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Research Article

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Frequency of Brain Metastasis in Breast Cancer Patients and Factors Leading to it

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Abstract

Objective: *Breast cancer is the second commonest cause of brain metastasis after lung cancer.10-16% of patients diagnosed with breast cancer ultimately develop brain metastasis. As most of chemotherapeutic drugs do not cross blood brain barrier despite adequate management of breast cancer risk of CNS relapse persist. Prognosis for breast cancer patients after developing brain metastases is poor. Therefore, we sought to determine the frequency of brain metastasis in Pakistani breast cancer survivors, how often brain metastasis is the first site of recurrence and what are the risk factors that indicate greater likelihood of this event occurrence so that more accurate screening for patients at risk can be established.*

Methods: *We retrospectively reviewed medical record of 507 patients with invasive breast cancer of all stages who received treatment in Liaquat National Hospital from January 2010 to December 2015. Patients who developed brain metastasis were identified and stratified according to risk factors.*

Result: *Out of 507 patients 51(10%) developed brain metastasis. 14 patients had brain metastasis as first site of recurrence. On univariate analysis negative hormone receptor status, triple negative and her2 enriched subtype, higher tumor size, lymph node positivity, stages 3 and 4, lymphovascular and peri nodal extension, shorter disease-free survival and recurrence with visceral metastasis had a statistically highly significant impact on brain metastasis occurrence, while young age at diagnosis (≤35 years), menopausal status, BMI and tumor histology showed no statistically significant impact.*

Conclusion: *Brain metastases are more frequent in triple negative, Her2Neu positive and Estrogen and Progesterone receptor negative patients. Other factors associated with higher risk of brain metastases in breast cancer patients include larger tumor size, positive axillary lymph nodes, higher stage and lymphovascular and periodontal invasion. Frequency of brain metastasis in breast cancer patients and factors leading to it.*

Introduction

Metastasis is the major cause of mortality and morbidity in breast cancer patients. Lung, liver and bones are the common sites of metastasis in breast cancer. Although brain metastasis is less common than bone and visceral metastasis, it is associated with more morbidity and mortality on comparison. In breast cancer patients 10-16% incidence of brain metastasis has been reported in several studies, 1,2,3,4 but this could be an under –estimation because most CNS metastasis are diagnosed in response to clinical symptoms rather than by routine screening, chances of missing sub clinical brain metastasis are always there and incidence of up to 18.9% asymptomatic brain metastasis in breast cancer patients on screening is reported in one study [1-4].

Incidence of brain metastasis in breast cancer patients has increased in last few decades probably because of increased overall incidence of breast cancer, improved survival because of better systemic therapy options, increased awareness of clinician and patient and improved imaging techniques [5].

As most chemotherapy drugs used in breast cancer management do not cross blood brain barrier, despite control of systemic disease risk of CNS relapse persist. The prognosis of patients who develop brain metastasis from Breast Cancer is generally poor, and the

median survival is 6–7 months (range, 2–16 months), with only approximately 20% of patients reaching 1 year of survival [6,7].

Multiple factors have been reported to be associated with increased rick of brain metastasis in breast cancer patients. Which include high tumor grade, a negative hormone receptor status, HER2 over expression tripe negative subtype, Axillary lymph node positivity, age younger than 35 years, Ki67 over-expression 8, disease free survival <2 years17, premenopausal status at diagnosis 18, visceral metastases and extensive extra cranial metastases [8-22].

As breast cancer is the second commonest cause of brain metastasis multiple researchers are trying to identify the most at risk breast cancer population upon which, like lung cancer the principles of screening brain MRI and prophylactic brain radiation can be applied to improve the prognosis. We designed this study to see the frequency of brain metastasis in Pakistani population and to identify clinical and biological features of patients who developed CNS metastases.

This will help us to identify the patients who are at increased risk of CNS metastases and our results can help in validation of screening models and prophylactic management to improve the survival and quality of life of these patients.

Materials and Methods

Study design

This is a retrospective study conducted at Liaquat National Hospital Karachi, Pakistan. Data of 507 diagnosed breast cancer patients of all stages treated from January 2010 to December 2015 was retrospectively analyzed for a minimum follow up of 2 years. Study was approved by ethical committee of Liaquat National Hospital Karachi. Patient's data collected with the approval of the institution review board and was maintained in a confidential manner. All breast cancer patients were pathologically confirmed, and metastatic lesions were confirmed by imaging and biopsy if possible. The Allred scoring system was used to assess the ER and PR status. In summary, a total Allred score was obtained by the summation of proportion score (PS) and intensity score (IS). A total score of 3 or more was considered as positive; scores 0 and 1 and 2 were considered negative [23]. The American Society of clinical Oncology / College of American Pathologists (ASCO / CAP) guideline recommendation were used to evaluate the HER2 Status [24]. Scores 0 and + 1 were considered negative; +2 equivocal; and+3 positive. Equivocal 2+ IHC was confirmed by FISH.

All the information available in the dataset was used exclusively for the purpose of this study and was not shared. Data was extracted and reviewed by two investigators on standardized data extraction form. All patients' demographics, clinical characteristics, pathologic characteristics, imaging studies and treatment methods were obtained. Based on age, stage, and receptor status patients were managed according to standard guidelines. Follow-up examinations were scheduled every three months in the first two years, then every six months for 3 years. On each visit patients were evaluated by history and physical examination. Blood workup and imaging done if indicated. Early stage patients who relapsed were confirmed by imaging and biopsy. Further treatment of these patients with either hormonal therapy or chemotherapy has been done according to receptor status, age, performance status, disease burden and symptoms. Patients which showed symptoms or signs of central nervous system involvement at any time were immediately evaluated by head CT and/or MRI with contrast. Histologic confirmation of brain lesions was not necessary. For patients who developed brain metastasis treatment modalities included symptomatic management with corticosteroids, WBRT, surgical resection, SRS, and/or systemic treatment at physician's discretion. Patient's demographics are displayed in Table 1.

Statistical analysis

Statistical analysis was done by using SPSS version [25]. Frequency and percentages were reported for qualitative while mean and standard deviation was presented for quantitative variable. Bivariate analysis was done using Pearson's chi square test and fisher exact test as appropriate. Univariate analysis was done using binary logistic regression. The estimates of the models are given as hazard ratio (HR) with 95% confidence intervals (95% CI).Significant variables were included for univariate analysis by taking 0.05 as level of significance [26-29].

Results

Patient's Characteristics

Total five hundred and seven patients were analyzed in this study. The median follow-up time of patients was 42 months (range, 24 to 84 months). Median age was 48.8 years and the median body mass index was 28.94 (15.77-62.43) [30].

Disease characteristics

Eighty-six percent (n=434) of the patient's had invasive ductal carcinoma and the remaining had other pathologies. Patient's demographics are shown in Table 1.

Table 1

Variables	Point Estimates
BMI (kg/m2) °	28.94±5.56
Age group	
<35 years	64(12.6%)
35-50 years	216(42.6%)
>50 years	227(44.8%)
Menopausal status	
Pre-Menopausal	240(47.3)
Peri Menopausal	8(1.6)
Post-Menopausal	259(51.1)
ER Status	
Positive	353(69.6)
Negative	154(30.4)

N0	144(28.4)
N1	213(42)
N2	88(17.4)
N3	62(12.2)
Absent	280(55.2)
Not Determined	45(8.9)
STAGE	
Stage-1	20(3.9)
Stage-2	158(31.2)

Stage-3	256(50.5)
Stage-4	73(14.4)

Brain metastasis occurred in 51(10.6%) patients as shown in Table 2.

Table 2: Total number of patients with brain metastases

Occured	51 (10.1)
Not occured	456 (89.9)

Disease recurrence was seen in 68(15.2%) patients. The sites of first recurrence in terms of frequency are shown in Table 3.

Table 3: Sites of First recurrence

Sites	n (%)
Brain	14(20.6)
Lung	17(25)
Liver	2(2.9)
Bone	2(2.9)
LN	5(7.4)
Chest wall	7(10.3)

There was significant association of brain metastasis with ER status (p=0.002), PR status (p=0.000), Her2neu (p=0.013), luminal sub types (p=0.000), ki67(0.002), AX LN (p=0.017), perinodal extension (p=0.000), Stage (p=0.000), disease free survival (p=0.000) and recurrence (p=0.000) as presented in Table 4 .While young age a t diagnosis (≤ 3 5 y e a r s) menopausal status, BMI, tumor histology and grade showed no statistically significant impact (p=0.10). Out of 154 patients with a negative ER status 25 (16.2%) developed brain metastasis as compared to 26 (7.4%) out of 353 ER positive patients. 19/118(16.1%) patients with Her2neu positivity developed brain metastasis as compared to 32/382(8.2%) with Her2Neu negative status. On subtype analysis only one patient with luminal a subtype developed brain metastasis, while triple negative had a highest incidence of brain metastasis 17.8% (16/90). Incidence of brain metastasis in Luminal B and Her2- enriched subtype was 11.2% (25/224) and 16.7% (9/54) respectively. Univariate analysis showed that females with positive ER were less likely (OR=0.410) to have brain metastasis as compared to Negative ER, Females with positive PR were less likely (OR=0.323) to have brain metastasis as compared to Negative PR. Females with luminal A (OR=0.036) and luminal B (OR=0.628) were less likely to have brain metastasis as compared to her 2 type, while females with Triple Negative were more likely (OR=1.081) to have brain metastasis as compared to her 2 type. Females with stage 1 (OR= 0.000), 2 (OR=0.067) and 3 (OR= 0.192) are less likely to develop brain metastasis as compared to stage 4. Detailed results of univariate and multivariate binary logistics are presented in Table 4 [31-33].

Median time to brain metastasis since initial diagnosis of breast cancer was 22.7 (1-72) months and median time to brain metastasis since first recurrence was 15.9 months (1-48).

Table 4: Univariate Analysis of association of different factors associated with brain metastases

Univariate				
	B	Odds Ratio	95% CI	P-Value
ER Status				
Positive	-0.891	0.410	0.228-0.737	0.003
Negative®		1		
PR Status				
Positive	-1.130	0.323	0.175-0.596	0.000
Negative®		1		
Her2Nue				
Positive	0.761	2.141	1.164-3.940	0.014
Negative®		1		
Disease Free				
NDFI	3.359	28.768	12.780-64.757	0.000
>2 years	3.092	22.023	9.416-51.511	0.000
<2 years®		1		
Sub Types				
Her 2 Type	3.318	27.60	3.403-223.859	0.002
Tripple Negative	3.396	29.83	3.880-229.45	0.001
Luminal B	2.853	17.33	2.322-129.45	0.005
Luminal A®		1		
KI67				
Not Determined	1.804	6.077	1.821-20.282	0.003
>50%	1.223	3.398	1.234-9.356	0.018
14-50%	1.379	3.972	1.559-9.869	0.003
<14%		1		
Perinodal Ext				
Not Determined	2.159	8.667	4.094-18.348	0.000
Present	0.000	1.000	0.485-2.064	1.000
Absent		1		
AX LN				
N3	0.702	2.018	0.592-6.877	0.262
N2	1.470	4.351	1.605-11.795	0.004
N1	1.162	3.198	1.281-7.981	0.013
N0®		1		
STAGE				
Stage-4	20.489	791250072.586818	NA	0.998
Stage-3	18.839	151881691.283581	NA	0.998
Stage-2	17.782	52793101.2483041	NA	0.998

Discussion

To date the value of diagnostic screening for brain metastases in breast cancer patients is unclear. There is a strong need for identification of those patients who are at a greater risk of developing brain metastasis because several studies have shown that brain metastasis has a very detrimental effect on cognitive function, quality of life and most important thing the survival. Considering these facts as in lung cancer can prophylactic cranial irradiation improve outcome in breast cancer patients needs to be further investigated. So, before proceeding towards screening brain imaging and prophylactic cranial irradiation in breast cancer patients we need to identify a group of patients which is at highest risk of brain metastasis to make this

consideration cost effective and fruitful.

In our study breast cancer patients with metastatic disease, ER, PR negative status and triple negative and her2 enriched tumor subtype exhibited a strong relationship with incidence of brain metastasis. So, our results confirm and extend the results of previous studies which evaluated the association between tumor subtype and brain metastasis among non-metastatic patients in which they reported that her 2 positive and triple negative patients are at highest risk of brain metastasis as compare to Luminal A or B 26. Also in metastatic disease triple negative and Her2 positive patients life time risk of brain metastasis of as high as 22-46% and 34-55% respectively has been reported [12,27,31]. In our study out of 73 stage 4 patients 24 (32.0%) developed brain metastasis. The incidence of brain metastasis was significantly higher with multiple sites of metastasis as compared to solitary site of metastasis. Our results match with other studies reporting higher risk of brain metastasis in patients with > 3 extra- cranial sites of involvement especially liver and bone [32,33]. In non-metastatic patient's recurrence increases the risk of brain metastasis also, as out of 448 non-metastatic patient's 57 patients relapsed later on and among them 26 (45.6%) developed brain metastasis. Relapse with Liver, bone and multiple sites had a highest propensity for brain metastasis as compared to local recurrence and lung only metastasis. Our study also confirmed that that TNBC is also associated with higher risk of developing BM as first site of recurrence, as compared to non-selected breast cancer patients [8,34,35].

In our study 14 patients had brain metastasis as first site of recurrence. Of these 14 patients 9 (64.2%) were triple negative, 4 patients were luminal B, out of which 3 were Her2neu positiveand 1 patient was from her2neu enriched type. So triple negative and her 2positive subtype hashighest propensity for recurrence in brain as first site and consideration of screening MRI brain in these patients can be worth taking [12]. Unlike previous reports we found no evidence indicating a correlation between the incidence of brain metastases and younger age at diagnosis.

Limitations of the study are that it's a retrospective study. Secondly some patients with Her2 Neu positive tumors didn't receive Trastuzumab.

Despite the limitations, our study provides insight into the epidemiology of brain metastases in breast cancer patients in Pakistan. It supports the consideration of studies evaluating the utility of screening MRI of the brain among patients at high risk of brain metastases, including those with HER2-positive or triple-negative subtypes, visceral recurrences and metastatic disease at presentation. The degree, to which earlier recognition of brain metastasis may have an impact on outcomes such as brain-directed neurosurgical or radio therapeutic treatment, quality of life, and cost-effective care, warrants further investigation.

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