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Research Article

Importance of Metastasis Site in Survival of Patients with Breast Cancer

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Abstract

Purpose: The purpose of this study is to analyze the survival rate of patients with metastatic breast cancer according to the location of metastases and to identify factors related to survival in these patients.

Methods: The data of 184 patients who were treated for metastatic breast cancer at the Cumhuriyet University Oncology Center between 2006 and 2013 were retrospectively reviewed.

Results: One hundred eighty-one patients (98%) in the study were female and three were male (2%). The median age at diagnosis was 51 years (range: 18-83 years). Following development of the first metastasis, median survival of the patients was 27 months (1-177 months), two-year survival was 55%, and five-year survival was 27%. The longest survival duration was in the patients with bone metastases, and the shortest survival was noted in patients with brain metastases. Age, menopausal status, diabetes mellitus, performance status, number of metastases (single organ vs. multiple organs), localization of the metastases (bone, liver, and brain metastasis), ER receptor status, grade, lymphovascular invasion, Ca 15.3 levels, and hemoglobin levels were the prognostic factors included in the univariate analyses. Based on the multivariate analyses, the independent prognostic factors affecting survival were diabetes mellitus, lymphovascular invasion positivity, high grade, hemoglobin levels < 12 g/dL, bone metastasis, and multiple organ metastases.

Conclusion: The duration of survival in patients with metastatic breast cancer greatly varies based on the site of metastasis. The study results showed that among all the prognostic factors that play significant roles on the survival of patients with metastatic breast cancer, post-menopause, presence of diabetes mellitus, lymphovascular invasion positivity, high disease grade, and multiple organ metastases represent the poor independent prognostic factors; whereas presence of bone metastasis is a good independent prognostic factor.

Keywords: Metastatic breast cancer; Prognostic factors

Introduction

Breast cancer is the most common cancer seen among women throughout the world. Today, metastasis can be seen at a rate of 6-10% of the patients upon diagnosis, despite the presence of advanced screening programs [1,2]. The disease is diagnosed at an early stage in most women; however, depending on the stage at diagnosis, 20-40% of these patients develop distant metastasis within five years [2,3]. Most of the metastases are seen within two or three years; however, they may also develop in the years following the initial diagnosis [2]. Distant organ metastases are frequently seen in the bones. Almost 70% of patients at an advanced stage develop bone metastases [4,5]. The other most common metastatic sites include the liver, lungs, and the brain.

Although adjuvant therapies significantly increase the survival of patients with breast cancer, the survival of these patients dramatically decrease after the development of metastases. The estimated five-year survival rate in these patients is 21% and median survival rates vary between nine months to three years [6,7].

The risk of metastasis in breast cancer is closely associated with the disease stage and the biological characteristics of the tumor. Each of the factors including the size of the tumor, nodal involvement, presence of lymphovascular and perineural invasion, tumor grade, receptor status of hormones such as estrogen and progesterone, and HER2 (human epidermal growth factor receptor-2) status represent independent prognostic factors for the development of relapse in the patients. Patients with metastatic breast cancer represent a heterogeneous patient group, since they have different patient characteristics and tumor biologies. The results of a recently published study show that the hormone receptor and HER2 status, location of the metastasis (visceral vs. non-visceral), performance status, disease-free duration, initial adjuvant therapy and the initial therapy given after the development of metastasis are factors affecting the prognosis in these patients [8].

The present study aims to assess the survival data of patients with metastatic breast cancer based on the localization of metastasis and to identify the prognostic factors that affect the survival in this patient group.

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Material and Methods

The medical data of patients who admitted to the Oncology Unit of Cumhuriyet University Faculty of Medicine between 2006-2013 were retrospectively analyzed. All of patients with metastatic breast cancer were accepted as eligible. Demographic, clinical, and pathological features of the patients were retrieved from the hospital records. The survival data of the patients were obtained from hospital records and unfollowed patients were contacted in order to obtain information about their conditions. Survival was defined as the time between the date of organ metastasis and last contact or death.

The performance status of the patients was evaluated by the ECOG (Eastern Cooperative Oncology Group) scoring system at the time of the metastases. The initial stage of disease was evaluated according to the 2010 TNM classification developed by the International Union against Cancer and the American Joint Committee on Cancer.

The biochemical evaluation of patients was completed by routine blood count and biochemical tests after diagnosed metastasis.

For statistical analysis, Statistical Package for Social Sciences (SPSS) for Windows 14.0 program was used. For descriptive statistics, the mean, standard deviation, frequency, and median were used. To compare quantitative data among groups, the Mann-Whitney U-test was used. The survival rates were calculated using the Kaplan-Meier analysis. Multivariate analysis (Cox regression analysis) was used for the evaluation of independent risk factors that had an effect on survival. P values ≤0.05 were accepted as statistically significant.

Results

Among 687 patients with breast cancer, the data of 184 patients who developed locoregional relapse and distant metastasis were analyzed in the present study. Of these patients, 181 (98%) were female and three (2%) were male. Median age at diagnosis was 51 years (range: 18-83 years). Clinical and demographical characteristics of the patients are summarized in table 1.

The first line treatments received by the patients after breast cancer diagnosis were as follows: surgical treatment was not preferred in 28 (16%) patients, 123 (67%) patients underwent modified radical mastectomy, and 32 (17%) patients underwent breast conserving surgery. Axillary treatment was not preferred in 32 (17%) patients, 145 (79%) underwent axillary dissection, and seven (4%) patients had sentinel lymph node sampling. Neoadjuvant chemotherapy was administered to 20 (11%) patients and 163 (89%) patients received adjuvant chemotherapy. Radiotherapy and hormonal therapy was administered to 106 (58%) and 108 (59%) patients, respectively. Treatments given after the development of metastasis were as follows: 105 (57%) patients received second line chemotherapy, 46 (24%) patients received third line chemotherapy, 19 (10%) patients received fourth line chemotherapy, 34 (19%) patients received second line hormonal therapy, and four (2%) patients received third line hormonal therapy. Palliative radiotherapy was given to 114 (62%) patients.

Metastasis was present at diagnosis in 44 (6%) patients; whereas 126 (18%) patients developed distant metastasis and 41 (6%) developed locoregional relapse in the mean follow-up duration of 54±1.6 months. Median interval for metastasis development was 27 months (1-207 months), and median interval for locoregional relapse development was 29 months (6-304 months). Sites of locoregional relapses included the chest/chest wall in 21 (53%) patients, chest/chest wall + lymph nodes in 10 (25%) patients, and only the lymph nodes in nine (22%) patients. The most common organ of distant metastasis was the bones, which was present in 111 (60%) patients. The other common distant organ metastases were respectively as follows: liver in 63 (34%) patients, lungs in 58 (31%) patients, and the brain in 49 (27%) patients. Single organ metastasis was seen in 75 (41%) patients, whereas 109 (59%) patients had multiple organ metastases.

Table 2 shows the comparison of survival durations based on the sites of metastases. While the patients with bone metastasis had

Table 1: Clinical and Demographic Characteristics.

	No. of patients (%)
Gender	
Female and Male	181 (98) and 3 (2)
Age	
≤50 years and >50 years	91 (49) and 93 (51)
Menopause status	
Premenopause vs postmenopause	84 (46) and 97 (54)
Comorbidity	73 (43)
Hypertention	51 (30)
Diabetes mellitus	24 (14)
Heart disease	11 (7)
ECOG[1] performance status	
ECOG 0-1	114 (62)
ECOG 2 and high	70 (38)
The initial stage	
Stage I	14 (7)
Stage II	35 (19)
Stage III	84 (46)
Stage IV	43 (23)
Unknown	9 (5)
Histopathology	
Invasive ductal carcinoma	146 (79)
Mixted type	14 (8)
Invasive lobular carcinoma	11 (6)
Other	13 (7)
Histopathologic feature	
Intraductal component	69 (75)
Multicentricity	25 (24)
Lymphovascular invasion	80 (69)
Perineural invasion	48 (46)
Grade	
Grade 1-2	104 (70)
Grade 3	44 (30)
Hormon status	
Estrogen receptor (-) and (+)	62 (35) and 116 (65)
Progesteron receptor (-) and (+)	71 (40) and 106 (60)
HER2 (-) and (+)	86 (52) and 78 (48)
Ca 15,3	
≤31 U/mL and >31 U/mL	92 (59) and 65 (41)
CEA ≤5 ng/dL and >5 ng/dL	112 (75) and 38 (25)
Hemoglobin	
<12 g/dL and ≥12 g/dL	67 (38) and 111 (62)

[1]ECOG PS: Eastern Cooperative Oncology Group performance status

Table 2: The comparison of survival durations based on the sites of metastases.

	The Median survival	The 2-year Overall survival	The 5-year overall survival	*P* value
Bone vs brain	31 vs 7 month	57% vs 12%	24% vs 0%	<0.001
Bone vs lung	31 vs 25 month	57% vs 51%	24% vs 12%	0.005
Bone vs liver	31 vs 13 month	57% vs 30%	24% vs 12%	<0.001
Bone vs LRR[1]	31 vs 32 month	57% vs63%	24% vs 22%	0.614
Brain vs lung	7 vs 25 month	12% vs 51%	0% vs 12%	0.015
Brain vs liver	7 vs 13 month	7% vs 30%	0% vs 12%	0.019
Brain vs LRR	7 vs 32 month	7% vs 63%	7% vs 22%	<0.001
Lung vs liver	25 vs 13 month	51% vs 30%	12% vs 12%	0.041
Lung vs LRR	25 vs 32 month	51% vs 63%	12% vs 22%	0.115
Liver vs LRR	13 vs 32 month	30% vs 63%	12% vs 22%	0.002

[1]LRR: Locoregional relaps

the longest median, two-year and five-year survival durations, the patients with brain metastasis had the shortest survival.

After the development of the first metastasis, the median survival of the patients was 27 months (1-177 months), two-year survival was 55%, and five-year survival was 27%. The prognostic factors that affected patient survival after the development of metastasis are shown in table 3. Univariate analyses showed that the age, menopausal status, diabetes mellitus, performance status, number of metastases (single organ vs. multiple organs), localization of the metastases (bone, liver, and brain metastasis), ER receptor status, grade, lymphovascular invasion, Ca 15,3 (cancer antigen) levels, and hemoglobin levels affected survival, whereas comorbidities, PR status, HER2 status, subgroups (luminal A, luminal B, triple (-), HER2+), perineural invasion, CEA (Carcinoembryonic antigen) levels (≤5 ng/mL vs >5 ng/mL), Ki-67 levels (≤14 vs.>14), lung metastasis, and disease free interval (disease free interval <12 vs. ≥12 months, <24 vs. ≥24 months) did not affect the survival duration after metastasis (p>0.050).

The independent prognostic factors that affected the survival time of the patients after development of metastasis are represented in table 4. Multivariate analyses showed that the presence of diabetes mellitus, lymphovascular invasion positivity, high grades, hemoglobin levels lower than 12 g/dL, bone metastasis, and multiple organ metastases were the independent prognostic factors affecting the survival.

Discussion

The overall survival duration of patients with breast cancer has significantly increased, parallel to the recent advances in early diagnosis techniques and adjuvant treatments. However, patients who develop metastasis still have varied survival durations. Some patients may die

Table 3: The prognostic factors that affected patients survival the development of metastasis in univariate survival analysis.

Univariate analysis	The 2-year survival	The median survival	*P* value
Age			
≤50 years vs >50 years	65% vs 46%	32 vs 20 month	0.023
Menopause status			
Premenopause vs postmenopause	62% vs 51%	32 vs 25 month	0.028
Diabtes mellitus			
No vs Yes	58% vs 32%	31 vs 18 month	0.012
ECOG PS[1]			
ECOG 0-1 vs ECOG 2 and high	67% vs 39%	45 vs 18 month	<0.001
Number of metastatic sites			
Single vs Multiple organ	65% vs 48%	47 vs 23 month	0.004
Bone metastases			
No vs Yes	47% vs 59%	20 vs 32 month	0.023
Liver metastases			
No vs Yes	62% vs 44%	32 vs 22 month	0.028
Brain metastases			
No vs Yes	60% vs 43%	32 vs 20 month	0.003
Estrogen receptor			
Negative vs Positive	44% vs 62%	21 vs 31 month	0.048
Grade			
Grade 1-2 vs Grade 3	65% vs 30%	36 vs 17 month	0.006
Lymphovascular invasion			
Negative vs Positive	55% vs 43%	29 vs 19 month	0.015
Ca 15,3			
≤31 U/mL vs >31 U/mL	61% vs 52%	36 vs 25 month	0.012
Hemoglobin			
<12 g/dL vs ≥12 g/dL	33% vs 70%	17 vs 37 month	0.002

[1]ECOG PS: Eastern Cooperative Oncology Group performance status

Table 4: The independent prognostic factors that affected the survival time of the patients after development of metastasis.

Multivariate analysis	*P* value	Hazard ratio	95% confidence interval
Menopause status			
Postmenopause vs premenopause	0.023	2.07	1.11-3.85
Diabetetes mellitus			
Yes vs no	0.006	2.71	1.37-6.29
Lymphovascular invasion			
Positive vs negative	0.004	7.71	1.39-5.30
Grade			
Grade 3 vs grade 1-2	0.017	2.09	1.14-3.84
Hemoglobin			
≥12 g/dL vs <12 g/dL	0.001	0.34	0.17-0.63
Bone metastasis			
Yes vs no	0.018	0.50	0.28-0.88
The number of metastasis			
Multiple vs single organ	0.018	2.14	1.14-3.99

in a very short time, while some others may live with the metastasis for many years. Therefore, metastatic breast cancer patients represent a heterogeneous group that involves different clinical entities. Due to the differences in survival durations, determining the prognostic factors for this patient group is of great importance.

Bone metastases represent the most common metastasis seen in patients with breast cancer. The bones are primarily the first site of metastasis in this patient group. After development of bone metastasis, patients generally have longer survival durations compared to the patients with other metastatic sites. The median survival of patients after development of bone metastasis is approximately two years and 20% of these patients live longer than five years [9]. In their study including 248 breast cancer patients with bone metastases, Yavas et al. reported that the median survival duration after the development of metastasis was 24 months. It was reported in the same study that the first site of metastasis was the bone in the majority of the patients [10]. In 110 breast cancer patients having bone metastasis alone (having no metastasis at any other region), Ahn et al. reported the median survival as 55.2 months [11]. In the current study, patients developing bone metastasis were seen to have statistically significantly longer survival after the development of metastasis, compared to the patients with brain, liver, or lung metastases. However, patients with locoregional relapse and patients with bone metastasis had similar survival times. Both sites had the longest survival durations; median survival: 32 and 31 months, two-year survival: 57% and 63%, and five-year survival: 24% and 22%, respectively.

Stereotactic radiosurgery or surgical applications may extend the survival time in a limited number of tumors; however, the survival in these patients is still very low after the development of brain metastasis. The one-year survival rate after development of brain metastasis is approximately 20% [12]. In a study performed by Niwińska et al. [13] in 222 breast cancer patients with brain metastasis, median survival of patients was found to be 7.5 months. Results of the present study also showed that the patients have quite a low survival duration after the detection of brain metastasis (median survival: seven months, two-year survival: 20%, five-year survival: 0%). Compared to the survival duration of patients developing bone, lung, liver metastasis, or locoregional relapse, patients with brain metastasis had statistically significantly shorter survival.

Like brain metastasis, hepatic metastasis is also generally associated with poor prognosis in patients with metastatic breast cancer. In 500 metastatic breast cancer patients having liver metastasis, Pentheroudakis et al. showed that median survival time was 16 months and five-year survival was 8.5% [14]. In the present study, the median survival of patients with liver metastasis was 13 months, and their two-year and five-year survival rates were 30% and 12%, respectively. When compared to the survival durations with other organ metastases, patients with liver metastasis were seen to have significantly shorter survival compared to the patients with bone, lung metastasis or locoregional relapse, and significantly longer survival compared to the patients with brain metastasis.

The lungs are also a common site of metastasis in patients with metastatic breast cancer. Kawano et al. performed a study in patients with hormone positive stage IV breast cancer (69 patients) and reported the median survival in patients with lung metastasis to be 37 months [15]. In the present study, patients with lung metastasis had a median survival of 25 months, and their two-year and five-year survival rates were 51% and 12%, respectively. Patients with lung metastasis had shorter survival times compared to the median and two-year survival in patients with bone metastasis or locoregional relapse, and longer survival compared to the patients with liver or brain metastasis. However, their five-year survival rate was similar to the rate in patients with liver metastasis.

Most researchers believe that the age of the patient at diagnosis is a prognostic factor affecting the survival. In the study performed by Largillier et al. [16] in 1038 patients with metastatic breast cancer, it was reported that the survival of patients above 50 years of age was shorter than the survival of patients aged below 50 years (median survival 20 and 31 months, respectively). Some studies have shown that premenopausal women had better prognosis than the postmenopausal women [2]. However, other studies do not support this finding [17,18]. In the present study, the univariate analysis showed that patients' age above 50 years and postmenopausal status affected the prognosis in a negative way; however, the multivariate analysis showed that only menopausal status was an independent prognostic factor. Some researchers associated the poor prognosis seen in patients with older ages to the comorbidities present in this patient group [7]. The current results showed that patients with comorbidities did not have significantly different survival rates; however, patients with diabetes had shorter survival than the other

patients. Additionally, presence of diabetes mellitus was found to be an independent prognostic factor. Different from the present study, in their study including 557 patients with metastatic breast cancer, Jung et al. revealed that the presence of hypertension was an independent prognostic factor associated with mortality and they did not show a relation between the presence of diabetes mellitus and survival [18]. Some studies showed that poor performance status of the patients is among the factors that negatively affect the prognosis [19,20]. In the present study, the univariate analyses demonstrated that the performance status was a factor affecting prognosis; however, such an affect was not confirmed by multivariate analyses.

Tumor biology is known to play a significant role in the disease prognosis and patient survival. Furthermore, various studies have shown that various parameters that play roles in tumor behaviors, such as tumor differentiation, lymphovascular invasion, and perineural invasion, and have effects on the prognosis. In their study comparing breast cancer patients who had metastasis at diagnosis and who developed metastasis later (370 patients), Jimeno et al. confirmed the relationship between survival and grade. According to that study, the poorly differentiated tumors continue their negative effects on survival even after the metastasis (median survival 37 vs. 21 months) [21]. In a study performed by Liu et al., the results in 135 patients with metastatic breast cancer were found similar to the above mentioned study; median survival was 29 months for grade 1 tumors, and 19 months for grade 2 and 6 months for grade 3 tumors [22]. The results of the present study also showed that the survival was negatively affected in patients having poorly differentiated tumors with lymphovascular invasion. Additionally, tumor grade was encountered as an independent prognostic factor in the multivariate analyses.

Both the hormone receptor status and HER2 status in patients with breast cancer have significant roles in the treatment decision and patient prognosis. Several studies have shown that ER- and/or PR- status is associated with poor treatment response and increased mortality risk in patients with metastatic breast cancer [7,23-25]. Takeuchi et al. performed a study in 345 Japanese women who had their first recurrence, and showed that ER- and PR- statuses were poor predictive factors for mortality [25]. Similarly, Jun et al. reported that both ER- and PR- status is associated with mortality in the multivariate analyses [18]. On the other hand, Chang et al. reported that only PR- status was an independent prognostic factor [7]. Ryberg et al. [26] performed a survival analyses in 469 metastatic breast cancer patients who were treated with epirubicin-based chemotherapy and reported ER- status to be a poor prognostic factor. However, different from the other studies, the current results did not show such a strong relation between the survival and hormone receptor status. Only the univariate analyses showed that ER+ status had positive effects on survival, but no statistical significance was seen in the multivariate analyses.

HER2 is a pro-oncogene and its overexpression is known to be associated with poor survival and prognosis in early stage diseases [27,28]. Its role in metastatic disease is yet to be discovered. The present study did not show a statistically significant relation between HER2 and survival; however, there are studies reporting that HER2 is a prognostic factor for survival. In their study, Yung et al. confirmed the relation between HER2+ status and mortality [18]. In the study performed by Ren et al. in 194 patients with metastatic breast cancer at diagnosis, different from the above mentioned study, a statistically significant relation was not observed between the survival and the absence of HER2 overexpression; however, this patient group was shown to have a slightly longer survival than the other patients [29]. Largillier et al. [16] have reported that median survival was not different between the patients with HER2+ and HER2- tumors; median survival was 22 and 29 months, respectively. This study also showed that HER2 status does not affect survival.

Several studies have investigated the effects of the time for metastases development and its localization on survival. These studies have generally shown that patients with longer intervals of metastasis development also had longer survival times [7,18,21,22,25]. Jimeno et al. [21] reported that the interval for metastasis development (<24 months vs. ≥24 months) has significant effects on the survival according to a univariate analysis. Chang et al. [7] grouped the interval for metastasis development as <12 months, 12-60 months, and >60 months and they obtained significant results in terms of survival. However, in the present study, no significantly different survival rates were observed when the interval for metastasis development was stratified as 12 and 24 months (<12 vs ≥12 months, <24 vs ≥24 months). The interval for metastasis development was not considered to be a prognostic factor in the current study.

Some studies report that similar to the interval for metastasis development, the number of metastasis, and localization of metastasis also affect survival [17,18,21,29]. Jimeno et al. [21] assessed the number of sites with metastasis development along with the interval for metastasis. Their results showed a statistically significant difference in the survival rates between the cases with single organ metastasis and multiple organ metastases. Additionally, the presence of ≥2 organ metastases was considered to be a poor prognostic factor. Similarly, in the present study, the number of metastases was found to be a prognostic factor affecting the survival in both univariate and multivariate analyses. In the study performed by Jun et al., presence of brain, bone, and liver metastases was observed to represent the prognostic factors that statistically significantly the survival, both in the univariate and the multivariate analyses [18]. Liu et al. [22] reported that the presence of liver metastases represented a poor prognostic factor. The present study revealed that the presence of bone, liver, and brain metastasis was among the factors affecting survival. Patients with bone metastasis had longer survival than the patients having metastasis in the other organs, and bone metastasis was also shown to be a good prognostic factor based on the multivariate analyses.

Although not always, the levels of tumor markers such as CEA and Ca15.3 can be elevated in patients with metastatic breast cancer after development of metastasis. The level of increase in tumor markers varies between the patients. In their study comparing the predictive and prognostic value of circulating tumor cells and tumor markers (CEA, CA15.3 and lactate dehydrogenase) in patients with metastatic breast cancer, Pierga et al. [30] showed that CEA and Ca15.3 levels above the normal interval were poor prognostic factors for progression-free survival according to the univariate analysis. In the current study, the researchers also assessed the effects of elevated tumor marker levels on survival. Based on the univariate analyses, only the level of Ca15.3 that is above the normal interval was found to

be a prognostic factor affecting survival. CEA levels above the normal interval did not affect survival.

It was shown that the hemoglobin levels measured at diagnosis can be associated with prognosis in many cancer patients [31-34]. A decrease can be expected in the hemoglobin levels of the patients with metastatic disease, since these patients receive strong treatments and it is highly possible that their hemodynamic balance may be altered. The results of this study show that hemoglobin levels in patients with metastatic breast cancer are strongly associated with the prognosis.

Conclusion

The results of the present study support the claim that patients with bone metastasis have the best survival rates, whereas the patients with brain metastasis have the shortest duration of survival. The duration of survival in patients with metastatic breast cancer greatly varies according to the localization of metastasis. The study results showed that among all the prognostic factors that play significant roles on the survival of patients with metastatic breast cancer, post-menopause, presence of diabetes mellitus, lymphovascular invasion positivity, high disease grade, and multiple organ metastases represent the poor independent prognostic factors; whereas the presence of bone metastasis is a good independent prognostic factor.

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