

## **Research Article**

# **A Study on Management and Treatment Outcomes of Metastatic Breast Cancer: Ten Years Experience in Alexandria University Hospitals**

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**Abstract:** Patients with metastatic breast cancer represent a heterogeneous group, whose prognosis and outcome may be dependent on multiple patient and tumor related factors. The objective of this retrospective study was to review demographic and clinico pathologic features and assesses treatment outcomes in primary metastatic breast cancer patients. During the period from January 2003 to December 2012, 302 patients with stage IV breast cancer at time of diagnosis treated at Clinical Oncology and Nuclear Medicine Department, Alexandria Main University Hospital were included in this analysis. Comprehensive clinico pathologic and treatment-related data were retrieved from medical records, survival outcomes were estimated and correlated to various prognostic and predictive factors. In results the median follow-up time was 16 months. The median progression free survival (PFS) after first line treatment was 10 months, while the median overall survival (OS) time was 18 months. Older age, positive hormonal receptor status and bone/soft tissue metastases only were associated with an improved survival. Whereas, menopausal status and loco regional treatment were not found to be statistically significant predictors of survival. In conclusion the general characteristics of the primary tumor are important for the prognosis and survival of patients with denovo metastatic breast cancer. These should be taken in account to achieve appropriate individualized therapeutic decisions.

**Keywords:** primary metastatic breast cancer, prognostic factors, survival

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## **INTRODUCTION**

Breast cancer (BC) is the most common cancer type and the second most common cause of death among all cancers in females [1, 2]. Despite advances in screening and early diagnosis, still approximately 6-10% of breast cancer patients present with metastatic disease at the initial diagnosis [3].

According to the National Population-based Registry program of Egypt 2008-2011, the incidence rate of breast cancer in Egypt in females is about 48.8 per 100,000, representing 32% of all female cancers [4]. Where, stages III and IV constitute 68% of all breast cancer cases [5, 6].

Primary metastatic BC (PMBC) is a heterogeneous disease comprising several subgroups based on the clinical presentation and the pathological, biological, and molecular characteristics of the tumor. Due to the heterogeneity of the disease, clinical behavior of PMBC is unpredictable [3, 7].

Many prognostic factors are thought to be responsible for determining survival in MBC. These include patient factors such as age, menopausal status, performance status, disease-free interval (DFI) and

treatment that patients have received. Furthermore, tumor characteristics such as site of disease, number of disease sites, tumor grade, hormone sensitivity, human epidermal growth factor receptor-2 (HER2) status and other biological characteristics are likely to be responsible [8].

Although, the survival of patients with metastatic breast cancer has improved over time, from approximately 16 months in the early 1990s to beyond 24 months in 2001, metastatic disease has traditionally been considered incurable [9, 10]. The primary goals of treatment in MBC are; maximizing the quality of life (QoL), prevention and palliation of symptoms and prolongation of survival [12, 13].

In contrast to early stage disease, for which level 1 evidence exists for the majority of treatment options, there are few therapeutic standards for advanced breast cancer[14]. Treatment choices for metastatic breast cancer include endocrine treatment, cytotoxic chemotherapy, targeted therapy, bisphosphonates, and supportive measures [15]. Treatment selection is based on tumor biology, to a similar extent as in the curative setting, with the choice

mainly depending on hormone receptor and HER2 status [16].

As such, the objectives of this study were to review the demographic and clinico pathologic features of primary metastatic breast cancer patients and to identify the outcome of the different treatment lines delivered and the factors affecting survival in this population.

#### **PATIENTS AND METHODS**

A total of 302 patients with stage IV breast cancer at time of diagnosis were included in the study. Those patients presented to the Department of Clinical Oncology and Nuclear Medicine of Alexandria Main University Hospital during the period from January 2003 to December 2012. Staging was based on clinical TNM classification. All information was obtained from medical records. Variables obtained from the registry included: gender, age at presentation, menopausal status, history and clinical picture, pathological findings (tumor histology, grade), hormonal receptor (ER/PR) status and HER2 receptor status, investigations done on diagnosis and treatment received. In this study, we took into consideration the initial metastatic sites that was categorized as single or multiple sites. Sites of metastasis were divided into: bone/soft tissue only, visceral only, a combination of bone and visceral and brain alone or in combination with other sites.

Median follow-up was calculated as the median observation time among all patients. Amongst the 302 patients, only 199 patients have completed their full treatment course and were included in further survival analysis. Treatment outcomes were demonstrated as tumor response (by physical examination and/or radiology according to the Response Evaluation Criteria in Solid Tumors (RECIST)), progression free survival and overall survival.

Progression free survival was defined as the interval between the start of treatment for MBC and the occurrence of disease progression or death for any cause, whichever occurred first. Overall survival was calculated from the date of diagnosis to that of death from any cause or that of the last follow-up.

Survival outcomes was analyzed on univariate analysis in relation to different prognostic factors: age, menopausal status, hormonal receptor status (ER/PR), number of metastatic site(s) at diagnosis, initial metastatic site, type of initial systemic treatment received and loco regional treatment

#### **Statistical analysis**

Data were analyzed using IBM SPSS software package version 20.0. Descriptive analysis of clinical and pathological characteristics was performed. All categorical data were described using numbers and

percentages. Quantitative data were presented using median and range or mean and standard deviation. Survival curves were determined by Kaplan-Meier method. The log-rank test of significance was used to compare and analyze the survival data among different subsets of patients. Differences were considered statistically significant when P value < .05; all P values were two-sided.

#### **RESULTS**

##### **Baseline patient characteristics**

In the present study, a total of 302 patients with primary metastatic breast cancer patients were analyzed. These constituted 7.9 % of all breast cancer cases. Almost all patients were females, most of which were postmenopausal. Patients' age ranged from 20 to 85 years old with a median age of 52. 231 patients were aged 40-65 years (76.5% of all patients).

As regards histology, IDC was the most common histologic type seen in 224 patients (74.5%), while only 4.3% of patients had ILC. Histologic grade was not identified in 171 patients (56.6%). Hormonal receptor status was unknown in 137 patients (45.4%), positive in 148 patients (49%) and negative in 17 patients (5.6%). While HER2 status was not identified in the majority (86.1 %), with only 3% of patients proved to be Her2 positive.

As regards investigations, bone scan was done in 60.3% of patients. Chest assessment was done by chest x-ray in 64.9% of patients, while abdominal assessment was done by ultrasound in 75.5 % of patients. Only 41 patients underwent testing for Ca15.3 and 16 patients were tested for CEA, out of which 25 (61%) and 6 (37.5 %) were elevated, respectively. Fine needle aspirate was the most common method of biopsy used in 133 patients (44%).

As regards the initial metastatic site, 196 patients (64.9%) presented by a single metastatic site. The most common site was bone and/or soft tissue only, reported in 181 patient (43.4%). The basic and clinical characteristics of the patients are presented in Table 1.

Concerning treatment received, 145 patients (48.0%) underwent loco regional treatment to the primary tumor, where surgery was the most common modality, employed in 127 patients. Most of those who received loco regional treatment received it at the time of diagnosis before metastatic work up were done (75.2%). Systemic treatment was given to 199 patients (65.9% of the total studied cases), half of which received only a single treatment line. Regarding type of systemic treatment, 47.7% of patients received both chemotherapy and hormonal treatment, while chemotherapy alone was given to 46.7% of patients, and a minority (5.5%) has received hormonal treatment only. Amongst those who received chemotherapy, anthracycline based chemotherapy was given to 89.0%

of patients in the first line, while in the second line, taxane based regimens were applied in 43% of patients followed by navelbine based regimens in 30%. In patients treated by hormonal treatment, tamoxifen was the main type used in the first line in 73.4% of patient, while non-steroidal aromatase inhibitors were the main

second line hormonal treatment used in 79.5% of patients. Palliative radiotherapy to either bone, brain or both was given to 141 patient (46.7% of total studied cases), while bisphosphonates were given to 31 patients (10.3% of total studied cases).

**Table-1: Basic and clinical characteristics' of primary metastatic breast cancer patients**

Variable	No.	%
<b>Age</b>		
<50 years	124	41.1
≥50 years	178	58.9
<b>Menstrual status (n = 301)</b>		
Pre/perimenopausal	106	35.2
Postmenopausal	149	49.5
Unknown	46	15.3
<b>Histological type</b>		
IDC	224	74.5
ILC	13	4.3
Unknown	65	21.5
<b>Histological Grade</b>		
G1	1	0.3
G2	114	37.7
G3	16	5.3
Unknown	171	56.6
<b>Hormonal receptor status (ER/PR)</b>		
Negative	17	5.6
Positive	148	49.0
Unknown	137	45.4
<b>Her2 receptor status (IHC)</b>		
Negative	33	10.9
Positive	9	3.0
Unknown	260	86.1
<b>No of metastatic site</b>		
1	196	64.9
≥2	106	35.1
<b>Initial metastatic site</b>		
Bone/Soft tissue only	131	43.4
Visceral only	88	29.1
Bone and visceral	69	22.8
Brain ± Others	14	4.6

**Survival estimates**

Only 199 patients who completed their full treatment course were included in survival analysis. The median follow-up time of our study was 16 months (range, 2 to 122 months). The median progression free survival (PFS) after first line treatment was 10 months. The 1-, 2-, and 5-year survival rates for our patients were 66.9 %, 39.2%, and 8.2%, respectively, while the median overall survival (OS) time was 18 months.

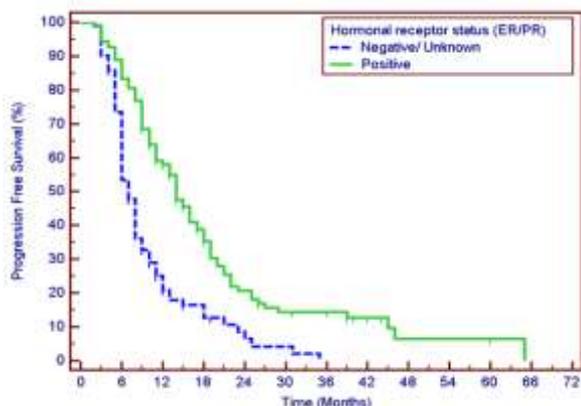
When age at diagnosis was correlated to OS, a better survival was seen to be significantly associated with increased age, and was particularly pronounced in patients above 65 years. (p = 0.028. Conversely, there was no statistically significant effect observed for menopausal status on OS. (p = 0.238)

When PFS and OS were evaluated according to hormonal receptor status, better survival outcomes were seen for hormonal positive patients. The median OS time was 25 months in hormonal positive patients, compared to 12 months in patients with negative/unknown hormonal receptor profile.(p<0.001)

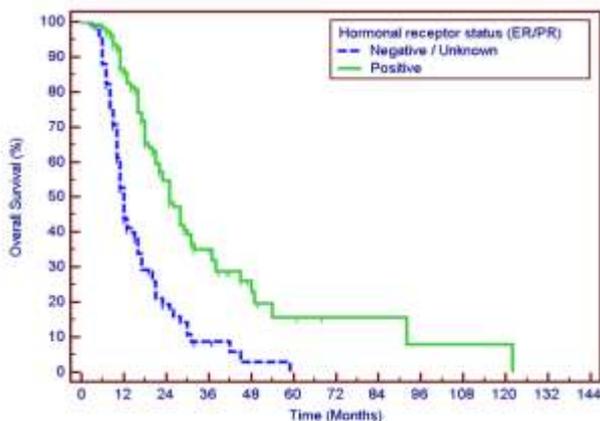
When correlating the number of sites of metastases on presentation to survival outcomes, our study has shown that multiple organ involvement significantly worsens PFS, without a significant effect on OS.(p=0.128)

Our study has also shown a significant effect on both PFS and OS according to the initial metastatic

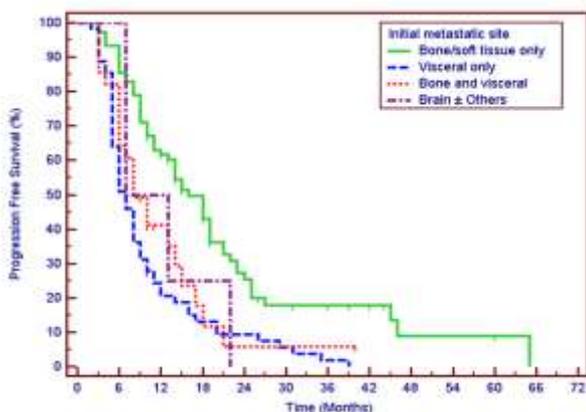
site. The longest OS was seen in patients with bone/soft tissue metastases only, with a median survival of 25 months compared to 12 months in patients with visceral metastases. ( $p < 0.001$ ).



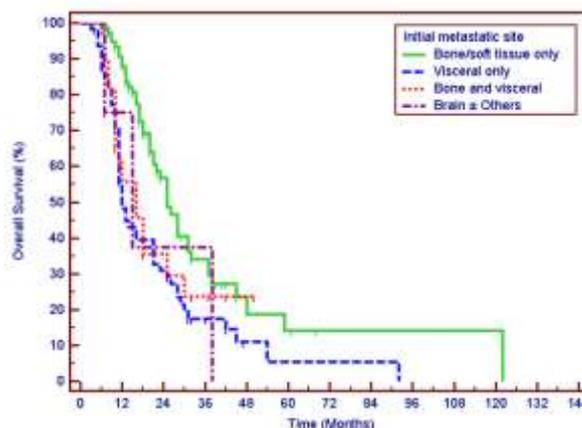
**Fig-1: Kaplan Meier survival curve for progression free survival by hormonal receptor status**



**Fig-2: Kaplan Meier survival curve for overall survival by hormonal receptor status**



**Fig-3: Kaplan Meier survival curve for progression free survival by initial metastatic site**



**Fig-4: Kaplan Meier survival curve for overall survival by initial metastatic site**

The type of initial line of treatment in hormonal positive patients was also found to have a significant effect on PFS, but not on OS. Those treated with hormonal treatment had the longest PFS and OS of 19 and 29 months, respectively, followed by those treated by both hormonal treatment and chemotherapy (16 and 26 months, respectively), while the worst survival was seen in those treated by chemotherapy only (6 and 21 months, respectively). When loco regional treatment was correlated to OS, no significant difference was found between those who received and didn't receive loco regional treatment. ( $p=0.213$ )

## DISCUSSION

Breast carcinoma is a clinically diverse and heterogeneous disease, and patients with metastatic disease have survival ranging from a few weeks to more than a decade [17]. Several studies have reported the survival of women with metastatic breast cancer to be predicted by a range of prognostic factors such as age at diagnosis, hormone receptor (HR) status, human epidermal growth factor receptor 2 (HER2) status, and site of metastases [3, 18].

Our study has reported median OS of MBC patients of 18 months, while the 5 year survival rate was 8.2%. When compared to literature, a longer median survival of patients with metastatic breast cancer who undergo treatment is reported, of about 24 months, while similarly only 5–10% of those patients survive more than 5 years [19].

The median age of patients in our study was 52 years at the time of diagnosis. Remarkably, 59 % of studied patients were  $\geq 50$  years, which is quite close to that reported by two different studies on MBC patients, where 64 or 70% of patients were over 50 years of age at diagnosis [17, 20]. In literature, conflicting data have been reported about the effect of age on survival. Dawood *et al.*; did not find age to be a prognostic factor for predicting survival, while the study of Largillier *et*

*al.*; reported poor prognosis with age over 50 years [3, 18]. However, it is broadly accepted that young age at diagnosis, particularly those younger than 35 years old, tend to have more aggressive disease and relative poor survival from diagnosis [21]. Remarkably, in our study, when age at diagnosis was correlated to OS, a better survival was seen to be associated with increased age, and was particularly pronounced in patients above 65 years.

Hormonal receptor status is a widely accepted prognostic factor in determining survival of MBC patients. Largillier *et al* reported the median survival time was >17 months in HR positive patients, and < 10 months in HR negative patients [18]. Chang *et al* also reported that the median survival time was 21 months for patients with estrogen receptor-positive MBC and 12 months for those presenting with an estrogen receptor-negative MBC [17]. Similarly, our study has shown better survival outcomes in terms of both PFS and OS for hormonal positive patients, with a median OS time of 25 months in hormonal positive patients compared to 12 months in patients with negative/unknown hormonal receptor profile.

On the other hand, despite HER2 positivity being primarily defined as a negative prognostic factor with HER2 positive PMBC patients expected to have a worse outcome than HER2-negative cases, studies have shown trastuzumab therapy compensated for the poorer prognosis of HER2-positive MBC [22]. Due to large amounts of missing data, we were unable to adjust for HER2 status in our models. Furthermore, we were unable to assess whether breast tumor subtypes had differing prognostic outcomes among women with de novo stage IV disease

When correlating the number of sites of metastases on presentation to survival outcomes, our study has shown that multiple organ involvement significantly worsens PFS, without a significant effect on OS. In literature, Andre *et al* in a study on breast cancer patients with synchronous metastases has shown the involvement of multiple organs to be one of the prognostic factors in multivariate analysis [23]. Additionally, several studies have shown the initial site of metastases to be one of most significant independent prognostic factors in MBC [18]. Similarly, in our study, the longest OS was seen in patients with bone/soft tissue metastases only, with a median survival of 25 months compared to 12 months in patients with visceral metastases. This is very close to the results reported by Chang *et al*, where patients with non-visceral metastases had a median OS of 23 months compared to 11 months in those with visceral metastases [17].

Treatment of metastatic breast cancer is complex. Clinical and biological characteristics of the tumor and the predilection of the patient for treatment

alternatives play a major role in treatment decisions [13].

Hormonal therapy is the standard of care in HR-positive PMBC without disseminated visceral metastasis. However, many clinicians prefer chemotherapy in initial treatments, even with only soft tissue/bone metastases, out of concern for the ineffectiveness of or the late response to hormone therapy. It is important to note however that 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 [24-26]. A review on multiple trials has also found that while initial treatment with chemotherapy rather than endocrine therapy may be associated with a higher response rate, the two initial treatments had a similar effect on overall survival [27].

Notably, in our study, the use of hormonal treatment as an initial sole line of systemic treatment was limited to 9 % of patients, while 38 % have received sequential endocrine therapy after chemotherapy as a first line treatment. A similar response rate was seen to both chemotherapy and hormonal treatment in first line. When correlating the type of initial line of treatment in hormonal positive patients to survival outcome, those treated with hormonal treatment had the longest PFS and OS, while the worst survival was seen in those treated by chemotherapy only. It is important however to note that the difference was statistically significant only on PFS.

Another major issue of debate in de novo metastatic breast cancer is the benefit of loco regional treatment for the primary tumor. Interestingly, although no guidelines recommend surgery as a routine practice in de novo stage IV breast cancer, various series reported the percentage of MBC patients undergoing surgery for the primary tumor to be 37% to 61.3% [28]. Even though various retrospective studies revealed a survival advantage to patients who underwent surgery [29], early results from prospective studies have shown no significant benefit to OS in patients who received loco regional treatment [30, 31]. Remarkably, loco regional treatment has been given to almost half (48 %) of patients included in our study. The majority of which (75%) have undergone surgery at presentation before metastatic work up was done. When loco regional treatment was correlated to OS, no significant difference was found between those who received and didn't receive loco regional treatment.

## CONCLUSION

In summary, this study has confirmed the general characteristics of the primary tumor are important in the prognosis and survival of patients with PMBC. This analysis has demonstrated that older age, positive hormonal receptor status and bone/soft tissue metastases only were associated with a better overall

survival. While, a better PFS only was seen in patients with a single metastatic site and those who have received hormonal therapy as an initial systemic treatment. On the other hand, menopausal status and loco regional treatment were not found to be statistically significant predictors of survival. We acknowledge that as a retrospective study, our study has a number of important limitations. These findings should be confirmed by more rigorous reporting and data monitoring in prospective trials of larger populations.

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