

## RESEARCH ARTICLE

# Differences in Prognostic Factors between Early and Late Recurrence Breast Cancers

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### Abstract

**Background:** Breast cancer (BC) is the most frequent malignancy among females and is a leading cause of death of middle-aged women. Herein, we evaluated baseline characteristics for BC patients and also compared these variables across early and late recurrence groups. **Materials and Methods:** Between 1995 to 2014, among female breast cancer patients referred to our oncology clinic, eighty-six were entered into our study. All had distant metastasis. 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. No recurrence was defined for survivors to a complete minimum of 10 years follow-up. Significant prognostic factors associated with early or late recurrence were selected according to the Akaike Information Criterion. **Results:** The median follow-up was 9 years (range, 1-18 years). During follow-up period, 51 recurrences occurred (distant metastasis), 31 early and 20 late. According to the site of recurrence, there were 51 distant. In this follow-up period, 19 patients died. Compared with the early recurrence group, the no recurrence group had lower lymph node involvement and more p53 positive lesions but the late recurrence group had lower tumor size. In comparison to no recurrence, p53 (odds ratio [OR] 6.94, 95% CI 1.49-32.16) was a significant prognostic factor for early recurrence within 5 years. **Conclusions:** Tumor size, p53 and LN metastasis are the most important risk factors for distance recurrence especially in early recurrence and also between of them, p53 is significant prognostic factor for early recurrence.

**Keywords:** Breast cancer - recurrence - p53 - tumor size

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### Introduction

Breast cancer (BC) is the most frequent malignancy among women that can be a leading cause of death through middle-aged women and this cancer accounts about one fifth of all female malignancy. BC is the leading cause of death in high income countries and second leading cause in low and middle income countries (Payandeh et al., 2015). Adjuvant chemotherapy and endocrine therapy for early BC have had a considerable impact on outcomes (Davies et al., 2011). Most relapses occur during the 2<sup>nd</sup> year after the treatment. Another peak is in the following 8 to 9.5 years. Then, the recurrence rate decreases. Of course, younger premenopausal women develop recurrence sooner (Yin et al., 2009). Multiple factors, such as race and ethnicity, are effective in BC survival. Also, tumor size and lymph node (LN) status are also directly related to the prognosis of BC (Omidvari et al., 2013). The involvement of the axillary LNs is the most important prognostic factor for recurrence in the early stages of BC according to the literature. Patients with cancer-positive LN have been reported to have a four to eight times higher

mortality rate in comparison to patients with negative LNs (Stankov et al., 2012). In patients with negative LN, tumor size is an independent prognostic factor of breast recurrence. Patients with tumors that were smaller than 1 cm in diameter had an overall 5-year survival rate of 99%, whereas patients with tumors of 3-5 cm in diameter had a survival rate of 86% (Carter et al., 1989). Tumor grade has also been widely accepted as a prognostic factor (Doussal et al., 1989). Approximately 15-23% of breast cancers over-express human epidermal growth factor receptor2 (HER2), a 185-kDa transmembrane tyrosine kinase, which is mainly found at the cell surface of tumor cells. HER2-positive breast cancer, featuring amplification of HER2/neu and negative expression of ER and PR, has the three following characteristics: rapid tumor growth, lower survival rate, and better response to adjuvant therapies (Wang et al., 2015).

Herein, we evaluated baseline characteristics for BC patients in Western Iran for the first time and also compared these variables in early recurrence, late recurrence and no recurrence for diagnosis of prognostic factors on distance recurrence.

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**Materials and Methods**

*Patients*

Between of 1995 to 2014, among referred BC patients to Oncology Clinic, Kermanshah, Iran, eighty-six female patients were entered to our study. We also deleted patients with metastasis at diagnosis. Baseline tumor characteristics for all patients were measured. Estrogen receptor (ER) and progesterone receptor (PR) positivity was defined as  $\geq 10\%$  positive tumor cells with nuclear staining. The human epidermal growth factor receptor 2 (HER2) positive was defined as either HER2 gene amplification by fluorescent *in situ* hybridization or scored as 3+ by IHC. In case of HER2 (+), fluorescent *in situ* hybridization was performed to determine HER2 positivity.

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). All patients had distant metastasis. 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. No recurrence was defined for survivors to complete minimum 10 years follow-up. According to the timing of first the recurrence, all patients were stratified into three groups (early recurrence (Group 1), late recurrence (Group 2), and no recurrence (Group 3) during the follow-up period).

*Statistical analysis*

We used Chi-square test for to compare baseline tumor characteristics and the binary logistic regression models

**Table 1. Adjutant Therapy for the Patients with Breast Cancer (n=86)**

Adjutant therapy		N (%)
Endocrine therapy	Yes	68 (79)
	No	18 (21)
Radiotherapy	Yes	58 (67.5)
	No	28 (32.5)
Chemotherapy	Yes	83 (96.5)
	No	3 (3.5)

**Table 2. Baseline Tumor Characteristics for Breast Cancer Patients According to Recurrence Pattern**

Variables	Early Recurrence (n=31)	Late Recurrence (n=20)	No Recurrence (n=35) Group2 <sup>#</sup>	Group 1 vs Group3 <sup>#</sup>	Group 2 vs Group1 <sup>#</sup>	Group 3 vs
Age				0.64	0.5	0.56
	<35(n=10)	3	3			
	$\geq 35$ (n=76)	28	17			
Tumor size(cm)*				0.003	0.36	0.06
	0.1-2(n=14)	4	5			
	2.1-5(n=46)	15	14			
	>5(n=9)	7	0			
Histological grade*				0.19	0.79	0.9
	I(n=7)	2	2			
	II(n=55)	21	14			
	III(n=12)	4	2			
ER*				0.3	0.18	0.5
	Positive(n=45)	15	13			
	Negative(n=39)	14	7			
PR*				0.8	0.45	0.25
	Positive(n=50)	19	12			
	Negative(n=34)	10	8			
HER2*				0.59	0.44	0.19
	Positive(n=18)	5	4			
	Negative(n=53)	22	12			
P53				0.28	0.16	0.005
	Positive(n=26)	5	6			
	Negative(n=33)	17	8			
LN involvement*				0.24	0.4	0.01
	Yes(n=46)	21	10			
	No(n=38)	8	10			
Laterality				0.98	0.21	0.16
	Right(n=42)	17	11			
	Left(n=44)	14	9			
History of breast cancer				0.43	0.39	0.57
	Yes(n=9)	4	1			
	No(n=77)	27	19			
Type of pathology				0.41	0.59	0.53
	IDC(n=84)	31	19			
	ILC(n=2)	1	0			

\*Values with missing data; <sup>#</sup>Chi-Square Test (P-value); Abbreviation: LN, Lymph Node; IDC, Invasive ductal carcinoma; ILC, Invasive lobular carcinoma

**Table 3. Binary logistic regression analysis comparing recurrence within 5 years of diagnosis or after 5 years of diagnosis with no recurrence**

Characteristics	Early recurrence OR* (95% CI)	P-value	Late recurrence OR (95% CI)	P-value
Tumor size*		0.62	n/a#	n/a#
0.1-2	3.63 (0.24-53.27)	0.34		
2.1-5	1.43 (0.17-11.45)	0.73		
>5	Reference			
P53		0.01		0.16
Positive	6.94 (1.49-32.16)		2.97 (.64-13.68)	
Negative	Reference		Reference	
LN involvement*		0.48		0.47
Yes	0.60 (0.14-2.46)		1.74 (0.38-7.87)	
No	Reference			

OR: odds ratio; Abbreviation: LN, Lymph Node; n/a, not applicable; \*Values with missing data; #A binary logistic regression model was selected using Akaike Information Criteria (AIC) in stepwise selection. Odds ratios are adjusted for all of the factors listed in the table

were employed to compare characteristics between the no recurrence and early or late recurrence groups. The significant prognostic factors associated with early or late recurrence were selected according to the Akaike Information Criterion. All statistical analyses were performed using the IBM SPSS statistics version 19 that  $p < 0.05$  was statistically significant.

## Results

The mean age at diagnosis was  $47.11 \pm 12.53$  years and the median age was 45 years (range, 27-79 years), 100% female, that the median follow-up was 9 years (range, 1-18 years). During follow-up period, 51 recurrences occurred (distant metastasis), 31 early recurrences and 20 late recurrences. According to the site of recurrence, there were 51 distant recurrences. In this follow-up period, 19 patients died.

All patients received mastectomy at the first diagnosis. Of 105 patients, 68 patients (79%) received endocrine therapy (tamoxifen or aromatase inhibitor). Fifty-eight patients (67.5%) were treated with radiotherapy and 83 patients (93.5%) received chemotherapy (Table 1).

Baseline tumor characteristics for BC patients according to recurrence pattern were listed and compared in the paired groups (Table 2). Compared with the early recurrence group, no recurrence group had lower LN involvement and more p53 positive but late recurrence group had lower tumor size.

Prognostic Factors using Binary Logistic Regression Model: In comparison to no recurrence, p53 (odds ratio [OR] 6.94, 95% CI 1.49-32.16) was significant prognostic factors for early recurrence within 5 years (Table 3).

## Discussion

BC is a heterogeneous disease and is currently divided into subtypes in accordance with the status of ER, PR and HER2 (Payandeh et al., 2015). Following primary treatment for early BC, systemic adjuvant therapy is given to reduce the risk of recurrence by targeting any undetectable micrometastatic deposits. Adjuvant systemic treatment may include endocrine therapy, chemotherapy and antibody therapy, depending on the presence or

absence of hormone receptors, HER2 status and the estimated risk of relapse (Thürlimann, 2007). Recurrent BC occurring after the initial treatment is associated with poor outcome. 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 (Perez-Rivas et al., 2014). Although ER negative tumors are commonly associated with a higher risk of early relapse (Hess et al., 2013). Data were available for 265 diagnosed patients with BC in other study that PR absence was found to be a negative prognostic factor in BC patients with ER-positive locoregional recurrence (Bogina et al., 2015). In our study, ER positive in early recurrence and late recurrence was more percentage but there was no significant correlation between of early recurrence or late recurrence and no recurrence. The results for PR positive are similar to ER positive. Therefore, difference between of our results with other results is probably because small sample volume, efficacy of other factors on recurrence or sequence of treatment. HER2 positive is the primary factor when considering whether or not patients should receive adjuvant endocrine therapy (Thürlimann, 2007) that in this study, HER2 positive in patients with early recurrence or late recurrence is less than no recurrence (18.5% vs. 32% and 25% vs 32%, respectively). A study (Boyages et al., 1990) reported that very young age (defined as 34 years of age or younger) was also a significant factor associated with the risk of breast recurrence. Very young patients comprised 8% of the patient population and accounted for 16% of breast recurrences. Fifteen of 61 very young patients (25%) developed a breast recurrence compared with 76 of 722 older patients (11%) ( $p = 0.001$ ). In our study, there was significant correlation between early or late recurrence with no recurrence for age.

A total of 1173 patients were treated with mastectomy alone and no adjuvant therapy. In this study (s). In our study, tumors less than 5 cm for early recurrence were more compared to late recurrence or no recurrence. Therefore, higher tumor size can be a risk factor for recurrence especially for early recurrence vs late recurrence that is this relationship spastically significant ( $P < 0.05$ ). LN positive was more for early recurrence compared to no recurrence ( $P < 0.05$ ), so LN positive is other risk factor. Other study (Diaconu et al., 2010)

included 144 patients in stage II BC, over a period of 5 years that in all these patients the first therapeutic option was surgery (radically modified mastectomy type Madden), followed by systemic chemotherapy-FAC or FEC, 6 cycles, and finally Tamoxifen. 34 out of them developed metastases in a period between 6 and 72 months, most of them in the first 26 months; 25 out of these 34 didn't have metastases in the axillary LNs, and in 18 patients ER and PR were highly positive. HER2 was negative or low expressed in patients with metastases. Our study after mastectomy, were treated with chemotherapy, radiotherapy and hormone therapy (a few patients were treated just with one or two from them) (Table 1). All patients developed metastasis that 31 patients between 0 to 5 years and 20 patients after 5 years. Of 43 patients with metastasis recurrence, 33 patients (76.7%) had HER2 negative. A study (Saxe et al., 1999) reported that oral contraceptive use, LN positive status, and tumor stage were associated with increased risk of recurrence. There is also a direct correlation of positive LN status with the risk of distant recurrence (Fisher et al., 1983). The extent of nodal involvement and the complete pathological response to neoadjuvant chemotherapy were the most important predictors of BC recurrence (Stankov et al., 2012). In a research was shown that tumor size, stage, and nodal involvement are routinely used to estimate the likelihood of BC recurrence and are relevant for both ER positive and -negative cancer. These clinical parameters are useful for predicting recurrence in the first 5 years after diagnosis. 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 (Sestak and Cuzick, 2015), and at last was shown that none of the immunohistochemical markers (ER, PR, HER2, Ki67) provided statistically significant prognostic information in years 5 to 10, except for nodal status and tumor size (Sestak et al., 2015). Also, recurrence was detected in 141 patient during follow-up that in this research, tumors recurred after 5 years more likely to have lower stage ( $p=0.05$ ), tumors without lymphovascular invasion ( $p<0.001$ ) and perineural invasion ( $p=0.01$ ), and also HER2 negative ( $p < 0.001$ ) (Oven Ustaalioglu et al., 2015). In a study with multivariate analysis, higher nodal stage (N0 vs N2, OR 3.189; N0 vs N3, OR 9.948), higher histologic grade (grade 1 vs grade 2, OR 3.896; grade 1 vs grade 3, OR 5.945), age  $>35$  years (OR 0.295), and receiving endocrine therapy (OR 0.293) affected early recurrence. Compared to no recurrence, receiving endocrine therapy (OR 0.285) was solely related to decreased risk of late recurrence. Increased risk of early recurrence was noted with the higher nodal stage when early and no recurrences were compared. This phenomenon was not found in late recurrence. In the last comparison between the early and late recurrence, higher nodal stage (N0 vs N3, OR 16.779) and higher histologic grade (grade 1 vs grade 3, OR 18.111) repeatedly weighted for early recurrence (Ahn et al., 2013). The p53 tumor suppressor protein is a principal mediator of growth arrest, senescence, and apoptosis in response to a broad array of cellular damage (Shafiee et al., 2015). In our study, tumor size, p53 and LN metastasis were the most important risk

factors for distance recurrence, respectively. Multivariate analysis showed that p53 is a significant prognostic factor (OR 6.94) for early recurrence vs no recurrence. Therefore, p53 positive increases early recurrence.

In conclusion, tumor size, p53 and LN metastasis are the most important risk factors for distance recurrence especially in early recurrence and also between of them, p53 is significant prognostic factor in early recurrence. Therefore, it is better that specialists at the first visit with diagnosis these factors, determine policy of treatment exactly. Also, it is recommended about prolongation of endocrine therapy to ten years more than five years that probably can prevent in early recurrence cases.

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