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Identification of Breast Cancer Patients at Risk for Bone Metastasis – A Case–Control Study

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Abstract

Introduction: Prognostic factors for metastatic breast carcinoma are a less studied topic than a prognostic factor for primary breast cancer. Bone is the most frequent site for metastasis in breast cancer patients. Bone metastasis decreases the survival and impacts the quality of life(QoL)in breast cancer patients. Therefore, the study to identify prognostic factors of this specific group of patients appears to be worthy of more detailed study. To the best of our knowledge, this is the first study of its kind in the North Indian population.

Materials and Methods: A retrospective case–control study was conducted at a tertiary cancer centerin Northern India between January 2011 and December 2015. All patients' clinical and demographic data were obtained from the medical record of the institute. The incidence and distribution of bone metastases from breast cancer were evaluated, and the correlation between diverse clinical-pathological parameters and bone metastases were analyzed in this study.

Results: A total of 363 patients were recruited, including 94 cases with bone metastases and 269 controls without bone metastases at presentation. Positive axillary lymph node status, higher stage tumors, HER2 neu-negative disease, and histological subtypes of tumor were found significant prognostic factors in univariate analysis associated with higher rates of bone metastasis. Luminal A(estrogen receptor-positive [ER+], progesterone receptor-positive [PR+], HER2–ve, Grade 1,2), and HER 2 enriched (ER –ve, PR–ve, and HER 2+) molecular subtypes are associated with increased risk of bone metastasis. None of the risk factors studied were significantly associated with bonemetastasis in binary logistic regression analysis.

Conclusion: Identification of breast cancer patients at risk for bone metastasis may aid in the prevention, prediction, detection, and early treatment of these lesions, thus providing improved survival and better QoL.

Keywords: Bone metastasis, risk factors, breast cancer.

Introduction

Bone metastasis is the most common site of spread in patients of breast cancer. In fact, up to 13.6% of breast cancer patients at 15 years of follow-up, in Stage I-III will develop bone metastasis[1].

Although not curable, bone as single metastatic site has a better prognosis than those with visceral or both bone and visceral metastasis. However, in breast cancer patients, the rate of 5-year survival is significantly decreased, and severe complications occur following bone metastasis[2].Skeletal metastasis is associated with notable impact on mobility, quality of life(QoL) due to metastatic bone pain[3, 4]. The overallmedian survival of boneonly metastatic breast cancer patient ranges from 40 to 65 months[5, 6].

Many factors seem to affect the metastatic pattern, which includes demographic, clinical, pathological, and genetics. Study of these factors associated with the development of bone metastasis will be of great importance. It will help in risk profiling and thus, early detection of bone metastasis in patients leading to survival benefit and better QoL.

Given the lack of Indian studies and none in our region in this field, we planned this study to identify risk factors for predicting bone metastasis in breast cancer patients in a group of North Indian population.

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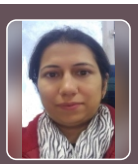
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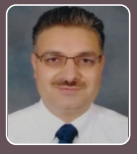
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Table 1: Basic clinical characteristics of the study population

Characteristics	Total number of patients (%)	Bone metastases group (n = 94)	No bone metastases group (n = 269)	*P** value (*P* - value)
Median age (years) 50				
Range (years) 30–80				
Mean±SD (years)	52.4±12.6	52.0±12.4	53.5±13.3	0.3*
Menopausal status				
Premenopausal	134 (36.9)	36 (9.9)	98 (27)	0.8#
Postmenopausal	229 (63.1)	58 (16)	171 (47.1)	
Family history				
Yes	03 (0.8)	0 (0)	3 (0.8)	0.5#
No	360 (99.2)	94 (25.9)	266 (73.3)	

*Student's*t* -test, #Chi-square test

Materials and Methods

A retrospective case–control study was conducted at a tertiary cancer center in Northern India, which provides comprehensive treatment and care to cancer patients. The study sample included database of patients who were diagnosed as breast cancer at the Department of Radiotherapy and Oncology between January 2011 and December 2015. Informed consent was taken from all the participants. The diagnosis was made based on the histopathological analysis of specimens harvested by biopsy or surgical resection. Bone metastasis was identified by bone scan. If necessary, local computed tomography and magnetic resonance imaging were performed to confirm the diagnosis. Patients with bone metabolic diseases, renal failure, and a second primary malignancy were excluded from this study.

All patients' clinical and demographic data were obtained from the medical record of the institute. The incidence and distribution of bone metastases from breast cancer were evaluated, and the correlation between diverse clinical-pathological parameters and bone metastases were analyzed in the study. A total of 363 patients were recruited in this study, including 94 cases with bone metastases and 269 controls without bone metastases at presentation. However, patients of breast cancer with metastasis to sites other than bone were also included in the control group.

Statistical analysis

All the statistical analysis was performed by open Epi-info version 7.2.2.6. Continuous data were demonstrated as means±standard deviation. First, the Chi-square test and student t-test were used to detect the differences between patients with and without bone metastases. Results which were found to be significant in Chi-square for more than two categories were further analyzed using posthoc test to identify the actual category with significant difference. Binary logistic regression model was then established to identify the independent risk factors for bone metastases in breast cancer. P < 0.05 was considered to be statistically significant.

Results

Patient's clinical characteristics

A total of 363 patients were recruited in this study, including 94 with bone metastases (15.33%) and 269 without bone metastases (84.67%). Patients' clinical characteristics are illustrated in Table1. The median age of the study population is 50 years (range 30–80 years).The mean age of patients with and without bone metastases was 52.0 ± 12.4 and 53.5 ± 13.3 years (P = 0.3), respectively. At the time of diagnosis, 63.1% of the patients were postmenopausal. Three patients had positive family history in no bone metastasis group and none in the bone metastasis group.

Distribution of bone metastases in patients with breast cancer

The most frequent site of bone metastases in our study population was spine involved in 47.8% patients commonly involving dorsolumbar vertebrae. The second common metastatic site was ribs in 27.6%, followed by pelvis in 24.4% with the involvement of acetabulum, iliac bone, and ischium. About36% patients had metastasis at multiple bony sites. Rarely involved sites were sternum in fifteen, skull in two, and scapula in one patient. About61% of our patients had bone only metastasis and the rest were associated with other visceral metastatic sites such as liver in 20%, lung in 12%, and brain in 5%.

Risk factors for bone metastases in breast cancer

To identify the potential risk factors for bone metastases, Chi-square test for dichotomous data and student t-test for continuous data were used for the analysis. Patients were categorized into the following breast cancer molecular subtypes: Luminal A(estrogen receptor-positive [ER+], progesterone receptor-positive [PR+], HER2–ve [HER2 neu-negative], and Grade 1,2), luminal B(ER+, PR+, HER 2–ve, and Grade 3), luminal HER2(ER +, PR+, and HER2+), HER2 +(ER –ve, PR –ve, and HER2+), and Basal Type (ER –ve, PR –ve, and HER2 –ve).

The results showed that significant difference was found inaxillary lymph node metastases, TNM stage grouping, HER 2 neu status and molecular subtypes between patients with and without bone metastases (P < 0.05) (Table 2).

Posthoc test was applied to find the difference between bone and non-bone metastasis among the different TNM stage grouping. There was significant difference between Stage II, III, and IV. After applying binary logistic regression in TNM stage grouping, it was observed that as the TNM stage increases, the risk of bone metastasis increases except for Stage I.

Thereafter, all the risk factors which were found significant on univariate analysis, i.e., axillary lymph node metastases, TNM stage grouping, HER 2 neu status, and molecular subtypes were analyzed using binary logistic regression model. None of the above risk factors were independent predictors for bone metastases in patients with breast cancer (Table 3).

Discussion

Breast cancer is a prime cause of cancer-related death in fairer sex worldwide. About 14% of the total cancer deaths in 2008 are attributed to breast cancer. About 50% of breast cancer cases and more than half (60%) of the deaths are estimated to occur in economically developing countries[7]. In many African and Asian countries, including India, incidence, and mortality rates have been rising [8]. Rising incidence in these populations may partially be attributed to increasing awareness and screening activity. Mammography may detect the disease at an early stage when effective treatment options

are available. However, as this approach is cost prohibitive, availability always remains an issue in most economically developing countries.

Bone metastasis from breast cancer is a widely studied subject, yet with no conclusive evidence pointing out the risk factors. One such ongoing prospective study aims to address the key issues including the association between lifestyle factors, genetic factors, the potential of metabolomic profiles for risk assessment and early detection and the signaling pathways affecting the metastatic tumormicroenvironment[9].

Bone only metastasis in breast cancer patients offers a better prognosis than patients with visceral disease. Cancer-induced bone disease carries an important risk of developing skeletal-related events that impact QoL[10]. Therefore, it becomes particularly important to distinguish patients according to their risk of developing bone metastasis.

The incidence of bone metastases from breast cancer at the primary diagnosis in our study was 56%, which was considerably higher than that reported from other countries[1,11].The distribution of bone metastatic sites in our study population is similar to the findings of Chen et al. in Chinese population. Chen et al. studied the clinical characteristics and risk factors for developing bone metastases in 327 patients with breast cancer. The spine was found to be the most common site for bone metastases, followed by ribs (57.5%), pelvis (54.1%), and sternum (44.3%).[11]. Their results indicate that axillary lymph node metastases and the concentrations of CA125, CA153, ALP, and hemoglobin were the independent risk factors for bone metastases in patients with breast cancer.

The mean age of the bone metastasis group was slightly lower than the non-bone metastasis group in our population, though not statistically significant. This may suggest that younger women may be at higher risk of developing bone disease. A similar trend was observed in a group of Chinese patients, but the mean age in their study population was 47.29 ± 10.59 which was lower than our population (52.0 ± 12.4)[11].

In the present study, involvement of axillary lymph nodes appears to be an important predictor of bone metastasis. Our results compare well with other studies that report similar observations[11,12,13]. In a study by Colleoni et al., 49.4% females had one to three and 31.9% had four or more positive axillary lymph nodes[12].Purushothamet al. in a study on 3553 patients of invasive breast cancer observed that large primary invasive tumor size, higher tumor grade, and positive axillary lymph nodes were important predictors of metastasis to all sites[14].

James et al. [13] presented data of 492 patients of metastatic breast cancer. Factors which were more likely associated with bone metastases were lower-grade primary tumor, ER-positive tumors, and lymph node-positive disease. Patient's age or the size of the primary tumor was not related to upfront presentation with bone metastases. In our study, grade was not found as a significant factor associated with bone metastasis. Four or more positive axillary lymph nodes at presentation and HER2 neu-negative disease were important predictors of bone metastasis.

Tumor subtype may be an important predictive factor for bone metastasis in breast cancer patients. Molecular subtype also came out to be a significant predictor of bone metastasis in breast cancer patients in our study population with luminal A and HER2 enriched tumors showing the greatest association with bone metastasis as compared to the other breast cancer subtypes. There is growing evidence suggesting that patterns of metastasis differ from breast cancer subtypes. Distant metastasis-free survival and pattern of distant metastases are influenced by tumor subtypes. Xiao et al. evaluated the relationship between molecular subtypes and distant metastatic sites and their prognostic significance. Hormonal receptor-positive (HR+)/HER2+ subtype significantly correlated with elevated bone metastasis risk, whereas HR−/HER2+ did not. Both HER2+ subtypes (HR+/HER2+ and HR−/HER2+) were significantly associated with higher rates of liver, brain, and lung metastases. Triple-negative tumors had a higher rate of brain, liver, and lung metastases, but a significantly lower rate of bone metastases than HR+/HER2− tumors[15].

In an attempt to find out the predictive factors for bone only metastasis in breast cancer patients, retrospective German multicenter study was done in 226 patients with boneonly metastases[16]. They concluded that breast cancer subtypes have the strongest influence on the development of osseous metastases. There was a highly significant difference between patients with triple-negative breast cancer or HER2 neu over expressing BC (11.4% boneonly metastases) and patients with luminal A or luminal B breast cancer (29.9% boneonly metastases). However,

Table 2: Clinical parameters of patients with or without metastasis (univariate analysis)

Characteristics	Total number of patients (%)	Bone metastasis group (n = 94)	Non bone metastasis group (n = 269)	Odd's Ratio (95%CI)	P-value[#]
Axillary lymph node metastases					
N0	123 (33.9)	20 (5.5)	103 (28.4)	0.44 (0.75–0.25)	0.001
N1-3	136 (37.5)	32 (8.8)	104 (28.7)	0.82 (1.4–0.48)	0.25
N4 and more	104(28.6)	42(11.6)	62(17.1)	2.7 (4.42–1.63)	<0.0001
TNM stage					
Stage 1	14 (3.9)	0 (0)	14 (3.9)		
Stage 2	148 (40.8)	20 (5.6)	128 (35.3)	0.3 (0.5–0.17	<0.0001
Stage 3	136 (37.5)	23 (6.3)	113 (31.1)	0.5 (0.8–0.3)	0.001
Stage 4	65 (17.9)	51 (14.1)	14 (3.9)	21.3 (43.1–11.04)	<0.0001
Nottingham grading					
Grade 1	87 (24)	22 (6.1)	65 (17.9)	1.0 (1.7–0.5)	0.9
Grade 2	189 (52)	48 (13.2)	141 (38.8)	1.0 (1.5–0.6)	0.8
Grade 3	87 (24)	24 (6.6)	63 (17.4)	1.1 (1.9–0.64)	0.7
ER					
Yes	198 (54.5)	45 (12.4)	153 (42.1)	0.7 (1.1–0.4)	
No	165 (45.5)	49 (13.5)	116 (32)		0.15
PR					
Yes	200 (55.1)	54 (14.9)	146 (40.2)	1.1 (1.8–0.7)	
No	163 (44.9)	40 (11)	123 (33.9)		0.63
HER2					
Yes	106 (29.2)	42 (11.6)	64 (17.6)		
No	257 (70.9)	52 (14.3)	205 (56.5)	2.6 (4.2–1.6)	<0.0001
Molecular subtype					
Luminal A	118 (32.5)	23 (6.3)	95 (26.2)	0.6 (1.0–0.3)	0.03
Luminal B	23 (6.3)	4 (1.1)	19 (5.2)	0.6 (1.7–0.2)	0.3
Luminal HER 2	55 (15.2)	18 (5)	37 (10.2)	1.5 (2.7–0.8)	0.21
HER 2 +	53 (14.6)	25 (6.9)	28 (7.7)	3.1 (5.7–1.7)	0.001
Basal type	113 (31.1)	24 (6.6)	89 (24.5)	0.7 (1.2–0.4)	0.21

[#]Chi-square test

Table 3: The risk factors for predicting bone metastases in patients with breast cancer (binary logistic regression)

	B	OR	Sig.	CI
Stage of breast cancer	0.6	0.1	0.9	0.00–0.00
Nodal status	1.2	0.2	0.4	0.54–2.47
HER2 neu status	0.8	0.4	0.06	0.37–2.54
Molecular subtype	0.8	0.4	0.05	0.44–1.02

B: Coefficient of regression, OR: Odds ratio

there was no significant difference between the subgroups luminal A, andluminal B/HER2+ or luminal B/HER2. The primary tumor stage, tumor histology, size, nodal staging, and grade of tumor did not seem to have a major influence on the development of bone only metastases in their study.

The correlation of receptor status was studied in Indonesian population by Irawan et al. and they did not find a significant relationship between ER/PR and HER2neu receptor status and bone metastasis[17]. However, the patient number was small to conclusively comment on the results.

ER/PR receptor status was not found to be a significant prognostic factor for bone metastasis in our study. Receptor status may be a predictor of survival more than determining the site of metastasis. In a study by Coleman and Rubens, there was no difference in estrogen or progesterone receptor status between bone only and bone and other metastatic site patients. However, ER-positive patients survived longer than those who were ER-negative[18]. Positive steroid receptor status was significantly associated with bone metastasis in breast cancer patients in another small study population[19].

Although univariate analysis points out few factors associated with risk of bone metastasis, none of the risk factors studied in our population were significantly associated with bone metastasis on binary logistic regression analysis. Increasing the sample size might ascertain more risk factors. As well as, in addition, other risk factors should have been studied such as alkaline phosphatase, CA125,CA153, and hemoglobin levels which have been identified important prognostic factors in other studies[11,20].The disease in older patients is known to behave differently than the younger age groups. However, in this study, the disease characteristics of all age groups are evaluated without any differentiation with regard to age.

Conclusions

In our study population, positive axillary lymph node status, higher stage tumors, HER2 neu-positive disease, and histological subtypes of tumor were found significant prognostic factors on univariate analysis associated with increased risk of bone metastasis. These findings can help to personalize and individualize adjuvant therapy, tumorfollow-up examinations and early identification of those at risk for bone metastasis. More such studies on this subject may help us improve our understanding of key aspects of bone metastases from breast cancer and thus, aid in the prevention, prediction, detection, and treatment of these lesions.

Clinical Message

Study of prognostic factors for bone metastasis may aid in identification of cancer breast patients who are at risk of developing bone metastasis. Positive axillary lymph nodes, advanced stage tumors, HER2 neu-positive disease, and luminal A subtypes of tumors may have an increased risk of bone metastasis.

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