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Clinicopathology Figures of Breast Cancer Women with Brain Metastasis and Invasive Ductal Carcinoma

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Abstract **Background:** Breast cancer (BC) metastasis to the central nervous system (CNS) or brain metastases include the clinically distinct situations of multiple brain metastasis (78%), solitary brain metastasis (14%), and leptomeningeal metastasis (8%). The aim of this study is to describe clinicopathologic features of patients with BC brain metastasis and to compare estrogen receptor (ER), progesterone receptor (PR), and Her2 expression in them. **Materials and Methods:** there were 16 patients with brain metastasis and we entered them to our study. Age, sex, kind of pathology, tumor markers, type of treatment, histological grade, size of tumor, laterality and other metastasizes were checked for the patients. ER and PR positivity was defined as ≥10% positive tumor cells with nuclear staining. HER2 positivity was defined as either HER2 gene amplification by fluorescent *in situ* hybridization or scored as 3+ by IHC. **Results:** The mean age at diagnosis for the patients was 42.2 years (±14.4) and range of 27 to 73 years that 100% were female. ER, PR, Her-2 and p53 positive for the patients were 43.7%, 56.3%, 43.7% and 37.5%, respectively. Three patients (18.7%) had grade I, nine patients (56.3%) had grade II and four patients (25%) had grade III. The mean OS was 24.7 months with survival rate of 50%. Lymph node metastasis for 13 patients (81.2%) was positive. **Conclusions:** The mean age for patients with brain metastatic BC at diagnosis is more between 45 to 52 years and also brain metastasis in BC occurs more in HER-2-overexpressing and TNBC. Size of tumor in BC patients >5 cm is a prognostic factor for brain metastasis.

Keywords: *brain metastasis, breast cancer, ER, Ki67*

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1. Introduction

Breast cancer (BC) screening and higher quality mammography have resulted in an increase in the diagnosis of ductal carcinoma in situ worldwide that is characterized by a number of genetic aberrations. Although improvements have been achieved in recent years, few genetic biomarkers are available to easily identify individuals at risk for BC or BC progression [1]. BC metastasis to the central nervous system (CNS) or brain metastases include the clinically distinct situations of multiple brain metastasis (78%), solitary brain metastasis (14%), and leptomeningeal metastasis (8%) [2,3]. Diagnosis of brain metastases is based on patient symptoms and neuroimaging. The most common clinical symptoms of parenchymal brain metastases include headaches and alterations in cognition, mental status, and behavior [3].CNS metastasis occur in 10%–16% of stage IV patients while they are found in ~30% of patients in autopsy series [2]. Several studies have reported that various prognostic factors (young age; receptor-negative tumors; elevated LDH; large tumor size; grade; lymphovascular invasion; number of positive lymph nodes; other sites of metastases, especially lung metastasis; HER-2 overexpressing metastatic BC; poor Karnofsky's performance status; etc.) are associated with higher incidence of dissemination to the CNS [4].

The aim of this study is to describe clinicopathologic features of patients with BC brain metastasis and to compare estrogen receptor (ER), progesterone receptor (PR), and Her2 expression in them.

2. Materials and Methods

2.1. Patients

Out of eight hundred patients with BC that referred to our Clinic between of 2005 to 2014, there were 17 patients with brain metastasis and we entered them to our study. Age, sex, kind of pathology, tumor markers, type of treatment, histological grade, size of tumor, laterality and other metastasizes were checked for the patients. The OS was estimated as the time from diagnosis of BC until

death from any cause or last follow-up for patients that were censored. The 3-year OS was concluded for the patients with at least one year follow up. ER and PR positivity was defined as ≥10% positive tumor cells with nuclear staining. HER2 positivity was defined as either HER2 gene amplification by fluorescent *in situ* hybridization or scored as 3+ by IHC. In case of HER2 2(+), fluorescent *in situ* hybridization was performed to determine HER2 positivity.

2.2. Statistic Analysis

The OS was plotted with GraphPad Prism 5 software by Log-rank test. The mean age and percentage of other variables was concluded by IBM SPSS V19 software that P≤0.05 was statistically significant.

Table 1. The characteristics for the breast cancer patients with brain metastasis (n=17)

Parameter	n(%)	Mean±SD	Range
Age(year)		47.0±14.0	27-73
Sex			
Male	0(0)		
Female	17(100)		
ER			
Positive	8(47.1)		
Negative	9(52.9)		
PR			
Positive	10(58.8)		
Negative	7(41.2)		
Her-2			
Positive	7(41.2)		
Negative	10(58.8)		
Ki67			
<10%*	4(23.5)		
≥10%	13(76.5)		
P53			
Positive	8(47.1)		
Negative	9(62.5)		
Histological Grade			
I	3(17.6)		
II	7(41.2)		
III	7(41.2)		
Size of Tumor(cm)			
0.1-2	4(23.5)		
2.1-5	6(35.3)		
>5	7(41.2)		
Laterality			
Right	11(64.8)		
Left	3(17.6)		
Both	3(17.6)		
Lymph node Metastasis			
Positive	12(70.6)		
Negative	5(29.4)		
Fatty Liver			
Positive	1(5.9)		
Negative	16(94.1)		
Hormone therapy			
Positive	13(76.4)		
Negative	4(23.6)		
Radiotherapy			
Positive	15(88.2)		
Negative	2(11.8)		
Chemotherapy			
Positive	17(100)		
Negative	0(0)		
Number of brain metastasis			
Single	6(35.3)		
Multiple	11(64.7)		
Mastectomy			
Yes	6(35.3)		
No	11(64.7)		

ER: Estrogen Receptor **PR:** Progesterone Receptor **Her-2:** Human Epidermal Growth Factor Receptor 2 * **low Ki67**

3. Results

The mean age at diagnosis for the patients was 42.2 years (±14.4) and range of 27 to 73 years that 100% were female (Table 1). ER, PR, Her-2 and p53 positive for the patients were 47.1%, 58.8%, 41.2% and 47.1%, respectively. We divided Ki67 to groups: Ki67<10% (low Ki67) was in 4 patients (23.5%) and Ki67≥10% (high Ki67) was in 13 patients (76.5%). Three patients (17.6%) had grade I, seven patients (41.2%) had grade II and seven patients (41.2%) had grade III. We divided size of tumor for the patients to 3 groups: 23.5% had between of 0.1-2 cm, 35.3% between of 2.1-5 cm and 41.2% >5 cm. 11 patients (64.8%) had right breast involvement, 3 patients (17.6%) had left and 3 patients (17.6%) both. Lymph node metastasis for 12 patients (70.6%) was positive and one patient had fatty liver. Out of 16 patients, 13 patients (76.4%) were treated with hormone therapy (tamoxifen or letrozole), 15 patients (88.2%) with radiotherapy and all patients with chemotherapy. Six patients (35.3%) had a single brain metastasis, whereas 11 patients (64.7%) had multiple metastases. Also, six patients (35.3%) had mastectomy. The median time from diagnosis of primary tumor to brain metastasis was 23 months.

Table 2.Drugs for brain metastasis (n=17)

Drug	n(%)
Sirolimus(Rapamycin)	5
Herceptin(Trastizumab)	7
Avastin(Bevacizumab)	5

Recently, to further specify the BC subtypes, the Cancer Genome Atlas (TCGA) performed microRNA and exome sequencing, defining four distinct BC subtypes: luminal A, luminal B, basal-like and HER2 type (Table 3) [5,6,7].

1. Luminal A (ER+ and/or PR+, HER2-, low Ki67)
2. Luminal B (ER+ and/or PR+, HER2+ (or HER2- with high Ki67))
3. Triple negative/basal-like(ER-, PR-, HER2-)
4. HER2 type (ER-, PR-, HER2+)

Table 3. Subtypes of Breast Cancer

Major molecular subtypes	n(%)
Luminal A	0(0)
Luminal B	9(53)
Triple negative	6(35.3)
HER2 type	2(11.7)

The Figure 1 shows the 3-year OS for BC patients with brain metastasis. The mean OS was 24.7 months with survival rate of 50%.

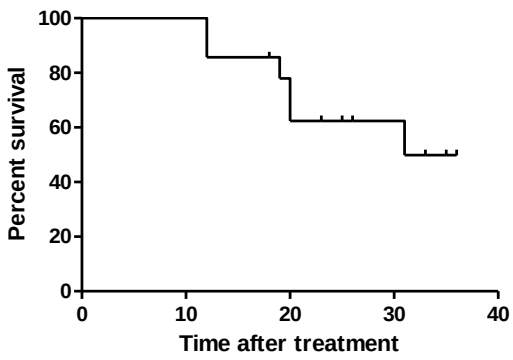

Figure 1. The 3-year OS for the breast cancer patients with brain metastasis

4. Discussion

BC is the most frequent malignancy among women that can be a leading cause of death through middle-aged women [8]. Patients with invasive ductal carcinoma present higher lymphatic involvement and worse prognosis than less common types of breast carcinoma [9]. Carcinomatous Meningitis (CM), a kind of brain metastases, refers to the multifocal seeding of the leptomeninges by malignant cells. CM occurs in approximately 5% of patients with BC [10]. Several publications have reported high rates of CNS recurrences in HER2-positive BC patients treated with trastizumab [11,12,13]. It has been reported that trastuzumab can penetrate into BC CNS metastasis as measured by PET scanning [14]. Amplification or overexpression of Her-2 correlates with a shorter disease-free and overall survival time and also appears to associate with a higher incidence of brain metastases [15]. Importantly, the incidence of breast to brain metastasis has recently increased due to the improved systemic treatments of primary and non-brain metastatic BC extending patient lifespan, particularly in patients with HER2-overexpressing and triple negative BCs [16,17]. In our study, 7 patients were treated by trastizumab. Therefore, these results show that trastizumab can probably increase brain metastasis in the patients with BC.

The median age of the patients at the diagnosis of brain metastases was 45 years (range, 26-78 years) [18] and other study reported that the median age at the time of diagnosis of brain metastases was 52 years [19]. Other study reported that the median age was 51 years (range 24-74) [20]. In our study, the mean age is 47 years (range, 27-73 years). Therefore, the mean age for patients with BC and brain metastases is more between 45 to 52 years (range 24-78).

s triple receptor-negative BC brain metastases developed earlier than in other receptor subtypes, occurring at a median interval of 22 months after primary diagnosis versus 51 months for all other subtypes [21].

Among the 152 patients, the number of luminal, HER-2-overexpressing, and triple-negative breast cancer (TNBC) subtypes were 60, 53, and 39 cases, respectively. Also, compared with the luminal subtype, brain metastasis occurs earlier in HER-2-overexpressing and TNBC subtypes. Trastuzumab can delay the occurrence of BM from advanced BC, and systemic therapy can improve the survival of patients after brain metastasis [22].

Leone et al. [20] reported that in the patients with brain metastasis, 61.9% had grade III, 42.9% ER+, 23.8% PR+ and 42.9% Her2+. In results of Shen et al. [23] have been written that most patients had invasive ductal histology (91%), grade III tumors (67%), and positive axillary lymph node (64%). Of the tumors, 56% were ER negative, 62% were PR negative, 44% were Her2 positive, and 28% were TN. In this study, all of patients were invasive ductal and also 56.3% patients had grade II, 43.7% ER+, 56.3 PR+, 43.7% Her2+, 81.2% positive lymph node and 31.2% TN. These results show that in patients with BC and brain metastasis, ER and HER2 are predominantly negative and more patients have lymph node metastasis, but grade II is more in our study, unlike other studies that is grade III.

A number studies [24,25,26] reported that large tumor size is a prognostic factor for brain metastasis in BC patients and in our study, more patients (43.7%) had tumor size>5 cm and our result confirms results of past studies.

The median survival of patients with metastatic BC is 2 to 3 years [27] and the 1-year survival rate of BC patients with brain metastasis is 20% [28]. The 3-year OS for our patients is 24.7 months with survival rate of 50% that it is probably combination of chemotherapy(phase 1- Temodar (because entering to the brain from the blood–brain barrier) and phase 2- irinotecan) with three drugs (Sirolimus, Herceptin and Avastin) in these patients is effective in increasing of the response rate or overall survival rate.

A study reported the median time from the diagnosis of BC until the development of brain metastasis was 32.24 months [20]. The Median time from the diagnosis of BC to the detection of brain metastasis was 30.2 months [29] but in our study the median time was 23 months and it is less than other studies.

5. Conclusions

The mean age for patients with brain metastatic BC at diagnosis is more between 45 to 52 years and also brain metastasis in BC occurs more in HER-2-overexpressing and TNBC. Size of tumor in BC patients >5 cm is a prognostic factor for brain metastasis. Physicians should consider that the OS of patients with brain metastases can increase with suitable drugs.

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