ORIGINAL ARTICLE

Detection of prognostic factors in metastatic breast cancer

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Background: The aim of this study was to detect prognostic factors in recurrent breast cancer metastasis. **Materials and Methods:** This retrospective cohort study employed data from 996 breast cancer patients of Isfahan Seyed-o-Shohada research center from 1998 to 2010. Stratified Cox proportional hazards model, marginal approach, was used to evaluate the prognostic value of estrogen receptor, progesterone receptor, tumor protein 53, human epidermal growth factor receptor type 2, diagnosis age, nodal ratio, tumor size, antigen Ki67, and cathepsin D. Survival curves were plotted using Kaplan-Meier method and log-rank test was carried out to compare survival in two categories of nodal ratio (≤0.25 vs. >0.25). **Results:** In simple Cox regression model, age ($P = 0.037$), nodal ratio ($P < 0.0001$), and Ki67 ($P = 0.032$) were associated with hazard of distant metastasis. Multiple analysis showed that patients with greater nodal ratio had significantly higher adjusted hazard of recurrent metastasis (Hazard ratio: 2.756, 95% Confidence interval: 1.017-7.467; $P = 0.046$). Tumor size was not an independent prognostic factor for recurrent metastasis. Comparing survival curves, there was significant difference between two categories of nodal ratio in the first ($P < 0.0001$), second ($P < 0.0001$) and third ($P = 0.024$) metastasis; survival was higher in-patients with nodal ratio <0.25. **Conclusion:** Our findings indicate that tumor size was insignificant; this raises the question about conventional premise of being a major prognostic factor for distant metastasis. Furthermore, nodal ratio is suggested to clinicians as a prognostic variable in follow-up of breast cancer patients; patients with higher nodal ratio have greater hazard of distant metastasis.

Key words: Axillary nodal ratio, breast cancer, distant metastasis, marginal approach, prognostic factor, stratified cox proportional hazards model, tumor size

INTRODUCTION

The most prevalent cancer among women after non-melanoma skin cancer is breast cancer and its incidence rate is increasing enormously. After lung cancer, the most of mortalities among 40-50-year-old women result from breast cancer and it accounts for 32% of female cancers.[1-4] Increase of cancer incidence has been reported in the most modern countries of Asia including, Japan, Singapore, Hong Kong and Taiwan. In contrast to reported pattern in West countries, breast cancer in modern Asian countries is appearing in young age.[5] Furthermore, unlike western countries, in which breast cancer incidence has been decreased or stable[6-8] it is increasing in majority of Asian countries in the last two decades.[9-12]

In Iran, cancer is the most common cause of death after coronary heart disease and accident.[13] Striking increase of cancer incidence has been reported in Iran.[14] Iranian women develop this disease at least one decade sooner and this makes the subject more important.[15] Incidence and mortality rate of breast cancer among Tehranian women were reported 26.4 and 5.8 in one hundred thousand in 1999, respectively.[16] Isfahan province is among Iranian cities with high-rate of cancer. According to statistics in 2005, 10% of all observed breast cancers in Iran had been seen in Isfahan.[17]

Among breast cancer patients, the primary tumor usually does not end in death; in fact distant metastases result in death.[18] Cancerous cells go to other parts of body through blood flow and lymphatic vessels and start to grow and form new tumors.[19] The percentage of breast cancer patients with high-risk of metastasis is about 30-50.[20] In the first 3 years after diagnosis, nearly 10-15% of breast cancer patients develop distant metastasis and it is also likely to happen 10 years after first detection.[21]

Speaking of these figures besides low-quality of patients' lives with metastasis, detection of prognostic factors is crucial.[22] Several studies have found that proportion of involved node (nodal ratio) has been an important prognostic factor.[23-25] Large tumor has the high-risk of metastasis in comparison with small ones.[20,26-31] Some other risk-factors are age, estrogen receptor (ER), and progesterone receptor (PR), human epidermal growth factor receptor type 2 (HER2), tumor protein 53 (p53), antigen Ki67, and cathepsin D.[32-37]

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Although, several studies have been undertaken to detect prognostic factors of metastatic breast cancer, most of these studies take in to account conventional risk-factors. In current study, we tried to evaluate not only conventional variables but also some other putative risk-factors like p53, HER2, Ki67, and cathepsin D. On the other hand, most of these researches studied only the first metastasis and used Cox proportional hazard models,[38-41] though each patient can experience multiple metastases. This is a direct way, which ignores the complexities such as the effect of first event on occurrence of next events. Furthermore, considering only the first event is not satisfying for evaluating the natural history of disease and all information is not considered.[42] There are different regression methods for multiple failures. These methods consider special construct of correlation between events for one subject, which are generalization of survival data analysis. One of non-parametric methods for multivariate failure time data is marginal approach in Cox proportional hazard function.[43] The aim of this study is identification of prognostic factors of metastatic breast cancer as a recurrent event using recurrent survival analysis in order to benefit from all existing information.

MATERIALS AND METHODS

Participants

This retrospective cohort study employed data from breast cancer patients admitted and treated at Isfahan Seyed-o-Shohada research center from 1998 to 2010 (range of diagnosis date: 5/11/98-21/9/2010). Follow-up cut-off date was May 14, 2011. All registered 1084 breast cancer patients of this center entered to the study. Among these patients, 88 individuals had metastasis at the time of entrance therefore they were withdrawn from the study and size of sample declined to 996.

Variables

Patient information had been extracted from computerized medical records, which included demographic information and tumor characteristics. Demographic background, including age and family history, was collected by interview. Tumor characteristics such as tumor size and status of ER, PR, p53, HER2, cathepsin D, Ki67 and also number of involved and dissected axillary lymph nodes were extracted from pathology report. Other information such as sites of metastasis and survival times was reported by physicians.

Survival time was defined as time between date of diagnosis and consecutive distant metastasis. Follow-up time was calculated starting at date of diagnosis with breast cancer until May 14, 2011 or last contact, whichever came earlier. Nodal ratio was defined as ratio of number of involved nodes to total number of disserted nodes.

Some of patients could not be followed-up and some other did not experience metastasis and the information of these patients was considered in analysis as censored data.

Statistical analysis

The outcome of interest was distant metastasis defined as spread of cancer to distant organs such as lung, bone, liver, and brain. Each patient could experience distant metastasis several times over the follow-up time.

Stratified Cox proportional hazards model, marginal approach, was employed to evaluate the prognostic value of ER, PR, p53, HER2, diagnosis age, nodal ratio, tumor size, Ki67, and cathepsin D using univariate analysis. In marginal stratified Cox model, each subject is considered in risk set for all failures regardless of number of experienced events. Marginal method allows the researcher to consider not only the order of failures, but also different types of failures.[44] The statistical details of this method is described in reference number 61 and briefly given in the appendix. Regression parameters were estimated by maximum partial likelihood method. *P* values were calculated from Wald Z statistics.

Proportional hazards assumption of the model assumes that the hazard proportion of one individual to any other one is independent of time. This assumption was confirmed by graphical methods (comparing-ln-ln survival curves or observed versus predicted curves) and goodness-of-fit test.

We used the cut-off point of 0.25 for nodal ratio, which has been confirmed by previous studies [23,24] and plotted Kaplan-Meier survival curves in first, second and third metastasis over time for two categories of patients (nodal ratio ≤0.25 vs. >0.25). Survival comparison between different categories was made using log-rank test. Tests were two-sided and significant level was established at 0.05. The analyses were performed using SAS 9.2 and SPSS 18.

RESULTS

Over 12 years, 996 breast cancer patients with a median age of 47 years (range: 22-86 years) registered at Isfahan Seyed-o-Shohada research center were studied. A total of 143 patients (14.3%) had metastatic breast cancer; 86 patients (8.6%) experienced metastasis once, 41 ones (4.1%) twice, 15 individuals (1.5%) three times and one of them (0.1%) four times. Diagnosis age for majority of patients was more than 40 years (73.8%). The percentage of patients with more than 2 cm tumor size was 78.7. Axillary Nodal ratio was more than 0.25 among 38.4% of patients [Table 1].

The median follow-up time was 6 years (range: 0.6-12.5 years).

Among patients with at least 2 years of follow-up ($n=848$), the percentage of patients with metastasis-free surviving at 2 year was 91.4% and the 5-year metastasis-free survival rate for patients with at least 5 years of follow-up ($n=605$) was 81.3%.

Median (range) interval between detection of breast cancer and first metastasis was 23.23 (0.43-103) months; It was 5.9 (0.03-95.87) months between the 1st and 2nd metastasis and 6.15 (0.1-40.9) months between 2nd and 3rd metastasis.

Lung, bone, liver, and brain metastasis were determined as major sites of metastasis and their frequencies were shown in Table 2. Considering some of patients experienced several metastases at each event, the most prevalent site of metastasis was bone in the first event (47.5%).

In univariate analysis, simple Cox regression model, age, and tumor size were entered into model as categorical variables. Results showed that age ($P = 0.037$), nodal ratio ($P < 0.0001$) and Ki67 ($P = 0.032$) were statistically significant. Patients who are less than 40 years old, have 33.5% higher Hazard of recurrent metastasis in comparison with more than 40-year-old patients. On the other hand, the risk of recurrent metastasis increased as the value of nodal ratio and Ki67 increased [Table 3].

Table 3 also shows the results of multiple survival analysis. ER, PR, p53, HER2, diagnosis age, nodal ratio, tumor size, Ki67, and cathepsin D were putative prognostic variables. First order interaction effect as the product of binary age and binary PR and also between binary age and Ki67 were considered in the model. Among all possible prognostic factors, nodal ratio was the only significant variable; patients with greater nodal ratio had a significantly higher adjusted hazard of recurrent metastasis (Hazard ratio = 2.756; 95% Confidence interval [CI]: 1.017-7.467). Tumor size was not an independent prognostic factor for recurrent metastasis.

Comparing survival into two categories of nodal

Table 1: Patient and tumor characteristics

Characteristic	No. of patients (%)
Number of metastasis	
0	853 (85.6)
1	86 (8.6)
2	41 (4.1)
3	15 (1.5)
4	1 (0.1)
Diagnosis age (years)	
≤40	259 (26.2)
>40	730 (73.8)
Family history	
Yes	181 (21.8)
No	649 (78.2)
Tumor size (cm)	
≤2	199 (21.3)
2<to≤5	586 (62.7)
>5	150 (16)
Tumor grade	
I	14 (10.4)
II	72 (53.3)
III	48 (35.6)
IV	1 (0.7)
Nodal ratio	
≤0.25	561 (61.6)
>0.25	349 (38.4)
Estrogen receptor	
Positive	516 (59.1)
Negative	357 (40.9)
Progesterone receptor	
Positive	511 (58.7)
Negative	360 (41.3)
p53	
Mutant	263 (34.7)
Non-mutant	495 (65.3)
HER2	
Positive	176 (56.1)
Negative	138 (43.9)
Cathepsin D	
Positive	637 (94.4)
Negative	38 (5.6)
Ki67	
≤20	337 (72.3)
>20	129 (27.7)

HER2=Human epidermal growth factor receptor type 2; p53=Tumor protein 53

Table 2: Sites of metastasis in each event

Site of metastasis	No. of patients (%)
First metastasis ($n=143$)	
Lung	30 (21)
Bone	58 (40.5)
Liver	30 (21)
Brain	4 (2.8)
Bone and liver	6 (4.2)
Lung and liver	2 (1.4)
Bone and lung	3 (2.1)
Lung and bone and liver	1 (0.7)
Others	9 (6.3)
Second metastasis ($n=57$)	
Lung	12 (21.1)
Bone	20 (35.1)
Liver	14 (24.6)
Brain	6 (10.5)
Lung and liver	2 (3.5)
Brain and bone and liver	1 (1.8)
Others	2 (3.5)
Third metastasis ($n=16$)	
Lung	5 (31.3)
Bone	3 (18.8)
Liver	5 (31.3)
Brain	3 (18.8)
Fourth metastasis ($n=1$)	
Lung	1 (100)

ratio (≤0.25 vs. >0.25) without adjustment for covariates, there was a significant difference between these two categories in the first ($P < 0.0001$), second ($P < 0.0001$), and third metastasis ($P = 0.024$); higher survival was seen in patients with nodal ratio <0.25.

Survival curves are shown in the Figures 1-3. The risk of first metastasis increased numerically faster in patients with nodal ratio >0.25 in comparison with nodal ratio <0.25. However, this difference decreased gradually in the next metastases.

DISCUSSION

In this study, high-nodal ratio was associated with a shorter survival from recurrent metastasis. According to the survival curve in the first metastasis, risk of metastasis in patients with nodal ratio >0.25 is significantly higher than nodal ratio <0.25. The risk decreased through next metastases (because of some patient's deaths) however, the difference remained significant. So this factor can be used to categorize patients into two different groups; a high-risk group with nodal ratio >0.25 and low-risk group with nodal ratio <0.25. Findings indicate that tumor size did not influence the hazard of distant metastasis. A possible explanation might be some breast cancer tumors behave aggressively despite being small.[45]

Our findings are in agreement with other studies in which only first metastasis was considered.[38-41,46-52] To the best

Table 3: Prognostic factors for distant metastasis, simple and multiple stratified Cox regression model, marginal approach

Characteristic	Simple Cox regression model			Multiple Cox regression model		
	Hazard ratio	*P* value	95% Confidence interval	Hazard ratio	*P* value	95% Confidence interval
Estrogen receptor						
Negative (ref)						
Positive	0.915	0.640	0.630-1.327	0.858	0.789	0.279-2.640
Progesterone receptor						
Negative (ref)						
Positive	0.723	0.085	0.500-1.046	0.779	0.803	0.110-5.536
p53						
Non-mutant (ref)						
Mutant	1.112	0.599	0.749-0.651	1.292	0.630	0.456-3.666
HER2						
Negative (ref)						
Positive	1.080	0.765	0.652-1.790	1.498	0.370	0.620-3.622
Age						
≤40 (ref)						
>40	0.665	0.037	0.453-0.976	0.603	0.631	0.077-4.734
Nodal ratio	4.332	<0.0001	2.785-6.740	2.756	0.046	1.017-7.467
Tumor size						
≤2 (ref)						
2<to≤5	1.576	0.105	0.910-2.731	2.523	0.094	0.854-7.454
>5	1.372	0.334	0.722-2.606	1.839	0.399	0.446-7.571
Ki67	1.016	0.032	1.001-1.031	1.007	0.851	0.940-1.078
Cathepsin D						
Negative (ref)						
Positive	0.966	0.927	0.460-2.026	0.284	0.080	0.070-1.160

HER2=Human epidermal growth factor receptor type 2; p53=Tumor protein 53

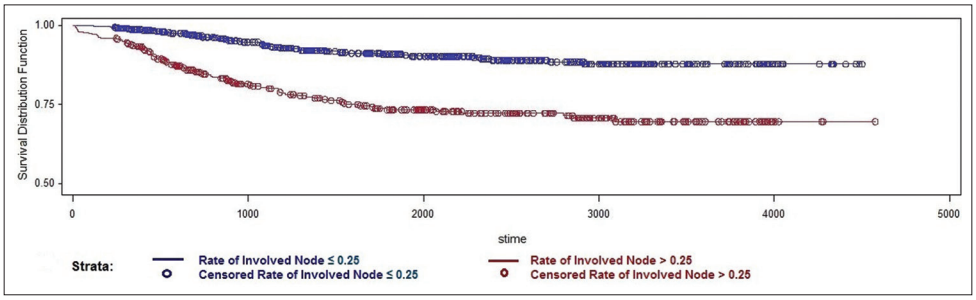

Figure 1: Survival curve in the first metastasis

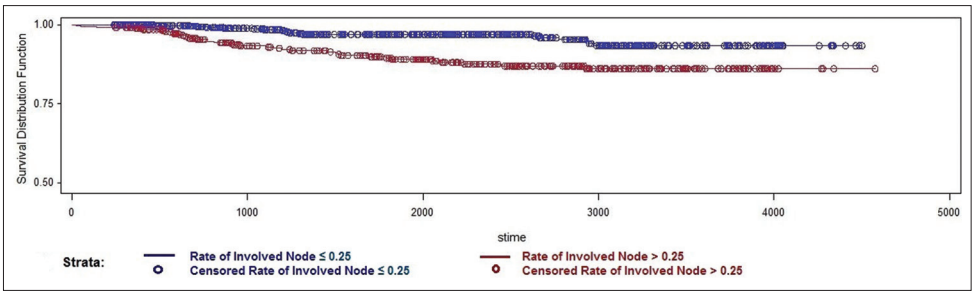

Figure 2: Survival curve in the second metastasis

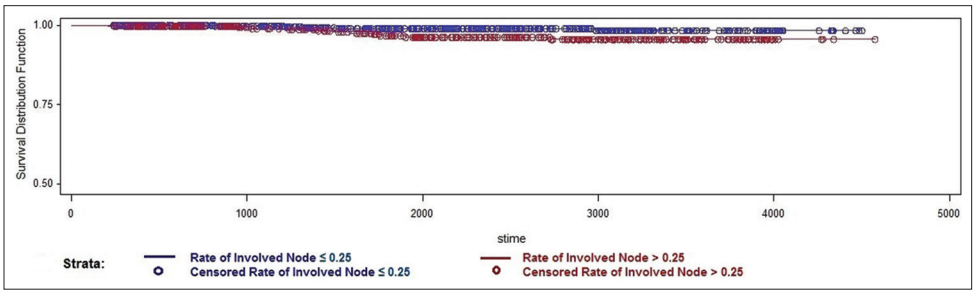

Figure 3: Survival curve in the third metastasis

of our knowledge, there are rare reports, which studied prognostic factors of metastatic breast cancer using recurrent survival analysis. However, there are several studies evaluated this issue by multivariate survival analysis. Although the significant factors and studied samples were different in these studies , they consistently comprised of axillary nodal ratio. Truong *et al*.[24] performed multivariate analysis on distant recurrence of 542 women who had pathologic T1-T2 breast cancer and one to three positive lymph nodes. It was indicated that patients with >25% positive lymph nodes, age ≥45 years, T2 classification of tumor, grade 3 and lymphovascular invasion had higher-risk of distant recurrence. In retrospective study, by Tausch *et al*.[53] lymph node ratio, age, PR, grade, and tumor stage were detected as prognostic factors of recurrent breast cancer among 7052 patients. Van der Wal *et al*.[25] examined 453 stage I or II breast cancer patients and found out lymph node ratio ≥0.2, ≥14 lymph nodes removed and vascular invasion increased risk of distant metastases in node positive patients. In multivariate Cox proportional hazard regression analysis of 205 breast cancer patients with stage II or III who treated with neoadjuvant chemotherapy, Keam *et al*.[23] reported that nodal ratio was prognostic factor for relapse free survival (RFS) besides initial clinical stage and ER. In univariate analysis, nodal ratio >0.25 was associated with shorter RFS.

Furthermore, several studies evaluated the prognostic value of number of involved nodes;[38-41] Voogd *et al*.[38] studied risk-factors for local and distant recurrence after breast-conserving therapy or mastectomy. Among 1,772 patients of two randomized clinical trial for stage I and II, the result of multivariate Cox proportional hazards survival analysis showed that large tumor size, positive nodal status, high-histological grade, and vascular invasion were highly associated with increased hazard of distant metastasis. In a study by Touboul *et al*.,[39] risk-factors for local recurrences and distant metastases after breast-conserving surgery and radiation therapy in 528 patients with stage I or II breast cancer were studied using multivariate generalization of the proportional hazards model. It was found that the hazard of distant metastasis increased by the number of involved axillary nodes, high-histological grade, and isolated local recurrence.

Tumor size has been an important prognostic factor of distant metastasis in several studies [24,38,40,41,51,54,55] however, this is not a fixed pattern. Other studies indicated that tumor size was not a significant factor in some subtypes of breast cancer.[39,56-60]

The present longitudinal study expanded the findings of previous studies by considering metastasis as a recurrent event and using relevant statistical models. Furthermore, the other strong point is studying the effect of some recent prognostic factors such as p53, HER2, Ki67, and cathepsin D besides conventional prognostic factors.

However, this study had some limitations. First of all, it feels a need for more information about tumor characteristic including, tumor grade. Information about tumor grade was available for few numbers of patients and it was not possible to consider in the model. Pathologic results including tumor grade imposed more cost on

patient however, it has an important role in decisions made by physicians and eventually on the survival of patients. Second in spite of adjustment for large spectrum of possible risk-factors, there is always the possibility of ignoring some influential factors; So using frailty models seems logical in order to account for variability due to unobserved factors. However, the multifarious nature of breast cancer metastasis makes detection of all risk-factors difficult.

In conclusion, insignificant tumor size in this study and some other studies raised the question about conventional premise of being a major prognostic factor for distant metastasis. High-nodal ratio was associated with an increased risk of recurrent metastasis in breast cancer patients. So it is suggested for clinical management and to clinicians as a prognostic factor in follow-up of breast cancer patients; patients with higher-nodal ratio have greater hazard of distant metastasis.

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APPENDIX

In marginal stratified Cox model, for k^{th} type of failure (k = 1,…, K), X_{ki} is supposed to be failure time of i^{th} subject (i = 1,…, n). For each $\tilde{X}_{ik}$, there is a two variable vector (X_{ki}, Δ_{ki}) in which $X_{ki} = \min(\tilde{X}_{ik}, C_{ki})$, C_{ki} is censored time and $\Delta_{ki} = 1$ if $X_{ki} = \tilde{X}_{ik}$ and 0 otherwise. If $\tilde{X}_{ik}$ is missing, C_{ki} will be 0. It means $\tilde{X}_{ik} = 0$ and $\Delta_{ki} = 1$ because $\tilde{X}_{ik}$ is positive. Now suppose $Z_{ki}(t) = (Z_{1ki}(t),\ldots, Z_{pki}(t))'$ is a $p \times 1$ vector of predictors for i^{th} subjects at $t \geq 0$ and k^{th} type of failure. Conditional on Z_{ki}, it is assumed that failure vector $\tilde{X}_{ik} = (\tilde{X}_{1i},\ldots, \tilde{X}_{ik})'$ and censor vector $C_i = (C_{1i},\ldots, C_{Ki})$, (i = 1,…,n) are independent. In addition, it is supposed (X_i, Δ_i, $Z_i(.)$), (i = 1,…, n), in case $Z_i = (Z'_{1i},\ldots, Z'_{Ki})'$, are independent identical distribution vectors with bounded covariance $Z_i(.)$.

For k^{th} type of failure of i^{th} subject, hazard function $\lambda_{ki}(t)$ is described as below:

$$\lambda_{ki}(t) = \lambda_{k0}(t) \exp\{\beta'_k Z_{ki}(t)\},\ t \geq 0$$

So that $\lambda_{k0}(t)$ is unspecified baseline hazard function and $\beta_k = (\beta_{1k}, \beta_{pk})'$ are failure-specific regression parameters.[61]

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