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Prognostic Factors in Breast Cancer Patients with Brain Metastases: Retrospective Analysis

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Background: Breast cancer is first cause of cancer-related deaths and it is estimated that 15% of breast cancer patients will develop brain metastases (BM). Its incidence differs according to many factors like molecular subtypes and burden and duration of systemic disease. Triple negative disease is an aggressive subtype with lifetime BM incidence of 25-46%. Survival of patients with BM is generally poor and affected by molecular subtypes, patient's performance, number and burden of visceral metastasis and resectability of brain lesions.
Aim: This analysis aimed at evaluating the prognostic factors in breast cancer patients with BM.
Methods: We retrospectively reviewed breast cancer patients' files treated at a single institute between January 2010 and December 2014. From 2095 files reviewed, 32 had BM. The clinico-epidemiological, pathological, treatment received and survival data were extracted and analysed.
Results: Median age at BM diagnosis was 49.5 years (range 27-69). Median time from breast cancer diagnosis to BM diagnosis was 16 months (95% CI: 13.23-18.77). Postmenopausal women represented 59% of patients and 56% of them had a good performance status (ECOG 1-2). The majority of patients had grade II disease and invasive ductal carcinoma (65.6% and 81.3%, respectively). The tumor subtype was hormone receptor positive/HER2-neu negative in 25%, triple negative in 25% and HER2-neu positive in 50%. More than 2/3 of patients presented with signs of increased intracranial tension. Seven (22%) patients had single BM lesion, 22 (69%) had multiple lesions and 3 (9%) had concomitant leptomeningeal metastases. Three (9%) patients underwent brain metastatectomy. The median progression free survival was 4.5 months (95% CI: 3.58-5.42) and was significantly longer among patients who underwent metastatectomy (p=0.023) and those with hormone receptor-positive disease (p=0.007). The median overall survival was 6.5 months (95% CI: 4.23-9.77) and was significantly longer in patients with better performance status (ECOG 1), hormone receptor-positive disease, low number of metastatic sites and brain metastatectomy (p=0.037, 0.045, <0.001 and 0.007; respectively).
Conclusion: Brain metastases in breast cancer patients is an indicator of short survival which is influenced by tumor subtype, performance status, burden of systemic disease and ability to perform metastatectomy.

Keywords: Metastatic breast cancer, Prognostic factors, Brain metastases
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INTRODUCTION

Brain metastases (BM) secondary to breast cancer affect badly the general condition of patients and may cause serious morbidity and eventually mortality if undiagnosed or not properly treated. Hence, it may be advisable to predict the occurrence of BM in breast cancer patients [1]. Early diagnosis of BM may help in improving treatment outcome and decreasing disease burden on the patients.

In breast cancer, BM is frequently encountered in later stages following metastases to other organs [2]. Brain metastases secondary to breast cancer is associated with poor survival of patients in general. The survival of these patients may be affected by factors including molecular subtypes, performance status, ressectability of BM and visceral metastasis burden. When detected, its treatment is usually difficult and unfortunately has reverse effects on life expectancy [3].

The aim of this study was to describe the pattern of BM in breast cancer patients and to evaluate factors associated with prognosis.

METHODS

The files of patients with breast cancer metastatic to the brain treated at the Department of Clinical Oncology and Nuclear Medicine, Ain Shams University in the period from January 2010 to December 2014 were retrospectively reviewed.

Adult patients (>18 years old) with pathologically proven breast cancer and radiological documentation of BM who had been followed up for at least 6 months were eligible for analysis. Patients without full medical data and those with previous or concurrent diagnosis of second primary malignancy were excluded.

The following was collected from the patients' files: personal, clinico-pathological and tumor related data as well as the treatment given and its outcome. Tumor

response was assessed using the Response Evaluation Criteria In Solid Tumors (RECIST) criteria.

Time to BM (TTBM) was defined as the time from primary breast cancer diagnosis to the date of BM diagnosis [4]. Progression-free survival (PFS) was defined as the time from BM diagnosis till progression or death and overall survival (OS) as the time from BM diagnosis till death.

Recorded data were analyzed using the statistical package for social sciences, version 20 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD) and qualitative data as frequency and percentage. Kaplan-Meier survival analysis was used to examine the distribution of time-to-event variables and log rank test to compare time-to-event variables by levels of a factor variable. P-value <0.05 was considered significant.

RESULTS

During the study period, 32 out of 2095 (1.53%) breast cancer patients developed BM.

Table 1: Personal and tumor characteristics of 32 patients at the time of diagnosis of brain metastases

Characteristic		
Age (years)		
Mean ± SD	48.7 ± 11.39	
Median (range)	49.5 (27 – 69)	
	No.	**%**
≤48	15	46.9
>48	17	53.1
Menopausal status		
Premenopausal	13	40.6
Postmenopausal	19	59.4
Family history of breast cancer		
Positive	2	6.3
Negative	30	90.3
ECOG performance status		
1	7	21.9
2	11	34.4
3	14	43.8
Tumor grade		
1	4	12.5
2	21	65.6
3	7	21.9
Histological subtype		
Invasive duct carcinoma	26	81.3
Invasive lobular carcinoma	3	9.4
Other*	3	9.4
Tumor subtype		
HR–positive / HER2-negative	8	25
Triple negative	8	25
HER2 –positive irrespective of HR status	16	50

***** Mixed, medullary, papillary and cribriform tumors; **ECOG**: Eastern Cooperative Oncology Group; **HR**: Hormonal receptor.

Personal and tumor characteristics of patients at the time of diagnosis of BM are shown in table 1. Only 2 cases had positive family history of breast cancer. Both cases were 41 years old. The 1st case had 1st degree breast cancer (mother) while the 2nd case had 2nd degree (aunt). None of the patients had grade 0 or 4 Eastern Cooperative Oncology Group (ECOG) performance scale.

Characteristics and treatment of BM are illustrated in table 2. The majority of patients presented with manifestations of increased intracranial tension (headache, vomiting and blurring of vision), had multiple BM and other distant metastatic sites, and received radiotherapy as the primary treatment for BM.

Table 2: Brain metastases' characteristics at presentation and their primary treatment

	No.	%
Presenting symptoms		
Manifestations of increased intracranial tension	22	68.7
Neurological deficit	5	15.6
Convulsions	1	3.1
Asymptomatic	4	12.5
Pattern of BM		
Single		
Frontal	5	15.6
Parietal	1	3.1
Occipital	1	3.1
Multiple	22	68.8
With leptomeningeal infiltration	3	9.3
Distant metastases at BM diagnosis		
No	9	28.1
Yes	23	71.8
Number of distant metastasis sites at BM diagnosis		
1	11	34.3
2	6	18.7
3	1	3.1
>3	5	15.6
Timing of metastases		
Metastatic from the start		
Brain	2	6.2
Bone, liver and lung	1	3.1
Lung	1	3.1
Developed metastases later on	28	87.4
Primary treatment of BM		
Surgery (mass excision)	3	9.4
Radiotherapy	26	81.2
Chemotherapy	3	9.4

BM: brain metastases

The median follow-up time was 10 months after diagnosis of BM. The Median Time to Brain metastasis (TTBM) was 16 months (95% CI: 13.23 -18.77). The median PFS of the 32 patients with BM was 4.5 months (95% CI: 3.576 -5.424) (figure1) and the median OS was 6.5 months (95% CI: 4.228-9.772) (figure 2). The 1-year survival rate was 23% and the 2-year was 3%.

Univariate analysis of PFS and OS is illustrated in table 3. Regarding PFS, it differed significantly according to the tumor subtype being shortest in patients with triple negative subtype. Significantly longer median PFS was observed in patients who underwent metastatectomy compared to patients with no metastatectomy. The other studied variables did not correlate significantly with PFS.

Regarding OS, it was significantly shorter in association with poorer performance status at BM diagnosis, triple negative subtype, no BM metastatectomy and higher number of other distant metastatic sites at BM diagnosis.

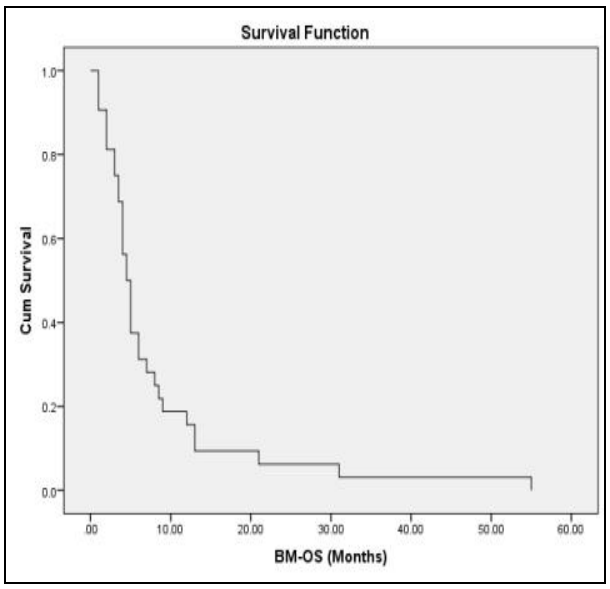

Figure 1: Progression free survival curve of 32 patients with brain metastases

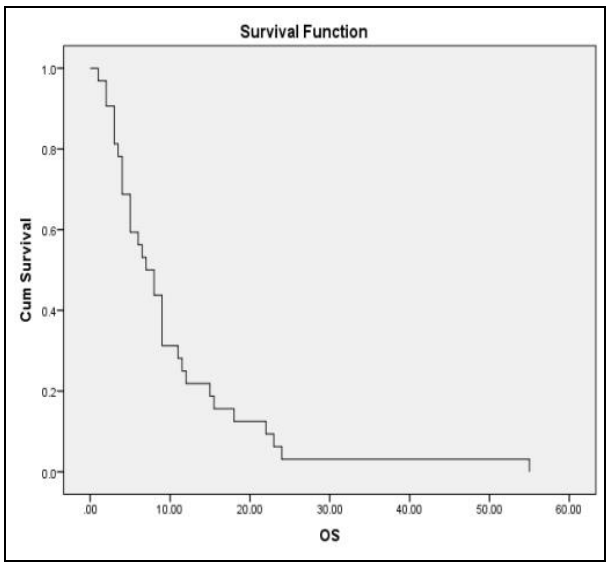

Figure 2: Overall survival curve of 32 patients with brain metastases

DISCUSSION

This was a retrospective analysis of 32 female patients with breast cancer metastatic to brain treated in a single institution.

This relatively low prevalence of BM could be attributed to the relatively short follow up period of patients. Also patients with files not containing full medical data were excluded.

In general, the characteristics of our study population were more or less similar to that reported in other studies. The median age at diagnosis of BM was 49.5 years which is similar to that reported by Ahn et al (48 years) [4] and Dayan et al (49 years) [1].

Fifty-nine percent of patients included in the current study were postmenopausal, similar to that reported by Gunduz et al (58%) [5]. Also, Yücel's et al found that postmenopausal women were more than premenopausal in their study [6].

In our study, the majority (78%) of patients had an ECOG performance scale >1 at the time of BM diagnosis which is close to the 72% reported by Ahn et al [4]. Similarly, in their literature review about BM of breast cancer origin, Rostami et al found that most patients presented with a higher (>70%) KPS score (equivalent to ECOG 0-1) [7]. In contrast, Yücel et al described that 68% of cases were ECOG ≤ 2 [6]. Poor performance status at presentation may be explained by lack of health education and socioeconomic factors leading to delay in seeking medical advice.

Grade 2 and 3 tumors represented 87% of our population which is higher than that reported by Rostami et al (73%) [7]. Invasive ductal carcinoma was the most prevalent histological diagnosis in our patients. A similar study, reported that invasive duct carcinoma constitute 81% and invasive lobular carcinoma constitute 7% in private pathological material [8]. This is going with most of studies discussing breast cancer metastasis [6, 7, 9].

Half of the patients in this study had HER2-positive irrespective of HR-status disease. This is consistent with the findings of Leone et al who observed HER2 overexpression in 45% of BM cases compared with the 20% incidence of HER2 overexpression in all cases with breast cancer, with 25% incidence of luminal A tumors, and 30% incidence of triple-negative disease [10]. This confirms that patients with HER2-overexpression are at increased risk of BM development and it is important to take this into consideration during individual's follow-up [10-12]. This may be contributed to the ability of HER2-cancer cell to spread hematogenously [13]. The pattern of BM in the current study is more or less similar to that described by Evans et al who reported 78% prevalence of multiple metastases, 14% solitary metastases and 8% leptomeningeal metastases [14]. Like what had been described in another study, the majority of the population of this study had pre-existing distant metastases to other sites at the time of BM diagnosis [15].

We found that only undergoing metastatectomy and hormone receptor-positive disease were associated with significantly better PFS. When breast cancer patients with BM were grouped according to the tumor subtype, Arslan et al found that PFS is shortest in patients with triple negative disease and longest in hormone receptor positive [16]. This was also in concordance with the study conducted by Huang et al [17].

The median OS in this study was 6.5 months and was significantly longer with better performance status, low number of other metastatic sites and metastatectomy. Shorter OS was observed in triple negative patients compared to hormone receptor-positive.

The significant relation between BM secondary to breast cancer and its biological subtypes has been described in many studies [13, 18-20]. In addition to the

Table 3. Univariate analysis of progression free survival and overall survival of 32 breast cancer patients with brain metastases

Variables	No. (%)	Progression free survival (months)		P value*	Overall survival (months)		P value*
		Median	95% CI		Median	95% CI	
Age at BM diagnosis							
≤48 years	15 (46.9)	4.5	3.08-5.92	0.44	3..8	0.99-6.61	0.345
>48 years	17 (53.1)	4.6	3.26-5.94		9	4.2-13.8	
Menstrual history							
Premenopause	13 (40.6)	5	3.85-6.15	0.411	10.26	2.56-24.9	0.537
Postmenopause	19 (59.4)	4.5	2.94-6.06		4	1-9.69	
ECOG performance status at BM diagnosis							
1	7 (21.9)	8	2.8-10.8	0.165	12	3-29.96	0.037
2	11 (34.4)	5.1	3.39-5.81		8	4.76-11.24	
3	14 (43.8)	4.1	1.67-5.33		6	3.25-8.75	
Tumor grade							
1	4 (12.5)	5	3.72-6.28	0.22	7	1.12-12.88	0.521
2	21 (65.6)	4.5	3.27-5.73		8	2.07-13.93	
3	7 (21.9)	3	0.06-5.94		6.5	2.65-10.35	
Histological subtype							
Invasive duct carcinoma	26 (81.3)	4.5	3.4-5.6	0.2	9	3.51-12.49	0.518
Invasive lobular carcinoma	3 (9.4)	3.00	1.05-7		8	5.6-10.4	
Others	3 (9.4)	13.00	4.55-17.55		5	2.99-10.61	
Tumor subtype							
HR-positive /HER2-Negative	8 (25)	6.50	2.27-10.14	0.007	9	7.66-10.34	0.045
Triple negative	8 (25)	3	0.92-5.08		4	2.7-6.3	
HER 2- Positive irrespective of HR status	16 (50)	4	3.72-5.28		8	5.65-11.35	
BM metastatectomy							
Yes	3 (9.4)	31	0-75.81	0.023	31	7.12-64.61	0.007
No	29 (90.6)	4.50	3.45-5.55		5	4.12-5.88	
Other metastatic sites at BM diagnosis							
Yes	23(71.9)	4.50	2.95-6.05	0.459	8	5.7-10.3	0.157
No	9(28.1)	6	3.08-8.92		5	2.93-7.07	
Number of other metastatic sites at BM diagnosis							
1	14 (43.8)	9	3.15-12.15	0.232	9	4.11-13.89	<0.001
2	11 (34.4)	7	6.3-7.7		7.5	5.07-9.93	
3	6 (18.8)	3.5	2.22-4.78		6	3.6-8.4	
4	1 (3)	1	0.35-1.35		4	4.31-8.44	
Multiple BM lesions							
Yes	25 (78.1)	5	3.38-6.62	0.192	6	5.03-6.97	0.586
No	7 (21.9)	4.5	2.74-6.26		9	6.43-11.57	

* Log rank test; **BM**: brain metastases; **CI**: confidence interval; **ECOG**: Eastern Cooperative Oncology Group; **HR**: hormone receptor

higher prevalence of BM in association with certain subtypes, these subtypes (triple negative) are associated with poorer survival [21].

Overall survival in our study was in agreement with that reported by Niwińska et al [22] and Yücel et al [6] (7.5 and 7 months, respectively).

Andrews et al reported that untreated metastatic breast cancer to brain has a median OS of 4 weeks which may be improved to 4-6 months with whole cranial irradiation. While in patients who had single brain lesion that can be surgically removed or who received stereotactic radiosurgery, the median OS improved dramatically to 16 months [23].

The 1- and 2-year survival rates in our study were 23% and 3% which is similar to the survival rates in Engel et al study with 20% and 2% [24]. These low survival rates were confirmed in other studies [25, 26].

As regard performance status, we found a statistically significant relation between ECOG performance status at BM diagnosis and survival which confirms the results of other studies that showed that poor performance status is one of the factors that negatively affect the survival [27-31].

There was a statistically significant relation between the tumor subtype and survival of breast cancer patients with BM included in this study, a finding that has been described by others [32, 33]. In particular, triple negative breast cancer is associated with dismal OS in patients with BM, ranging from 3 to 4 months [34]. The risk of developing BM is higher among HER2-positive patients, however their survival after BM diagnosis is better than the triple negative and luminal subtypes [35]. Some studies reported that the interval for metastasis development, the number of metastasis, and localization

of metastasis also affect survival [36-38]. Furthermore, the presence of bone and liver metastases was found to be prognostic factor that statistically affect the survival of BM patients [39]. In congruence, the higher the number of metastatic sites other than BM in our patients the shorter the OS.

As regard brain mass excision, our finding support the conclusion of a study done by Yaeger and Nair [40] in which the presence of a single metastatic lesion in the presence of well-controlled systemic cancer was the best indicator for surgical therapy and was predictive for better survival following resection. This is also supported by the study performed by Patchell et al, in which the addition of surgery followed by radiotherapy compared to WBRT alone reduced significantly the local recurrence in patients with single brain metastases and improved survival [41].

Prognostic factors that determine the survival of breast cancer patients with BM have been investigated in many studies and some developed prognostic scoring models [29]. The most significant prognosis predictors were age, tumor subtype and performance status [42].

Limitations of the current study include being a retrospective one that included a relatively small sample size.

Conclusion

BM is an indicator of short survival which is influenced by tumor subtype, performance status, burden of systemic disease and the ability to perform metastatectomy. Larger prospective studies are needed to document these findings

Acknowledgement

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Conflict of interest

The authors have no conflict of interest.

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