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The analysis of prognostic factors and treatment outcomes in breast cancer patients with brain metastasis

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Abstract

Aim: Breast cancer (BC) is among the most common causes of brain metastasis (BM). Brain metastasis leads to severe morbidity and mortality. Brain metastasis-related survival is not common despite all treatments. The aim of the present study is to compare the short-term or long-term surviving patients who underwent radiotherapy due to BM in our clinic regarding treatment modalities, and clinic-pathological characteristics as well as to investigate the factors that influence overall survival and progress for BM development.

Materials and Methods: The data of 167 patients who were referred to radiotherapy due to BM were analyzed retrospectively. The patients were allocated to two groups: ones who survived less than, or more than, 14 months. The treatment, patient, and tumor characteristics were evaluated.

Results: The frequencies of a better Karnofsky performance scores (p=0.001), her-2 positivity ($p < 0.001$), the presence of a single BM (p=0.048), an absence of leptomeningeal disease (p=0.033), an absence of extracranial metastasis (p=0.033) and having received systemic therapy following BM ($p < 0.001$) were higher in the group that survived longer. In the group that survived longer, having stage T1-2 disease and being under 40 years of age, and, in the group that survived less, receiving systemic therapy following BM development were found to be the factors effective on overall survival (OS).

Conclusion: To the best of our knowledge, this is the first study to compare the prognostic features of breast cancer patients with BM who survived short-term or longer. In our single-center retrospective study, for the group that survived longer, having T1-2 stage disease and being under 40 were the independent predictive factors for OS in multi-variable analyses. Further studies are required to determine the groups that will have a longer change of survival and plan to receive more aggressive therapies.

Introduction

Breast cancer (BC) is the second leading cause of brain metastasis (BM) following lung cancer [1]. The ratio of BM is increasing today. This may be associated with prolonged survival due to better control of extracranial disease and early detection of these lesions through the developments in imaging techniques [2]. This rate may rise to 30% in an autopsy series although it is seen in 10-15% of BC [3, 4, 5]. It leads to severe morbidity and mortality [6].

Several risk factors including a young age, a higher grade, her-2 positivity, axillary node positivity, and being triple negative were determined in the development of BM [4, 7, 8]. The median time between BC and BM development is usually 2-3 years [4], and 16 months after the development of systemic disease [9]. This time may vary depending on subtypes [10].

The treatment of BM includes surgical therapy or local radiotherapy (RT) (conventional, stereotactic radiosurgery (SRS), and stereotactic body radiotherapy (SBRT)) [10]. Many factors including the performance of the patient, her-2 status, systemic disease status, and the number of BM should be considered when making treatment decisions [2, 11].

Survival is short despite all the treatments. It is 6 months with RT and 2 months without RT [10]. However, a median overall survival was shown to prolong life up to 14 months in certain subtypes and through multi-modal therapies [2]. It is difficult to predict outcomes in BM. Therefore, some prognostic models are available. In 1997, Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) was applied on patients with BM [12]. This index was updated as Graded Prognostic As-

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sessment (GPA). Through a retrospective study conducted with 4259 patients with BM, the disease-specific GPA performance score, based on the performance score in BC patients, genetic subtype, and age has begun to be used [13]. Sperduto et al. described novel prognostic factors such as the number of BM and extra-cranial metastasis (ECM) and included in updated breast-GPA [14].

In the literature, few studies are available that have investigated long-term survival in BM. In this study, the aim was to compare the treatment modalities and clinicopathological features of the patients who were given RT due to BM in our clinic and who had short- or long-term survival, and to investigate the factors that influence OS and BM development time. The present study is expected to contribute to determine the group that would achieve long survival through the treatment of BM, to evaluate the natural course of BM and to determine the groups that need more aggressive therapies.

Materials and Methods

The data for 877 patients who were applied RT for BM in our clinic between January 2010 and December 2020 was retrospectively analyzed and 167 BC patients with BM were included in the study. Female patients who were above 18 years, whose diagnosis of BC was confirmed histopathologically and who were free of other malignities were included in the study. The presence of BM was determined through magnetic resonance imaging (MRI) and/or histopathologically. Central nervous system (CNS) metastasis was interpreted as the presence of parenchymal or leptomeningeal involvement.

As median OS was shown to prolong up to 14 months through multi-modal treatment [2], patients were allocated to two groups as the ones who survived shorter or longer than 14 months.

The data for the patient and tumor characteristics were obtained from medical records. The time of the diagnosis, age at the time of the diagnosis, date, and place of the first metastasis, date of BM, number of metastases, age at the time of metastasis, treatments applied for BM, systemic therapies before or after BM, vital status and dates of death of the last control were evaluated. Besides, the clinic-pathological characteristics of the tumor at the time of the diagnosis (grade, stage, lymph node involvement, lymphovascular invasion (LVI), perineural invasion (PNI), extracapsular invasion (ECI), Ki-67, estrogen/progesterone receptor positivity (ER/PR) and her-2 positivity) were evaluated for all patients.

Her-2 was accepted to be positive if the her-2 gene was shown to be 3(+) immuno-histochemically (IHC) or the her-2 amplification was shown in fluorescence insitu hybridization (FISH). Breast cancer subtypes were classified into four groups as luminal A (ER/PR (+), her-2(-)), Luminal B (ER/PR (+), her-2(+)), her-2(+)(ER/PR (-), her-2(+)) and triple negative (ER/PR/her-2 (-)) according to the hormone status in IHC.

Breast-GPA and RPA were estimated for all the patients. With RPA, the patients were classified into 3 groups: Class I (Karnofsky performance score (KPS) $\geq$70, age $<$ 65, primary lesion is under control and no extracranial metastasis); Class III, KPS $<$ 70, Class II, others [12]. The Breast-GPA scoring was done based on the scoring system of Sperduro et al. KPS, subtype, age, presence of ECM and number of BM were scored. The patients were allocated to 4 groups as those scored 0-1, 1.5-2, 2.5-3 and 3.5-4. The higher scores were correlated with a good prognosis [14] (Table 1).

Ethics committee approval was obtained prior to the study (2021/3368). The study was conducted in accordance with the principles of the recent Helsinki Declaration. Written informed consent was not obtained from the patients due to the nature of the study.

Survival

The primary endpoint of this study was to determine the survival rates in the patients with BM who survived less or longer than 14 months. The secondary primary endpoint of this study was to evaluate prognostic factors in patients with BM. Overall survival was estimated as the duration between the diagnosis of BM and death or the last control. Brain metastasis-free interval (BMFI) was defined as the duration from the diagnosis of primary breast cancer to the diagnosis of BM. Metastasis-free interval (MFI) was defined as the duration from the diagnosis of primary breast cancer to the time of the first metastasis.

Statistical Analysis

The patient characteristics were summarized as number (%) for the categorical variables and median for the continuous variables. Tumor, patient, and treatment characteristics between two groups were evaluated with a chi-square test. Survival rates were calculated with the Kaplan-Meier method. The survival differences between the two groups were evaluated with a log-rank test. In the uni- and multivariable analyses, the Cox proportional hazard models were used. In the uni-variable analysis, p values $<$ 0.20 were included in the multi-variable analysis. The p level of $<$ 0.05 was accepted as statistically significant. All the statistical analyses were done by using SPSS (Statistical Package for Social Sciences) version 13.

Results

Of 167 patients, 70.1% (n:117) survived less than 14 months. The median duration of the follow-up was 8.04 months (0.30-111.97) in the whole group. Sixteen patients (9.6%) were alive. In the group that survived for a shorter period, the median age was 51 (range: 32-85), and in the group that survived longer, median age was 48 (range: 22-74). A comparison of the patient and treatment characteristics is presented in Table 2.

Karnofsky performance score was better in the group that survived longer (p=0.001). In the group that survived longer, the her-2 positivity (p $<$ 0.001), the presence of a single BM (p=0.048), the absence of leptomeningeal disease (LMD) (p=0.033), the absence of ECM (p=0.033) and the ratio of receiving systemic therapy following BM (p $<$ 0.001) were greater. No difference was found between groups regarding the menopause status, the T stage, the N stage, the grade, the LVI, the PNI, and hormone positivity. While the ratio for being triple negative was 17.1%

Table 1. Updated graded prognostic assessment scoring for breast cancer patients with brain metastasis

Factor	0	0.5	1.0	1.5	Patient Score
KPS	≤60	70-80	90-100	NA	Sum total
Subtype	Basal	Luminal A	NA	Her2, Luminal B	
Age	≥60	< 60	NA	NA	
Number BM	> 1	1	NA	NA	
ECM	Present	Absent			

KPS: Karnofsky Performance Score, BM: Brain metastasis, ECM: Extracranialmetastasis, NA: not applicable

Table 2. Patient and treatment characteristics

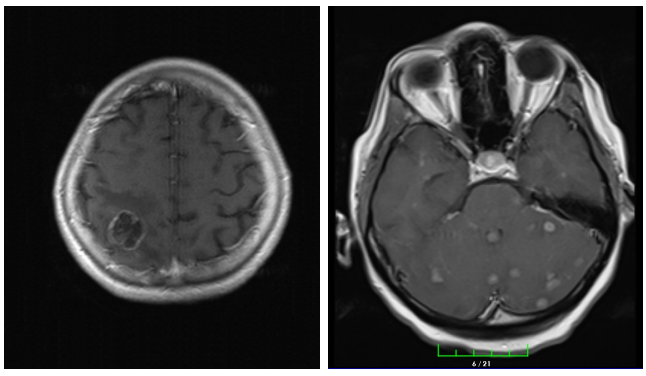
		Group with short survivaln(%)	Group with long survivaln(%)	P value
KPS	< 70	28(23.9)	1(2)	0.001*
	≥70	89(76.1)	49(98)	
Age at firstbrainmetastasis	<40	24(20.5)	15(30)	0.184
	≥40	93(79.5)	35(70)	
Menopause	Premenapose	63(53.8)	30(60)	0.463
	Postmenapose	54(46.2)	20(40)	
T stage	T1-2	81(69.2)	29(58)	0.161
	T3-4	36(30.8)	21(42)	
N stage	N0-1	43(36.8)	19(38)	0.879
	N2-3	74(63.2)	31(62)	
Stage	Stage 1-2	27(23.1)	9(18)	0.465
	Stage 3-4	90(76.9)	41(82)	
Grade	Grade 1	4(4.1)	4(9.3)	0.250
	Grade 2-3	93(95.9)	39(90.7)	
LVI of primary breast lesion	Absent	19(31.7)	7(29.2)	0.823
	Present	41(68.3)	17(70.8)	
PNI of primary breast lesion	Absent	36(63.2)	6(26.1)	0.003*
	Present	21(36.8)	17(73.9)	
Her-2 expression of primary breast lesion	Negative	81(69.2)	19(38)	<0.001*
	Positive	36(30.8)	31(62)	
Triple negativity of primary breast lesion	Yes	20(17.1)	3(6)	0.057
	No	97(82.9)	47(94)	
HR of primary breast lesion	Negative	39(33.3)	13(26)	0.349
	Positive	78(66.7)	37(74)	
Number of lesions	Single	27(23.1)	19(38)	0.048*
	Multiple	90(76.9)	31(62)	
Presence of LMD	Absent	101(86.3)	50(100)	0.003*
	Present	16(13.7)	0	
Presence of ECM	Absent	13(11.1)	12(24)	0.033*
	Present	104(88.9)	38(76)	
Systemic treatment after the diagnosis of BMs	Yes	79(67.5)	49(98)	<0.001*
	No	38(32.5)	1(2)	
GPA	Group 1-2	84(71.8)	17(34)	<0.001*
	Group 3-4	33(28.2)	33(66)	
RPA	Class I-II	91(77.8)	49(98)	0.001*
	Class III-IV	26(22.2)	1(2)	
Treatment	WBRT	108(92.3)	39(78)	0.062
	SRS	2(1.7)	2(4)	
	WBRT+SRS	0(0)	1(2)	
	Surgery+WBRT	7(6)	7(14)	
	Surgery+WBRT+SRS	0(0)	1(2)	

KPS: Karnofsky Performance Score, BM: Brain metastasis, ECM: Extracranial metastasis, LVI: Lymphovascular invasion, PNI: Perineural invasion, HR: Hormone receptor, LMD: Leptomeningeal disease, BM: Brain metastasis, GPA: Graded Prognostic Assessment, RPA: Recursive Partitioning Analysis, WBRT: Whole brain radiotherapy, SRS: Stereotactic radiosurgery,*Statistically significant

Table 3. TableCaption

		Group with short survivalMedian OS p value		Group with long survival Median OS p value	
KPS	<70	1.18	<0.001*	15.44	<0.001*
	≥70	5.58		28.68	
Menapose	Premenapose	4.86	0.110	29.14	<0.001*
	Postmenapose	2.49		24.24	
Age at first brain metastasis	<40	4.86	0.442		0.414
	≥40	3.61			
T stage	T1-2	5.15	0.103	43.86	0.020*
	T3-4	2.79		24.24	
N stage	N0-1	4.79	0.963	43.23	0.024*
	N2-3	2.79		24.14	
Her-2 expression of primary breast lesion	Negative	3.45	0.224	43.11	0.011*
	Positive	5.58		25.09	
Presence of LMD	Absent	4.76	0.001*	28.28	0.001*
	Present	1.38		28.68	
Presence of ECM	Absent	8.18	0.125	33.08	0.631
	Present	3.45		24.14	
Systemic treatment after the diagnosis of BMs	Yes	7.19	<0.001*	28.68	<0.001*
	No	1.28		15.50	
GPA	Group 1-2	2.79	<0.001*	22.96	<0.001*
	Group 3-4	8.87		62.26	
RPA	Class I-II	5.22	<0.001*	28.68	<0.001*
	Class III	1.15		15.44	
Number of lesions	Single	9.52	0.005*	33.08	0.005*
	Multiple	2.79		23.78	
BM, site of first metastasis	Yes	6.83	0.006*	43.23	0.006*
	No	3.02		23.22	

KPS:Karnofsky Performance Score, ECM:Extracranial metastasis, LMD: Leptomeningeal disease, BM: Brain metastasis , GPA: Graded Prognostic Assessment, RPA: Recursive Partitioning Analysis, *Statistically significant



(a) (b)

Figure 1. MRI image of single (a) and multiple (b) brain metastases

in the group that survived less, it was 6% in the group that survived longer (p=0.057).

In the whole group, 1,2 and 5-year OS were 38.5%, 18.2% and 5%, respectively. Median OS was 4.20 months in the group that survived shorter and 28.69 months in the group that survived longer. The BMFI and MFI were median 45.40 and 22.73 months in the group that survived shorter, they were 35.05 and 24.60 months, respectively in another group (Figure 2).

For the uni-variable analyses, in the group that survived shorter, KPS≥70 ($p < 0.001$), brain metastasis' being the first site of metastasis (p=0.006), the presence of a single metastasis (p=0.005), the absence of LMD (p=0.001), receiving systemic therapy following BM ($p < 0.001$), the GPA score of Group 3-4 ($p < 0.001$), the RPA of Class I-II ($p < 0.001$) were found to positively affect the OS. In the group that survived longer, KPS≥70 ($p < 0.001$), being under 40 years of age (p=0.020), beingT1-2 stage(p=0.024), beingN0-1 stage(p=0.011), receiving systemic therapy following BM (p=0.001), the GPA score of Group 3-4 ($p < 0.001$), the Class I-II RPA of Class I-II ($p < 0.001$) were found to positively affect the OS (Figure 3).

When the BMFI was analyzed, in the patients that survived shorter, being under 40 (p=0.002), having stage T3-4

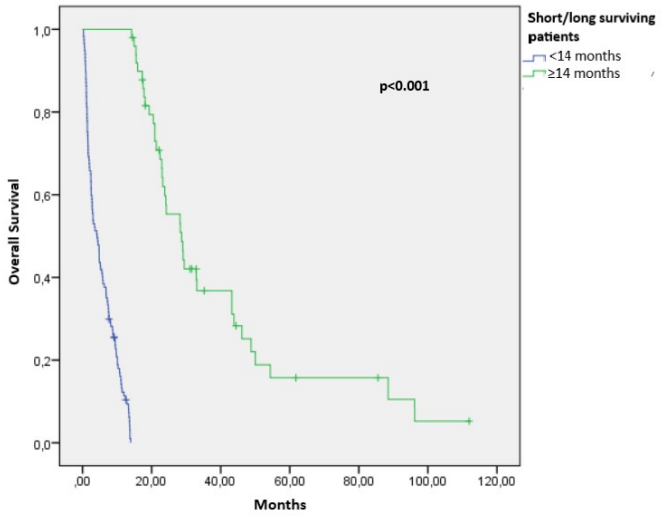


Figure 2. Overall survival curve in long or short survival groups

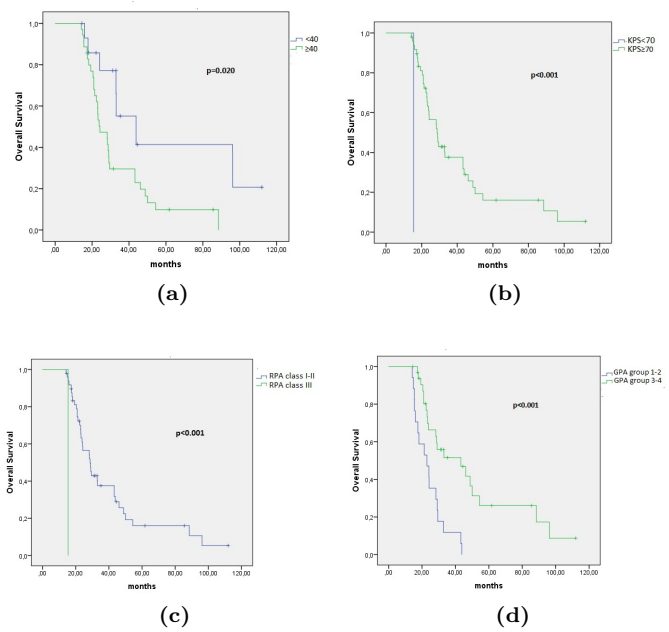


Figure 3. Kaplan-Meirer curves by age (a), karnofsky performance score (b), Recursive partitioning analysis (c), and Graded prognostic assessment (d) in patients with long-term survival with brain metastases

disease (p=0.008), having stage N2-3 disease (p=0.001), being triple negative (p=0.038) and ER/PR negative (p=0.008); in the patients who survived longer, having stage N2-3 disease (p=0.002) negative factors were found.

When MFI was analyzed, in the patients that survived shorter, being under 40 (p=0.006), having stage T3-4 disease (p=0.019), having stage N2-3 disease (p=0.003) were found; in the patients who survived longer, having stage N2-3 disease (p=0.002) negative factors were found.

In the multi-variable analysis, in the group that survived shorter, receiving systemic therapy following BM (HR: 4.490; 95%Cl: 2.638-7.640; p < 0.001), in the group that survived longer, being under 40 (HR: 2.943; 95%Cl: 1.175-7.373; p=0.021) and having T1-2 disease (HR:2.669; 95%Cl:1.158-6.154; p=0.021) were found to be factors that positively affect OS.

Discussion

In 19.04% of the patients who were treated due to BM in our clinic during the recent 10 years, the primary site of metastasis was the breast. Breast cancer with BM is an important factor for morbidity and mortality. In the present study, we aimed to evaluate the factors that are effective on OS and BM development by making a comparison between the patients with BM who survived less or longer than 14 months. When the whole group was analyzed, in the multi-variable analyses, her-2 positivity, the absence of leptomeningeal involvement, and receiving systemic therapy after detection of BM were found to be associated with OS. In the group that survived longer, the her-2 positivity, presence of a single metastasis, the absence of LMT, receiving systemic therapy, and the absence of extracranial metastasis were observed more when compared to the group that survived for a shorter period.

There are differences in the frequency of BM and survival among different primary breast cancer types. The ratio of BM was higher in the groups with her-2 positivity and triple negative groups [6]. In the past, while survival rates were poor before any transtuzumab treatment, today, the longest survival rates may be seen in her-2 (+) group (2). Median OS was 11.6 months in her-2 (+) group, and 4.6 months in triple (-) group [7]. Similar to the literature, in our cohort, while the OS was 13.7 months in the her-2 (+) group, it was 5.15 months in her-2 (-) group (p < 0.001), 4.86 months in triple (-) group, and 9.46 months in the group that was not triple (-). The ratio of her-2 positivity was greater in the group that survived longer as compared to another group. All her-2 (+) patients received transtuzumab. The median OS was found to be 12.8 months in the patients treated with transtuzumab and 4 months in those not treated with transtuzumab (15). Although BM may develop in 30-35% of her-2 (+) BM, routine imaging is not recommended [16]. Imaging is done when patients become symptomatic. In our study, her-2(+) patients constituted 40.1% of the whole study population. The frequency of BM may be found less as routine cerebral imaging is also not done in the groups with increased likelihood of BM.

In the study conducted with the aim of showing the effects of subtypes on BMFI, Sperduto et al. showed that the duration was 27.5 months in the basal group, 35.8 months in her-2(+) group, 47.4 months in luminal B, and 54.4 months in luminal A [17]. The median time to the BM development from the diagnosis of BC was 34 months and the median time to BM development from the diagnosis of systemic diseasewas 16 months (9). In our study, the BMFI was 41.82 months in the whole group, 45.40 months in those who survived short and 35.05 months in those who survived longer. The MFI was found to be 23.32 months, 22.73 months and 24.60 months, respectively.

In the study of Witzel et al. conducted with 1712 patients,

the shortest survival rate was shown in the LMD when compared to the parenchymal metastasis and the median OS was found to be 3.9 months [7]. In the patients with BM, the presence of LMD was shown to cause a death risk 2.52- fold greater as compared to 1-3 metastases [2]. In our study, while the median OS was 1.38 months in the group with LMD, it was found to be 9.79 months in those without LMD ($p > 0.001$). While involvement was present in 13.7% of those who survived less, the LMD was not detected in long survivors.

The ratio of receiving systemic therapy after the diagnosis of BM was greater in the group that survived longer (67.5% vs 98%). In the uni-variable analyses, it was found to be effective on the OS both in the whole group ($p < 0.001$) and in the groups that survived less ($p < 0.001$) and longer ($p=0.001$). In multi-variable analyses, while it was quite significant in the whole group and those who survived short, this effect could not be shown in those who survived long. Receiving systemic therapy after BM was associated with better survival rates in the literature also (13.0 months vs 3.4 months) [7]. Similarly, Lee et al. also showed that almost half of the patients received palliative chemotherapy and the duration of survival was 7.8 months in those who received chemotherapy as compared to those who did not and who survived 3.6 months [18].

A young age is among the risk factors for BM development [4, 7, 8]. Very young patients have more aggressive malignancies [19]. Despite the presence of different references as 45 or 50 in different studies, a young age at the diagnosis of BM was found to be associated with better survival rates [15, 20, 21]. On the contrary, studies are also available that do not show the effect of age (5). Consistently with the literature, in our study, although the duration to BM and the first metastasis was shorter in the patients under 40, OS after BM development was observed to be better. Being under 40 had a positive effect also in those who survived longer ($p=0.020$, 43.86 months vs 24.24 months), the same effect was shown also in multi-variable analysis ($p=0.021$).

Prognostic models such as RPA and GPA are available for the prediction of survival in patients who develop BM. In the RPA analysis conducted by Gasper et al., the survival rates for RPA Class I, II and III were 7.1 months, 4.2 months and 2.3 months. These rates were 24.24 months, 9.79 months and 1.18 month in our study [12]. The median survival was 6, 12.9, 23.5, and 36.3 months according to the 0-1, 1.5-2, 2.5-3, 3.5-4 scores, respectively according to the Breast-GPA index [14]. These rates were 1.51, 6.27, 13.70, and 20.92 months in our whole cohort. With the groups that survived shorter or longer, the RPA Class I-II and GPA Group 3-4 were more frequent in those who survived longer as compared to those who survived shorter ($p=0.001$ ve $p < 0.001$). In the uni-variable analyses, while the GPA Group 3-4 and RPA Class I-II positively affected survival both in the whole group and in the group that survived shorter or longer, this effect could not be shown in the multi-variable analyses. It was suggested that our low median survival rates may be associated with a higher number of patients with KPS < 70.

The limitations of our study were the relatively low number of patients and retrospective design of the study. In addition, we included the data of the patients who were registered with RT in our clinic rather than the whole number of patients who were treated in our hospital. The number of SRS/SBRT was quite low as stereotactic radiotherapy had not been applied in our clinic until recently. Consequently, we could not compare the effects of the treatment modalities on OS. Further studies are required to determine the features and differences of BC patients with BM who survive longer. Further knowledge can be obtained through collecting pool data together with other centers.

The BM of breast cancer is a challenging condition with its treatments and outcomes. In conclusion, to the best of our knowledge, this is the first study that compares the prognostic features of the BC patients with BM who have short or long survival duration. In our single-center, retrospective study, having stage T 1-2 disease and being under 40 were found to be the independent predictive factors for those who survived longer in the multi-variable analyses. Further studies are required to determine the groups in which long survival will be possible and which would receive more aggressive therapies.

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