

**Introduction:** Breast cancer (BC) is a heterogeneous disease. Several subgroups have been identified, according to the clinical presentation and radiographic, pathological, biological, and molecular characteristics of the tumor. Intrinsic genetic heterogeneity may be responsible for these differences. To date, little is known about the clinical features and outcome of patients with primary metastatic BC (PMBC) defined as those presenting with stage IV disease.

**Material and methods:** Between September 2007 and May 2011, BC patients who were admitted to a clinic were assessed. Patients with PMBC were included in this retrospective analysis. The patients' demographic characteristics, treatment schedules, and survival data were recorded.

**Results:** Of 2478 BC patients, 102 (4.1%) with PMBC were included in the analysis. The median age of the patients was 50 (26–90) years. Only four patients (3.9%) had previously undergone mammography. The median progression-free survival (PFS) and overall survival (OS) were 30 and 66 months, respectively. The PFS and OS were unaffected by age, menopausal status, ECOG, histology, or tumor grade. Both PFS and OS were affected by HR status (log rank  $p = 0.006$ , log rank  $p = 0.04$ ), HER2 status ( $p = 0.001$ ,  $p = 0.005$ ), site of metastasis ( $p = 0.01$ ,  $p = 0.04$ ), radiotherapy ( $p = 0.04$ , OS  $p = 0.03$ ), and bisphosphonate treatment ( $p = 0.02$ ,  $p = 0.006$ ). PFS was greater in the hormone therapy group (43 months,  $p = 0.03$ ) while OS was greater in the patients that received chemotherapy (76 months,  $p = 0.01$ ).

**Conclusions:** Mammography should be given greater emphasis, considering its importance in the prevention of PMBC. As a treatment option for bone and soft tissue metastatic PMBC patients, hormone therapy should be effective as a first-line treatment.

**Key words:** primary metastatic breast carcinoma, demographic characteristics, mammography, factors affecting survival.

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# Assessment of general characteristics of patients with primary metastatic breast carcinoma: single center experience

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## Introduction

Breast cancer (BC) is the most common cancer in women in almost all countries, including developing countries. In 2008, 1,380,000 new cases and 458,000 BC deaths were noted worldwide, with 332,000 new cases and 89,000 deaths in the European Union [1, 2]. Breast cancer is a heterogeneous disease with several subgroups based on the clinical presentation and radiographic, pathological, biological, and molecular characteristics of the tumor [3].

Approximately 5–10% of BC is metastatic at diagnosis; of these, approximately one-fifth of the patients survive for five years. As there are significant variations in the outcome of early BC among different regions, the burden of primary metastatic BC (PMBC) may differ from that of early disease [1]. The general characteristics of the primary tumor are important in the prognosis and survival of patients with MBC [4].

Despite a reduction in BC mortality by 15% due to increased awareness of BC and widespread screening by mammography, the literature lacks data suggesting that mammography reduces the incidence of advanced BC [5]. The prevalence of metastatic disease is high because many women live with the disease for several years. There is, however, a significant lack of accurate data on the prevalence in the great majority of countries, since most cancer registries do not capture relapses [1].

Little is known about the clinical features and outcome in patients with PMBC. The aim of this analysis was to evaluate the demographic characteristics of PMBC patients and the factors that may affect progression-free survival (PFS) and overall survival (OS).

## Material and methods

Between September 2007 and May 2011, BC patients who were admitted to the Clinical Medical Oncology Department of the Ankara Oncology Education and Research Hospital (Ankara, Turkey) were assessed in this retrospective analysis. Patients with PMBC were included in this analysis. Patients were considered to have PMBC if a distant metastasis was evident at the time of the initial diagnosis of BC. Patients with an ipsilateral axillary lymph node metastasis at the time of diagnosis were not included in the PMBC group. Patients were considered to have recurrent metastatic BC (RMBC) if the metastasis had developed during the follow-up period for localized BC. Patients with RMBC were excluded from the analysis. The age, menopausal status, Eastern Cooperative Oncology Group (ECOG) performance status, tumor histological

subtype, grade of tumor, and type of metastasis (visceral, bone/soft tissue, and visceral plus bone/soft tissue) were recorded from the patients' medical records. Treatment schedules and the duration and response to treatment were also recorded.

Chemotherapy (cyclophosphamide, Adriamycin and taxanes) was used as the first line treatment in patients with visceral metastasis [hormone receptor (HR) negative or positive and if they were human epidermal growth factor receptor 2 (HER2) negative]. Targeted therapy (trastuzumab) was added to the chemotherapy for HER2 positive patients.

Both chemotherapy and targeted therapy were used for HR negative and HER2 positive patients with only bone and soft tissue metastasis. Hormone therapy (tamoxifen in premenopausal patients and anastrozole or letrozole in postmenopausal patients) or chemotherapy was used as a first line treatment option based on oncologist preference if patients were HR positive and HER2 negative.

The PFS was calculated from the date of first diagnosis until disease progression or death. OS was calculated from the date of first diagnosis till death for any reason, or until the date of last contact.

### Statistical analysis

For statistical analysis, SPSS for Windows ver. 15.0 (SPSS, Chicago, IL, USA) was used. Descriptive statistics for discrete variables were compared with the median (minimum-maximum) as categorical variables, and the number of cases (%) is shown. Categorical variables were tested for a significant association with PFS or OS using log-rank tests of Kaplan Meier survival curves. For each variable, the average PFS and OS times were calculated;  $p < 0.05$  was considered statistically significant.

### Results

Between September 2007 and May 2011, a total of 2478 BC cases were admitted to our medical oncology clinic; 102 (4.1%) of those who were identified PMBC as patients were included in this analysis.

All of the patients were female; the median age was 50 years (range: 26–90). Three patients were 30 years old or younger, 44 were between 31 and 49 years, 38 were between 50 and 69 years, and 17 patients were older than 70 years. More than half of the patients (58.8%) were postmenopausal. The median age of menopause was 51 (range: 43–55) years.

Only four (3.9%) patients had had previous mammographic screening.

The ECOG performance status was 0-1, 2, and 3 in 71 (69.6%), 26 (25.5%), and 5 (4.9%) patients, respectively.

In all, 92.2% (94) patients had not undergone primary surgical treatment. As primary surgical treatment, a modified radical mastectomy was performed in three (2.9%) patients and a lumpectomy in five (3.1%). The histological subtypes seen were invasive ductal carcinoma (no special type), invasive lobular carcinoma, or other types in 91 (89.2%), 8 (7.8%), and 3 (3.0%) patients, respectively.

Only one patient had a grade 1 tumor, 25 patients had grade 2 tumor, and 59 patients had a grade 3 tumor; the tumor grade was undetermined in 17 patients.

The tumors were positive for HR and HER2, either by immunohistochemical or chromogenic *in situ* hybridization methods, in 76.5 and 42.2% of cases, respectively.

When evaluated together, the tumors were negative for both HR and HER2 in 11 cases (10.8%), HR-negative and HER2-positive in 13 (12.7%), HR-positive and HER2-negative in 48 (47.1%), and both HR- and HER2-positive in 30 cases (29.4%) (Table 1).

The metastatic sites were visceral, bone/soft tissue, or visceral with bone/soft tissue sites in 21 (20.5%), 43 (42.2%), and 38 (37.3%) patients, respectively. Most of the visceral metastatic patients (11/13, 84.7%) were negative for HR and positive for HER2 (Table 2).

The median PFS and OS were 30 (range: 1–97) and 66 (range: 1–143+) months, respectively (Figs. 1 and 2). Both PFS and OS were unaffected by age ( $p = 0.2$  for both), menopausal status ( $p = 0.09$  and  $0.9$ , respectively), ECOG performance status ( $p = 0.07$  and  $0.4$ , respectively), histology ( $p = 0.3$  and  $0.6$ , respectively), and tumor grade ( $p = 0.2$  and  $0.7$ , respectively).

**Table 1.** Demographic characteristics of the patients

	n (%)
<b>Median age (years, range)</b>	50 (26-90)
< 30 years	3 (2.9)
31–49 years	44 (43.1)
50–69 years	38 (37.3)
> 70 years	17 (16.7)
<b>Menopausal status</b>	
premenopausal	42 (41.2)
postmenopausal	60 (58.8)
<b>ECOG</b>	
ECOG 0-I	71 (69.6)
ECOG II	26 (25.5)
ECOG III	5 (4.9)
<b>Type of histology</b>	
Invasive ductal	91 (89.2)
Invasive lobular	8 (7.8)
other	3 (3.0)
<b>Grade of histology</b>	
grade I	1 (1.0)
grade II	25 (24.5)
grade III	59 (57.8)
unspecified	17 (16.7)
<b>Hormone receptor</b>	
positive	78 (76.5)
negative	24 (23.5)
<b>HER2 (IHC and CISH)</b>	
positive	43 (42.2)
negative	59 (57.8)
<b>Receptor combinations</b>	
HR(-)HER2(-)	11 (10.8)
HR(-)HER2(+)	13 (12.7)
HR(+)-HER2(-)	48 (47.1)
HR(+)-HER2(+)	30 (29.4)

ECOG – Eastern Cooperative Oncology Group, HR – hormone receptor, HER2 – human epidermal growth factor receptor 2, IHC – immunohistochemical, CISH – chromogenic *in situ* hybridization

**Table 2.** Presence of visceral metastasis according to receptor profile in primary metastatic breast carcinoma patients

Visceral metastasis	Absent n (%)	Present n (%)	
HR(-)/HER2(-)	3 (27.2%)	8 (72.8%)	11
HR(-)/HER2(+)	2 (15.3%)	11 (84.7%)	13
HR(+)/HER2(-)	25 (52%)	23 (48.0%)	48
HR(+)/HER2(+)	13 (43.3%)	17 (56.7%)	30
Total n (%)	43 (42.15%)	59 (57.85%)	102

HR – hormone receptor, HER2 – human epidermal growth factor receptor 2

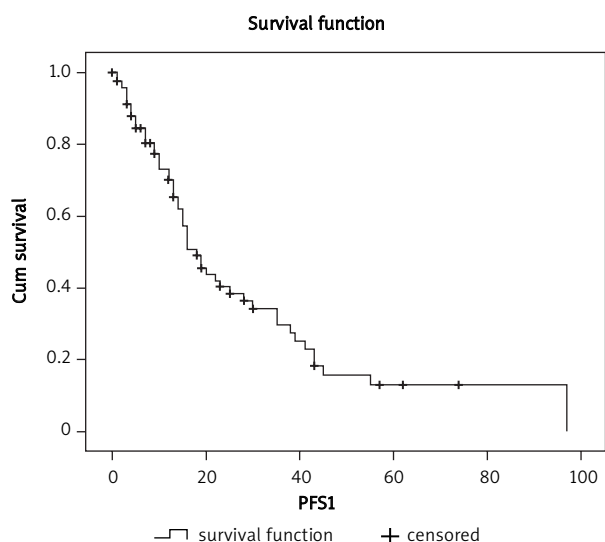
When PFS and OS were evaluated according to estrogen receptor (ER) and progesterone receptor (PR) status, median PFS of the PR positive patients was not different from that of the PR negative subjects ( $p = 0.440$ ). In contrast, the PFS of the ER positive patients was significantly longer than

that of the ER negative patients ( $p = 0.011$ ). We found that PR and ER status do not have a significant effect on OS ( $p = 0.551$  and  $p = 0.114$ ).

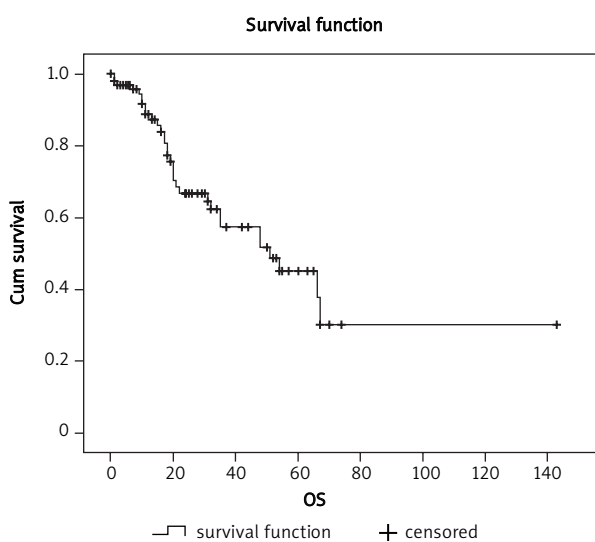
The median PFS of the HR positive and negative patients were 34 (1–97) and 15 (1–39) months, respectively. The median OS of the HR positive and negative patients were 73 (8–143) and 41 (1–67) months, respectively.

Significant effects on both PFS and OS were noted for HR status ( $p = 0.006$  and  $0.04$ , respectively) HER2 status ( $p < 0.001$  and  $0.005$ , respectively), site of metastasis (visceral or bone/soft tissue metastasis;  $p < 0.01$  and  $p = 0.04$ , respectively), previous radiotherapy ( $p = 0.04$  and  $0.03$ , respectively), and bisphosphonate therapy ( $p = 0.02$  and  $0.006$ , respectively) (Figs. 3 and 4).

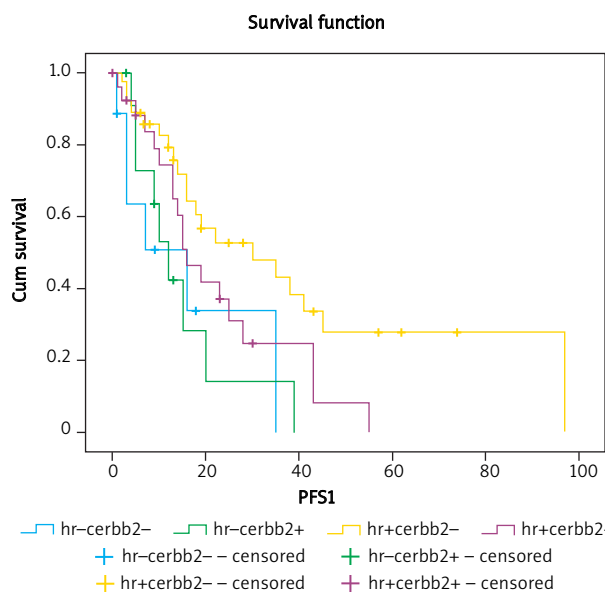
The PFS and OS were longer in patients with a metastasis only to bone or soft tissue, as compared to patients with only visceral metastases (40 vs. 13 months, and 79 vs. 34 months,  $p < 0.001$  and  $0.03$ , respectively).



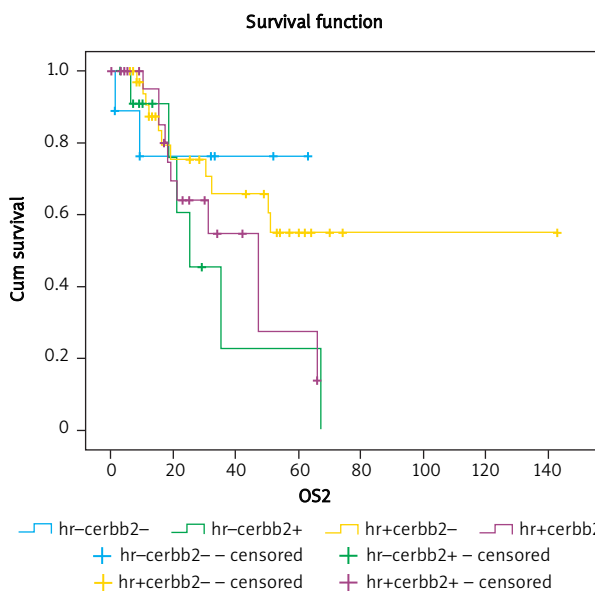
**Fig. 1.** Kaplan-Meier curve showing the rate of PFS in the patients



**Fig. 2.** Kaplan-Meier curve showing the rate of OS in the patients



**Fig. 3.** Kaplan-Meier curves showing the rate of PFS by HR and HER2 status



**Fig. 4.** Kaplan-Meier curves showing the rate of OS by HR and HER2 status

**Table 3.** Factors affecting progression-free survival and overall survival in primary metastatic breast carcinoma

Variables	PFS (months)	<i>p</i>	OS (months)	<i>p</i>
Median (range)	30 (1–97)		66 (1–143)	
Age		0.2		0.2
Menopausal status		0.09		0.9
ECOG performance status		0.07		0.4
Type of histology		0.3		0.6
Grade of histology		0.2		0.7
HR(+)	34 (1–97)		73 (8–143)	
HR(–)	15 (1–39)	0.006*	41 (1–67)	0.04*
HER2(+)	20 (1–55)		37 (6–67)	
HER2(–)	38 (1–97)	0.04*	93 (1–143)	0.04*
Visceral only metastasis	13 (1–38)		34 (1–70)	
Bone/soft tissue only metastasis	40 (1–97)	0.001*	79 (8–143)	0.03*
Radiotherapy (+)	34 (1–97)		70 (8–143)	
Radiotherapy (–)	15 (1–38)	0.005*	33 (1–70)	0.02*
Bisphosphonate (+)	35 (1–98)		72 (8–143)	
Bisphosphonate (–)	13 (1–38)	0.01*	31 (1–70)	0.006*
Hormone therapy	43 (1–62)		46 (16–62)	
Chemotherapy	32 (1–97)		76 (1–143)	
Chemotherapy and targeted therapy	15 (2–30)	0.03*	23 (10–35)	0.01*

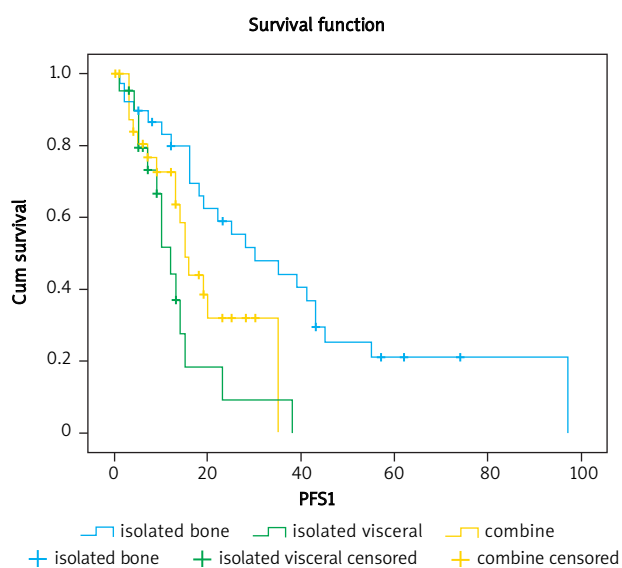
ECOG – Eastern Cooperative Oncology Group, HR – hormone receptor, HER2 – human epidermal growth factor receptor 2, \*statistically significant

Both PFS and OS were longer in the group that had received radiotherapy (34 vs. 15 months, and 70 months vs. 33 months,  $p < 0.005$  and  $0.02$ , respectively). Bisphosphonate therapy was also associated with a longer PFS and OS (35 vs. 13 months, and 70 vs. 33 months,  $p < 0.01$  and  $0.006$ , respectively).

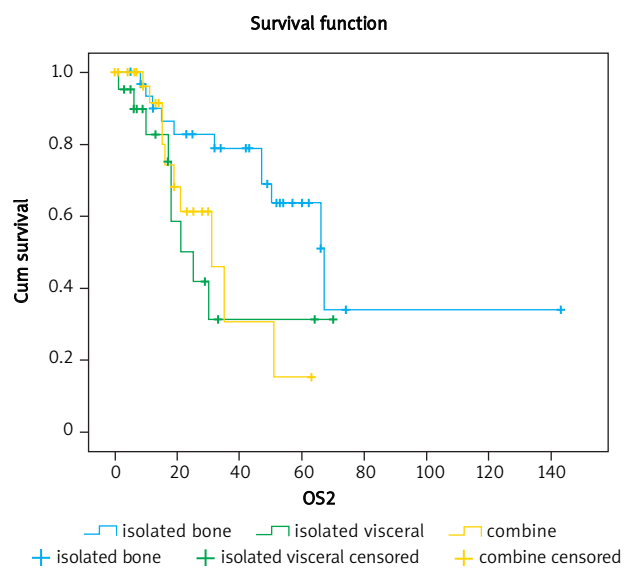
Progression-free survival was better in the hormone therapy (tamoxifen, anastrozole and letrozole) group, while the OS was better in the patients who received chemotherapy

(cyclophosphamide, Adriamycin and taxanes) ( $p = 0.03$  and  $< 0.01$ , respectively).

The PFS was longest in the hormone therapy group and shortest in the chemotherapy plus targeted therapy (trastuzumab) group (43 vs. 15 months, respectively;  $p = 0.03$ ). On the other hand, OS was longest in those patients who received chemotherapy (76 months) and shortest in patients who received chemotherapy plus targeted therapy (23 months;  $p < 0.01$ ) (Table 3).



**Fig. 5.** Kaplan-Meier curves showing the rate of PFS by metastasis region



**Fig. 6.** Kaplan-Meier curves showing the rate of OS by metastasis region

## Discussion

Breast cancer is a heterogeneous disease, and the clinical course and prognosis for each patient may vary according to the characteristics of the tumor [6]. The incidence of PMBC was reported to be between 0 and 11.5% in the EURO-CARE study [7]. This incidence was reported as 8.9 and 6% in reports from Spain and the US, respectively [8, 9]. In this analysis, we found an incidence of PMBC of 4.1%.

The risk of BC increases with age. Two different studies reported that 64 or 70% of MBC patients were over 50 years of age [10, 11]. One study indicated that PMBC patients were older (median age: 61 years) than RMBC patients, and that 77.3% of them were postmenopausal [9]. In our analysis the median age of the patients was 50; 54% of them were older than 50 years, and 58.8% of the patients were postmenopausal. Age was not directly correlated with PFS or OS. A possible reason for that may be that although many patients in our analysis were elderly, their visceral metastasis rate was low and their bone and soft tissue metastasis rate was high, giving them a better average ECOG performance status.

The best screening method for BC is mammography, which has a sensitivity of 77–95% and specificity of 94–97%. Annual or biannual mammography screening is advised for women between 40 and 50 years of age. However, women usually do not attend screening programs because of a lack of education and information. We also noted inadequate mammography screening in our analysis [12–14].

Performance status is an important parameter in the initiation and continuation of a treatment. In other MBC studies, the ECOG performance status was 0 or 1 in 58–89.3% of PMBC patients [11, 15]. Sezgin *et al.* [16] showed that a lower performance status was correlated with a worse outcome.

We also found a relatively good performance status for the PMBC patients in our analysis (ECOG of 0 or 1 in 69.6% of the cases). This might be due to the preponderance of bone and soft tissue metastases, since this kind of metastasis would not highly affect organ functions, and would have a relatively slower clinical progression compared to visceral metastases. In this analysis, we also found a longer PFS and OS in HR-positive patients. Additionally, and as found in the literature, HER2 positivity was correlated with a shorter PFS and OS in our analysis. We also found that the incidence of bone metastases was high (52%) in the HR-positive/HER2-negative subgroup [6, 10, 17].

As expected, visceral organ metastases were common in the HR-negative/HER2-positive group (84.7%). These results may explain the better outcome for HR-positive PMBC and worse outcome for HER2-positive PMBC. Studies including PMBC patients reported that the PFS was < 24 months in patients with a liver or other solid organ metastasis, but > 24 months in patients with soft tissue/bone metastases only [18]. The detrimental effect of visceral organ metastases is supported by a study from Turkey [16]. In this analysis, we also found a longer PFS and OS in patients with only soft tissue/bone metastases.

Bisphosphonate treatment was also correlated with a better outcome in our analysis. Besides anti-resorptive effects, bisphosphonates also have anti-tumor effects, which may explain these better outcomes. In the ZO-FAST

trial, zoledronic acid treatment was correlated with a 41% relative risk reduction in disease progression [19]. Similarly, zoledronic acid treatment was correlated with lower recurrence rates, and a 36% relative risk reduction in disease progression, even in premenopausal early BC patients [20].

Palliative radiotherapy was correlated with improved PFS and OS in our analysis. Most of the patients who received radiotherapy presented with bone and soft tissue metastases, so they also received zoledronic acid therapy. This may explain the better outcome in patients receiving radiotherapy.

Trastuzumab, either alone or in combination with chemotherapy, yielded better outcomes for HER2-positive MBC patients, including PMBC cases [21].

Since HER2 positivity is a negative prognostic factor, HER2-positive PMBC patients were expected to have a worse outcome than HER2-negative cases. However, trastuzumab therapy was shown to compensate for the poorer prognosis of HER2-positive MBC in previous studies [22, 23].

We found the longest PFS in patients treated with hormone therapy, and the shortest in patients treated with chemotherapy plus targeted therapy. Patients treated with targeted therapy (e.g., trastuzumab) had the worst OS. In contrast to the literature, we did not find any advantage of adding trastuzumab to chemotherapy. This might be due to the worse prognostic features in the HER2-positive patient cohort, due to the retrospective nature of the analysis. We also could not compare treatment with or without trastuzumab, since there were not enough HER2-positive patients treated without trastuzumab.

Treatment choices for PMBC were found to be more aggressive than for RMBC in the literature. The addition of chemotherapy to hormone therapy and combination regimens was preferred more often in PMBC patients, even if they were strongly HR-positive [9]. Although hormone therapy is the standard of care in HR-positive PMBC without disseminated visceral metastasis, many clinicians prefer chemotherapy in initial treatments, even in PMBC patients with only soft tissue/bone metastases, out of concern for the ineffectiveness of or late response to hormone therapy. Even after treatment with first-line chemotherapy, maintenance with chemotherapy was reported as the treatment of choice, although it was not an evidence-based recommendation [1, 9, 17].

In this analysis, we found the longest PFS in patients treated with hormone therapy and the shortest in patients treated with chemotherapy plus targeted therapy. This suggests that chemotherapy is not an ideal choice for PMBC patients. Previous studies have shown that hormone therapy, even as a first-line therapy, had a better outcome compared to chemotherapy in postmenopausal women with advanced BC [9, 24].

Radiation therapy or bisphosphonates, along with endocrine therapy or chemotherapy, can palliate pain from bony complications. Systemic treatment depends upon HR status, the rate of disease progression, and patient willingness to tolerate the adverse effects of treatment. Endocrine therapy is generally better tolerated than chemotherapy. In women with rapidly progressive disease, it may be better to initiate treatment with chemotherapy, which is more likely to induce a timely response. Trastuzumab with or without

chemotherapy is a reasonable choice for the initial treatment of metastatic disease overexpressing HER2. Trastuzumab can be used in combination with endocrine therapy for susceptible tumors [25].

The PFS and OS of the patients who underwent primary surgical treatment were not different from those of the patients did not undergo surgical treatment in a series of 61 subjects [26]. In another study the median OS of patients who underwent primary surgical treatment was not significantly different from that of patients who did not. Nevertheless, the authors concluded that surgery should improve the survival in patients with stage IV BC [27]. In our analysis, few patients underwent surgery and so we could not assess the difference.

In conclusion, we found in this analysis that HR positivity, HER2 status, and the site of metastasis were associated with PFS and OS in PMBC patients. As an option, in bone and soft tissue metastatic PMBC, hormone therapy would be effective as the first choice of treatment. Palliative radiotherapy and bisphosphonate treatment of bone metastases should not be neglected. Mammography should be given greater importance in the prevention of PMBC. Our report is a rather small retrospective analysis. These findings should be confirmed with more rigorous reporting and data monitoring in prospective trials of larger populations.

*The authors declare no conflict of interests.*

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