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.

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. Nearly 70% of advanced breast cancers occurs with bone metastasis.

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.

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. 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 or 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).

### Table 1. Characteristics of the patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical Stage</th>
<th>Histopathological type</th>
<th>Lung metastasis</th>
<th>Liver metastasis</th>
<th>Bone metastasis</th>
<th>Estrogen Receptor (ER)</th>
<th>Progesterone receptor (PR)</th>
<th>c-erbB-2</th>
<th>Cathepsin D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean ± SD</td>
<td>47.8 ± 9.0y</td>
<td>Female: 196 (99.5%)</td>
<td>Male: 1 (0.5%)</td>
<td>0 (in situ carcinoma): 1 (0.5%)</td>
<td>157 (79.7%)</td>
<td>176 (89.3%)</td>
<td>149 (75.6%)</td>
<td>28 (50.9%)</td>
<td>38 (69.1%)</td>
<td>19 (34.5%)</td>
<td>27 (49.1%)</td>
</tr>
<tr>
<td>Median</td>
<td>47 years</td>
<td>196 (99.5%)</td>
<td>1 (0.5%)</td>
<td>1 (in situ carcinoma)</td>
<td>50 (26.7%)</td>
<td>53 (27.8%)</td>
<td>53 (27.8%)</td>
<td>11 (22.9%)</td>
<td>7 (11.8%)</td>
<td>9 (17.3%)</td>
<td>13 (23.6%)</td>
</tr>
<tr>
<td>Minimum</td>
<td>28 years</td>
<td>196 (99.5%)</td>
<td>1 (0.5%)</td>
<td>0 (in situ carcinoma)</td>
<td>17 (9.2%)</td>
<td>17 (9.2%)</td>
<td>17 (9.2%)</td>
<td>7 (14.3%)</td>
<td>6 (10.3%)</td>
<td>6 (11.5%)</td>
<td>7 (13.0%)</td>
</tr>
<tr>
<td>Maximum</td>
<td>77 years</td>
<td>196 (99.5%)</td>
<td>1 (0.5%)</td>
<td>1 (in situ carcinoma)</td>
<td>50 (26.7%)</td>
<td>53 (27.8%)</td>
<td>53 (27.8%)</td>
<td>11 (22.9%)</td>
<td>7 (11.8%)</td>
<td>9 (17.3%)</td>
<td>13 (23.6%)</td>
</tr>
<tr>
<td>Skewness</td>
<td>0.462</td>
<td>196 (99.5%)</td>
<td>1 (0.5%)</td>
<td>0 (in situ carcinoma)</td>
<td>50 (26.7%)</td>
<td>53 (27.8%)</td>
<td>53 (27.8%)</td>
<td>11 (22.9%)</td>
<td>7 (11.8%)</td>
<td>9 (17.3%)</td>
<td>13 (23.6%)</td>
</tr>
<tr>
<td>Histopathological type</td>
<td>Invasive ductal carcinoma</td>
<td>196 (99.5%)</td>
<td>1 (0.5%)</td>
<td>0 (in situ carcinoma)</td>
<td>50 (26.7%)</td>
<td>53 (27.8%)</td>
<td>53 (27.8%)</td>
<td>11 (22.9%)</td>
<td>7 (11.8%)</td>
<td>9 (17.3%)</td>
<td>13 (23.6%)</td>
</tr>
<tr>
<td>Lobular carcinoma</td>
<td>11 (5.6%)</td>
<td>196 (99.5%)</td>
<td>1 (0.5%)</td>
<td>0 (in situ carcinoma)</td>
<td>50 (26.7%)</td>
<td>53 (27.8%)</td>
<td>53 (27.8%)</td>
<td>11 (22.9%)</td>
<td>7 (11.8%)</td>
<td>9 (17.3%)</td>
<td>13 (23.6%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>12 (6.1%)</td>
<td>196 (99.5%)</td>
<td>1 (0.5%)</td>
<td>0 (in situ carcinoma)</td>
<td>50 (26.7%)</td>
<td>53 (27.8%)</td>
<td>53 (27.8%)</td>
<td>11 (22.9%)</td>
<td>7 (11.8%)</td>
<td>9 (17.3%)</td>
<td>13 (23.6%)</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>4 (2.0%)</td>
<td>196 (99.5%)</td>
<td>1 (0.5%)</td>
<td>0 (in situ carcinoma)</td>
<td>50 (26.7%)</td>
<td>53 (27.8%)</td>
<td>53 (27.8%)</td>
<td>11 (22.9%)</td>
<td>7 (11.8%)</td>
<td>9 (17.3%)</td>
<td>13 (23.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (6.6%)</td>
<td>196 (99.5%)</td>
<td>1 (0.5%)</td>
<td>0 (in situ carcinoma)</td>
<td>50 (26.7%)</td>
<td>53 (27.8%)</td>
<td>53 (27.8%)</td>
<td>11 (22.9%)</td>
<td>7 (11.8%)</td>
<td>9 (17.3%)</td>
<td>13 (23.6%)</td>
</tr>
</tbody>
</table>

**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. Preliminary studies showed that the incidence of metastasis from breast cancer was associated with the ER/PR expression and tumor stage. Axillary nodal involvement is the best prognostic indicator and is believed to be the sign of the early systemic spread.

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...
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 Dharmais 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.

**REFERENCES**