

RESEARCH COMMUNICATION

Patterns of Metastasis and Survival in Breast Cancer Patients: A Preliminary Study in an Iranian Population

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Abstract

Due to lack of sufficient data on characteristics of breast cancer patients and risk factors for developing metastasis in Iran this study was designed to understand clinical aspects impacting on survival. A cross-sectional study on breast cancer patients was conducted in an oncology clinic of the university hospital between 1995 and 2010. Data were retrieved from medical records and included age, menopausal status, tumor diameter, number of involved nodes, histopathological type, estrogen and progesterone receptor expression, c-erbB-2, primary and secondary metastasis sites, overall survival, disease free interval and type of chemotherapy protocol. The results were analyzed with SPSS 13 software. The mean age of the patients was 49.2 (27-89) years. The primary tumors were mainly ER positive (48%) and PR negative (49.3%). The status of lymph nodes dissected and examined in these patients was unknown in 19 patients (25.3%) while 18 patients (24%) had positive lymph nodes with no report on the number of involved nodes. All of the patients had received antracyclin based chemotherapy in an adjuvant or metastatic setting. Adjuvant hormonal therapy was administered to receptor positive patients. In average, overall survival after recurrence was 30 months (95% CI 24.605-35.325) for non-skeletal versus 42 months (95% CI 31.211-52.789) for skeletal metastasis (P= 0.002). The median survival was also greater for receptor positive patients; 39 months (95% CI 33.716-44.284) for PR+ versus 26 months (95% CI 19.210-32.790) for PR- (P=0.047) and 38 months (95% CI 32.908-43.092) for ER+ versus 27 months (95% CI 18.780-35.220) for ER- patients (P=0.016). No relation was found between site of first metastasis and hormone receptor, age, tumor diameter, DFI and menopausal status. Sites of metastasis were independent of age, size of the tumor, menopausal and hormone receptor status in this study. Overall survival provided significant relations with respect to receptor status and bone metastasis.

Keywords: Breast cancer - bone metastasis - survival - receptor status - Iran

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Introduction

Breast cancer is a disease with a higher incidence in hematogenous spread. Nearly 70% of advanced breast cancers lead to bone metastasis (Irawan C, et al. 2003). Patients suffering metastatic breast carcinoma express a highly variable clinical course and outcome. Intrinsic genetic heterogeneity of the primary breast tumor may have a role in this variability and could explain it in part (Chang et al., 2003).

The survival of patients with metastases is variable ranging from few months to many years. The ability to predict prognosis and response to treatment has significant impact on patient management. It is well established that estrogen receptor (ER) status and site of presentation of metastatic disease have the greatest impact on patient survival along with additional contributions made by patient age, disease-free interval and histological grade. Bone is the most common site of metastases in patients with breast carcinoma, so patients with bone metastases

make up the largest single group of patients presenting metastatic disease (James et al., 2003).

In this study, traditional factors such as ER and PR status, lymph node status, clinical stage and size of the primary tumor, patient age, overall survival and disease free interval and the presence of metastases at sites other than bone have been assessed.

Materials and Methods

A cross-sectional study on breast cancer patients was conducted in an oncology clinic of university Hospital between 1995 and 2010. Data were retrieved from medical records and consisted of age, menopausal status, tumor diameter, number of involved nodes, histopathological type, estrogen receptor (ER) and progesterone receptor (PR) expression, c-erbB-2, primary and secondary metastasis sites, overall survival, disease free interval and type of chemotherapy protocol.

Patients suffering from metastatic disease following

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a previous diagnosis of breast carcinoma and patients with metastatic disease at the time of initial diagnosis of breast cancer were enrolled. All patients were investigated for metastatic disease due to a clinical symptom or sign and assessed in the bones, chest and liver. In the first instance, plain radiographs were used to assess the chest and bones. Bone scan and computed tomography (CT) were used when the diagnosis was uncertain or equivocal. The presence of liver metastases was determined using ultrasound or less frequently CT. Sites of metastatic disease at first presentation were recorded.

Tumor markers were recorded at the time of first presentation. The markers routinely measured at our clinic are carcinoembryonic antigen (CEA) and cancer antigen 15.3 (CA15.3). CEA was said to be elevated above a value of 10 ng/ml and CA15.3 was elevated above a level of 25 U/ml.

Pathological data were obtained from the patients' previous mastectomy or wide local excision specimens. Histological grade, lymph node status, tumor size, ER status and tumor type were recorded for each patient where possible. Unfortunately lymph node involvement was determined correctly only in a few patients through pathological reports. ER and PR status was determined using immunohistochemical methods.

Recurrences were defined as skeletal or non-skeletal (brain, liver, lung, and other organs). Sites of recurrences were documented by physical examination, X-rays, and/or other imaging modalities. Patients were classified with skeletal metastases if these were the only sites of involvement; otherwise, they were categorized with non-skeletal metastases.

Overall survival was defined as the time from first time of visiting the patient to the last contact with poor performance or death. Disease free interval (DFI) was defined as the time from first time of visiting the patient to the first time that metastasis was confirmed by radiological methods.

Primary tumor size and the number of positive axillary lymph nodes were extracted from the medical records. The DFI was divided into six groups (<12 months, 12–24 months, 25–36 months, 37–48 months, 49–60 months and > 60 months). Data were analyzed by SPSS 13 software.

Results

A total of 75 metastatic breast cancer cases were recruited in the 1995–2010. The patients were between 27 and 89 years old with a mean age of 49.17. The median age at initial diagnosis of the primary tumor was 49 years. The majority of patients were at age \geq 50 years. Invasive ductal carcinoma was the most common histopathological type. The expression of ER, PR, c-erbB-2, and Ki67 were evaluated in the majority of patients. The primary tumors were mainly ER positive (48%), PR negative (49.3%).

The status of lymph nodes dissected and examined in these patients was unknown in 19 patients (25.3%), 18 patients (24%) had positive lymph nodes with no report on the number of involved nodes. All of the patients received antracyclin based chemotherapy for adjuvant or metastatic setting, and adjuvant hormonal therapy was administered

Table 1. The Characteristics of 75 Metastatic Patients are Summarized

Characteristics of the Patients		
Age	Mean	49.17
	Median	49
	Mode	50
	Std. Deviation	12.497
	Min	27
	Max	89
Menopausal Status	Prem	38(50.7%)
	Post	30(40.0%)
	Peri	2(2.7%)
	Unknown	5(6.7%)
Tumor Diameter	1-1.9 cm	5(6.7%)
	2-2.9cm	10(13.3%)
	3-3.9cm	16(21.3%)
	4-4.9cm	17(22.7%)
	T4	4(5.3%)
	Unknown	23(30.7%)
Receptor Status	ER Pos.	36(48.0%)
	ER Neg.	34(45.3%)
	Unknown	5(6.7%)
	PR Neg.	37(49.3%)
	Unknown	5(6.7%)
First Secondary Metastasis	nonskeletal	33(44.0%)
	skeletal	29(38.7%)
Primary Metastasis		13(17.3%)
Disease Free interval	<12m.	10(13.2%)
	12-24m	21(28.8%)
	25-36m>	13(17.3%)
	37-48m	7(9.3%)
	49-60	2(2.7%)
	>5years	4(5.3%)
	Unknown	18(24.0%)

*Pos, Positive; Neg, Negative; m, month; ER, Estrogen Receptor; PR, Progesteron Receptor

to receptor positive patients. Thirteen patients were metastatic when visited for the first time. In the other patients the sites of first recurrence were mainly visceral in 33 patients (44%) including local recurrence in 7 (9.3%), and lymph node recurrence in 3 (4%), and skeletal in 29 (38.7%) patients. The median overall survival after recurrence was 30 months (95%CI 24.605–35.325) for non-skeletal versus 42 months (95%CI 31.211–52.789) for skeletal metastasis ($P=0.002$). The median survival for receptor positive patients was 39 months (95%CI 33.716–44.284) for PR+ versus 26 (95%CI 19.210–32.790) for PR- ($P=0.047$) and 38(95%CI 32.908–43.092) for ER+ versus 27 months (95%CI 18.780–35.220) for ER- patients ($P=0.016$). We found no correlation between site of first metastasis and hormone receptor, age, tumor diameter, DFI and menopausal status.

Discussion

This is a report of 75 metastatic breast cancers from Iran in respect with demographic, clinical and survival findings. Breast carcinoma is a clinically diverse and

heterogeneous disease, and patients with metastatic disease have survival ranging from a few weeks to more than a decade (Chang et al., 2003; James et al., 2003). Although breast cancer is the first in Iranian women, but studies describing the epidemiologic, etiologic and clinicopathologic features of the disease are lacking (Harirchi et al., 2011).

It has been shown that traditional prognostic markers including ER status of the primary tumor, lymph node involvement, and site of recurrence have potential in predicting survival in patients with metastatic breast carcinoma (Chang et al., 2003; James et al., 2003). So we proposed to determine the relation between these findings and patient survival. Lymph nodes assessment was inaccurate in respect with the number of resected or involved nodes. ER, PR and recently Her2, Ki67 and P53 status were determined. It has been reported that ER positive breast carcinoma tends to recur more frequently in bone, whereas ER negative tumors tend to recur in visceral sites. However, we found no significant relation between hormone receptors and site of metastasis. This was the same when we grouped the patients into visceral and non-visceral (skeletal, local and lymph node recurrence) metastasis. This may be related to low number of patients or other undefined etiologies.

Another study in 433 women confirmed the reports that patients with metastatic disease who had ER negative tumors, visceral metastases, and shorter DFI had significantly worse survival (Insa A, et al.1999). The survival of our patients with positive hormone receptors like patients with bone metastasis was higher than hormone negative or visceral metastasis. So absence of relation between hormone receptors and the site of metastasis must be studied in other centers with higher number of patients.

One of the strongest traditional prognostic factors in patients with metastatic breast carcinoma is the site of recurrence. Women with bony metastases have a higher life expectancy compared to patients with visceral metastases (Solomayer et al., 2000). Similar to other studies, we found higher survival rate in patients with skeletal metastasis ($P=0.002$).

Coleman and coworkers reported that survival for women with bone metastases was significantly worse over the age of 70 years (Coleman et al., 1998). Although it is difficult to explain the role of treatment or other factors in the increased likelihood of dying (James J J, et al.2003), this may be true in our patients but we had a few patients over 70 years old to determine this factor in survival analysis.

Previous investigators also have demonstrated that ER is important in determining prognosis in patients with metastatic breast disease (Chang et al., 2003). As with other reports our hormone receptor positive patients had higher survival rate compared to hormone receptor negative patients ($P=0.016$ for ER+ and $P=0.047$ for PR+). While the incidence of ER and PR+ patients were higher over the age of 50 in some studies (Balleine et al., 1999), Pourzand and coworkers (2011) reported younger women had more likely PR+ tumors. Hormone receptors may alter survival, and induce better response to therapy

in receptor positive patients (Singhakowinta et al., 1976; Kohil et al., 1985). The absence of relation between receptor status and pattern of metastasis may be linked with unknown factors such as genetics and molecular mechanisms among Iranian patients.

Tumor size and axillary lymph node status at the time of diagnosis also have been investigated as prognostic factors at the time of recurrence. According to Robertson and coworkers, once a patient develops metastatic disease then neither the lymph node status nor the size of the primary tumor is relevant as predictors of survival (Robertson et al., 1999).

In other studies, the reported incidence of bone metastasis was only 8% in cases with negative nodes which increased to 18-27% in patients with 1 to 3 or < 4 positive lymph nodes (Irawan et al., 2003). We could not determine the relation between number of involved nodes and metastasis pattern because the pathologic reports were inadequate in respect with the number of resected or involved nodes. This is one of the most important short coming of this study. Histopathological type and grade have been known to be important prognostic factors. Grade 1 and 2 ductal or lobular carcinomas provide better prognosis compared to grade 3 tumors (James J J, et al.2003). We lacked adequate number of reports for statistical analysis

It has been previously observed that older women are more likely to have metastatic disease that remains confined to bone (Coleman et al., 1998), but other studies showed that presentation with bone metastases was not related to the patient's age or the size of the primary tumor (De la Monte et al., 1988). We also did not find any correlation between age and bone metastasis.

The evaluation of newer biologic markers in primary breast tumors may facilitate assessment of outcome and prognosis. Hence treatment options for patients with metastatic breast carcinoma may be based on biologic factors. Although metastatic breast carcinoma usually leads to mortality, knowledge of prognosis and life expectancy is one of the most frequently asked questions in daily practice and has critical importance to both the patient and their families and after patients develop recurrent disease, the individual biologic characteristics of the primary tumors provide the clinician with required information in making more specific assessments. They allow patients to plan better priorities for the rest of their lives, and to make adequate preparation for death, a necessity that often is overlooked by the medical community (Chang et al., 2003).

Reports' analyzing a large number of patients with lymph node positive breast disease demonstrates that biologic factors of the initial primary tumor are indeed associated with post-recurrence outcome and the prognosis for these women is determined strongly by intrinsic molecular characteristics of the primary tumor.

In conclusion, sites of metastasis were independent to age, size of the tumor, menopausal and hormone receptor status in this study. Overall survival provided significant correlation with receptor and bone metastasis. Due to lack of sufficient data we are required to conduct many basic and clinical studies in Iranian patients suffering from

breast cancer to determine etiologic and molecular factors responsible for this disease.

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