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Original Research Article

Determining characteristics of cerebral metastasis from breast cancer

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ABSTRACT

The aim of this study was to evaluate the characteristics of cerebral metastasis from breast cancer. This cross sectional study was conducted on patients with cerebral metastasis from breast cancer in Shahid Sadoughi hospital from 2014 to 2020 and was conducted on 37 patients with mean age 50.83± 14.58. Negative estrogen receptor/ progesterone receptor and Ki67 > 50 was seen in 54.1 %, 62.2 %, and 10.8 % of patients, respectively. The most common cerebral tumor was brain with frequency of 63.6 %. There was no significant difference between age range less and more than 50 years regarding cerebral metastasis and location of cerebral tumors (p-value >0.05). The most location of cerebral metastasis was brain. Furthermore, cerebral metastasis and location of cerebral tumors were not influenced by age range of patients.

***Keywords*:** Cerebral metastasis from breast cancer, estrogen receptor, progesterone receptor

INTRODUCTION

Breast cancer is the most malignancy in women [1], containing almost one third of all illnesses in women [1-3]. It is the leading cause of cancer death among Iranian women [4]. Recent studies have shown that survival rate of patients with breast cancer is increasing due to improvement of systemic therapies; causing a number of these patients

experiences cerebral cancer before death. Studies have shown that 15-30 % of metastatic cases of breast cancer develop brain metastasis during the course of disease. Studies have also reported that cerebral metastasis is associated with poor prognosis and neurological impairments (cognitive and sensory functions) [5,6]. In addition, it affects quality of life and life expectancy of many patients. The neurological symptoms of cerebral metastasis are headache, nausea, vomiting, limb paralysis, dizziness, seizures and impaired vision. Therapeutic approaches including radiotherapy and surgery are effective in treatment of metastatic cerebral tumors [7]. Furthermore, breast cancer cells based on gene expression pattern have different signaling pathways for metastasis and show different clinical outcomes [7], Therefore assessment of molecular biomarkers in breast cancer tissue for predicting the outcome of disease and decision making for optimal treatment is valuable [8]. According to studies, decision regarding treatment of breast cancer is commonly made according to expression of these biological markers [9], particularly Estrogen Receptor (ER), Progesterone Receptor (PR), and Ki67 [10]. ER and PR status are beneficial markers to predict the response to endocrine therapy. Expression of positive ER/PR in breast tumors is associated with response to hormone therapy. Moreover, these tumors have better prognosis than tumors with negative ER/PR [11]. Ki67 as a non-histone nuclear protein is linked to proliferation of cells [12,13]. Expression of Ki67 as a prognostic marker is associated with higher histological grade and shorter disease free and overall survival and worse clinical outcomes [13].

Given that few studies have been conducted regarding the characteristics of brain metastasis from breast cancer [14,15] and no comprehensive studies were conducted in this regard in our region, the aim of this study was to evaluate determining the characteristics of cerebral metastasis from breast cancer in shahid Sadoghi hospital, Yazd, Iran.

MATERIALS AND METHODS

This cross sectional study was conducted on 37 patients with cerebral metastasis from breast cancer in Shahid Sadoughi hospital in 2020. After approving current study by ethical committee of Islamic Azad University (IR.IAU.Khuisf.REC.1398.269), data

including age, number of involved lymph nodes, tumor metastasis, and location of cerebral tumors were extracted from medical records in Shahid Sadoughi hospital from 2014 to 2020. Patients with incomplete medical records were excluded from study.

Expression of biomarkers including ER, PR and Ki67 was assessed through immunohistochemical technique. In this method, thick histological sections (4µm) were mounted on poly-L-lysin slides. These slides were dewaxed with xylene and then rehydrated. Sections were placed with H_2O_2 (3 %) for 15 min. For antigen retrieval, the slides were put in citrate buffer and boiled (15 min). After washing with PBS, blocking of non-specific binding site was done. Then, the sections were exposed to primary antibody monoclonal mouse anti human1D5, monoclonal mouse anti human PGR 636, and monoclonal mouse anti human MIB-1 (Dako Company) for staining of ER, PR and Ki67 antigens. In the next step, secondary antibody sheep anti mouse, anti-rabbit horseradish peroxidase and 3, 3-diamino-benzidine tetrahydrochloride (sigma) was used. Then hematoxylin was applied for counterstaining of sections and in the next step, dehydration and mounting process was done.

Statistical analysis

Data were entered to SPSS, version 21. Chi square test, Anova and T test were used for analysis of data. $P<0.05$ was assumed significant.

RESULTS

Current study was conducted on 37 patients with mean age 50.83± 14.58 and age range 20 - 85 years old. Furthermore, 44 cases of cerebral metastasis were observed in these patients (cerebral metastasis was observed in more than one site in many patients). Frequency distribution of variables such as estrogen receptor, progesterone receptor, Ki67, location of brain tumor and metastasis is shown in Table 1.

Comparison between variables such as cerebral metastasis and location of cerebral tumors in terms of age range is shown in Table 2. As shown in Table 2, no difference was seen between variables such as cerebral metastasis and location of cerebral tumor in terms of age range (p-value>0.05).

Comparison of biomarker expression including ER, PR, Ki67 and location of

cerebral tumors in terms of the number of involved lymph nodes is shown in Table 3. As shown in Table 3, no significant difference was found between biomarkers expression including PR, ER, and Ki67 regarding the number of involved lymph nodes (p-value>0.05). In addition, there was no significant difference between location of cerebral tumor in terms of the number of involved lymph nodes (p-value >0.05).

Comparison of biomarkers expression including PR, ER, and Ki67 in terms of location of cerebral tumors is shown in Table 4. As shown in Table 4, no remarkable difference was found between biomarkers expression in terms of location of cerebral tumors (p-value>0.05). Furthermore, we did not find significant difference between cerebral tumors regarding metastasis (lung and bone) (p-value= 0.41).

Table 1: Frequency distribution of variables in breast cancer patients

Receptors	Frequency (Percent)
ER	
Negative	20 (54.1)
Positive	17 (45.9)
Total	37 (100)
PR	
Negative	23 (62.2)
Positive	14 (37.8)
Total	37 (100)
Ki67	
< 14	22 (59.5)
15-50	11 (29.7)
> 50	4 (10.8)
Total	37 (100)
Location of brain tumor	
Brain	28 (63.6)
Cerebellum	10 (22.7)
Brainstem	6 (13.6)
Total	44 (100)
Location of metastasis	
No metastasis	28 (75.7)
Bone	5 (13.5)
Lung	4 (10.8)
Total	37 (100)

Table 2: Comparison between variables in terms of age range

Variable	Age		X^2	p-value
	Over 50 years	Under 50 years		
Cerebral metastasis				
No	12 (60)	7 (41.1)	1.588	0.208
Yes	8 (40)	10 (58.9)		
Total	20 (100)	17 (100)		
Location of brain tumor				
Brain	14 (60.8)	14 (66.6)	0.557	0.749
Cerebellum	5 (21.7)	5 (23.8)		
Brainstem	4 (17.5)	2 (9.6)		
Total	23 (100)	21 (100)		

DISCUSSION

Recently, the incidence of cerebral metastasis from breast cancer is increasing. Anders *et al.*, reported that approximately 10 % to 15 % of women with metastatic breast cancer develop cerebral metastasis [14]. In our study, the most common site of cerebral tumor was brain. Gohari *et al.* assessed frequency of patients with cerebral malignancy from breast cancer and reported that the most common involved site was brain; which was consistent with our study [15]. Rostami *et al.*, assessed cerebral metastasis in patients with breast cancer and reported that the most common site for metastasis was cerebellum [16]. McArthur *et al.*, reported that cerebellum was involved in one-third of cerebral metastasis from breast cancer [17]. Yamada *et al.*, also reported that cerebellum was the most common metastatic site of breast cancer [18]. Therefore, according to these studies, brain and cerebellum are the most common involved site.

Moreover, frequency distribution of biomarkers in breast cancer patients showed that ER^- and PR^- were observed in 54.1 % and 62.2 % of patients. This finding indicated that majority of patients with cerebral metastasis have ER^-/PR^-. In addition, no remarkable difference was seen between biomarkers expression in terms of location of cerebral tumor. Few studies have assessed relation between biomarkers expression and type of cerebral tumors. Hulsbergen *et al.*, in a study evaluated cerebral metastasis of breast tumors and reported ER^- and PR^- was observed in 46.6 % and 61.6 % of patients, respectively [19], which approximately was similar to our study. Salhia *et al.*, assessed patients with cerebral cancer from breast cancer and reported that majority of these patients had ER receptor [20]. Shen *et al.*, assessed clinicopathological characteristics of 140 patients with cerebral metastasis of breast cancer in MD Texas Anderson and reported that expression of ER^- and PR were observed in 56 %, and 62 % of patients, respectively [21]. This finding was almost similar to our study. Koniali *et al.*, assessed risk factors for breast cancer brain metastasis and observed relation between ER expression and cerebral metastasis [22]. Evan *et al.*, also achieved same findings and reported that cerebral metastasis was more common in women with ER expression [23].

According to these findings, the status of hormone receptors expression was the most important risk factor for cerebral metastasis. Furthermore, in different subtypes of breast cancer, the likelihood of cerebral metastasis is different [24-26]. Hulsbergen *et al.*, reported ER, PR, and Her2 expression can be different in primary breast cancer and distant metastasis. It appears that this discordance happen in all metastatic sites and may affect subtype-directed management strategies [19]. Hosonoga *et al.*, also reported that cerebral metastasis from breast cancer happens in patients with certain subtypes of breast tumor [7].

In current study, the most involved site in patients with cerebral metastasis from breast cancer was bone and lung, respectively. Nasiri *et al.* conducted a study on 1615 patients with breast cancer in Omid hospital during 2001 to 2011 and observed that among them, 446 patients had metastasis. In addition, the most involved location in these patients was bone, which was consistent with our study

[27]. Irwani *et al.*, assessed metastasis in Indonesian breast cancer patients and reported that most involved site was bone [28]. The finding of this study was also consistent with our study. Maria Lelekakis *et al.*, assessed metastasis in breast cancer patients and reported that majority of patients with metastatic disease have bone involvement, whereas lungs and liver are the other common targets [29]. Therefore according to these findings, it seems that bone was the most common metastatic site in breast cancer patients. Other studies have also shown higher risk of cerebral cancer of breast tumors. [30,31], visceral and lymph node as first sites of metastasis [32].

The mean age of patients in our study was 50.8±14.58 years old. In addition, no significant difference was seen between cerebral metastasis and location of cerebral tumors in age range less and more than 50 years old. Rostami *et al.*, evaluated cerebral metastasis in patients with breast cancer and reported that this mean age is 50.3 years old, which was consistent with our study [16]. Gohari *et al.*, assessed cerebral metastasis of breast cancer and reported that the mean age of patients was 52.4 years old [15]. Therefore according to findings of our study and other studies, it seems that the mean age of patients with cerebral metastasis from breast cancer was ≥ 50 years.

Moreover, in our study, no remarkable difference was seen between biomarkers expression in terms of the number of involved lymph nodes. Sofi and colleagues reported no relation between ER and PR expression and lymph node metastasis, which was consistent with our study [32]. But Sheikhpour *et al.*, reported that ER overexpression was associated with reduced lymph node metastasis [1]. It seems that the most reason of this difference between two studies was related to different sample size. Sheikhpour *et al.*, conduced this study on 184 patients; whereas we performed current study on 37 patients [1].

Table 3: Comparison of biomarker expression and location of brain tumor in terms of the number of involved lymph nodes

Variables	The number of involved lymph nodes			p-value
	0	1	2	
ER				
Negative	1 (25)	16 (57.1)	3 (60)	0.549
Positive	3 (75)	13 (42.9)	2 (40)	
Total	4 (100)	28 (100)	5 (100)	
PR				
Negative	2 (50)	18 (64.2)	3 (60)	0.859
Positive	2 (50)	10 (35.8)	2 (40)	
Total	4 (100)	28 (100)	5 (100)	
Ki67				
< 14	0 (0)	18 (62)	4 (80)	0.202
15-50	2 (66.3)	8 (27.5)	1 (20)	
> 50	1 (33.7)	3 (10.5)	0 (0)	
Total	3 (100)	29 (100)	5 (100)	
Location of cerebral tumor	2 (66.7)	22 (62.8)	4 (66.6)	
Brain	1 (33.4)	7 (20)	2 (33.4)	0.714
Cerebellum	0 (0)	6 (17.2)	0 (0)	
Brainstem	3(100)	35 (100)	6 (100)	
Total				

Table 4: Comparison of biomarkers expression including PR, ER, and Ki67 in terms of location of cerebral tumors

Variables	Brain	Cerebellum	Brainstem	Total	p-value
PR					
Negative	17 (63)	6 (22.2)	4 (14.8)	27 (100)	0.959
Positive	11 (64.7)	4 (23.5)	2 (11.8)	17 (100)	
ER					
Negative	15 (60)	6 (24)	4 (16)	25 (100)	0.189
Positive	13 (68.4)	4 (21)	2 (10.6)	19 (100)	
Ki 67					
< 14	18 (69.2)	6 (23)	2 (7.8)	26 (100)	0.386
15-50	7 (50)	3 (21.5)	4 (28.5)	14 (100)	
> 50	3 (75)	1 (25)	0 (0)	4 (100)	

CONCLUSION

According to these findings, the most location of cerebral metastasis was brain. Furthermore, cerebral metastasis and location of cerebral tumors were not influenced by age range of these patients. In addition, the expression of biomarkers and the number of involved lymph nodes did not affect location of cerebral tumors. Perhaps, the small sample size is the reason of this issue. It is proposed this study is done on larger sample size in future.

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