

## Investigation of Prognostic Factors and Survival without Recurrence in Patients with Breast Cancer

### Abstract

**Background:** One of the major consequences of breast cancer is the recurrence of the disease. The objective of present study was to estimate the 7-year survival without recurrence as well as the effective prognostic factors in recurrence. **Materials and Methods:** This historical cohort survival analysis was conducted on 1329 patients diagnosed with breast cancer in Motahari Breast Clinic, Shiraz, Iran between 2004 and 2011. We estimated the rate of survival without recurrence through the Kaplan–Meier method and the difference between the survival curves was investigated using the log-rank test. Furthermore, Cox regression model was used to model the effective factors in local recurrence as well as metastasis. **Results:** The mean age of the patients was  $54.8 \pm 11.4$  years. Estrogen receptor positive, progesterone receptor positive, and human epidermal growth factor receptor-2 positive were observed in 70.6%, 66.6%, and 34.4% of the cases, respectively. The mean of the follow-up period was  $3.7 \pm 1.8$  years in all patients. The results of the Kaplan–Meier method revealed 1-, 3-, 5-, and 7-year rate of survival without recurrence as 96.4%, 78.4%, 66.3%, and 54.8%, respectively. There was a significant relationship between survival without recurrence and histology grade (hazard ratio [HR] = 1.66,  $P = 0.009$ ), neural invasion (HR = 1.74,  $P = 0.006$ ), and progesterone receptors (HR = 0.69,  $P = 0.031$ ). **Conclusion:** In this study, the rate of survival without recurrence in breast cancer was 54.8%. Among factors, histology grade and neural involvement at the time of diagnosis increased the chance of recurrence and progesterone receptors caused a longer interval between diagnosis and recurrence.

**Keywords:** Breast cancer, chemotherapy, radiotherapy

### Introduction

Breast cancer is the most prevalent type of cancer among women and is the second cause of death due to malignancies after lung cancer.<sup>[1]</sup> Every year, 100,000 new cases of breast cancer are diagnosed, and nearly 30,000 patients die because of this disease in the United States.<sup>[2,3]</sup> In Iran, cancer has the first rank among women's cancers<sup>[4]</sup> and is the third cause of death after cardiovascular diseases and accidents.<sup>[5]</sup> Furthermore, annually, 8090 new cases resulting in Iran and more than 1300 deaths per year by breast cancer is reported.<sup>[6]</sup>

Recurrence is defined as the relapse of breast cancer after the initial treatment and is classified into three categories. In local recurrence, cancer cells reappear in their original site, which is mostly due to the failure in the initial treatment. In regional recurrence, the cancer cells spread

to the lymph nodes and mostly involve the chest wall muscle, lymph nodes inside the breast, and nodes surrounding the neck. Finally, in metastasis, the cancer cells spread to the other organs and mostly spread from the lymph nodes to the bones. In fact, the major concern after treating the breast cancer is local as well as regional recurrence of the disease which, eventually, leads to metastasis and death.<sup>[7]</sup> The 5- and 10-year survival rates of local recurrence have been reported as 35–75% and 25–55%, respectively. Moreover, local recurrence mostly leads to metastasis; as a result, treatment of local recurrence should be considered.<sup>[8]</sup> Overall, identifying new effective factors in prognosis and recurrence of disease could be helpful in preventing of recurrence of disease which, finally, leads to death. In fact, 70–80% of the patients suffering from breast cancer could be treated in the primary stages of disease.<sup>[9]</sup>

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In general, various factors, such as status of axillary lymph nodes, vascular as well as lymphatic invasion, tumor size (risk of recurrence is positively correlated with tumor size), histologic grade (it is based on three components: Tubule formation, nuclear pleomorphism, and mitotic index which has three grades of well-differentiated, moderately differentiated, and poorly differentiated), epidermal growth factor (C-erbB-2, ERBB2, Her2/neu) that is an oncogene located on the long arm of chromosome 17, and type of surgery, affect the prognosis of breast cancer.<sup>[10-13]</sup> Furthermore, one of the methods for diagnosis of breast cancer is fine needle aspiration (FNA) which was performed as a diagnostic method in the present study.

Because of the high rate of breast cancer and its present status and the importance of prognostic information, and also, due to the lack of data about prognostic factors and survival without recurrence in patients with breast cancer in Iran, this study aims to estimate the 7-year rate of survival without recurrence and its effective prognostic factors. In this study, 1-, 3-, 5-, and 7-year rates of survival without recurrence have been estimated among the breast cancer patients in Motahari Breast Clinic, Shiraz, Iran from 2004 to 2011.

## Materials and Methods

The present retrospective cohort study was conducted in patients with breast cancer which was diagnosed through FNA method from 2004 to 2011. The patient's profiles had been completed in Motahari Breast Clinic, Shiraz University of Medical Sciences, Shiraz, Iran. This center is a nonreferral governmental center. Over these 7 years, 1800 cases of breast cancer had been identified, 1329 cases were entered the present research. Patients without recurrent breast cancer who were diagnosed between 2004 and 2011 were eligible and selected to participate in the study. Moreover, exclusion criteria were previous or coexisting cancers other than breast cancer and many missing data in their clinical and demographic records at diagnosis. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences.

In this study, the time of diagnosis was considered as the initial event and the time of recurrence (local or metastatic) which led to further surgery, chemotherapy, radiotherapy, or death was considered as the end point event. Besides, the cases that had no end point events due to the end of the study, losing the follow-up, or death resulting from other causes were considered as the censored data. Data were gathered from patients' profiles in breast clinic. The profiles of patients that were followed for 6 months were investigated, and the final status of each patient was asked by phone call. The study objectives were explained to the patients, and informed consent was obtained. The patients were assured of the confidentiality of information. The studied factors included patient's age, menarche age, body mass index (BMI), type of surgery,

chemotherapy, radiotherapy, histology of tumor, histologic grade of tumor, lymphatic system involvement, vascular and neural involvement, the number of involved lymph node, tumor size, estrogen and progesterone receptors and epidermal growth factor (human epidermal growth factor receptor-2 [HER-2]).

Studied profiles in this study that do not have enough data to extracted, were considered as the censored data and only those cases with complete information were entered in final analyses. The rate of survival without recurrence was determined through the Kaplan–Meier method and the survival curves were compared using the log-rank test. In addition, Cox regression model was used to model the data. Moreover, constancy of the hazard ratio (HR) which is one of the presuppositions of the Cox model was investigated through the graphical model of  $\log(-\log [t])$  on  $\log (t)$  and the parallelism of the curves in this graph shows the constancy of the HR. All statistical analyses were performed through the SPSS software for Windows (version 20, SPSS Inc., Chicago, IL, USA) and  $P < 0.05$  was considered as statistically significant.

## Results

Of 1800 profiles in breast clinic 471 profiles were excluded because do not have enough data to extracted, had no end point events due to the end of the study, or dead from other causes, so, 1329 (73.8%) were investigated completely. Table 1 shows the characteristics of studied patients. Mean and median of follow-up period were  $3.7 \pm 1.8$  and 3.4 years, respectively. In addition, the mean age of the patients was  $54.8 \pm 11.4$  years, and they were mostly over 35 years old.

According to results of Kaplan–Meier test, 1-, 3-, 5-, and 7-year rates of survival without recurrence were 96.4%, 78.4%, 66.3%, and 54.8%, respectively. Moreover, univariate analysis revealed a significant relationship between recurrence and the rate of survival without recurrence based on the histology grade ( $P = 0.012$ ), lymphatic involvement ( $P = 0.001$ ), vascular involvement ( $P = 0.032$ ), neural involvement ( $P = 0.000$ ), tumor size ( $P = 0.04$ ), the number of involved lymph glands ( $P = 0.000$ ), and epidermal growth factor ( $P = 0.016$ ). However, no significant relationship was found between recurrence and the patients' age, menarche age, BMI, type of surgery, chemotherapy, radiotherapy, tumor histology, and estrogen as well as progesterone receptors. To model of effective factors in the rate of survival without recurrence, the variables with  $P < 0.2$  in the univariate analysis were entered into the Cox model by assuming the constancy of the HR. These variables were age, type of surgery, histology, histology grade, lymphatic involvement, vascular involvement, neural invasion, tumor size, the number of involved lymph nodes, and estrogen, progesterone, and HER-2 receptors. In this study, backward

**Table 1: Characteristics of 1800 studied patients with breast cancer in Motahari breast clinic of Shiraz University of Medical Science between 2004 and 2011**

Variables	n (%)
Age (year)	
20-34	47 (2.6)
>35	1748 (97.4)
Menarche age (year)	
<12	172 (9.7)
12-15	1382 (77.7)
>15	129 (7.3)
unknown	96 (5.4)
BMI (kg/m <sup>2</sup> )	
≤25	916 (52.1)
25-29.9	560 (31.8)
≥30	283 (16.1)
Type of surgery	
Mastectomy	1064 (66)
Quadrectomy	549 (34)
Radiotherapy	1008 (63)
Chemotherapy	1366 (76.8)
Tumor histology	
Ductal	1407 (88.1)
Lobular	170 (10.6)
Other	20 (1.3)
Tumor histology grade	
Grade I	490 (33.8)
Grades II and III	961 (66.2)
Lymph tract involvement	826 (52.2)
Vascular involvement	306 (19.4)
Nervous involvement	257 (16.3)
Tumor size (cm)	
<2	169 (10.9)
2-5	1280 (82.7)
>5	98 (6.3)
Number of lymph glands	
N0 (none)	773 (50.7)
N1 (1-3)	378 (24.8)
N2 (4-9)	244 (16)
N3 (>10)	130 (8.5)
Estrogen receptor positive	1099 (70.6)
Progesterone receptor positive	955 (66.6)
HER-2 receptor positive	248 (34.4)
Type of recurrence	
Local	184 (44)
Metastasis	234 (56)
Sites of metastasis	
Liver	34 (14.5)
Brain	18 (7.7)
Bone	115 (49.1)
Lung	48 (20.5)
Other body organs	19 (8.1)

BMI: Body mass index, HER-2: Human epidermal growth factor receptor-2

stepwise (likelihood ratio) was used and the results are presented in Table 2. Moreover, the results of the Cox

**Table 2: Modeling the factors affecting the breast cancer rate of survival without recurrence using the Cox regression model**

Variable	HR	95% CI	P
Histology grade			
Grade I	Reference	1.13-2.442	0.009
Grades II and III	1.666		
Neural involvement			
No	Reference	1.16-2.54	0.006
Yes	1.740		
Progesterone receptor			
Negative	Reference	0.49-0.99	0.031
Positive	0.694		
HER-2 receptor			
Negative	Reference	0.95-1.86	0.092
Positive	1.334		

HR: Hazard ratio, CI: Confidence interval, HER-2: Human epidermal growth factor receptor-2

regression model revealed the HR of 1.666 for histology grade ( $P = 0.009$ ), 1.74 for neural involvement ( $P = 0.006$ ), and 0.694 for progesterone receptor ( $P = 0.031$ ). Moreover, HR for HER-2 receptor was 1.33; however, this relationship was not statistically significant.

## Discussion

Recurrence of disease is one of the major problems in patients with breast cancer during the first 2 years after diagnosis. Now, considering advanced surgical techniques and complementary therapies, the rate of breast cancer recurrence has decreased. Our study showed that 7-year rate of survival without recurrence in studied patients was 54.8%. The histology grade, lymphatic involvement, vascular involvement, neural involvement, tumor size, the number of involved lymph glands, and epidermal growth factor were significant factors in relation to recurrence and age, menarche age, BMI, type of surgery, chemotherapy, radiotherapy, tumor histology, estrogen and progesterone receptors were not in relation to recurrence. In addition, only histology grade, neural invasion, and progesterone receptors were independently significant predictors of survival without recurrence.

Kheradmand *et al.*,<sup>[12]</sup> showed no significant correlation between age, weight, tumor size, nodal status, stage, grade and histology of tumor and locoregional recurrence and survival in 114 patients with breast cancer underwent mastectomy and they showed menarche age as an important risk factor for breast cancer. In agreement with Kheradmand *et al.*, we found no significant correlation between age, BMI, tumor histology and recurrence. However, in contrast to their results we found a significant correlation between tumor size and grade of tumor with recurrence, also, we did not found any significant correlation between menarche age and recurrence. The differences between these two studies

may explain by different in sample volume. In our study, similar to other studies<sup>[14,15]</sup> no significant relationship was found between the rate of surgery and the rate of survival without recurrence but in Brewster *et al.*,<sup>[14]</sup> a significant relationship was found between the rate of surgery and the rate of survival without recurrence. In addition, in our study like Brewster *et al.*,<sup>[14]</sup> study tumor histology was not significantly relation with the rate of survival without recurrence and histology grade was significantly related.

The findings of this study showed no significant relationship between radiotherapy and chemotherapy with the rate of survival without recurrence, which is consistent with the results of other studies.<sup>[9,14,16-19]</sup> Nevertheless, Clark *et al.* diagnosed a significant relation between radiotherapy and chemotherapy with the rate of survival.<sup>[20]</sup> Differences between the present study and Clark *et al.*, study can be explain by the difference between studied population, whereas in our study women without recurrence were studied but study sample in Clark *et al.*, the study included women with recurrent breast cancer.

The results of the present study, like Fathi *et al.*,<sup>[21]</sup> study a significant relationship between the rate of survival without recurrence and lymphatic involvement, vascular, and neural invasion was observed. The rate of survival without recurrence and tumor size were significantly related in Clark *et al.*,<sup>[20]</sup> Hajihosseini *et al.*,<sup>[22]</sup> and Karimi *et al.*,<sup>[23]</sup> Also, our result was dissimilar to other studies that show no significant relationship between tumor size and survival without recurrence.<sup>[9,12,24]</sup>

In the present study, a significant relation was observed between the lymph nodes involvement and the rate of survival without recurrence, which is in the line with finding of Clark *et al.* investigation<sup>[18]</sup> whereas, the lack of relation was reported in two surveys in Iran.<sup>[12,22,24]</sup> In the present study, no significant relation was diagnosed between estrogen and progesterone receptors with the rate of survival without recurrence similar to other studies.<sup>[16,18,24]</sup> Furthermore, the findings of the present study on the contrary to those of other studies<sup>[18,24]</sup> revealed a significant relationship between HER-2 receptor and the rate of survival without recurrence. These differences between findings in the present study with other reported studies may be due to the difference between studied population whereas in our study women without recurrence treated with any treatment regimens were studied but study samples in other studies were women with postmastectomy locoregional recurrence or received limited treatment regimens.

Cox regression analysis revealed histology grade as an important prognostic factor; in a way that in comparison to Grade I, Grades II and III increased the HR of breast cancer recurrence to 1.66-folds, which is consistent with the results of other studies.<sup>[13]</sup> Dislike to Karimi *et al.*,<sup>[23]</sup> findings, our results showed that neural involvement,

as an important prognostic factor, caused a 1.74-fold increase in the HR of breast cancer recurrence. Moreover, our findings showed progesterone receptor as one of the prognostic factors which caused a 30% decrease in the HR of recurrence. In addition, HER-2 receptor was marginally significant, while Fathi *et al.* did not find HER-2 as a prognostic factor.<sup>[21]</sup>

Some of the limitations could be addressed in the present study. Selection bias could be a potential source of bias, despite the fact that eligibility criteria were performed to minimize the bias, inter observational in breast cancer diagnosis can be lead to bias. Incomplete records and lack of access to other data centers can be noted as other main limitations in this study.

## Conclusion

Findings of our study confirmed that histologic grade, neural involvement, and HER-2 were risk factors and progesterone receptor was considered as the protective factor of recurrence. It can be concluded that the accurate identification of tumor grade, pathological examination, and precise identification of the hormone receptors are helpful in prediction of high-risk group.

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## Conflicts of interest

There are no conflicts of interest.

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