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Identification of the Risk Factors of Bone Metastatic among Breast Cancer Women in Al-Bashir Hospital

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Abstract

Background: Bone metastasis with advance cancer stage forms approximately 85% of all cases. Breast cancer patients frequently suffer from bone pain, functional impairment due to bone metastasis which impacts negatively on their quality of life. **Subjects and Methods:** A retrospective study of breast cancer patients who have bone metastasis at diagnosis or developing bone metastasis during 5 years from breast cancer diagnosis (2011-2016) and who received zometa 4 mg monthly in radiotherapy department was included and conducted in 2017. We reviewed 107 female with breast cancer diagnosed by bone scan and/or PET scan as cases of bone metastasis enrolled. Questionnaire was designed to document all variables besides, demographic data which contain (age, histopathology reading invasive ductal carcinoma, invasive lobular carcinoma or others, ER status, PR status, Her2neu status and lymph node status & stage, Onset of metastasis, Menopausal Status & finally No. of metastasis site). **Results:** We noticed that the highest percentage of patients diagnosed as bone metastasis were 45 years and more, and 86% of them were invasive ductal carcinoma; regarding hormonal status we noticed that ER, PR status was positive in 90.7% and 82.2% of cases respectively, Her2neu receptors were amplified in 26.2% of them, positive lymph nodes were seen positive in 80.4% of cases and 31.8% of them were shown (N3) stage; we noticed that the only risk factor of bone metastasis is PR+ significantly associated with lesions multiplicity (0.049). There is no significant association between ER, PR, Her2neu, lymph nodes and menopausal status and onset of bone metastasis, also age, ER, Her2neu, lymph nodes and menopausal status are not associated significantly with No. of metastatic lesions. **Conclusion**: PR+ is significantly associated with lesions multiplicity (0.049), which is considered as a risk factor of bone metastasis in our study.

Keywords

Risk Factors, Bone Lesion, Breast Cancer, Metastatic, Zometa

1. Introduction

Breast cancer is the most common cancer among women. Recently, although breast cancer has excellent prognosis due to advances in management and treatment, a significant number of patients suffer from complication of bone metastasis. It is estimated 70% of women with advanced breast cancer [1].

The most prevalent solid tumors having metastasis to the bone are in breast, prostate and lung. Patients with bone metastasis complain skeletal-related events (SREs) like pain, pathological fracture, spinal cord compression which need emergency treatment and adversely affect their quality of life [2].

Skeleton is the most common metastatic organ for breast cancer, which has better prognosis than visceral metastases. Patients with bone-only metastasis are also in need of effective treatment to prolong survival. Endocrine therapy is the most important treatment for bone metastatic patients. Endocrine therapy is proper for ER-positive patients. The patients with initial osteoblastic metastasis should not be treated with salvage chemotherapy or anti-HER2 treatment, only if osteolytic metastasis or visceral metastasis is observed. Bisphosphonates are just auxiliary drugs in bone metastasis, which should not be abused [3].

Another treatment of bone metastasis from solid tumor is zometa (bisphosphonates); 4 mg is infused around 15 to 30 minutes every 3 to 4 weeks for patients having metastatic bone lesions with creatinine clearance (CrCl) greater than 60 mL/min which is recommended in conjunction with standard cancer therapy [4]. In 2016, the result of a retrospective survey conducted in China for bone metastatic management showed that patients on continuous bisphosphonates treatment more than 6 months were associated significantly with a reduced risk of SREs ($p < 0.05$) [5].

In addition, in another study that discussed bone metastases treatment in 228 Japanese women, zometa 4 mg monthly over a year can significantly reduce the risk of SREs and delay the onset of the first SRE compared to placebo: $p = 0.027$, $p = 0.003$ respectively [6].

In 2015, a meta-analysis presented randomized adjuvant bisphosphonate trials among breast cancer conducted in last 20 years which showed for all patients that, there were significant borderline reductions with the addition of bisphosphonates at 10 years for distant recurrence, bone recurrence, breast cancer mortality and all-cause mortality but specific highly significant reductions in postmenopausal women ($p = 0.002$) [7].

According to the risk factors for bone metastasis among breast cancer patients who were treated with bone-modifying agents (BMAs), the skeletal-related events (SREs) like extraskeletal metastases, elevated serum calcium levels, were

considered as risk factors which need vigorous observation to detect [5].

This study is the first study in oncology radiology department of Al Bashir Hospital that tries to identify the most important factors that may affect the incidence of bone metastasis among Jordanian women suffering from breast cancer. Beside, this study is illustrated as a profile of the breast cancer cases associated with bone metastasis in this department during last 5 years.

The purposes of this study are:

1) To identify the profile of the breast cancer cases associated with bone metastasis in radiation oncology department during last 5 years.

2) To find the most important factors that may affect the incidence of bone metastasis among breast cancer patients.

3) To identify factors which affect the multiplicity of bone lesions in bone metastasis cases.

2. Subjects and Methods

This is a retrospective study conducted in 2017. All adult breast cancer patients with bone metastasis at diagnosis or developing bone metastatic during 5 years from breast cancer diagnosis (2011-2016) and who received zometa 4 mg monthly for bone metastasis in radiotherapy department in Al Bashir hospital were included: bone metastasis diagnosed by bone isotope scan, CT scan, MRI or by PET.

Data was collected from patient‘s files after taking their consent form them, data was collected during 6 months by the author herself. 107 breast cancer patients who diagnosed as bone metastasis by methods mentioned above were enrolled in the study. All independent variables were assessed through reading patient's file. Questionnaire was designed to document all variables besides, demographic data which contains (age, histopathology results, ER, PR and Her2neu status, stage of the tumor by (TNM) staging system, Onset of metastasis, Menopausal Status & finally No. of metastasis site). All questioners were filled without missing data, using SPSS version 16.0 for data analysis. The associations between variables tested by (X2) Chi-square statically; P value less than 0.05 represented a significant difference throughout the data analysis. We used the average to substitute the indeterminate data.

3. Results

107 breast cancer patients who diagnosed by bone scan and/or PET scan as cases of bone metastasis were selected in the study. Patients' age ranged from (26 - 76) years old with mean of (49.9 ± 9.901), patients characteristics in details were appeared in Table 1. In which, the authors noted that the highest percentage of patients who diagnosed as a bone metastasis cases were 45 years and more, 86% of them were invasive ductal carcinoma, regarding hormonal status we noticed that ER, PR status was positive in 90.7% and 82.2% of cases respectively, Her2neu receptors were amplified in 26.2% of them, Luminal A forms the highest molecular

Table 1. General characteristics of breast cancer patients.

Variables	No.	%
Age of patients		
<45 years	35	32.7
≥45	72	67.3
Histopathology		
IDC	92	86.0
ILC	12	11.2
Others	3	2.8
ER status		
Negative	10	9.3
Positive	97	90.7
PR status		
Negative	19	17.8
Positive	88	82.2
Her2neu status		
Non amplified	79	73.8
Amplified	28	26.2
Molecular subtype		
Luminal A	76	71
Luminal B	23	21.5
Her2nue	5	4.7
Basal	3	2.8
Lymph nodes status		
Negative	21	19.6
Positive	86	80.4
LN stage		
N0	21	19.7
N1	32	29.9
N2	20	18.6
N3	34	31.8
Onset of metastasis		
At diagnosis	44	41.1
After treatment	63	58.9
Menopausal status		
Pre-menopause	61	57.0
Post-menopause	46	43.0
No. of metastasis site		
Multiple	71	66.4
Single	36	33.6

subtype in our sample, positive lymph nodes seen positive in 80.4% of cases and 31.8% of them shown (N3) stage, while we can see that 57% of bone metastasis case were in premenopausal period.

Factors affect onset of the metastasis:

In Table 1 we notice that about 59% of breast cancer cases diagnosed as bone metastasis cases after treatment (surgery, chemotherapy and radiotherapy) and 41% of cases diagnosed as bone metastasis at first presentation.

In Figure 1 we find that 69.8% of the metastatic cases suffered from signs of metastasis in 1 - 5 years after diagnosis and in Figure 2 we noticed that 18.2% of them shown signs of bone metastasis in less than one year after diagnosis.

In Table 2 we noticed that, the highest percentage of metastasis appears in age groups (less than 45 and 45 and more) in (After Treatment) category, there is no significant association between age and onset of metastasis.

Also, there is no significant association between ER, PR, Her2neu, luminal subtype, lymph nodes and menopausal status and onset of bone metastasis as shown in Table 2.

The highest percentage of bone lesions that appears in after treatment categories were single lesions (87.8%), the No. of lesions associated significantly with the onset of metastasis appearance ($p = 0.005$). we did not include histopathological subdivision in association with onset of metastasis because we mentioned it in table for description purposes.

Factors affect bone lesions multiplicity:

In Table 2 we noticed that 66.4% of metastasis cases diagnosed primary as a case of bone metastasis with multiple lesions in same bone or multiple bones.

Table 3 showed that Age, ER, Her2neu, luminal subtype, lymph nodes and menopausal status not associated significantly with no. of metastatic lesions. In same table we can noticed that PR status significantly associated with lesions multiplicity (0.049), in which we can notify that the highest percentage of positive PR receptors associated with multiple bone metastasis lesions (70.5%).

4. Discussion

The current study includes breast cancer patients who have bone metastasis and treated by BMAs like zometa and radiation therapy in our department during the time of data collection. In our study, we notice that about 59% of breast cancer cases diagnosed as bone metastasis cases after treatment (surgery, chemotherapy and radiotherapy) and 41% of cases diagnosed as bone metastasis at first presentation.

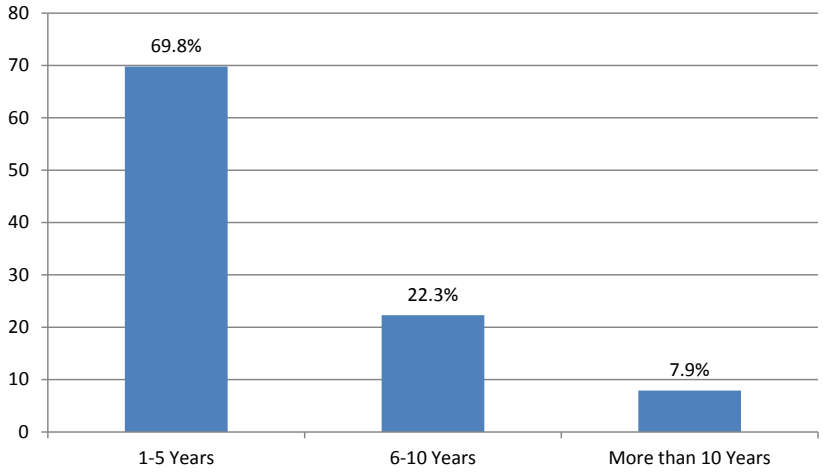

Figure 1. Distribution of cases by time of metastasis occurrence after treatment.

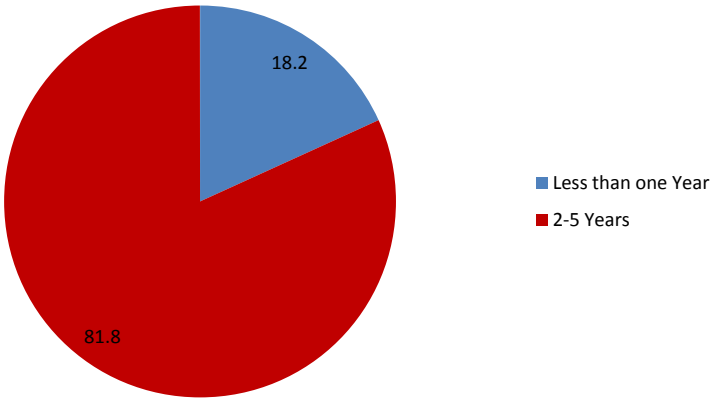

Figure 2. Distribution of cases by onset of metastasis during first 5 years.

Table 2. Variables affect onset of the metastasis.

	Onset of metastasis						
Variable	**At diagnosis**		**After treatment**		**Total**		
	No.	**%**	**No.**	**%**	**No.**	**%**	**P Value**
Age							
Less than 45	11	31.4	24	68.6	35	32.7	
45 and more	33	45.8	39	54.2	72	67.3	0.115
ER							
Positive	41	42.2	56	57.8	97	90.6	
Negative	3	30	7	70	10	9.4	0.453
PR							
Positive	39	44.3	49	55.7	88	82.2	
Negative	5	26.3	14	73.7	19	17.8	0.148
Her2 nue							
Positive	15	53.5	13	46.5	28	26.1	
Negative	29	36.7	50	63.3	79	73.9	0.119
Luminal subtype							
Luminal A	29	61.8	47	38.2	76	76.8	
Luminal B	13	56.5	10	43.5	23	23.2	0.118
Lymph node							
N0	5	23.8	16	76.2	21	19.6	
N+	39	45.3	47	54.7	86	80.4	0.072
Menopausal status							
Pre-menopause	25	41	36	59	61	57	
Post-Menopause	19	41.3	27	58.7	46	43	0.973
No. of lesions							
Single	8	22.2	28	87.8	36	33.6	
Multiple	36	50.7	35	49.3	71	66.4	0.005

Table 3. Factors affect bone lesions multiplicity.

Variable	No. of bone lesions						P Value
	Single lesion		Multiple lesions		Total		
	No.	%	No.	%	No.	%	
Age							
Less than 45	10	28.5	25	71.5	35	32.7	
45 and more	26	36.1	46	63.9	72	67.3	0.439
ER							
Positive	30	30.9	67	69.1	97	90.6	
Negative	6	60	4	40	10	9.4	0.064
PR							
Positive	26	29.5	62	70.5	88	82.2	
Negative	10	52.6	9	47.4	19	17.8	0.049
Her2 nue							
Positive	10	35.7	18	64.3	28	26.1	
Negative	26	32.9	53	76.1	79	73.9	0.787
Luminal subtype							
Luminal A	23	30.3	53	69.7	76	76.9	
Luminal B	8	34.8	15	65,2	23	23.1	0.682
Lymph node							
N0	7	33.3	14	66.7	21	19.6	
N+	29	33.7	57	66.3	86	80.4	0.973
Menopausal status							
Pre-menopause	20	32.7	41	77.3	61	57	
Post-menopause	16	34.7	30	65.3	46	43	0.839

In Ontario, Canada (2016); the probability of bone metastasis was 6.5%, 10.3%, and 11.3% for the first recurrence among 2097 breast cancer women after 5, 10 and 15 years from diagnosis respectively, and 8.4%, 12.5%, and 13.6% for any bone recurrence [8], the results of our study were the inverse of the Canadian, the incidence of bone metastases at 5, 10, and more than 10 years after breast cancer diagnosis decreased with time proceeding after diagnosis and it were 69.8%, 22.3% and 7.9% respectively, the difference in the results may be related to the difference in the sample size or variability of nature of the disease between the countries.

Regarding to ER, PR, Her2neu, lymph nodes and menopausal status, we found that there is no significant association between receptors status and bone metastasis which is not consist with Irawan and his colleagues study in 2016 that shown the ER+ was the determinant that was associated with increasing bone metastasis incidence [9].

The study of Chiu and his colleague's research in 2017, showed that association between ER positive with bone metastasis [10].

Regarding to Multiplicity of bone lesions, the results of our study were compatible with Koizumi and his colleagues who conducted a research about breast cancer patients undergoing treatment developed bone metastasis in 2003, at the Cancer Institute Hospital, in Tokyo, the result showed; the percentage of single metastatic bone lesions was (41%) that was (33.6%) in our study and the percentage of multiple metastatic bone lesions was (59%) that was (66.4%) in our study [11].

According to the factors that may affect bone lesions multiplicity; we noticed that 87.8% the patients in (After Treatment) category of metastasis onset shown single metastatic lesion, while we can see that slightly more than half of patients that diagnosed as bone metastatic case (At diagnosis) shown multiple bone lesions. The No. of metastatic lesions was significantly associated with the onset of metastasis appearance ($p = 0.005$).

In our study, variables like age, ER, Her2neu, lymph nodes and menopausal status not associated significantly with no. of metastatic lesions. But PR status significantly associated with lesions multiplicity ($p = 0.049$), in which we can notify that the highest percentage of positive PR receptors associated with multiple bone metastasis lesions (70.5%).

Regarding to Su Jin Lee and his colleagues study (2011), 122 patients with breast cancer, bone metastasis were most common among patients who have positive hormonal receptors types than in the other subtypes like HER2+ and triple negative, and patients with HR+ have favourable clinical outcome rather than other groups [12].

Regarding to median survival rate in Daniel *et al.* study that include 87 patients, cervical segment of the spine shown the shorter rate while estrogen positive receptors patients shown the highest. Also, the multiplicity of bone metastasis doesn't significantly affect survival comparing to single bone lesion [13].

However, in interpretation of our results, the previous studies providing additional data regarding risk factors of bone metastatic like positive hormonal receptors which is associated with increase the incidence of bone metastatic that are remarkable to predict whose patients are most vulnerable to bone metastasis and identify them to be more cautious when treat them and follow up more carefully to detect bone metastatic in early stage to achieve more benefits from treatment.

The limitation of this study that the small number of patients included make our findings need more advance study that may describe some questionable points in our study. Besides, in spite of the retrospective nature of this study, it provides additional data regarding risk factors of bone metastasis. Thus, additional studies are needed to detect the risk factors of bone metastases among breast cancer.

5. Conclusions

107 breast cancer patients having bone metastasis were included in this study, the highest percentage of patients diagnosed as a bone metastasis cases were 45 years and more, and 86% of them were invasive ductal carcinoma; regarding hormonal status we noticed that ER, PR status was positive in 90.7% and 82.2% of cases respectively, Her2neu receptors were amplified in 26.2% of them, positive lymph nodes were seen positive in 80.4% of cases and 31.8% of them were shown (N3) stage, while we can see that 57% of bone metastasis case were in premenopausal period. About 59% of breast cancer cases were diagnosed as bone metastasis cases after treatment and 41% as bone metastasis at first presentation. 57.2% of the metastatic cases suffered from signs of metastasis in 1 - 5 years after diagnosis and 18.2% of them showed signs of bone metastasis in less than one year after diagnosis.

The highest percentage of bone lesions that appeared after treatment categories was single lesions (87.8%), and the No. of lesions was significantly associated with the onset of metastasis appearance ($p = 0.005$).

In our study we noticed that the only risk factor of bone metastasis is PR+ significantly associated with lesions multiplicity ($p = 0.049$).

So we need more researches with large sample size to generalise these results and to confirm the finding. So when identifying the risk factors of bone metastasis among breast cancer patients, we predict a plan for treatment and do proactive measurement to decrease the complication of it that affects negatively on quality of life.

Conflict of Interest

There is not any conflict of interest like financial interest may benefit, directly or indirectly to publish the research results.

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