

Factors Associated with Bone Metastasis in Breast Cancer: A Preliminary Study in an Indonesian Population

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ABSTRACT

Aim: to know the characteristics of breast cancer patients with bone metastasis and its risk factors.

Methods: this was a cross-sectional study on breast cancer patients in Dharmais Cancer Hospital between 1998 and 2002. Data were retrieved from medical records and consisted of age, history of hormonal contraceptive use, histopathological type, estrogen receptor (ER) and progesteron receptor (PR) expression, c-erbB-2 and cathepsin D expressions.

Results: a total of 197 cases were recruited between the study period. Almost all patients were women with a mean age of 47 years old. The majority of patients were between 36 and 55 years old (69.1%) with a peak between 46 and 50 years. About 70% of the patients had already had advanced diseases (III and IV). Invasive ductal carcinoma was the commonest histopathological type (80%). The expression of ER, PR, c-erbB-2, and cathepsin D were evaluated in 55 patients. Metastases were found to occur in bone (24.4%), lungs (20.8%), and liver (10.7%). Among patients with bone metastasis, 36 patients (75%) were more than 40 years old and 32 (66.7%) had invasive ductal carcinomas. There was a significant correlation ($p=0.011$) between bone metastasis and histopathological type. No significant correlation was found between the use of hormonal contraceptives, ER/PR expression, c-erbB-2 and cathepsin D and bone metastasis.

Conclusion: most breast cancer patients came in an already advanced stage, either locally or distant metastasis. The most common site of metastasis was the bone, followed by lungs and liver. Histopathological type of invasive ductal carcinoma was associated to the higher incidence of bone metastasis. Further studies are needed to identify patients with high risk of bone metastasis. There is also a need to evaluate predictive factors for the occurrence of bone metastasis at earlier stage.

Key words: breast cancer, bone metastasis, risk factors, invasive ductal carcinoma.

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INTRODUCTION

Breast cancer is a disease with a high tendency of hematogenous spread. Many breast cancer patients who do not show distant metastasis after locoregional therapies eventually died because of disease recurrence or distant metastasis. Locoregional recurrence may occur in one-third of patients who have received primary therapy. The cumulative incidence of bone metastasis in patients with positive nodes was reported to be as high as 14.9% after 2 years and 40.8% after 10 years of treatment.¹ Nearly 70% of advanced breast cancers occurs with bone metastasis.²

Although bone metastasis cannot be cured, the median survival of the patients could be expected between 2 to 3 years and 40% of the patients could survive for 5 years with serious morbidity consequences such as fracture, bone marrow compression, severe pain and hypercalcemia.³

The reported incidence of bone metastasis was only 8% in cases with negative nodes and increased to 18-27% in patients with 1 to 3 or ≤ 4 positive lymph nodes. Histopathological type and grade are known as important prognostic factors. Grade 1 and 2 ductal or lobular carcinomas have better prognosis than grade 3 tumors.⁴ Several clinicopathologic studies have shown that estrogen receptor contents, low histopathology grade and the expression of parathyroid hormone-related peptide are risk factors for bone metastasis.

In Indonesia, data on the characteristics of breast cancer patients and risk factors for developing bone metastasis are limited. This study was aimed to know the characteristics of breast cancer patients with bone metastasis and its risk factors.

METHODS

Patients Recruitment

This was a cross-sectional study on breast cancer patients in Dharmais Cancer Hospital between 1998 and 2002. Patients basic data were obtained from the

medical record which consisted of age, gender, the use of hormonal contraceptive by female patients, menopausal status, family history of cancer, course of the disease and previous treatment, clinicopathologic staging, histopathological type and grade. The expression of estrogen receptor (ER), progesterone receptor (PR), c-erbB-2, and cathepsin D were also evaluated but was not routinely done at that time.

Statistical Analysis

Descriptive analysis was done to examine the profile and characteristics of patients on admission and at the follow-up. Correlation between bone metastasis and several risk factors (age, contraceptive methods, histopathological type, ER/PR, c-erbB-2 and cathepsin D) were tested with the Chi-square test. A p value below 0.05 was considered significant.

RESULTS

A total of 197 patients' data between 1998 and 2002 were collected. Almost all patients were women with a mean age of 47 years. Most patients (69.1%) were between 36-55 years old with a peak between 46-50 years old (Figure 1). Patients usually came in advanced stages (III and IV). Histopathological type was predominated by invasive ductal carcinoma. Most metastases occurred in the bone, followed by the lungs and liver (Table 1). Immunohistochemistry staining for ER, PR, c-erbB-2, and cathepsin D were done in 55 specimens. The results are shown in Table 1.

Among 48 patients who suffered from bone metastasis, 36 patients (75%) were more than 40 years old and 32 (66.7%) had invasive ductal carcinoma histopathology (Table 2). Among all factors, only histopathological type which showed significant correlation with the occurrence of bone metastasis (Table 3).

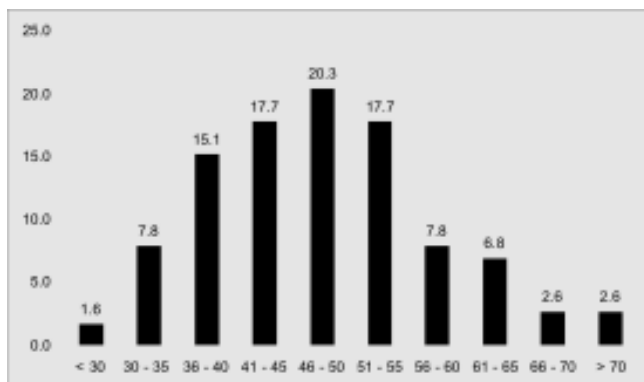


Figure 1. Patients' distribution based on age group

Table 1. Characteristics of the patients

Variables	
Age	Mean 47.8 ± 9.0 years Median 47 years Minimum: 28 years Maximum: 77 years Skewness: 0,462
Sex	Female: 196 (99,5%) Male: 1 (0.5%)
Clinical Stage	0 (in situ carcinoma): 1 (0.5%) I: 7 (3.6%) II: 49 (24.9%) III: 69 (35.0%) IV: 70 (35.5%) No data: 1 (0.5%)
Histopathological type	Invasive ductal carcinoma: 157 (79.7%) Lobular carcinoma: 11 (5.6%) Adenocarcinoma: 12 (6.1%) Mucinous adenocarcinoma: 4 (2.0%) Others: 13 (6.6%)
Lung metastasis	Negative: 156 (79.2%) Positive: 41 (20.8%)
Liver metastasis	Negative: 176 (89.3%) Positive: 21 (10.7%)
Bone metastasis	Negative: 149 (75.6%) Positive: 48 (24.4%)
Estrogen Receptor (ER)	Negative: 28 (50.9%) Positive - weak: 11 (20.0%) Positive - moderate: 8 (14.5%) Positive - strong: 8 (14.5%)
Progesteron receptor (PR)	Negative: 38 (69.1%) Positive - weak: 6 (10.9%) Positive - moderate: 8 (14.5%) Positive - strong: 3 (5.5%)
c-erbB-2	Negative: 19 (34.5%) Positive: 36 (65.5%)
Cathepsin D	Negative: 27 (49.1%) Positive: 28 (50.9%)

DISCUSSION

Prognostic factors have been widely used in the management of breast cancer which consists of tumor size, nodal status, steroid hormone receptor status and tumor grading.⁵ Preliminary studies showed that the incidence of metastasis from breast cancer was associated with the ER/PR expression and tumor stage.^{2,6} Axillary nodal involvement is the best prognostic indicator and is believed to be the sign of the early systemic spread.⁷

However, it should be noted that most cases in international studies were performed on early stage breast cancer patients. The study from The International Breast Cancer Study Group (IBCSG), for instance, was done in 6792 female patients with operable breast cancer; 89.4% of them underwent total mastectomy and axillary

Table 2. Characteristics of patients with bone metastasis

Variables		n	%
Age	≤ 40 years	10	20,8%
	> 40 years	36	75%
	No data	2	4,2%
Contraceptives	Hormonal	6	12,5%
	Non-hormonal	6	12,5%
	No data	36	75%
Histopathology	Invasive	32	66,7%
	Non-invasive	16	33,3%
ER expression	Positive	7	14,6%
	Negative	5	10,4%
	No data	36	75%
PR expression	Positive	2	4,2%
	Negative	10	20,8%
	No data	36	75%
c-erb-B2 expression	Positive	8	8,3%
	Negative	4	16,7%
	No data	36	75%
Cathepsin D expression	Positive	6	12,5%
	Negative	6	12,5%
	No data	36	75%

Table 3. Correlation between bone metastasis and risk factors

Variables		Bone metastasis (n)		p value
		(+)	(-)	
Age	≤ 40 years	10	35	0.463
	> 40 years	36	111	
Contraceptives	Hormonal	6	27	0,297
	Non-hormonal	6	16	
Histopathology	Invasive	32	125	0.011*
	Non-invasive	16	24	
ER expression	Positive	7	20	0.346
	Negative	5	23	
PR expression	Positive	2	15	0.199
	Negative	10	28	
c-erb-B2 expression	Positive	8	28	0.603
	Negative	4	15	
Cathepsin D expression	Positive	6	22	0.600
	Negative	6	21	

nodes dissection, whereas the other 10.6% underwent lumpectomy.¹ In contrast with many studies, our study showed that about 70% of patients came in an already advanced stages (III-IV) and 35% of them were metastasized. With this high proportion of advanced stage cases, the nodal involvement was not relevant to be used as a prognostic indicator. The expression of ER, PR, c-erbB-2, and cathepsin D showed no correlation with metastasis occurrence. This could be due to the limited number of cases which underwent immunohistochemical evaluation.

Other factors which have frequently been associated with bone metastasis is histopathological type. A study in Japan showed that the growth pattern and the presence of fibrotic focus in invasive ductal carcinoma were significantly correlated with early occurrence of bone metastasis. The presence of fibrotic focus is also associated with osteolytic bone metastasis.⁸

Compared to the IBCSG study, the population of this current study tended to be younger. The IBCSG study showed that 4.6% of patients were less than 35 years old, 39% were between 35-49 years, 30% were between 50-59 years, and 25.6% were more than 60 years old. Our study showed that 9.4% of patients aged less than 35 years, 53.1% of patients aged 35-60 years, 25.5% aged 51-59 years and 12% were more than 60 years old.

CONCLUSION

Our preliminary study has shown that most breast cancer patients in Dharmas Cancer Hospital came in already advanced stage and 24.4% of them suffer from bone metastasis. Analysis of common risk factors did not show a significant correlation with the occurrence of bone metastasis, except histopathological type. Further studies are needed to identify patients with high risk of bone metastasis. There is also a need to find predictive factors for the occurrence of bone metastasis at an earlier stage of disease.

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