ORIGINAL RESEARCH

Long-term survival of breast cancer patients with brain metastases: subanalysis of the BMBC registry

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Background: Up to 30% of metastatic breast cancer (BC) patients develop brain metastases (BM). Prognosis of patients with BM is poor and long-term survival is rare. Identification of factors associated with long-term survival is important for improving treatment modalities.

Patients and methods: A total of 2889 patients of the national registry for BM in BC (BMBC) were available for this analysis. Long-term survival was defined as overall survival (OS) in the upper third of the failure curve resulting in a cut-off of 15 months. A total of 887 patients were categorized as long-term survivors.

Results: Long-term survivors compared to other patients were younger at BC and BM diagnosis (median 48 versus 54 years and 53 versus 59 years), more often had HER2-positive tumors (59.1% versus 36.3%), less frequently luminal-like (29.1% versus 35.7%) or triple-negative breast cancer (TNBC) (11.9% versus 28.1%), showed better Eastern Cooperative Oncology Group (ECOG) performance status (PS) at the time of BM diagnosis (ECOG 0-1, 76.9% versus 51.0%), higher pathological complete remission rates after neoadjuvant chemotherapy (21.6% versus 13.7%) and lower number of BM (n = 1, BM 40.9% versus 25.4%; n = 2-3, BM 26.5% versus 26.7%; n ≥4, BM 32.6% versus 47.9%) (P < 0.001). Long-term survivors had leptomeningeal metastases (10.4% versus 17.5%) and extracranial metastases (ECM, 73.6% versus 82.5%) less frequently, and asymptomatic BM more often at the time of BM diagnosis (26.5% versus 20.1%), (P < 0.001). Median OS in long-term survivors was about two times higher than the cut-off of 15 months: 30.9 months [interquartile range (IQR) 30.3] overall, 33.9 months (IQR 37.1) in HER2-positive, 26.9 months (IQR 22.0) in luminal-like and 26.5 months (IQR 18.2) in TNBC patients.

Conclusions: In our analysis, long-term survival of BC patients with BM was associated with better ECOG PS, younger age, HER2-positive subtype, lower number of BM and less extended visceral metastases. Patients with these clinical features might be more eligible for extended local brain and systemic treatment.

Key words: brain metastases, breast cancer, long-term survivors

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INTRODUCTION

The incidence of brain metastases (BM) from breast cancer (BC) is increasing, treatment options are limited and the management of those patients is a major challenge in clinical daily routine.[1] Furthermore, the patients' prognoses are poor and could not be significantly improved over the past decades.[2]

Many prognostic factors are known to be associated with a higher risk of developing BM such as young age, higher tumor stage at diagnosis, histological grade, tumor size, tumor biology and nodal status.[3]

Triple-negative and HER2-positive subtype are predictive factors for developing BM.[4] BM rates of 25%-46% for patients with metastatic triple-negative breast cancer (TNBC) and 30%-50% in patients with metastatic HER2-positive BC have been published.[5]

Despite commonly known short median survival times of BC patients with BM differing between 7 and 8 months, long-term survivors with survival rates longer than 2 years represent around 25% of the whole cohort as shown in a former analysis of the BMBC registry in 2018 with a total of 1712 patients.[2] Nonetheless, therapeutic options for systemic therapy of BM and clinical management of BMBC patients remain unsatisfactory and the overall survival (OS) rates are still poor.

Until now only fewer data have been published concerning long-term survival among BMBC patients. Altundag et al.[6] described a cohort of 82 BC patients with BM with long-term survival defined as survival of >18 months. Murthy et al. reported nine patients with long-term survival longer than 5 years among 66 BMBC patients.[7]

Identifying the factors associated with long-term survival could help optimize diagnostic and therapeutic options for those patients who are more eligible for extended treatment modalities.

In the large BMBC registry, a German multicenter registry, the clinical data of BMBC patients are documented and, simultaneously, translational projects on available tumor samples of BMBC patients are carried out.

The aim of this retrospective analysis was to characterize the cohort of long-term survivors in the BMBC registry defined as survival in the upper third of the failure curve due to a lack of a commonly accepted definition in published data and to identify the clinical factors associated with long-term survival among those patients.

PATIENTS AND METHODS

Patients in the national multicenter BMBC registry registered before the 5 December 2020 were included in this analysis. The aims of the evaluation were as follows:

1. To assess the OS and progression-free survival (PFS) after diagnosis of BM in the updated number of patients of the BMBC registry.
2. To characterize the OS, and short-term and long-term survival after diagnosis of BM in an explorative analysis regarding different clinical parameters: Age at first diagnosis of BC and of BM, number of BM, localization of BM, tumor grading, histological tumor type, Eastern Cooperative Oncology Group (ECOG)/Karnofsky performance status (PS) at the time of BM diagnosis, existence of leptomeningeal metastases, maximum diameter of BM at first BM diagnosis, neurological symptoms at first diagnosis of BM, extracranial metastases (ECM) at the

time of BM diagnosis, localization of ECM, year of diagnosis, therapies of BM (first therapy of BM).
3. Comparison of the OS (categorized in long-term and short-term survival) after diagnosis of BM between the groups of BC subtypes (HER2-positive, luminal-like, TNBC).

Biological subtypes were defined as HER2-positive, TNBC [estrogen (ER)- and progesterone (PR)-negative, and HER2-negative] and luminal-like (ER- and/or PR-positive, HER2-negative; luminal A- and B-like subtypes were evaluated together because of the missing values of tumor grading causing an issue in the strict distinction of luminal A-like and luminal B-like patients).

Continuous data were summarized using the number of available data, mean, standard deviation, median, minimum and maximum for each group. Categorical and ordinal data were summarized using the number and percentage of patients in each group. OS was defined as the time interval from first diagnosis of BM to death due to any reason.

PFS was defined as the time interval from first diagnosis of BM to first progress of BM or ECM or death due to any cause. Further, Kaplan—Meier curves, the median survival times and the survival rates after 2, 3 and 4 years with the corresponding 95% confidence intervals (CIs) were determined. Differences in the survival curves were tested by the log-rank test. Univariate and multivariate Cox proportional hazards models for OS were carried out to report hazard ratios with the corresponding 95% CIs and to adjust for the covariates. For the analysis of the time intervals from first diagnosis of BC to diagnosis of BM, cumulative incidence rates were determined with the diagnosis of ECM as competing risk. Differences in the cumulative incidence curves were tested by Gray's test.

Long-term survival was defined as OS in the upper third of the failure curve resulting in a cut-off of 15 months. Short-term survival, therefore, was defined as OS <15 months. Patients censored at a time point lower than 15 months were automatically assigned to the group of short-term survivors.

Univariate and multivariate logistic regression analyses were carried out to report odds ratios with the corresponding 95% CIs.

All reported P values were two-sided, and the significance level was set at 0.05. CIs symmetrically cover 95%. Adjustment for multiple testing was not planned. The data were analyzed using SAS® (Statistical Analysis Software, SAS Institute, Cary, NC) version 9.4 with SAS Enterprise Guide Version 7.1 and 8.3 on Microsoft Windows 10 Enterprise. Ethical approval: FF42/2013, Ethikkommission at the Landesärztekammer Hessen.

RESULTS

Patients' characteristics

Clinical data of 2889 patients from the BMBC registry were available for the analysis. Survival in the upper third of the survival curve resulted in an OS >15 months. A total of 887

patients could be categorized as long-term survivors. Accordingly, all patients living <15 months were included in the group of short-term survivors (n = 2002).

In the overall cohort (n = 2889), the median age at BC and BM diagnosis was 52 and 57 years, respectively. A total of 1667 (60.1%) of the patients were hormone receptor (HR)-positive (ER- and/or PR-positive), 1105 (39.9%) were HR-negative (ER- and PR-negative), 1091 (41.8%) patients were HER2-positive and 1522 (58.2%) were HER2-negative. A total of 442 (15.3%) of the patients showed a leptomeningeal disease at the time of BM diagnosis. A total of 1484 (56.9%) of the patients had 1-3 BM and 1122 (43.1%) had >4 BM at first diagnosis. ECM at the time of BM diagnosis could be detected in 2304 (79.8%) of the patients. The majority of the patients (58.9%; n = 763) had a good PS (ECOG 0-1) at the time of BM diagnosis.

Detailed patients' characteristics of the overall cohort as well as in short-term and long-term survivors are shown in Table 1.

Survival analysis

Median survival in the overall cohort was 7.5 months (95% CI 6.9-8.0 months) overall, 13.2 months (95% CI 11.4-14.4 months) in HER2-positive, 6.1 months (95% CI 5.4-7.3 months) in luminal-like and 4.5 months (95% CI 4.0-5.1 months) in TNBC patients (P < 0.0001, Figure 1). The association between OS and other clinicopathological parameters is shown in Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2023.101213 (univariate and multivariate Cox regression analysis). Median PFS was 5.0 months overall, 7.3 months in HER2-positive (95% CI 6.5-7.9 months), 4.5 months (95% CI 4.0-5.1 months) months in luminal-like and 3.5 months (95% CI 3.2-4.0 months) in TNBC patients (P < 0.0001, Figure 2). Time from BC diagnosis until diagnosis of BC according to tumor subtype is shown in Supplementary Figure 1, available at https://doi.org/10.1016/j.esmoop.2023.101213.

Median OS in long-term survivors was about two times higher than the cut-off of 15 months, 30.9 months [interquartile range (IQR) 30.3 months] overall, 33.9 months (IQR 37.1 months) in HER2-positive, 26.9 months (IQR 22.0 months) in luminal-like and 26.5 months (IQR 18.2 months) in TNBC patients. Within the group of long-term survivors, estimated 2-year survival rates depending on different subtypes were 70.2% (95% CI 65.8% to 74.1%) for HER2-positive, 58.6% (95% CI 51.9% to 64.7%) for luminal-like and 55.3% (95% CI 44.8% to 64.6%) for TNBC patients. Looking at the probability of a 4-year survival the following results were estimated: 31.7% (95% CI 27.1% to 36.4%) for HER2-positive, 23.1% (95% CI 17.4% to 29.2%) for luminal-like and 17.2% (95% CI 9.6% to 26.7%) for TNBC patients (table not shown, see Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101213).

Comparison of patients' characteristics between long-term and short-term survival.

Long-term survivors compared to other patients were younger at BM diagnosis (median 53 years versus 59 years, P < 0.001). 59.1% (n = 492) of the long-term survivors had a HER2-positive, 29.1% (n = 242) had a luminal-like and 11.9% (n = 99) had a TNBC subtype. More than half of the long-term survivors (53.1%) had a poorly differentiated primary tumor (G3). Compared to other patients, long-term survivors showed better ECOG PS at the time of BM diagnosis (ECOG PS 0-1, 76.9% versus 51.0%), higher pathological complete remission (pCR) rate after neoadjuvant chemotherapy (21.6% versus 13.7%) and lower number of BM (n = 1 BM, 40.9% versus 25.4%; n = 2-3, BM 26.5% versus 26.7%; n ≥4, BM 32.6% versus 47.9%) (P < 0.001). Moreover, long-term survivors had leptomeningeal metastases (10.4% versus 17.5%) and ECM (73.6% versus 82.5%) less often, asymptomatic BM more often at the time of BM diagnosis (26.5% versus 20.1%) and more often received radiotherapy and surgery for the BM than radiotherapy alone (38.5% versus 16.9%) (P < 0.001, Table 1). In univariate analysis we carried out a logistic regression analysis showing the same prognostic factors being statistically significant for a long-term survival above 15 months (for details see Table 2).

Multivariate analysis. In multivariate analysis (Table 3), the following factors were confirmed to be associated with longer survival (P < 0.001): younger age [<60 versus ≥60, odds ratio (OR) 0.59], better PS (ECOG 0-1 versus ECOG 2-4, OR 0.45), lower number of BM (1 versus 2-3 versus ≥4, OR 0.79, 0.46), positive HR status (positive versus negative OR 1.87), positive HER2 status (positive versus negative OR 2.74), no ECM at the time of BM diagnosis (yes versus no OR 0.65) as well as chemotherapy application after the BM diagnosis (yes versus no OR 2.19). In contrast, pCR rates after neoadjuvant therapy of primary BC (yes versus no, OR 1.8, P = 0.069), leptomeningeal disease (yes versus No, OR 0.99, P = 0.949) and clinical symptoms at BM diagnosis (yes versus no, OR 0.94, P = 0.726) were not associated with a categorization in the group of long-term survivors.

DISCUSSION

In our analysis of 2889 BC patients with BM, 887 patients showed a long-term survival, defined as survival in the upper third of the failure curve, resulting in survival above 15 months in the present analysis. There is no generally accepted definition for long-term survival with BM irrespective of primary tumor type in published data. Long-term survival times between 12 months,[8] 24 months[9] and up to 5 years[10] can be found in the literature. A median OS of BC patients with BM ranging between 6 months for the triple-negative subtype and 21 months for the triple-positive subtype was reported in the SEER database.[11] A survival of >15 months can be therefore regarded as long in this group of real-world patients with poor prognosis. Creating a dichotomic system for survival times could prove helpful for the daily clinical routine in order to help choose eligible patients for certain therapy strategies and predictions of estimated survival prognosis. Nonetheless, there are certain limitations to such a categorization system including

Table 1. Comparison of patients' characteristics between short-term and long-term survival categorical parameters

Parameter	Category	Short-term survivors N = 2002 (%)	Long-term survivors N = 887 (%)	Overall N = 2889 (%)	P value[a]
Age at first diagnosis of BC, years	Median	54.0	48.0	52.0	<0.001
Age at diagnosis of BM, years	Median	59.0	53.0	57.0	<0.001
HER2-status at diagnosis of BC	Negative	1180 (65.1)	342 (42.8)	1522 (58.2)	<0.001
	Positive	633 (34.9)	458 (57.3)	1091 (41.8)	
	Missing	189	87	276	
Hormone receptor status	Negative	826 (42.8)	279 (33.1)	1105 (39.9)	<0.001
	Positive	1104 (57.2)	563 (66.9)	1667 (60.1)	
	Missing	72	45	117	
Tumor subtype[b]	HER2+	668 (36.3)	492 (59.1)	1160 (43.4)	<0.001
	Luminal-like	657 (35.7)	242 (29.1)	899 (33.6)	
	TNBC	517 (28.1)	99 (11.9)	616 (23.0)	
	Missing	160	54	214	
Pathological tumor stage after neoadjuvant therapy	ypT0	83 (13.7)	60 (21.6)	143 (16.2)	<0.001
	ypTis	33 (5.4)	22 (7.9)	55 (6.2)	
	ypT1	174 (28.7)	95 (34.2)	269 (30.4)	
	ypT2	180 (29.7)	58 (20.9)	238 (26.9)	
	ypT3	71 (11.7)	22 (7.9)	93 (10.5)	
	ypT4a-c	52 (8.6)	14 (5.0)	66 (7.5)	
	ypT4d	13 (2.1)	7 (2.5)	20 (2.3)	
	Missing[c]	1396	609	2005	
Tumor grading	G1	34 (1.9)	12 (1.5)	46 (0.8)	0.019
	G2	723 (39.5)	362 (45.4)	1085 (41.3)	
	G3	1073 (58.6)	424 (53.1)	1497 (57.0)	
	Missing	172	89	261	
ECOG (Karnofsky performance status)	ECOG 0 (100%)	95 (10.6)	90 (22.6)	185 (14.3)	<0.001
	ECOG 1 (80%-90%)	362 (40.4)	216 (54.3)	578 (44.6)	
	ECOG 2 (60%-70%)	296 (33.0)	76 (19.1)	372 (28.7)	
	ECOG 3 (40%-50%)	113 (12.6)	15 (3.8)	128 (9.9)	
	ECOG 4 (10%-30%)	31 (3.5)	1 (0.3)	32 (2.5)	
	Missing	1105	489	1594	
Number of BM	1	453 (25.4)	337 (40.9)	790 (30.3)	<0.001
	2-3	476 (26.7)	218 (26.5)	694 (26.6)	
	≥4	853 (47.9)	269 (32.6)	1122 (43.1)	
	Missing	220	63	283	
Leptomeningeal disease (clinical diagnosis)	No	1652 (82.5)	795 (89.6)	2447 (84.7)	<0.001
	Yes	350 (17.5)	92 (10.4)	442 (15.3)	
Cytological confirmed meningiosis at diagnosis of BM	No	1743 (88.6)	816 (93.3)	2559 (90.0)	<0.001
	Yes	224 (11.4)	59 (6.7)	283 (10.0)	
	Missing	35	12	47	
Local treatment of BM	Surgery only	88 (5.7)	47 (5.7)	135 (5.7)	<0.001
	RT only	1184 (77.3)	462 (55.8)	1646 (69.8)	
	Surgery and RT	259 (16.9)	319 (38.5)	578 (24.5)	
	Missing	471	59	530	
ECM at diagnosis of BM[d]	No	351 (17.5)	234 (26.4)	585 (20.2)	<0.001
	Yes	1651 (82.5)	653 (73.6)	2304 (79.8)	
	Missing	0	0	0	

BM, brain metastases; ECM, extracranial metastases; ECOG, Eastern Cooperative Oncology Group; NCTX, neoadjuvant chemotherapy; pCR, pathological complete remission; RT, radiotherapy; TNBC, triple-negative breast cancer.
[a]Fisher's exact test resp. Chi-square test between short-term and long-term survivors.
[b]If HER2-status at diagnosis of BC was unknown, but anti-HER2-targeted therapy was given, the subtype was set to HER2-positive.
[c]Missing data include patients without NCTX and patients with NCTX and missing information about pCR.
[d]Diagnosis of ECM not later than 60 days after diagnosis of BM.

censored patients in the survival curve being automatically assigned to the group of short-term survivors due to missing data. But an additionally carried-out Cox regression analysis for the whole cohort supported the results regarding prognostic factors (data not shown, see Supplementary data Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2023.101213). This should be taken into consideration while interpreting categorized survival times.

Regarding our analysis, several factors were associated with long-term survival, including younger age (below 60), a good ECOG PS, asymptomatic BM, HER2-positive subtype, achieving a pCR after neoadjuvant chemotherapy, a limited number of BM, the absence of leptomeningeal metastases and no ECM at the time of BM diagnosis.

Our findings are in line with results of descriptive analyses of other groups.[12] Altundag et al.[6,13] reported in a retrospective study of 420 BM BC patients with a survival longer than 18 months that younger age, ER-positive subtype and a limited number of BM were associated with longer survival. Lee et al. showed that PS, number of BM, treatment modalities and systemic chemotherapy after BM were associated with better prognosis and therefore longer survival but reported that only 23.1% of the patients survived longer than 12 months.[12]
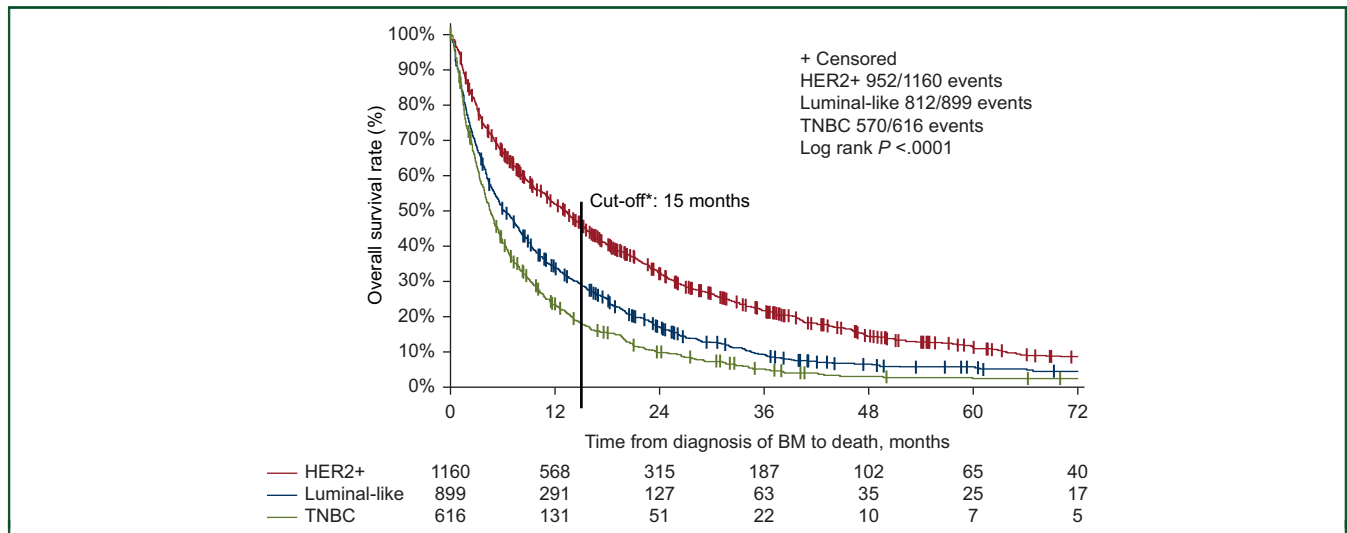
Figure 1. OS in the overall cohort according to tumor subtypes.
*Previously published figure[25] was updated by adding a line with the cut-off of 15 months dividing the patients into groups of long-term versus short-term survivors which corresponds to an OS in the upper third versus the two lower thirds of the failure curve.
BM, brain metastases; OS, overall survival; TNBC, triple-negative breast cancer.

Sperduto et al.[14] also reported a median survival time in BC patients with BM differing between 3.4 and 25.3 months depending on different factors such as PS, age and subtype and therefore established the first diagnosis-specific graded prognostic assessment (GPA) score in order to identify BC patients with longer survival being eligible for treatment. There are various prognostic scores that have been developed trying to categorize patients in different prognostic groups including many of those clinical parameters named. The GPA breast score in its updated version,[15] for example, includes ECOG status, BC subtype, age, number of BM and ECM in the calculation. However, our group has already shown that the sensitivity and specificity of all published scores are limited.[16,17] The probability of classifying patients with survival above 12 months in the best prognostic group

differed between a specificity of 68.7% for the breast GPA compared with 48.1% for the updated breast GPA and 21.8% for the original GPA.[16] Thus, patients might be also categorized in groups that do not reflect their prognosis by calculating scores with clinical parameters. Therefore, we aimed to further investigate a cohort of long-term survivors with BM in the BMBC registry. Indeed, in our analysis, we found that in addition to already published parameters, a pCR rate after neoadjuvant chemotherapy was associated with longer survival rates in case of BM disease in univariate analysis but not in multivariate analysis. This could be explained by pCR depending on different covariates such as subtype, grading and lymph node status. In two large neoadjuvant chemotherapy trials (n >3000 patients), we reported that a non-pCR was associated with a higher
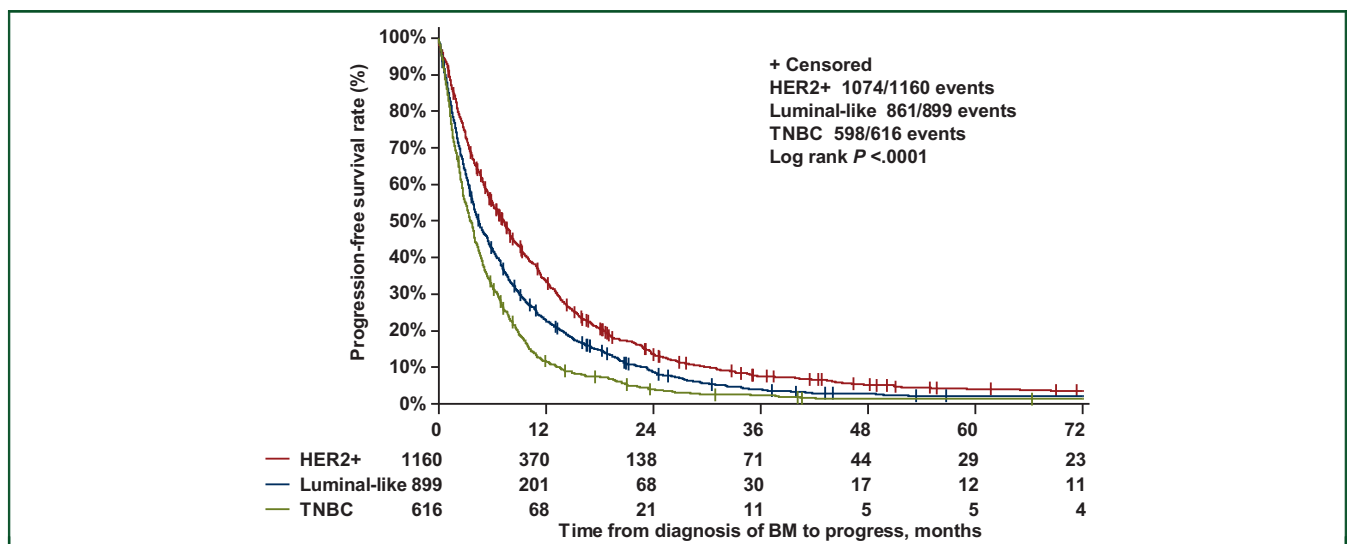

Figure 2. Progression-free survival (time from diagnosis of BM to progress of BM, 25 ECM or death) in the overall cohort according to tumor subtypes.
BM, brain metastases; TNBC, triple-negative breast cancer.

Table 2. Probability of long-term survival according to different clinical parameters (univariate logistic regression analysis)

Parameter at diagnosis	Category	Number of events (%)	Odds ratio[a]	95% CI	P value
Age[b]	<60 years	608 (37.0)			
	≥60 years	279 (22.4)	0.49	0.42-0.58	<0.001
ECOG[b]	0-1	306 (40.1)			
	2-4	92 (17.3)	0.31	0.24-0.41	<0.001
Hormone receptor	Negative	279 (25.2)			
	Positive	563 (33.8)	1.51	1.27-1.79	<0.001
HER2 receptor	Negative	342 (22.5)			
	Positive	458 (42.0)	2.50	2.11-2.96	<0.001
Biological Subtype	HER2+	492 (42.2)			
	Luminal-like	242 (26.9)	0.50	0.41-0.60	<0.001
	TNBC	99 (16.1)	0.26	0.24-0.33	<0.001
Number of BM	1	337 (42.7)			<0.001
	2-3	218 (31.4)	0.62	0.50-0.76	<0.001
	≥4	269 (24.0)	0.42	0.35-0.52	<0.001
pCR (ypT0)	No	218 (29.4)			
	Yes	60 (42.0)	1.73	1.20-2.51	0.003
Leptomeningeal metastases	No	795 (32.5)			
	Yes	92 (20.8)	0.55	0.43-0.70	<0.001
Clinical symptoms[b]	No	235 (36.9)			
	Yes	652 (29.0)	0.70	0.58-0.84	<0.001
ECM[b]	No	234 (40.0)			
	Yes	653 (28.3)	0.59	0.49-0.72	<0.001
Chemotherapy after diagnosis of BM	No	388 (22.0)			
	Yes	499 (44.2)	2.8	2.38-3.30	<0.001
Endocrine therapy	No	649 (26.0)			
	Yes	238 (60.7)	4.4	3.53-5.49	<0.001
HER2-targeted therapy	No	429 (20.4)			
	Yes	458 (58.0)	5.37	4.50-6.41	<0.001

BM, brain metastases; CI, confidence interval; ECM, extracranial metastases; ECOG, Eastern Cooperative Oncology Group; pCR, pathological complete remission; TNBC, triple-negative breast cancer.
[a]An odds ratio ≥1 means to have a higher probability to be assigned to the group of long-term survivors.
[b]At diagnosis of BM.

probability of developing BM as the first site of metastatic disease.[18]

Interestingly, we could not confirm leptomeningeal metastases and asymptomatic BM as independent prognostic variables for survival in multivariate analysis after having shown an association with longer survival in univariate analysis. Other reports also show that there are a few patients with leptomenigeal metastases with a reported 1-year survival rate of 20%.[19] In line with those results, 6.4% of our patients among the long-term survivors had cytologically confirmed leptomeningeal disease, showing that even in the group of a leptomeningeal disease with poor prognosis with a reported median survival time of 3-4 months a subgroup with a better prognosis exists.[11]

In the univariate analysis, we could confirm that patients with asymptomatic BM had a higher chance of achieving a long-term survival above 15 months. One of the possible reasons for no significant association in the multivariate analysis could be a small number of patients with asymptomatic BM at first diagnosis in the BMBC registry. Furthermore, we could show that a lower number of BM was associated with a higher probability of achieving a long-term survival. In our previous analysis of patients with asymptomatic BM, a significant correlation between asymptomatic BM and lower number of BM could be shown.[17] Therefore, our analysis provides a rationale for modern study concepts investigating early detection approaches of BM. Until now, it

is unclear whether there is a gain in survival time or a lead-time bias due to the earlier detection of BM.

In addition, we observed that receiving systemic therapy, namely chemotherapy, endocrine or targeted therapy, was associated with long-term survival in univariate and/or multivariate analysis. This could be explained by a better visceral disease control and therefore longer survival.[20]

Several targeted therapeutic options and novel agents especially in the HER2-positive subgroup such as trastuzumab deruxtecan[21,22] and tucatinib[23] have also shown an intracranial effect of systemic therapies. The application of this treatment options could result in a relevant further improvement of survival of patients with BM of BC.

Concerning tumor biology, our analysis indicates that patients with HER2-positive and HR-positive tumors were more often represented in the group of long-term survivors in our analysis in contrast to patients with TNBC tumors who had a lower probability of long-term survival which is in line with published data.[20,24] A different mechanism of tumor cell dissemination in the brain depending on tumor subtype can be assumed. The value of clinical data might be limited to further understand the nature of long-term survival in BC patients with BM.

Therefore, the translational research project of the BMBC registry aims at setting up a scientific base for research

Table 3. Probability of long-term survival according to different clinical parameters (multivariate logistic regression analysis)

Parameter at diagnosis	Category	Odds ratio[a]	95% CI	P value
Age[b]	<60 years	1		
	≥60 years	0.59	0.44-0.79	<0.001
ECOG[b]	0-1	1		
	2-4	0.45	0.33-0.61	<0.001
Hormone receptor status	Negative	1		
	Positive	1.87	1.39-2.50	<0.001
HER2 status	Negative	1		
	Positive	2.74	2.06-3.64	<0.001
Number of BM	1	1		<0.001
	2-3	0.79	0.55-1.13	0.191
	≥4	0.46	0.33-0.65	<0.001
pCR	No	1		
	Yes	1.8	0.995-3.38	0.069
Leptomeningeal metastases	No	1		
	Yes	0.99	0.64-1.53	0.949
Clinical symptoms[b]	No	1		
	Yes	0.94	0.66-1.34	0.726
ECM[b]	No	1		
	Yes	0.65	0.46-0.93	0.017
Chemotherapy after diagnosis of BM	No	1		
	Yes	2.19	1.64-2.92	<0.001

BM, brain metastases; CI, confidence interval; ECM, extracranial metastases; ECOG, Eastern Cooperative Oncology Group; pCR, pathological complete remission.
[a]An odds ratio ≥1 means to have a higher probability to be assigned to the group of long-term survivors.
[b]At diagnosis of BM.

projects to explore factors associated with BM development and prognosis depending on BC subtypes.

Conclusions

In conclusion, our analysis showed that several clinical factors such as younger age, better PS, lower number of BM, positive HR status, positive HER2 status, no ECM at the time of BM diagnosis as well as application of the systemic treatment after the BM diagnosis were associated with long-term survival in BC patients with BM.

Further research should be carried out to better understand those factors associated with long-term survivor with BM. Our results provide a rationale for the design of studies to prove intensified treatment strategies in this patient cohort.

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