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Original Article

Association of Estrogen Receptor, Progesterone Receptor, and Human Epidermal Growth Factor Receptor 2 Expression with Breast Cancer Metastasis in Iran

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Abstract

Background: Metastasis is an important factor in the survival estimate of patients with breast cancer. The present study aimed to examine the frequency of epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR) expression in relation to the metastatic site, pattern, and tumor size in patients with metastatic breast cancer (MBC).

Methods: In this retrospective study, the medical records of patients diagnosed with MBC at Motahari Clinic (Shiraz, Iran) during 2017-2019 were examined. Metastasis was confirmed using computed tomography, and a total of 276 patients were included in the study. Based on the expression of receptors, the patients were categorized into luminal A, luminal B, HER2, and TNBC groups. The frequency and percentage of receptors in relation to the metastatic site, size, and pattern were compared using the Chi square test. $P<0.05$ was considered statistically significant.

Results: The frequency of receptor positivity in the 276 selected medical records were of the subtype HER2-enriched (n=48), luminal A (n=43), luminal B (n=146), and TNBC (n=39). The most common metastatic sites were the bones (47.1%), lungs (34.4%), liver (27.9%), brain (20.3%), and other organs (12.7%). The first site of metastasis occurred in the bones (36.6%), lungs (17.4%), liver (15.6%), brain (10.5%), and other organs (7.6%). The frequency of receptor expression was different in relation to the first metastatic site (P=0.024). There was a statistically significant difference between the frequency of receptor expression in patients with bone (P=0.036), brain (P=0.031), and lung (P=0.020) metastases. The frequency of receptor expression was also significantly different in relation to the size of liver metastasis (P=0.009). Luminal A and B subtypes showed higher rates of bone metastasis as the first metastatic site.

Conclusion: The difference in the frequency of receptor expression in relation to the metastatic site and tumor size can be used as predictive and prognostic factors in patients with breast cancer.

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Keywords ● Breast neoplasms ● Neoplasm metastasis ● Receptors ● Progesterone

What's Known

- Breast cancer is the most common type of cancer in women. It has metastatic potential and is the principal determinant of patient survival.
- The expression of human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR) has been associated with patient survival and metastatic sites.

What's New

- The bone is a common site for metastasis. Luminal A and B subtypes show higher rates of bone metastasis.
- The frequency of HER2, ER, and PR expression differs at the first metastatic site, in patients with bone, brain, or lung metastasis, and in relation to the size of liver metastasis.

Introduction

Breast cancer (BC) is the most common type of cancer in women worldwide. The lifetime risk of developing BC is about 12%, i.e.,

approximately one in eight women.[1] In 2019, the United States recorded 1,762,450 new cancer cases and 606,880 cancer deaths, of which BC alone accounted for 30% of all new cases and the second leading cause of death in women.[2] The age-standardized rate of developing BC in Iranian women is estimated at 27.4%, the lowest in the Middle East.[3] Nonetheless, BC is the most common type of cancer in Iranian women, and the majority of cases are diagnosed at advanced stages with an upward trend in mortality rates.[4, 5] One of the important factors in determining disease stage and mortality rate in patients with BC is distant metastasis, affecting about 6-60% of patients.[6] The prognosis of patients with metastatic breast cancer (MBC) is site-dependent. Patients with bone metastasis have the best prognosis, and those with brain metastasis have the worst.[7]

Recently, research studies have focused on the metastatic ability of BC tumors as a prognostic factor. Several MBC risk factors have been suggested, such as patients' age, race/ethnicity, cigarette smoking, history of cancer in first-degree relatives, endogenous hormones, menopause, breastfeeding duration, and tumor histopathology, size, and grade.[8] Molecular studies have shown that biological subtypes of BC are important predictors of metastasis. The subtypes include luminal A, luminal B, and triple-negative breast cancer (TNBC)/basal-like, which are classified based on the expression of receptors, i.e., human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR).[9]

ER is a nuclear hormone receptor that acts as a transcription factor, and PR plays a role in ER signaling. Both the ER and PR are important drivers of BC development.[10] Patients with ER^+ and PR^+ respond to endocrine therapy, but not to cytotoxic chemotherapy and are thus, less likely to achieve a complete response.[11] On the other hand, $HER2^+$ is highly proliferative with higher histological grade and aggressive biological and clinical behavior.[12] TNBC subtype is biologically aggressive and has a high mortality rate and earlier recurrence.[13] Consequently, these are important contributors to disease recurrence and overall survival (OS).[14]

There is a significant association between the site and pattern of metastasis and disease survival and recurrence rates. There is also emerging evidence on the biological nature of MBC.[15] Hence, in the present study, we examined the frequency of HER2, ER, and PR expression in patients with MBC and their association with the metastatic site, size, and pattern. The outcome of the study demonstrates whether these receptors can be used as effective markers for the prediction of the disease and to monitor and follow-up patients with MBC.

Materials and Methods

In this retrospective study, the medical records of patients diagnosed with MBC during 2017-2019 were examined. The patients were treated at Shahid Motahari Clinic affiliated with Shiraz University of Medical Sciences, Shiraz, Iran. The inclusion criteria were being diagnosed with BC for less than 10 years, with at least one apparent site of metastasis, and a complete medical record. Metastasis was confirmed using computed tomography (CT) scanner (GE BrightSpeed, Milwaukee, WI, USA) with 512×512 matrix size and 10 mm slice thickness. The diagnosis of BC and metastasis was confirmed by three attending radiologists using CT imaging. Based on the convenient sampling method, medical records of 276 patients that fulfilled the inclusion criteria were selected. The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (code: IR.Sums.Med.Rec.1398.118). Written informed consent was obtained from the patients including permission for anonymized use of the results for research purposes and publications.

Based on pathology reports, the data associated with the metastatic site (the brain, liver, lungs, bones, etc.), size (<2 cm, 2–4 cm, >4 cm), and pattern were extracted from the medical records. In addition, the status of the three receptors (HER2, ER, PR) was noted. Patients with ER^+ and/or PR^+ and $HER2^-$ were classified as luminal A subtype, those with ER^+ and/or PR^+ and $HER2^+$ as luminal B subtype, ER^- and/or PR^- and $HER2^+$ as HER2–enriched subtype, and ER^-, PR^-, and $HER2^-$ as TNBC subtype.[9]

Statistical Analysis

The data were analyzed using SPSS software, version 21.0 (IBM Corp. Armonk, NY, USA). A Chi square test was used to compare the frequency of variables between the study groups. Descriptive data were expressed as frequency and percentage. $P<0.05$ was considered statistically significant.

Results

The frequency of receptor positivity from the 276 selected medical records were of the HER2-enriched (n=48), luminal A (n=43), luminal B (n=146), and TNBC (n=39) subtype. The most common sites of single or multiple metastases

were the bones (n=130, 47.1%), lungs (n=94, 34.4%), liver (n=77, 27.9%), brain (n=56, 20.3%), and other organs (n=35, 12.7%) (figure 1). The first site of metastasis occurred in the bones (n=101, 36.6%), lungs (n=48, 17.4%), liver (n=43, 15.6%), brain (n=29, 10.5%), and other organs (n=21, 7.6%). Note that the medical records of 34 (12.3%) patients did not include complete information about the first metastatic site.

The frequency of receptor expression at different metastatic sites and their categorization based on the site of the first metastasis and pattern is shown in figure 2 and table 1, respectively. As shown in the table, there was a statistically significant difference between the frequency of receptors in relation to the first metastatic sites (P=0.024). Luminal A and B subtypes showed higher rates of bone metastasis as the first metastatic site. There was a statistically significant difference between the frequency of receptors in patients with bone (n=130, P=0.036), brain (n=56, P=0.031), and lung (n=94, P=0.020) metastases. The frequency of receptors was significantly different in relation to the size of liver metastasis (P=0.009), while no difference was observed in relation to the size and pattern of other metastatic sites (P>0.05).

Discussion

The results of the present study showed that the most common metastatic sites were the bones followed by the lungs, liver, and brain. Similarly, a previous population-based study reported that distant metastases at the first diagnosis of BC were to the bones, lungs, liver, and brain, respectively.[16] Another study reported that the bones followed by the brain, liver, and lungs are the most common metastatic sites.[17] Weilbaecher and colleagues also reported

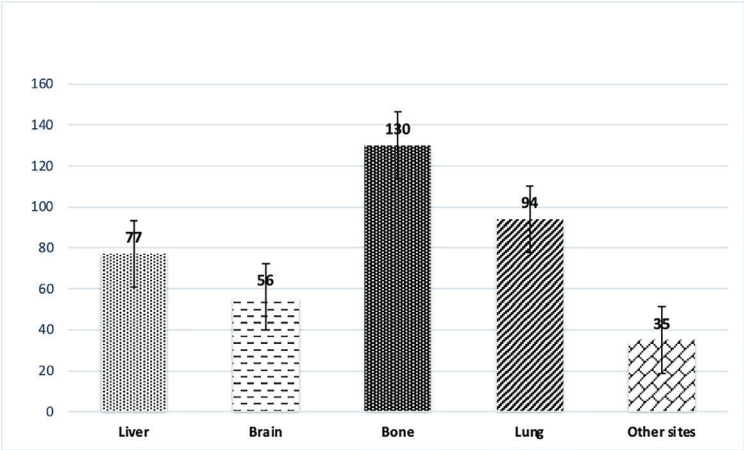

Figure 1: The figure shows the frequency of metastases to different sites in patients with breast cancer. The most common sites were the bones, lungs, liver, and brain, respectively. Metastases to other sites were less frequent.

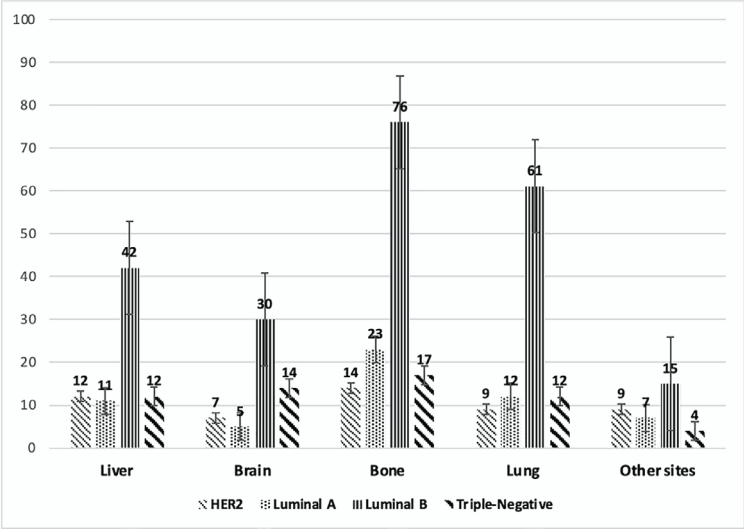

Figure 2: The figure shows the frequency of BC subtypes at different metastatic sites in patients with breast cancer. Luminal B is the most frequent subtype at all metastatic sites. The results of the Chi square test showed significant differences between the frequency of receptor expression in the bones (P=0.036), brain (P=0.031), and lungs (P=0.020).

Table 1: The frequency of BC subtypes in relation to the metastatic site, pattern, and tumor size

Variable		Categories	Total	HER2†	Luminal A	Luminal B	Triple-negative	P value*
Site of first metastasis		Brain	29 (100%)	5 (17.20%)	3 (10.40%)	15 (51.70%)	6 (20.70%)	0.024
		Liver	43 (100%)	10 (23.20%)	3 (7.0%)	22 (51.20%)	8 (18.60%)	
		Bone	101 (100%)	8 (7.90%)	22 (21.80%)	64 (63.40%)	7 (6.90%)	
		Lung	48 (100%)	10 (20.80%)	5 (10.40%)	25 (52.10%)	8 (16.70%)	
		Other sites	21 (100%)	6 (28.60%)	3 (14.30%)	9 (42.80%)	3 (14.30%)	
		Not reported	34 (100%)	9 (26.50%)	7 (20.60%)	11 (32.30%)	7 (20.60%)	
Liver metastasis	Presence of metastasis	Positive (27.9%)	77 (100%)	12 (15.60%)	11 (14.30%)	42 (54.50%)	12 (15.60%)	0.912
		Negative	199 (100%)	36 (18.10%)	32 (16.10%)	104 (52.20%)	27 (13.60%)	
	Metastatic pattern	Necrotic	18 (100%)	2 (11.10%)	2 (11.10%)	11 (61.10%)	3 (16.70%)	0.927
		Hypervascular	11 (100%)	1 (9.10%)	2 (18.20%)	7 (63.60%)	1 (9.10%)	
		Hypovascular	48 (100%)	9 (18.70%)	7 (14.60%)	24 (50%)	8 (16.70%)	
	Tumor size	≤2 cm	41 (100%)	5 (12.20%)	5 (12.20%)	27 (65.80%)	4 (9.80%)	0.009
		2–4 cm	17 (100%)	2 (11.80%)	2 (11.80%)	12 (70.50%)	1 (5.90%)	
		≥4 cm	19 (100%)	5 (26.30%)	4 (21.10%)	3 (15.80%)	7 (36.80%)	
Brain metastasis	Presence of metastasis	Positive (20.3%)	56 (100%)	7 (12.50%)	5 (8.90%)	30 (53.60%)	14 (25%)	0.031
		Negative	220 (100.0%)	41 (18.60%)	38 (17.30%)	116 (52.70%)	25 (11.40%)	
	Metastatic pattern	Necrotic	16 (100%)	2 (12.60%)	3 (18.70%)	8 (50%)	3 (18.70%)	0.102
		Hemorrhagic	4 (100%)	0 (0.0%)	2 (50%)	0 (0.0%)	2 (50%)	
		Hypervascular	24 (100%))	3 (12.50%)	0 (0.00%)	14 (58.30%)	7 (29.20%)	
		Dural	4 (100%)	0 (0.0%)	0 (0.00%)	4 (100%)	0 (0.0%)	
		Leptomeningeal	7 (100%)	2 (28.60%)	0 (0.00%)	3 (42.80%)	2 (28.60%)	
		Hypovascular	1 (100%)	0 (0.0%)	0 (0.00%)	1 (100%)	0 (0.0%)	
	Tumor size	≤2 cm	19 (100%)	3 (15.80%)	0 (0.00%)	11 (57.90%)	5 (26.30%)	0.516
		2–4 cm	31 (100%)	3 (9.70%)	4 (12.90%)	15 (48.40%)	9 (29%)	
		≥4 cm	6 (100%)	1 (16.70%)	1 (16.70%)	4 (66.60%)	0 (0.0%)	
Bone metastasis	Presence of metastasis	Positive	130 (100%)	14 (10.80%)	23 (17.70%)	76 (58.40%)	17 (13.10%)	0.036
		Negative	146 (100%)	34 (23.30%)	20 (13.70%)	70 (47.90%)	22 (15.10%)	
	Metastatic pattern	sclerotic	57 (100%)	7 (12.30%)	8 (14.00%)	34 (59.70%)	8 (14.00%)	0.937
		Lytic	32 (100%)	3 (9.40%)	7 (21.90%)	17 (53.10%)	5 (15.60%)	
		Mixed	41 (100%)	4 (9.70%)	8 (19.60%)	25 (61%)	4 (9.70%)	
	Tumor size	≤2 cm	78 (100%)	11 (14.10%)	15 (19.20%)	43 (55.10%)	9 (11.60%)	0.520
		2–4 cm	41 (100%)	3 (7.30%)	6 (14.60%)	27 (65.90%)	5 (12.20%)	
		≥4 cm	11 (100%)	0 (0.0%)	2 (18.20%)	6 (54.50%)	3 (27.30%)	
Lung metastasis	Presence of metastasis	Positive	94 (100%)	9 (9.50%)	12 (12.80%)	61 (64.90%)	12 (12.80%)	0.020
		Negative	182 (100%)	39 (21.40%)	31 (17%)	85 (46.70%)	27 (14.90%)	
	Metastatic pattern	Cavitary	2 (100%)	0 (0.0%)	1 (50%)	1 (50%)	0 (0.0%)	0.950
		Lymphangitic	19 (100%)	1 (5.30%)	2 (10.50%)	14 (73.70%)	2 (10.50%)	
		Single	15 (100%)	2 (13.30%)	2 (13.30%)	10 (66.70%)	1 (6.70%)	
		Multiple	57 (100%)	6 (10.50%)	7 (12.30%)	35 (61.40%)	9 (15.80%)	
		Cavitary/Multiple	1 (100%)	0 (0.0%)	0 (0.0%)	1 (100%)	0 (0.0%)	
	Tumor size	≤2 cm	64 (100%)	5 (7.80%)	7 (11%)	42 (65.60%)	10 (15.60%)	0.505
		2–4 cm	16 (100%)	1 (6.20%)	3 (18.80%)	10 (62.50%)	2 (12.50%)	
		≥4 cm	14 (100%)	3 (21.40%)	2 (14.30%)	9 (64.30%)	0 (0.0%)	
Other sites	Presence of metastasis	Positive	35 (100%)	9 (25.70%)	7 (20%)	15 (42.90%)	4 (11.40%)	0.381
		Negative	241 (100%)	39 (16.20%)	36 (14.90%)	131 (54.40%)	35 (14.50%)	
	Tumor size	≤2 cm	14 (100%)	6 (42.90%)	2 (14.20%)	6 (42.90%)	0 (0.0%)	0.103
		2–4 cm	13 (100%)	2 (15.40%)	3 (23.10%)	7 (53.80%)	1 (7.70%)	
		≥4 cm	8 (100%)	1 (12.50%)	2 (25%)	2 (25%)	3 (37.50%)	

*Chi square test (significance level: P<0.05), †Human epidermal growth factor receptor 2

the bone as the most common site of MBC.[18] Although the following order of metastatic sites in various studies was different, in these as well as in the present study, the primary site of metastasis in MBC patients was the bone. It has been reported that patients with bone metastasis have the best prognosis compared to other metastatic sites.[7]

The site and pattern of metastasis are important predictors of patient survival, clinical outcome, and response to treatment.[19] Therefore, it is of great importance to understand factors influencing the site and pattern of metastasis in patients with MBC. It has been suggested that organ-specific metastasis depends on extrinsic factors (e.g., circulation patterns) and

intrinsic factors capable of interacting with the host micro-environment that allow cancer cells to cross physical barriers and survive in distant sites.[20] In this regard, biological subtypes have been suggested as an important factor.

In our study, the most common BC subtypes were luminal B, HER2–enriched, luminal A, and TNBC, respectively. Association between these subtypes and metastatic sites showed that the frequency of receptors at different sites was not the same. We found that luminal A and B had the highest frequency in patients with bone or lung metastasis. The frequency of luminal B compared to other subtypes was significantly higher in patients with bone, brain, or lung metastasis and the difference was statistically significant. We recommend that the status of these receptors is used to monitor and follow-up BC patients. For example, our results showed a higher risk of bone metastasis in women with BC in the luminal B group. Therefore, women with luminal B subtype should be specifically and precisely evaluated in terms of bone metastasis. Our findings were confirmed in a retrospective study of the medical records of 168 patients with recurrent BC.[21] Kim and colleagues showed that bone metastasis was commonly observed in patients with luminal B (63.2%), HER2–enriched (57.9%), and luminal A (42.4%) subtypes. Moreover, most liver metastases occurred in those with luminal B (40.0%) and HER2–enriched (31.6%) subtypes with a statistically significant difference. In line with our results, they also showed that the frequency of receptor expression at different metastatic sites was dissimilar.[21] Pareek and others showed that bone metastasis, with an incident rate of 25.5%, was more prevalent in ER^+ tumors,[22] which is in line with the results of the present study. Jung and colleagues suggested that patients with MBC to the brain had a higher frequency of HER2 conversion (23.8%) and thus suggested the need for a biopsy in cases with resistance to anti-HER-2 treatment.[23] Their findings indicate the significance of evaluating these receptors for the successful treatment of patients with MBC.

In the present study, the frequency of receptors in relation to the site, size, and pattern of metastasis was compared. The results showed a significant difference in the frequency of receptor types in relation to the frequency of the first metastatic site in patients with bone, brain, or lung metastasis. A similar observation was made in terms of metastatic size in which luminal A and B subtypes had a higher rate of bone metastasis (as the first metastatic site) than liver metastasis. These findings are indicative of the usefulness of evaluating receptor positivity in patients with MBC, especially in those with bone, brain, or lung metastasis. A previous study also stated the significance of receptor expression on disease progression, patient survival, and prognosis in relation to metastatic sites.[24] Analysis of 3,726 patients with early-stage of BC showed a higher rate of brain, lung, and distant nodal metastases and a lower rate of bone metastases in patients with TNBC than those with luminal A subtype.[25] Generally, luminal A and B subtypes are suggested to have a better prognosis and response to endocrine treatments because of the positivity of ER and/or PR receptors,[26] while patients with ER^- and PR^- may experience earlier relapse.[27] Nonetheless, it is advantageous to differentiate between luminal A and B subtypes, since luminal B has a poor prognosis than luminal A and additional local and systemic treatments are required in cases with luminal B subtype.[9]

Our results showed a significant difference in the frequency of receptors in relation to metastatic sites. A previous study reported that luminal subtypes are more frequently observed at certain metastatic sites (i.e., the bones) with a better prognosis than HER2–enriched and TNBC subtypes, which have a higher frequency in brain metastasis.[28] TNBC and HER2–enriched subtypes show similar clinical/pathological characteristics and are suggested to have a poor prognosis and shorter OS, partly because of their association with brain metastasis[29] and the role of HER2 expression in mediating pathways related to aggressive tumor behavior and brain metastasis, including matrix metalloproteinase (MMP) and heterodimers heregulin (HRG).[30] It has also been suggested that patients with $HER2^+$ should be screened for brain metastasis in order to improve their survival through the diagnosis of occult brain metastasis[31] and anti-HER2 treatment.[32] This is while TNBC is considered a distinct cancer type and heterogeneous disease,[33] and its treatment remain a clinical challenge due to the lack of a molecular target and the short disease-free duration, despite its chemosensitivity.[34] A previous study reported that angiopoietin–2 increases the permeability of the blood-brain barrier by impairing tight junction protein structures, resulting in the colonization of TNBC cells in the brain.[35] A combination of ixabepilone-capecitabine and platinum with anti-angiogenic drugs is suggested for the treatment of TNBC,[34] although the best treatment approach for each subtype is still under investigation.

One of the limitations of the present study was the use of convenient sampling rather than the randomized sampling method. Besides, the

single-center study design increased the risk of confounding bias on the results. Furthermore, the patients were not followed up after treatment, and we did not evaluate the effect of variables such as metastatic site and biological subtypes on patient survival.

Conclusion

Bone metastasis is found to be the most common metastatic site, and luminal B is the most frequent biological subtype. Biological subtypes show preferential distant metastasis sites in patients with MBC and vary in relation to the size of liver metastasis. For the first time in Iran, all four molecular subtypes were compared in relation to the metastatic site, pattern, and tumor size in women with MBC. Further studies are required to establish the effect of preferential distant metastasis sites of biological subtypes on patient survival and prognosis and its implication for future treatment strategies.

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Conflict of Interest: None declared.

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