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ORIGINAL ARTICLE

Prognostic importance of steroid receptor status for disease free and overall survival after surgical resection of isolated liver metastasis in breast cancer patients

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Summary

Purpose: *Breast cancer (BC) is the most common malignancy among women, while isolated operable liver metastases (LMs) from BC are very rare and occur in only 1-5% of the patients. Besides, positive steroid receptor (SR) status for oestrogen and/or progesterone is known as a factor which improves disease free survival (DFS) and overall survival (OS). The primary aim of this study was to examine the impact of SR status on DFS and OS after liver metastasectomy in female patients with primary BC.*

Methods: *We analyzed 32 medical records of female patients diagnosed and treated for primary BC with LMS as the first and only site of disease progression, at the Institute of Oncology and Radiology of Serbia (IORS), during 2006-2009. All of them underwent primary BC surgery as well as LMs resection.*

Results: *Patients with metachronous BC and LMs and positive SR status in both BC and LM (BC+/LM+) had a median time from BC to LM occurrence (TTLM) of 36 months, compared to BC+/LM- and BC-/LM- subgroups, whose medians for TTLM were 30.5 and 14.5 months, respectively ($p<0.01$). For all patients, positive SR status showed high correlation with longer DFS and OS after LM resection (medians according survival analysis for DFS/OS in subgroups BC-/LM-, BC+/LM- and BC+/LM+ were 10/19, 25/45, 50/not reached months respectively; $p<0.01$ for DFS/OS). Cox regression analysis confirmed that the subgroup of patients with BC-/LM- had 10.8 and 18.8 higher risk of events for DFS (disease relapse or death) and event for OS (death only), respectively, compared to BC+/LM+ subgroup of patients.*

Conclusion: *Positive SR status in BC and LM has a high impact not only on time from BC to LM occurrence, but also on longer DFS and OS after LM resection.*

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

Introduction

Positive ER and/or PR receptors status in primary BC is one of the best established prognostic factors, linked with longer DFS and OS. Also, the expression of SR plays an extremely important role in treatment decision by helping select patients who could benefit from endocrine therapy [1,2].

In 10-40% of metastatic disease, there is a certain transition in SR status between primary breast tumors and metastases [3,4]. This change could be caused by chemotherapeutic agents effect, genetic drift occurring during tumor progression or in case when the metastatic process

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is driven from the very beginning by the clone with the more aggressive phenotype [5]. The main significance of this transition is that it gives the possibility to identify patients who could benefit from additional hormonal therapy.

Despite advances in early detection and modern treatment, around 30% of BC patients will develop distant metastases. Among all metastasized patients, 40-50% of them will have the liver affected [6]. In 12-15% of metastatic patients liver will be the first site of disease progression, while in 5% of the patients it will remain an isolated progression site [7]. Unfortunately, at the time of diagnosis, only 5% of liver tumors are operable [8].

The 5-year OS in BC patients is around 80% [9]. Patients with LMs live around 14 months, and less than 20% of them will survive longer than 36 months [10]. Standard treatment options for metastatic disease include chemotherapy and/or hormonal therapy, although complete remission of the secondary tumor is very rare. Surgical resection of LMs improves the 5-year OS in BC patients by 20-37% (median 20-32 months), compared to patients without surgery [11-13].

The main aim of this study was to examine the impact of SR status on DFS and OS after liver metastasectomy in female patients with primary BC. Additionally investigated were the correlation between SR status in BC and in LMs and characteristics of the disease and its treatment.

Methods

Patient selection

We analysed the medical records of 32 female patients treated at the IORS between February 2006 -December 2009. All patients were diagnosed with primary BC and had operable LMs, as the first and only metastatic site. LMs were diagnosed synchronously with the primary breast tumor (at the same time) or metachronously (during disease-free, follow up period). We defined TTLM as the period between diagnosis of primary BC and confirmation of LMs.

Primary disease treatment

Depending on the primary breast tumor size, patients underwent radical mastectomy or breast-conserving surgery. Based on tumor histological features, standard adjuvant chemotherapy was administered, with addition of hormonal therapy for patients with SR positive tumors and/or trastuzumab for patients with HER2 positive tumors. Radiotherapy was delivered to patients who had tumor size >5 cm, radical mastectomy with ≥4 positive lymph nodes or breast-conserving surgery (quadrantectomy).

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 exact determination of localization, size and number of LMs, as well as their relationship to blood vessels and bile ducts. Patients underwent anatomical liver resection (resection of segments or lobes), metastasectomies (non-anatomical liver resection) or radiofrequency ablation with biopsy of metastases.

Postoperative treatment after liver metastases resection

According to standard protocols, treatment after LMs resection was continued using systemic chemotherapy, hormonal and/or targeted therapy.

Histology and immunohistochemistry

All specimens from both primary tumors and LMs have been reviewed at the Department of Pathology, IORS, by a consultant pathologist. SR status was determined by immunohistochemistry; we used DAKO primary antibodies: Monoclonal Mouse Anti-Human Estrogen Receptor α, Clone 1D5 and Monoclonal Mouse Anti-Human Progesterone Receptor, Clone PgR 636. For interpretation of the results, score for proportion staining (score 0-5) and score for staining intensity (score 0-3) were defined (Table 1) [14]. By adding both scores together, the maximum score was 8 and as a cut-off value we used score 4. Samples having ER or PR score ≥4 were classified as SR positive.

Steroid receptor subgroups

According to the SR status of the primary tumor and LMs, all patients were stratified into three groups:

1. BC+/LM+: patients with an unchanged positive SR status (positive in both BC and LM).
2. BC+/LM-: patients with SR status in liver being changed compared to breast tumor (positive in BC and negative in LM).
3. BC-/LM-: patients with an unchanged negative SR status (negative in both BC and LM).

Table 1. Scoring system for steroid receptor immunohistochemistry results

Score for proportion staining	*Score for staining intensity*
0 = No nuclear staining	0 = No staining
1 = <1% nuclei staining	1 = Weak staining
2 = 1-10% nuclei staining	2 = Moderate staining
3 = 11-33% nuclei staining	3 = Strong staining
4 = 34-66% nuclei staining	
5 = 67-100% nuclei staining	

From: Leake R, Barnes D, Pinder S et al. Immunohistochemical detection of steroid receptors in breast cancer: a working protocol. J Clin Pathol 2000; 53:634-635 [14].

Table 2. Patient age and characteristics of disease (primary BC and LMs) and treatment (BC and LM treatment) in total according to SR subgroups

Characteristics	*Total*	*ER & PR for BC/LM*			*Test*
		BC+ / LM+	*BC+ / LM-*	*BC- / LM-*	
Age (years)					
Mean (SD)	51.7 (11.2)	50.9(14.3)	52.2(10.6)	51.5(10.9)	
Median (range)	49 (29-73)	50 (29-71)	50 (40-73)	47.5 (38-70)	ns
BC & BC Stage and treatment characteristics					
BC histology, N (%)					
Ductal	19(59.4)	4(57.1)	8(61.5)	7(58.3)	ns
Lobular	13(40.6)	3(42.9)	5(38.5)	5(41.7)	
T in TNM staging, N (%)					
T1	5(15.6)	1(14.3)	2(15.4)	2(16.7)	
T2	23(71.9)	6(85.7)	10(76.9)	7(58.3)	ns
T4	4(12.5)	-	1(7.7)	3(25.0)	
Lymph nodes, N (%)					
Positive	22(68.8)	3(42.9)	9(69.2)	10(83.3)	ns
Negative	10(31.2)	4(57.1)	4(30.8)	2(16.7)	
Breast surgery, N (%)					
Sparing (T≤3cm)	17(53.1)	7(100)	7(53.8)	3(25.0)	p<0.01
Radical (T>3cm)	15(46.9)	-	6(46.2)	9(75.0)	
Postoperative BC therapy					
With adj. chemotherapy	23(71.9)	3(42.9)	9(69.2)	11(91.7)	ns§
With adj. hormonotherapy	18(56.2)	6(85.7)	12(92.3)	-	p<0.01§
With adj. radiotherapy	21(65.6)	5(71.4)	9(69.2)	7(58.3)	ns§
Period from BC to LM (TTLM)					
With period from BC to LM, N (%)					
No (synchronous LM)	3 (9.4)	-	3(23.1)	-	ns
Yes (metachronous LM)	29 (90.6)	7(100)	10(76.9)	12(100)	
Period from BC to LM (months)*, N (%)					
Mean (SD)	30.76 (23.4)	44.6 (33.9)	33.4 (19.9)	20.5 (14.2)	p<0.05
Median (range)	25 (8-120)	36 (18-120)	30.5 (10-72)	14.5 (8-48)	
Period from BC to LM (categories), N (%)					
≤24 months#	17 (53.1)	1 (14.3)	7 (53.8)	9 (75.0)	p<0.05
>24 months	15 (46.9)	6 (85.7)	6 (46.2)	3 (25.0)	
LM & LM treatment characteristics					
Number of LM, N (%)					
1	16(50.0)	4(57.1)	8(61.5)	4(33.3)	ns
≥2	16(50.0)	3(42.9)	5(38.5)	8(66.7)	
Size LM (cm)					
Mean (SD)	2.8 (1.2)	2.3 (1.4)	3.0 (1.4)	2.9 (0.8)	ns
Median (range)	2.6 (1-6)	1.5 (1-4.5)	2.7 (1.2-6)	3 (1.8-4)	
Type of LM surgery, N (%)					
Resection	30(93.8)	6(85.7)	13(100)	11(91.7)	ns
Ablation	2(6.2)	1(14.3)	-	1(8.3)	
Postoperative LM therapy, N (%)					
With adj. chemotherapy	32(100)	7(100)	13(100)	12(100)	-
- FAC	9(28.1)	1(14.3)	6(46.2)	2(16.7)	
- CMF	4(12.5)	2(28.6)	2(15.4)	-	ns
- Taxol	17(53.1)	4(57.1)	5(38.5)	8(66.7)	
- Capecitabine	2(6.2)	-	-	2(16.7)	
With hormonotherapy	7(21.9)	7(100)	-	-	p<0.01§
Total, N (%)	32 (100)	7 (100)	13 (100)	12 (100)	-

ns:not statistically significant, BC:primary breast cancer; LM:liver metastases, SD:standard deviation.
*Period from BC to LM for patients with metachronous LM; # including patients with synchronous LM; § compared to patients without current therapy

Statistics

Descriptive methods of statistical analysis were used (frequencies, percents, mean, median, standard deviation, and range). Statistical tests were used for normality data testing (Kolmogorov–Smirnov, Shapiro-Wilk) and comparison of disease (BC,LM) and treatment characteristics among SR subgroups (Kruskal-Wallis, Wilcoxon rank sum, Fisher exact test). The statistical level of significance was set at $p<0.05$ and the Bonferroni correction was used for multiple testing at the same set of data. Methods of survival analysis were used to investigate the impact of SR status on DFS and OS after liver metastasectomy (Kaplan-Meier product-limit method; median of survival analysis with corresponding 95% CI; log-rank test; univariate Cox proportional hazard regression models; hazard ratio (HR) with the corresponding 95% CI; Wald and Likelihood ratio test). The statistical analysis was done with the program R [15].

Results

All patients were female. Their age, characteristics of disease (BC,LM) and treatment details are shown in Table 2 (in total and according to 3 SR subgroups). During and after BC treatment, SR status remained stable in 19/32 (59.4%) of the patients (Figure 1).

All patients with BC+/LM+ and more than a half (53.8%) of patients with BC+/LM- had breast-conserving surgery, while the majority of patients with BC-/LM- (75%) had radical mastectomy ($p<0.01$, Table 2). Adjuvant chemotherapy was administered to 71.9% of the patients; adjuvant hormonal therapy was administered to 85.7% and 92.3% of the patients in BC+/LM+ and BC+/LM- subgroups, respectively ($p<0.01$; Table 2).

After adjuvant treatment, during the follow-up period, metachronous LMs occurred in 29/32 (90.6%) patients, within a median of 25 months; in 17 of those patients this period was shorter or equal to 24 months. Statistically significant difference was confirmed for TTLM between all subgroups of SRs (medians TTLM for BC+/LM+, BC+/LM- and BC-/LM- were 36.0, 30.5 and 14.5 months respectively; $p<0.05$; Table 2), as well as for frequencies of TTLM categories (TTLM ≤24 months for BC+/LM+ , BC+/LM- and BC-/LM- were 14.3, 53.8 and 75.0% respectively; $p<0.05$; Table 2).

Survival analysis for TTLM is shown in Tables 3, 4 and Figure 2. Patients without synchronous LM from the BC-/LM- subgroup had the shortest TTLM, while the longest TTLM was observed in the BC+/LM+ subgroup (medians TTLM for BC-/LM-, BC+/LM- and BC+/LM+ were 14.5, 30.5 and 36 months respectively; $p<0.01$; Table 3).

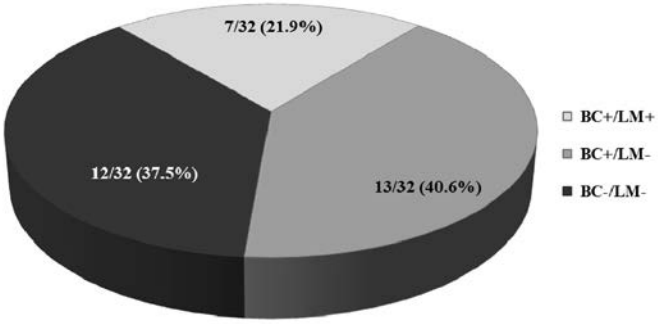

Figure 1. Percent distribution of steroid receptor subgroups.

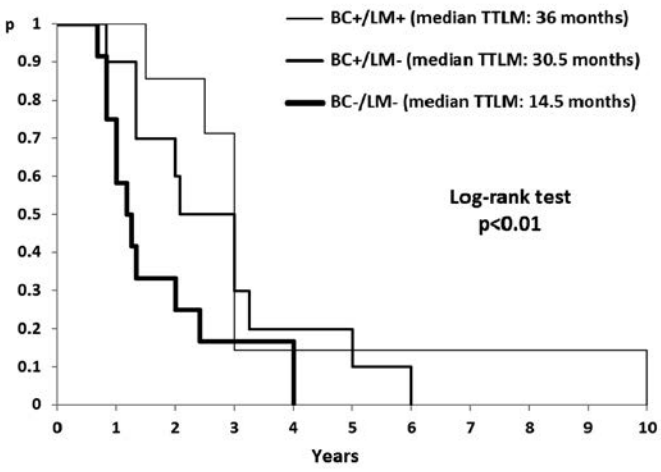

Figure 2. Kaplan-Meier plot of TTLM according steroid receptor subgroups.

Univariate Cox regression analysis confirmed that the BC-/LM- subgroup had 2.8-fold higher risk for LM occurrence compared to BC+/LM+ subgroup of patients without synchronous LM ($p<0.01$; Table 4).

Patients in the BC-/LM- subgroup were more common to have two or more LMs (66.7%, Table 2). They also had a bigger size of liver metastases (median 3 cm, Table 2), but without statistically significant difference compared to the BC+/LM+ and BC+/LM- subgroups. Predominant type of LM operation was resection (93.8%, Table 2). All patients received postoperative chemotherapy, while hormonal therapy received patients with stable positive SRs in the subgroup BC+/LM+ (Table 2).

The results of analysis of the correlation between survival after LM operation (DFS and OS) and SRs subgroups are shown in Tables 3,4,5 and Figures 3,4. Statistical analysis confirmed that patients with BC-/LM- had the shortest, while BC+/LM+ had the longest DFS and OS (medians for DFS/OS in subgroups BC-/LM-, BC+/LM- and BC+/

LM+ were 10/19, 25/45, 50/not reached months respectively; p<0.01;Table 3,Figures 3,4). Additional analysis for pairs of BC/LM subgroup also confirmed that BC+/LM- group had a statistically significant longer DFS and OS, compared to the BC-/LM- (Table 3, Figures 3,4).

Univariate Cox regression analysis showed that patients with BC-/LM- had 10.8 and 18.7-fold higher risk for DFS-event (disease relapse and/or death) as well as for OS-event (death) respectively, compared to patients with BC+/LM+ (p<0.01; Table 4).

Discussion

LMs in BC patients represent poor prognostic factors for both DFS and OS. Standard treatment options for metastatic disease include chemotherapy and/or hormonal therapy, but despite multidisciplinary approach, median OS is still poor and ranges between 2 and 3 years [2,8]. Surgical resection of LMs from BC is still a very controversial topic of discussion, due to the diversity of the metastatic pattern in different organs but also because the existence of metastases reflects disseminated disease in which a local treatment modality is inconclusive. However, many studies advocate the benefit of metastasectomy, which in these patients does improve the OS in around 30% [11-13].

One of the most accurate prognostic factors in BC is the status of ER and PR in the primary tumor [16]. Among numerous studies, one conducted in MD Anderson Cancer Centre, found that patients with ER/PR negative receptors had significantly shorter median OS of (28.3 months), comparing to SR positive patients whose median OS was 76.8 months [16]. The results of another study by Martinez et al. also confirmed the longer OS (37.2 months in SR positive patients), but also showed that ER/PR positive tumors had less aggressive phenotype. Furthermore, patients with SR positive tumors achieved better response to neoadjuvant chemotherapy [17]. Similar results have been reported in a paper by Elias et al., who showed median OS in SR positive patients was 44

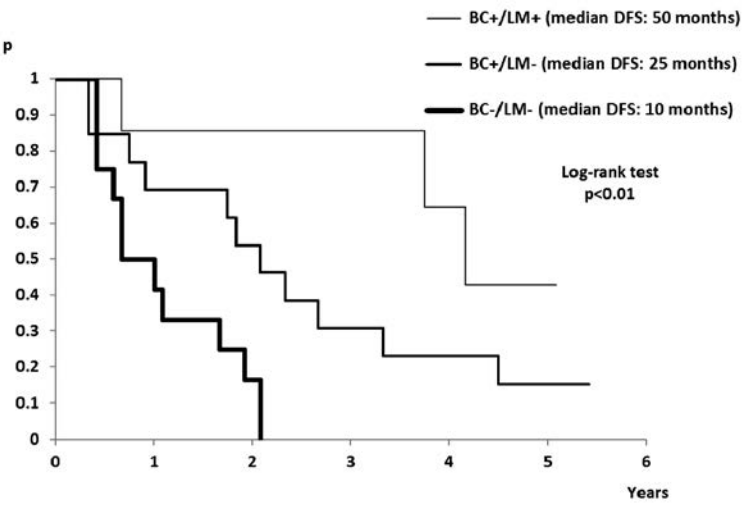

Figure 3. Kaplan-Meier plot of DFS according steroid receptor subgroups.

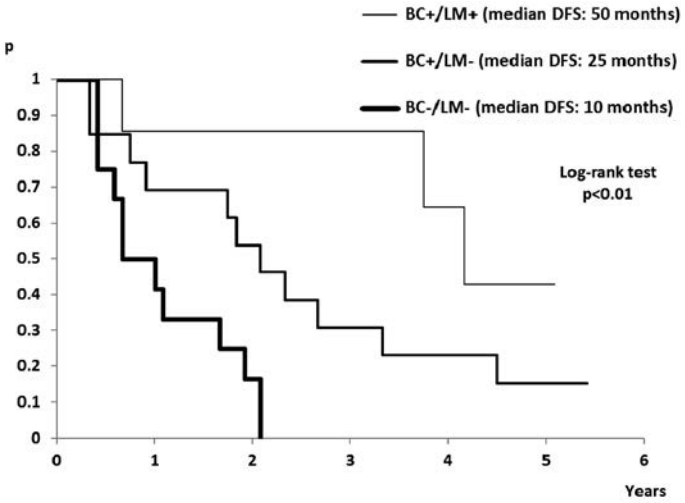

Figure 4. Kaplan-Meier plot of OS according steroid receptor subgroups.

Table 3. TTLM, DFS and OS according to steroid receptor subgroups

Survival analysis descriptive data	*Total*	*ER & PR for BC/LM*			*Log-rank, p*
		BC+ / LM+	*BC+ / LM-*	*BC- / LM-*	
TTLM*					
N (%)	29 (90.6)	7(100)	10(76.9)	12(100)	
Median (95%CI)	25 (16-36)	36 (≥30)	30.5 (≥16)	14.5 (≥12)	<0.01
DFS					
N (%)	32(100)	7(100)	13(100)	12(100)	
Median (95%CI)	22.5 (12-40)	50 (≥45)	25 (≥11)	10 (≥7)	<0.01
OS					
N (%)	32(100)	7(100)	13(100)	12(100)	
Median (95%CI)	37 (≥23)	Not reached	45 (≥18)	19 (≥11)	<0.01

*Only for patients with metachronous LM. For abbreviations see text

Table 4. Univariate Cox regression analysis for TTLM, DFS and OS according steroid receptor subgroups

Time to event	*HR (95%CI)*	*Wald test for HR*	*Likelihood ratio test for HR*
TTLM*			
BC+/LM- : BC+/LM+	1.31 (0.5-3.6)	ns	p<0.05
BC- /LM- : BC+/LM+	2.8 (1.0-7.6)	p<0.01	
DFS			
BC+/LM- : BC+/LM+	3.13(0.9-11.3)	ns	p<0.01
BC- /LM- : BC+/LM+	10.8 (2.6-44.4)	p<0.01	
OS			
BC+/LM- : BC+/LM+	4.7 (0.6-38.5)	ns	p<0.01
BC- /LM- : BC+/LM+	18.7 (2.3-153.4)	p<0.01	

ns: not statistically significant; for other abbreviations see text. *Only for patients with metachronous LM.

months, and only 19 months in SR negative ones [18].

In recent years, many studies have studied the importance of SR status not only in the primary tumor, but also in metastases. It is shown that tumor biology changes and between 18 to 54% of metastatic patients will experience a transition in ER/PR status [19-21]. In accordance to that, the assessment of hormonal status in metastasis provides information that enables optimization of therapy, which could improve the survival. One Japanese study which included 35 BC patients who underwent resection of LMs pointed out that SR status is a valid prognostic factor by both univariate and multivariate analysis. The group of patients whose SR status changed to positive in metastasis had significantly longer both OS and DFS, compared to BC-/LM- group. That result additionally highlighted the favorable impact of positive SR on prognosis, even if occurred at a later stage [22].

Similarly, the focus of our study was to examine the impact of SR status in primary BC and in LMs on DFS and OS. Transition of SR status from positive in primary tumor to negative in LMs was recorded in 40.6% of the patients.

We found statistically significant differences in medians for DFS/OS in subgroups BC-/LM-, BC+/LM- and BC+/LM+, which were 10/19, 25/45, 50/not reached months, respectively (p<0.01; Table 3, Figures 3,4). These results clearly support the thesis of good prognostic value of positive SR status in LMs.

Moreover, not only the importance of surgical LM resection was studied, but also the significance of LM biopsy. It has been shown that patients who developed metastases in the liver during the first 3 years of BC diagnosis and underwent liver biopsy, had a benefit in the sense of longer survival simply because of the availability of additional treatment options [23]. In addition, our article shows that in the group of 8 patients with SR positive primary BC and LMs occurrence in the first 2 years, only one patient had a change of SR status. On the other hand, out of 12 patients with disease progression in the liver recorded 24 months after the BC diagnosis, half of them had transition from SR positive to SR negative. This

Table 5. Results of statistical analysis according to pairs of BC/LM subgroups

Parameters	*Test*
Breast surgery	Fisher Exact Test
BC+/LM+ vs BC+/LM-	ns**
BC+/LM+ vs BC-/LM-	p= 0.0031**
BC+/LM- vs BC-/LM-	ns**
Period from BC to LM (months)*	Wilcoxon rank sum test#
BC+/LM+ vs BC+/LM-	ns**
BC+/LM+ vs BC-/LM-	ns**
BC+/LM- vs BC-/LM-	ns**
Period from BC to LM (categories)	Fisher Exact Test
BC+/LM+ vs BC+/LM-	ns**
BC+/LM+ vs BC-/LM-	ns**
BC+/LM- vs BC-/LM-	ns**
TTLM	Log-rank test
BC+/LM+ vs BC+/LM-	ns**
BC+/LM+ vs BC-/LM-	ns**
BC+/LM- vs BC-/LM-	ns**
DFS	Log-rank test
BC+/LM+ vs BC+/LM-	ns**
BC+/LM+ vs BC-/LM-	p=0.0006**
BC+/LM- vs BC-/LM-	p=0.0142**
OS	Log-rank test
BC+/LM+ vs BC+/LM-	ns**
BC+/LM+ vs BC-/LM-	p=0.0008**
BC+/LM- vs BC-/LM-	p=0.0046**

For abbreviations see text. ns: not statistically significant; *Period from BC to LM for patients with metachronous LM; # Wilcoxon rank sum test with continuity correction; ** According Bonferroni correction (p<0.05/3=0.0167).

phenomenon can be a result of a long-term hormonal therapy, as seen in tamoxifen use in the adjuvant setting. After a certain period of time the primary tumor is gradually losing ER, becoming insensitive to tamoxifen and continues to grow. A similar theory can be applied to metastasis [24]. In recent years, the development of hormonal drug resistance in SR positive BC as well as its overcoming remains a hotspot in translational research.

Conclusion

This study showed that the status of ER and/or PR could have a prognostic value in BC patients with isolated LMs, as both DFS and OS were shown to be significantly longer in patients with positive SR status in primary and/or secondary tumors. Median time from BC diagnosis to LMs occurrence in patients with positive BC and LM was 36 months, which was significantly longer compared to patients from BC+/LM- and BC-/LM- subgroups, where it was 30.5 and 14.5 months, respectively. Similarly, patients with negative SR status in breast and in liver cancers had the worst prognosis, with median OS 19 months, while patients with positive SR status in primary and secondary tumor had median OS longer than 50 months. Patients diagnosed with ER/PR positive BC, but whose LM showed transition in the SR status towards negative, had median DFS/OS of 25/45months.

Although additional research on this topic is necessary on a larger group of patients, our results certainly contribute to a better understanding of the prognostic importance of SR status for DFS and OS after surgical resection of isolated LM in BC patients

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Conflict of interests

The authors declare no confict of interests.

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