

The recurrence frequency of breast cancer and its prognostic factors in Iranian patients

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ABSTRACT

Background: Recurrent breast cancer (BC) after initial treatments is usually associated with poor outcome. The objective of this study is to evaluate baseline characteristics of BC patients to determine their prognostic influence of recurrences. **Materials and Methods:** In this retrospective study of 481 BC patients, 182 patients who had recurrence within the first, second, or third 5 years after diagnosis were included in the study. The significant prognostic factors associated with late or very late recurrence were selected according to the Akaike Information Criterion. Early recurrence was defined as initial recurrence within 5 years following curative surgery irrespective of site. Likewise, late recurrence was defined as initial recurrence after 5 years. Also, very late recurrence was defined as initial recurrence after 10 years. **Results:** During the follow-up period, 182 recurrences occurred (local recurrence or distant metastasis). All patients were treated with chemotherapy and radiotherapy and the patients with estrogen receptor (ER)- or progesterone receptor (PR)-positive had hormone therapy. There was a significant correlation between histological grade and receptors status with recurrence. In binary logistic regression analysis, ER and PR were significant prognostic factors for early recurrence. **Conclusion:** High histological grade and immunohistochemical markers (ER- and PR-negative or human epidermal growth factor receptor 2-positive) are risk factors for recurrence, especially in early recurrence and also between of them, ER is the more significant prognostic factor in early recurrence.

Key words: Breast cancer, estrogen receptor, lymph node, recurrence

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INTRODUCTION

Breast cancer (BC) screening and high-quality mammography have resulted in increase in the diagnosis of ductal carcinoma of breast worldwide. Estrogen receptor (ER) positivity predicts response to endocrine therapy such as antiestrogen (tamoxifen) and trastuzumab therapy (Herceptin) for tumor with the

human epidermal growth factor receptor 2 (HER2) overexpression.^[1] Up to 75% of BCs express ER and/or the progesterone receptor (PR).^[2] Adjuvant chemotherapy and endocrine therapy for early BC have had a considerable impact on outcomes.^[3] Therefore, higher rates of pathological complete response can be achieved when selecting for certain BC subtypes and treatment regimens.^[4] The timing of distant recurrence also varies according to the subtype and is nonproportional – while ER-negative and HER2-positive BCs have higher recurrence rate within the first 5–7 years with an up to 3-fold higher risk, a lower

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annual hazard rate for ER-positive tumors exists for the first 5 years after diagnosis.^[5] For women with hormone receptor-negative disease, the risk of recurrence is confined mostly to the first 5 years after diagnosis and relapse rates fall rapidly thereafter,^[6,7] but women with HR-positive tumors remain at risk for late recurrences, and the annual rate is in excess of 2% for at least 15 years, even after 5 years of tamoxifen therapy.^[8]

The involvement of the axillary lymph nodes (LNs) is the most important prognostic factor for recurrence in the early stages of BC according to the literature. Patients with positive axillary LNs have been reported to have a four to eight times higher mortality rate in comparison to patients with negative LNs^[9] and in patients with negative LN, tumor size is an independent prognostic factor of breast recurrence^[10] and also tumor grade has also been widely accepted as a prognostic factor.^[11]

The aim of the study is to evaluate baseline characteristics for BC patients in Iran and also compared these variables in early recurrence, late recurrence, and very late recurrence for diagnosis of prognostic factors of recurrences.

MATERIALS AND METHODS

In this retrospective study, 481 BC patients who were admitted to the Hazrat-e-Rasoul Hospital, Tehran, were investigated. Of all patients, 299 patients were excluded that had the short follow-up after diagnosis and did not have the recurrence, but 182 patients who had the recurrence within the first, second, or third 5-year period after diagnosis entered to our study. The data for those patients who had recurrent BC were analyzed, including patient's age, primary tumor size, stage, axillary LNs, the presence of ER and PR; and HER2 receptors. The site of recurrence was classified as local (ipsilateral breast or chest wall), regional (ipsilateral axillary, infraclavicular, internal mammary, or supraclavicular), or distant metastasis (any other site). Early recurrence was defined as initial recurrence within 5 years following curative surgery irrespective of site. Likewise, late recurrence was defined as initial recurrence after 5 years. Furthermore, very late recurrence was defined as initial recurrence after 10 years. According to the timing of the first recurrence, all patients were stratified into three groups (early recurrence [Group 1], late recurrence [Group 2], and very late [Group 3] during the follow-up period). ER and PR positivity was defined as $\geq 10\%$ positive tumor cells with nuclear staining. The HER2-positive was defined as either HER2 gene amplification by fluorescent *in situ* hybridization or scored as 3+ by immunohistochemical (IHC). For HER2 (+2), fluorescent *in situ* hybridization was performed to determine HER2 amplification.

We used Chi-square test for to compare baseline tumor characteristics, and the binary logistic regression models were employed to compare characteristics between early recurrence (up to 5 years) with late (5–10 years) or very late (10–15 years) recurrence groups. The significant prognostic factors associated with late or very late recurrence were selected according to the Akaike Information Criterion. All statistical analyses were performed using the IBM SPSS statistics software version 19 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

The median age at diagnosis was 47.0 ± 13.1 , 100% female. During the follow-up period, 182 recurrences occurred (local recurrence or distant metastasis). All patients were treated with chemotherapy and radiotherapy and the patients with ER- or PR-positive had hormone therapy. Furthermore, HER2-positive patients received Herceptin® (trastuzumab). The patients were divided into two age groups, age < 40 or age ≥ 40 [Table 1]. There was a significant correlation between histological grade and receptors with recurrence ($P < 0.05$). Grade III was more in early recurrent patients compared to late recurrence and also in early recurrence compared to very late recurrence. In addition, ER- or PR-positive is less in the patients with early recurrence compared to late recurrence or very late recurrence. HER2-positive was less in the patients with very late recurrence compared to late recurrence or early recurrence.

Prognostic factors using binary logistic regression model

In comparison to late recurrence, ER (odds ratio [OR] 0.33, 95% confidence interval [CI] 0.17–0.63) and PR ([OR] 0.44, 95% CI 0.23–0.84) were significant prognostic factors for early recurrence [Table 2]. In addition, in comparison to very late recurrence, ER ([OR] 0.30, 95% CI 0.10–0.86) was significant prognostic factors for early recurrence.

DISCUSSION

The BC screening and higher quality mammography have resulted in an increase in the diagnosis of ductal carcinoma of breast worldwide that is characterized by a number of genetic aberrations. Although improvements have been achieved in recent years, few genetic biomarkers are available to easily identify individuals at risk for BC or BC progression.^[12] BC is a heterogeneous disease and is currently divided into subtypes in accordance with the status of ER, PR, and HER2.^[13] Recurrent BC occurring after the initial treatment is associated with poor outcome and a bimodal relapse pattern after surgery for primary tumor has been described with peaks of early and late recurrence occurring at about 2 and 5 years, respectively.^[14]

Table 1: Baseline tumor characteristics for breast cancer patients according to recurrence pattern (n=182)

Variables	Up to 5 years: Group 1 (n=87)	5-10 years: Group 2 (n=75)	10-15 years: Group 3 (n=20)	Group 1* versus Group 2	Group 1* versus Group 3	Group 2* versus Group 3
Age						
<40 (n=50)	23	21	6	0.481	0.471	0.531
≥40 (n=132)	64	54	14			
Histological grade						
I (n=8)	0	5	3	0.037	0.000	0.187
II (n=122)	57	50	15			
III (n=52)	30	20	2			
Tumor size (cm)						
≤3 (n=41)	17	20	6	0.187	0.229	0.484
>3 (n=67)	70	55	14			
LN* involvement						
Yes (n=108)	55	43	10	0.273	0.200	0.368
No (n=74)	32	32	10			
Number of ILNs**						
≤3 (n=41)	17	19	5	0.127	0.207	0.505
>3 (n=67)	38	24	5			
Receptors						
ER+ (n=101)	36	51	14	0.001	0.019	0.547
ER- (n=81)	51	24	6			
PR+ (n=104)	41	50	13	0.009	0.116	0.543
PR- (n=78)	46	25	7			
HER2+ (n=78)	38	36	4	0.347	0.041	0.021
HER2- (n=104)	49	39	16			

*Lymph node, **Involved lymph nodes, #Chi-square test. ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2

Table 2: Binary logistic regression analysis comparing recurrence within after 5 years of diagnosis or recurrence after 10 years of diagnosis with up to 5 years of diagnosis

Variables	5-10 OR* (95% CI)	P	10-15 OR* (95% CI)	P
Receptors				
ER+	0.33 (0.17-0.63)	0.001	0.30 (0.10-0.86)	0.025
ER-	Reference		Reference	
PR+	0.44 (0.23-0.84)	0.013	0.48 (0.17-1.31)	0.155
PR-	Reference		Reference	
HER2+	2.99 (0.85-11.02)	0.245	3.10 (0.95-10.04)	0.059
HER2-	Reference		Reference	
Histological grade				
I	NA#	NA#	NA#	NA#
II				
III				

#A binary logistic regression model was selected using Akaike Information Criterion in stepwise selection. ORs are adjusted for all of the factors listed in the table. ORs: Odds ratios; NA: Not applicable; CI: Confidence interval; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human epidermal growth factor receptor 2

In a study,^[15] data for patients with BC showed that PR absence was found to be a negative prognostic factor in BC patients with ER-positive locoregional recurrence, but another study, reported that none of IHC markers (ER, PR, HER2) provided statistically significant prognostic information in years 5–10.^[16] Other study reported that ER-negative tumors are commonly associated with a higher risk of early relapse.^[17] In our study, ER- and PR-positive rate were less in patients with early recurrence, and there was a significant correlation

between hormone receptor positivity and late or very late recurrence ($P < 0.05$). In addition, binary logistic regression analysis showed that ER-and PR-negative is prognostic factors in early recurrent patients compared to late recurrent group or ER-negative in very late recurrent group. Therefore, ER- and PR-positive are effective factors for recurrence in BC patients. Despite the fact that most BC patients have ER-positive tumors, up to 50% of the patients are or soon develop resistance to endocrine therapy.^[18] HER2 positivity is the primary factor when considering whether or not patients should receive adjuvant Herceptin therapy.^[19] In our study, HER2-positivity was less in patients with very late recurrence compared to early or late recurrence and these differences were statistically significant ($P < 0.05$) and in this study, HER2-positive patients received Herceptin, and also binary logistic regression analysis showed that HER2-positive is prognostic factors in early recurrent patients compared to very late recurrent group. A number of studies,^[18,20-22] reported that HER2 activation is one of the major mechanisms contributing to endocrine resistance. Therefore, based on our result and other results, it is probably HER2, or Herceptin therapy with their endocrine resistance in BC patients can cause high recurrences especially after 10 years of the first treatments [very late recurrence compared to late or early recurrence in Table 1]. A study,^[23] showed that age is a risk factor for recurrence in BC patients, and younger patients had more recurrence compared to older patients (25% vs. 11%). In our study, of 182 recurrent

patients, 50 patients had age <40 years (27.5%) and 132 had ≥40 years (72.5%), and there was a significant correlation between age and recurrence in three groups. Therefore, age alone is not a risk factor for recurrence.

There is also a direct correlation between LN involvement and the risk of distant recurrence.^[9] Distant recurrence has been associated with large tumor size, poorly differentiated disease, and nodal involvement, and these factors are believed to be correlated also with late metastasis.^[16] A study showed that early recurrence associated with unregulated stress response signaling and certain clinical parameters, such as molecular subtypes, tumor size, and grade; while late recurrence associated with mesenchymal characteristics of the tumor epithelium and gene expression alterations in the adjacent tumor stroma.^[24] In our study, there was a significant correlation between axillary LN involvement or tumor size and recurrence. There was also the correlation between histological grade and early recurrence. In future studies, should measure Ki67, p53, and other genes in BC patients to determine the correlation between them and recurrence rate.

To conclude, high histological grade and IHC markers (ER- and PR-negative or HER2-positive) are risk factors to determine the risk of recurrence, especially early recurrence and between them; ER is the more significant prognostic factor.

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Conflicts of interest

There are no conflicts of interest.

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