THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2023.94803
Med Bull Sisli Etfal Hosp 2023;57(4):479–484

Original Research

Retrospective Analysis of Parameters Affecting Metastatic Breast Cancer

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Abstract

Objectives: While metastatic breast cancer (MBC), which is the most common cause of death in women, has been seen as an incurable surgical problem in the past decade, as the heterogeneous nature of breast cancer becomes clear with increasing molecular studies and advances in oncological protocols, life expectancy is increasing. In this study, we aimed to examine the clinicopathological features of the patients we followed up with MBC.

Methods: Patients who were operated on with the diagnosis of breast cancer in our hospital between 2018 and 2023 and who were later found to have metastases were retrospectively analyzed from the database. The age of the patients, the histological and molecular type, stage and grade of the tumor, the time from diagnosis to metastasis, the location of metastasis, the duration of treatment and follow-up were investigated. Patients who were operated on in other centers and/or were out of follow-up were excluded from the study. For the statistical analysis of the findings, number cruncher statistical system (NCSS) 2020 statistical software (NCSS LLC, Kaysville, Utah, USA) was used at a significance level of 0.05.

Results: Metastasis was detected in 77.1% (n=37) of a total of 48 female patients, and recurrence was found in 22.9% (n=11). The mean age of the patients was 57 years. There was no statistically significant difference between the patients in terms of demographics. When evaluated according to the TNM stage, 24.3% (n=9) of the patients were in the early stage and 75.7% (n=28) were in the locally advanced stage; the number of locally advanced patients was found to be higher than the early stage. In histology examination, 27.1% (n=13) of the patients were luminal A, 31.3% (n=15) luminal B, 16.7% (n=8) HER2 positive, and 25% (n=12) triple negative. Ki67 was higher than 14% in 64.6% (n=31) patients. Breast conserving surgery was performed in 41.6% (n=20) of the patients, and mastectomy was performed in 58.3% (n=28) patients. Metastasis in 34.2% (n=13) of the cases within 1–2 years, in 42.1% (n=16) within 2–5 years, and in 23.7% (n=9) after 5 years took place. Sites of metastasis were bone (37.7%, n=28), liver (28.9%, n=11), brain (10.5%, n=4), and lung (7.9%, n=3). More than one metastasis site was observed in 21.05% (n=8) of patients with metastases. There was no statistically significant difference between luminal A, luminal B, HER 2 groups and triple-negative breast cancer in terms of metastasis time and location ($p>0.05$). Adjuvant hormone therapy was more common in the luminal A group, whereas neoadjuvant therapy was more common in the HER2+ group. A total of 20 deaths were observed in 48 patients (41.7%). The median disease-free survival was 64 months.

Conclusion: Despite all the developments in metastatic breast cancer, the 5-year survival rate is 27%. Targeted personalized therapies may be promising when the mechanism of metastasis and specific pathways in breast cancer emerge.

Keywords: Heterogeneous nature, metastatic breast cancer, targeted therapies

Please cite this article as "Burcu B, Ertas I, Sener A, Demircioglu ZG, Cerekci E, Kaya C. Retrospective Analysis of Parameters Affecting Metastatic Breast Cancer. Med Bull Sisli Etfal Hosp 2023;57(4):479–484".

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Submitted Date: May 09, 2023 **Revised Date:** July 11, 2023 **Accepted Date:** July 17, 2023 **Available Online Date:** December 29, 2023

Breast cancer (BC), the most common cancer in women, was diagnosed in over 2.26 million new cases worldwide in 2020, and ranked fifth in cancer-related mortality, causing 685,000 deaths worldwide.[1] Locoregional recurrences occur in 5–15% of women diagnosed with breast cancer, while distant metastases occur in 15–30% of cases.[1,2] The risk of recurrence or metastasis is highest in the first 2 years after treatment in the hormone-negative group, while in the hormone-positive group, this risk remains constant for a long time, and late recurrences are more common.[1] Despite an increase in survival times due to developing treatments, 20–30% of patients with early breast cancer still die from metastatic disease. In less developed countries, 20–30% of patients have metastases at the time of diagnosis, and it is expected that the global death rate due to MBC will be approximately 805,116 by 2030.[3]

The prognosis of MBC is affected by many clinicopathological features, including age, race, performance status, tumor size, pathology, lymph node status, and the number and location of metastases.[4] While the overall 5-year survival rate in stage 1 is 99%, it drops to 27% when distant metastases are detected.[5] Systemic treatments for metastatic breast cancer include endocrine therapy, chemotherapy (CT), and target-directed therapies with the primary goal of palliation.

Due to the dramatic decrease in survival rates in metastatic disease, it is essential to identify parameters that may predict recurrence/metastasis more explicitly and develop treatment methods that prevent it. In our study, we aimed to identify factors that may be responsible for the development of metastasis and contribute to the literature to increase survival in this disease.

Methods

This study was conducted with a total of 48 female patients in a single center. Breast cancer patients who developed metastasis or recurrence between 2018 and 2023 were retrospectively screened from the database. The patients' age, histological and molecular type of the tumor, grade, time from diagnosis to metastasis, site of metastasis, and treatment and follow-up periods were investigated. Treatment was initiated for all patients after diagnosis was confirmed by a council decision. Patients who underwent surgery at other centers and those who were lost to follow-up during treatment were not included in the study. Ethics committee approval was obtained from the ethics committee on April 04, 2023, with the number 3863. Our study was carried out in accordance with the Declaration of Helsinki.

Statistical Analysis

While evaluating the findings obtained in the study, number cruncher statistical system (NCSS) 2020 statistical software (NCSS LLC, Kaysville, Utah, USA) program was used for statistical analysis. Shapiro–Wilktest and box plot graphics were used to evaluate the conformity of the data to the normal distribution. The Mann–WhitneyU test was used to evaluate the non-normally distributed variables according to two groups. Variables that do not show normal distribution; Kruskal–Wallis test was used in the comparison of three groups and above. Chi-square test, Fisher'sexact test, and Fisher's Freeman Halton test were used in the comparison of qualitative data.

Results

In 77.1% (n=37) of the patients, metastasis was detected, while recurrence was observed in 22.9% (n=11). The patient's ages ranged from 31 to 85 years, with a mean age of 57. When tumor histology was examined, 83.3% (n=40) were invasive ductal carcinoma (IDC), 10.4% (n=5) were invasive lobular carcinoma (ILC), 2.1% (n=1) were metaplastic carcinoma, 2.1% (n=1) were mucinous carcinoma, and 2.1% (n=1) were of other types. The mean tumor size was 32.40±22.29. In subgroup analysis, 27.1% (n=13) of the patients were luminal A, 31.3% (n=15) were luminal B, 16.7% (n=8) were HER2-positive, and 25% (n=12) were triple-negative breast cancer (TNBC) (Fig. 1). Ki-67 value was above 14% in 64.6% of the patients (n=31). 5% of the patients (n=5) had low, 47.9% (n=23) had intermediate, and 41.7% (n=20) had high-grade differentiation. With respect to the type of surgery, 41.6% (n=20) of the patients underwent breast-conserving surgery and 58.3% (n=28) underwent mastectomy. 81.3% (n=39) of the patients received radiotherapy (RT), 79.2% (n=38) received CT, and 37.5% (n=18) received hormone therapy (HT). The metastasis occurred within 1–2 years in 34.2% (n=13) of the cases, within 2–5

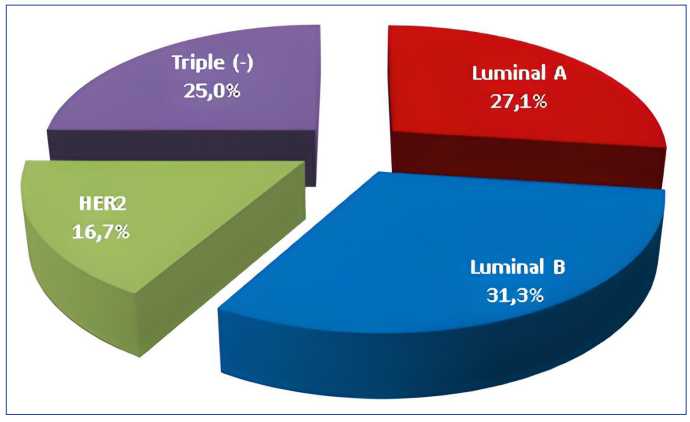

Figure 1. Ratio of subgroups.

years in 42.1% (n=15), and after 5 years in 23.7% (n=9). The sites of metastasis were bone 37.7% (n=28), liver 28.9% (n=11), brain 10.5% (n=4), and lung 7.9% (n=3). Multiple sites of metastasis were observed in 21.05% (n=8) of the patients with metastasis.

The average time to recurrence was 50 months, and the average follow-up period for all patients with metastasis/recurrence was 30 months. It was observed that 41.7% (n=20) of the patients had died. There was no statistically significant difference in age, metastasis and recurrence status, grade, tumor type, and size among groups (p>0.05). There was no statistically significant difference in terms of metastasis time and site between the luminal A, luminal B, HER 2+ groups, and TNBC (p>0.05) (Table 1). Adjuvant HT was more common in the luminal A group, while neoadjuvant therapy was more common in the HER2+ group. Axillary lymph node involvement, tumor location, type of surgery, RT and KT rate, recurrence time, metastasis site and time, mortality rate, and follow-up time did not show statistically significant differences among subgroups (p>0.05). The metastasis rate was found to be statistically significantly higher in the ex-group compared to the control group (p=0.016; p<0.05). The axillary lymph node involvement rate of the cases in the metastasis group was statistically significantly higher than that of the cases in the recurrence group (p=0.010; p<0.05). Adjuvant CT was administered to 89.2% of patients with metastasis. The rate of receiving CT in metastatic cases was statistically significantly higher than that in the recurrence group (p=0.005; p<0.01).

There was no statistically significant difference in terms of the site of metastasis (bone, liver, and brain) according to tumor type (p>0.05) (Table 2).The rate of lung metastasis in patients with metaplastic carcinoma and mucinous tumor was statistically significantly higher than that in patients with IDC and ILC tumor types. The rate of lung metastasis in patients with IDC tumor type was statistically significantly higher than that in patients with ILC tumor type (p=0.006; p<0.01).

In total, 20 deaths were observed in 48 patients (41.7%). The mean disease-free survival was 64 months. In the luminal A group, 7 patients (53.8%) were alive, and 6 patients had died with a mean survival time of 48 months. In the luminal B group, 9 patients (60%) were alive, and 6 patients had died with a mean survival time of 51 months. The mean survival time was 86 months in the HER2 + group, and 6 patients (75%) were alive while 2 patients had died. The mean survival time in the TNBC group was 59 months; 6 patients (50%) were alive, and 6 patients had died. When the sur-

Table 1. Comparison of patients according to subtypes

Ages and tumor characteristics n=48	Group				p
	Luminal A (n=13)	Luminal B (n=15)	HER2 (n=8)	Triple (-) (n=12)	
Age					
Medt±Sd	56.54±12.87	62.27±14.11	56.13±13.83	59.92±14.19	[a]0.653
Median (Min-Max)	57 (31–79)	59 (42–84)	55 (41–76)	61 (36–85)	
Metastasis/recurrence					
Metastasis	13 (100)	12 (80.0)	4 (50.0)	8 (66.7)	[b]0.572
Recurrence	1 (7.7)	3 (20.0)	4 (50.0)	4 (33.3)	
Both	1 (7.7)	1 (6.7)	0	0	
Grade					
High	3 (23.1)	1 (6.7)	0 (0.0)	1 (8.3)	[b]0.178
İntermediate	7 (53.8)	7 (46.7)	6 (75.0)	3 (25.0)	
Poor	3 (23.1)	7 (46.7)	2 (25.0)	8 (66.7)	
Tumor type					
Intraduktal (IDC)	11 (84.6)	12 (80.0)	7 (87.5)	10 (83.3)	[b]0.574
Intralobular (ILC)	1 (7.7)	3 (20.0)	0 (0.0)	1 (8.3)	
Metaplastic	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	
Musinous	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Other	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	
Tumor diameter (n=47)					
Med±Sd	29.00±13.45	31.27±13.87	45.86±47.79	29.67±15.82	[a]0.912
Median (Min-Max)	25 (8–54)	30 (13–60)	30 (5–150)	26.5 (8–65)	

[a]KruskalWallistest; [b]Fisher Freeman Halton test; IDC: İnvasive ductal; ILC: Intraductal carsinom carcinoma.

Table 2. Comparison of metastasis sites by tumor type

Metastasis site	Tumoral type				p
	IDC (n=40)	ILC (n=5)	Metaplastic (n=1)	Musinous (n=1)	
Bone					
No	8 (25.0)	0 (0.0)	0 (0.0)	1 (100.0)	[b]0.515
Yes	24 (75.0)	3 (100.0)	1 (100.0)	0 (0.0)	
Liver					
No	23 (71.9)	2 (66.7)	1 (100.0)	1 (100.0)	[b]1.000
Yes	9 (28.1)	1 (33.3)	0 (0.0)	0 (0.0)	
Brain					
No	28 (87.5)	3 (100.0)	1 (100.0)	1 (100.0)	[b]1.000
Yes	4 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Lung					
No	31 (96.9)	3 (100.0)	0 (0.0)	0 (0.0)	[b]0.006**
Yes	1 (3.1)	0 (0.0)	1 (100.0)	1 (100.0)	

[b]Fisher Freeman Halton Test, IDC:Intraduktalcarsinom; ILC: Intraductal carsinom.

vival rates were evaluated by the LogRank test according to groups, there was no statistically significant difference in survival rates (p=0.745; p>0.05) (Fig. 2).

Discussion

Approximately 90% of deaths related to breast cancer occur due to metastasis.[6] A review reported that the 5-year overall survival rate for MBC is only 22.8%.[7] It is estimated that 20–30% of all patients diagnosed with BC will develop metastasis.[7] In the United States alone, it has been reported to cause 41,000 cancer-related deaths per year.[7,8] While the expected lifespan varies in different series, the general consensus is an average of 2–3 years for the years 1995–2013.[3] While in some studies, triple metastatic sites are reported in 74% of patients, this rate remains at 40% in Türkiye.[9]

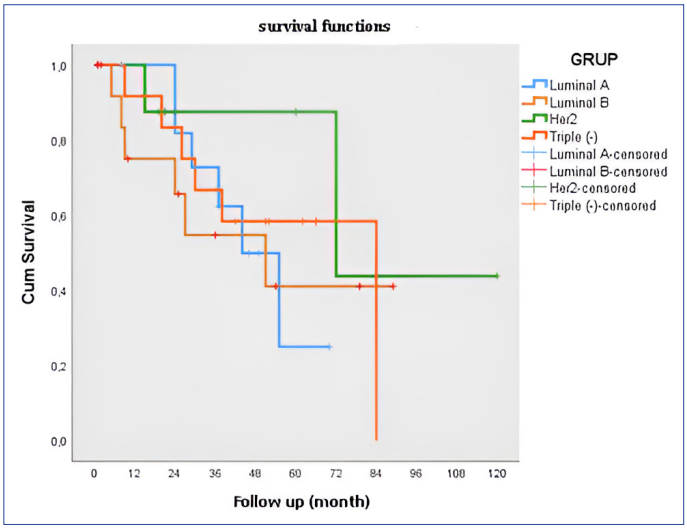

Figure 2. Survive analysis of subgroups.

The development of metastasis in breast cancer is a heterogeneous condition that may be related to the tumor, the patient, and the treatment method.[10] Although it is not yet clear exactly which patients will develop metastasis, some predictive parameters are known.[10,11]

Unlike most malignancies, BC spreads through the lymphatic route rather than the hematogenous route.[6] Depending on the localization of the tumor cell, it progresses to the lymph node, the sentinel lymph node, and then to the efferent lymphatic system.[6] As stated in the "seed and soil" theory, organ-specific metastases are thought to occur not randomly, but rather due to the appropriate organ microenvironment allowing for the growth of tumor cells.[7,11] The process of progressing from lymph node metastasis to organ metastasis has not yet been fully elucidated.

When metastatic BC histology was examined, the most common type was ductal carcinoma, and in our study, 83.3% of the patients were ductal type.[1,12] Medullary and metaplastic carcinoma associated with the basal-like subtype and with poor prognosis was found in 4.2% of our patients who developed metastasis, and no significant correlation was found with the prognosis.[12](p<0.05) However, in our study, a medullary and metaplastic carcinoma type significant correlation was found between the presence of lung metastasis (p=0.006). BC was basically clinicopathologically, as first described in 2000,[11] gene expression profiles and receptor status (estrogen [ER], progesterone receptor [PR], human epidermal growth factor 2 [HER2].[11] Systemic treatment in metastatic breast cancer is shaped according to subtypes; while CT is preferred in the TNBC group, HER2 overexpressing type anti-HER2 drugs, endocrinotherapy in HR+BC will be considered in primary care

treatment.[4,9,10] It was reported that 70% of all MBCs were HR+, and this rate was 58.3% in our study.[4]

TNBC and HER2+ MC have the highest incidence of metastasis in the first 2 years.[2] Similarly, in our study, 50% of HER2+ patients and 62.5% of TN patients had metastasis within the first 2 years. Many studies have shown that HR+ patients have a higher rate of recurrence/metastasis after 5 years compared to HR- patients.[2] In our study, 53.9% of Luminal A patients had metastasis after 5 years. According to NCCN data, 83% of breast cancers are diagnosed in women over the age of 50 years, which is consistent with the mean age of 59 in our study.[1] All recurrence cases were late (after 2 years) and had a moderate to high differentiation. Ki67 was high in 81.8% of cases and 45.45% were HR+. HR+ status may be related to late recurrence. However, it is noteworthy that the risk of recurrent MBC increases after 5 years of endocrine therapy in HR+ BC.[13] The subtext of these late recurrences may be related to the low-grade and slow expression of HR+BC cells compared to other types.[4] Hormone receptor-positive and HER2+ subtypes have relatively longer survival expectations.[4,14] Kim et al.[14]showed that HR+ patients had the longest metastasis-free survival time and the lowest mortality, with an average survival time of 20 months. They also found that a short time to metastasis was associated with young age and initial visceral metastasis. The average survival time was 40 months in patients with bone metastasis but dropped to 14 months in those with visceral metastasis.[14] In the literature, the average survival time is 21 months,[15] and the 5-year survival rate for MBC is 29%.[1] Waks et al.[16] reported that brain metastasis occurs in 10–20% of cases. In this study, the average survival times were 9 months for isolated lung metastasis, 13 months for isolated liver metastasis, and 4 months for isolated brain metastasis; 2 out of 4 patients in the isolated liver metastasis group and 3 out of 3 patients in the isolated brain metastasis group died. Except for the results due to the low number of patients in some groups (excluding bone metastasis), the overall survival times are consistent with the literature.

ER/PR+ type is generally associated with bone metastasis, while HER2+ and TNBC groups are known to have more visceral organ metastasis.[10] In MBC patients, bone metastasis is the most common, with some studies reporting a rate of 75%.[7] When the bone metastasis profile was examined, it was found that luminal A and B subtypes were the most common, with a survival time of 24–26 months.[6] In our study, bone metastasis was present in 58.3% of the entire group and was the most common metastatic site. There was no difference observed in the metastatic sites based on the hormone profile. The mean survival time of 22 patients with isolated bone metastasis was 19.6 months, which is consistent with the literature.

Studies have reported that patients with lung metastasis often have TNBC and are strongly associated with epidermal growth factor receptor (EGFR) expression.[11] In some series, EGFR/HER2 positivity was found in 75.8% of patients with primary lung metastasis.[6] Looking at the largest studies, TNBC is the most common subtype after luminal B for primary lung metastasis.[10] The rate of primary liver metastasis was 15–32%, and the rate of brain metastasis was 4–10%.[11] The 5-year life expectancy for metastatic breast cancer is 8.5%, which is extremely short.[7] In our study, 7.9% of patients had lung metastasis, 28.9% had liver metastasis, and 10.5% had brain metastasis. Liver metastases are more common in the HER2+ group and are also frequent in recurrences.[10] In many studies, there was no significant difference in metastasis and recurrence sites between luminal A and luminal B subtypes. The lack of a significant relationship between the location of metastasis and hormone profile in our study may be related to the limited number of cases.

In our study, locally advanced breast cancer was more common than in early-stage breast cancer patients. Poor histological type, large tumor size, and higher incidence of metastasis in advanced breast cancer are consistent with other studies.[17,18] Apart from all histopathological types and factors, axillary lymph node involvement at the time of diagnosis is one of the most important prognostic factors for distant metastasis.[16,19] It was found to be associated with patients with distant metastasis and, therefore, mortality in our patient group. Of the 20 patients who had ex, 19 were metastatic, and the average survival time of all patients was 64 months.

Although there was no statistically significant difference in terms of survival between subgroups, the HER2-overexpressing group and luminal B group were relatively higher than the others, and it was thought that this could be related to the difference in sensitivity to CT, but a definite explanation could not be found in our study. We know the heterogeneous molecular structure of BC through its subtypes. Studies on molecular markers have shown that there are different types of metastasis depending on the subtypes of BC. Clarifying gene analyses and thus molecular signaling pathways will enable the development of targeted therapies and reduce the risk of death due to metastasis and recurrence.

Conclusion

As the molecular codes and patient-specific genetic maps of BC become clearer, targeted agents appear to be able to change the course of this dramatic disease. In this study, the positive contribution of surgical local control to surviv-

al was repeated. With studies to be conducted with larger case series, especially the identification of factors that can lead to recurrence or metastasis in subgroups, more improvements can be made in preventing recurrence and metastasis and improving survival.

Disclosures

Ethics Committee Approval: Ethics Committee approval was obtained from the Sisli Hamidiye Etfal Training and Research Hospital ethics committee on 04/04/2023 with the number 3863.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – B.B.; Design – A.S.; Supervision – C.K.; Materials – Z.G.D.; Data collection &/or processing – E.C.; Analysis and/or interpretation – I.E.; Literature search – B.B.; Writing – B.B.; Critical review – I.E.

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