of 54 patients with LM resection [10]. Our results showed that hormonotherapy was directly related to the ER/PR status, which was confirmed with the univariate but not with the multivariate analysis.

Patients with HER2-positive status have worse prognosis [12,14,15]. All HER2-positive patients in our study received adjuvant targeted therapy (trastuzumab), thus no statistically significant difference has been shown in relation to time to LM, DFS and OS.

Time to LM was a precise prognostic factor, as shown in another study [2]. Our patients who developed LM 2 years after their primary BC had significantly better survival compared to those with earlier development of LM, as well as those with solitary compared to those with multiple metastases. This is in accordance with results of other researchers [2,4].

It is very important to make a good plan for LM resection. LM surgery is just one of the treatment modalities, but not the only one. At our institute, whenever possible, we perform liver resection (anatomical or non-anatomical), trying to preserve as bigger liver volume as possible. Radiofrequency ablation is a palliative, not curative, and technically easier interventional method, but still whenever possible, resection of LM should be done [16].

Conclusion

In properly selected patients with LM, LM resection increases OS. Also, smaller primary tumor, longer time period to development of LM, solitary LM and positive hormone receptor status of the primary BC and LM, represent good prognostic factors, predicting longer DFS and OS after LM resection.

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