RESEARCH ARTICLE

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Effecst of Patho- Biological Factors on the Survival of Recurrent Breast Cancer Cases

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Abstract

Background: Recurrence of breast cancer after treatment is generally due to loco-regional invasion or distant metastasis. Although patients with metastasis are considered incurable, existing treatments might prolong a patient's life while also improving its quality. Choice of approach for individual patients requires identification of relevant survival factors. This study concerns factors influencing survival after recurrence in Iranian breast cancer patients. **Methods:** This study was performed on 442 recurrent breast cancer patients referred to the Cancer Research Center of Shahid Beheshti University between 1985 and 2015. After confirming recurrence as a distant metastasis or loco-regional invasion, the effects of demographic, clinic-pathologic, biological, type of surgery and type of adjuvant treatment on survival were evaluated using univariate and multivariate stratified Cox models. **Results:** The mean survival after recurrence was 18 months (5 days to 13 years), 219 patients (70.42%) survived two years, 75 patients (24.12%) survived from 2 to 5 years, and 17 patients (5.47%) survived more than 5 years. In this study, it was found through univariate analysis that the factors of age, lymph node status, DFI, place of recurrence and nodal ratio demonstrated greatest influence on survival after recurrence. On multivariate analysis, the most important factors influencing survival were the place of recurrence and the lymph node status. **Conclusion:** The results of this study enhance our knowledge of effects of different factors on survival of patients after breast cancer recurrence. Thus, they may be used to inform treatment choice.

Keywords: Recurrent breast cancer- survival- prognosis

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Introduction

Breast cancer is the most common cancer in women around the world (Ferlay et al., 2015) including Iranian women, however, the prevalence age of Iranian women for this disease is ten years below the prevalence age of women in advanced and developed countries (Yavari et al., 2003; Harirchi et al., 2004). 30-40% of breast cancer patients experience metastasis during their follow-up. The pique of recurrence is 2 to 3 years after treatment (Dawood et al., 2010; Fodor et al., 2011).

Despite the incurability of metastatic disease, identifying the methods to promote increased survival and improved quality of life for patients with metastatic breast cancer is the main objective of the studies that have been done so far in this field. The goal of this retrospective study is to investigate the factors influencing the survival of patients with recurrent breast cancer.

In previous studies, factors such as biological characteristics of tumor and the comparison of different subtypes (luminal A, B), HER2 positive and triple negative were studied. Also, there were studies on the effects of lymph node status, surgical method, disease stage, patient age, DFI on the evaluation of tumor's tendency towards metastasis. However, the effects of these factors on the survival of patients after recurrence have been given more attention in this study. Previous studies investigating the effective factors of survival in metastatic breast cancer patients, the factors included the place of metastasis, the extent of metastasis (visceral metastasis vs. bone metastases), HER2 receptor and performance status.

DFI, the previous adjuvant treatment and metastatic therapy have been effective in survival of patients (Beslija et al., 2009). Some studies also found that factors such as age, black race, socioeconomic status and BMI were effective on survival (Hortobagyi et al., 1983; Vincent et al., 1986; Bradley et al., 2002; Berclaz et al., 2004; Grau et al., 2005; Lagerlund et al., 2005; Loi et al., 2005; Tao et al., 2005; Whiteman et al., 2005; Bouchardy et al., 2006; Dalton et al., 2006; Caan et al., 2008; Cluze et al., 2009; Rezaianzadeh et al., 2009).

In fact, different studies did not report the same risk factor and effective factor, thus, more studies are needed in different societies in order to find more effective factors

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while finding more effective solutions in order to increase patients' survival.

Materials and Methods

This study was performed on 442 recurrent breast cancer patients who had been referred to the Cancer Research Center of the Shahid Beheshti University between 1985 to 2015. After initial treatment, including surgical and adjuvant therapy, 442 patients experienced recurrence during the follow-up. Upon confirmation of cancer recurrence; loco-regional recurrence, visceral metastasis and bone metastasis were treated and patients were followed up. At the end of the follow-up period the factors influencing survival after recurrence were evaluated based on patient's death or condition in the last visit.

Patients' information was extracted from the records of Shahid Beheshti Cancer Research Center, which included demographic data (age), tumor characteristics (tumor size, estrogen receptor status, progesterone, HER2), stage of disease, lymph vascular invasion, lymph node status, nodal ratio (ie. the ratio of the number of involved lymph nodes to the total number of removed lymph nodes), primary surgery method (mastectomy or breast preservation surgery), the location of metastasis, DFI (disease free survival), adjuvant treatments (chemotherapy and Radiotherapy). Subsequently, the effect of these factors on survival (the time between the diagnosis of metastasis and the occurrence of death or not in the last visit at the end of the follow-up period (2016, March 19th)) was evaluated using the analysis of univariate and multivariate Stratified cox-model.

In Statistical analysis Using a stratified Cox proportional hazards model to assess the patient's age at the time of diagnosis, disease stage, lympho-vascular invasion, primary tumor size, lymph node involvement, DFI (disease free survival), the location of metastasis (visceral, bone, loco-regional), biological categorization of tumors including luminal A (ER and PR Positive and HER2 negative), luminal B (ER and PR positive and HER2 positive), HER2 n reach (ER and PR negative and HER2 positive) and triple negative (ER and PR and HER2 negative) on survival was applied using univariate and multivariate analyses and P values of 0.05. We used 0.25 cut-off point to analyze the nodal ratio which was proved in previous study (21.22) and Kaplan Meyer curve of survival was drawn based on effective factors on survival after recurrence (Figure 1). Comparison of survival was performed in a different categorization using a log -rank test. Table 3: life table performed for 2,5years survival

The analysis was performed using the STATA software version 16. This study have been performed in accordance with Declaration of Helsinki.

Results

Of 3449 breast cancer patients who had been referred to the Cancer Research Center of Shahid

Beheshti University between 1985 and 2015, 442 patients had recurrences.

Table 1. Prognostic Factors for Survival in Recurrent Breast Cancer Patients (Univariate Cox Regression Analysis)

Factors	Haz. Ratio	p>z	95%con.interval
Age			
<40	1		
>=40	2.675737	0.041	1.041227-6.876087
Stage			
1	1		
2	1.176159	0.697	0.5197839-2.661396
3	1.759438	0.14	0.8309554-3.725378
Grade			
1	1		
2	1.394477	0.503	0.5272838-3.687891
3	2.512724	0.066	0.9399615-6.717065
LVI *			
negative	1		
positive	2.10547	0.561	1.248773-3.549886
Receptors			
Luminal A**	1		
Luminal B***	1.842634	0.085	0.9184965-3.696584
Triple negative****	1.482221	0.268	0.7385408-2.974758
Her2 n reach*****	1.739194	0.12	0.8659807-3.492914
Tumor size			
<2cm	1		
2-5cm	1.016194	0.959	0.548013-1.884352
>5cm	1.256021	0.502	0.6457379-2.443081
Lymph node			
Negative	1		
Positive<4node	2.337451	0.008	1.249909-4.371266
Positive>4=node	2.745066	0	1.574971-4.78446
DFI******			
<2year	1		
>=2year	0.6323073	0.018	0.4328129-0.9237537
Chemotherapy			
Negative	1		
Positive	2.313931	0.46	0.2494663-21.46293
Radiotherapy			
Positive	1.616843	0.463	0.448723-5.825821
Place			
loco regional	1		
Bon	1.924987	0.066	0.9568276-3.872771
Visceral	4.027297	0	2.242385-7.232979
Surgery			
BCS 1	1		
MRM 2	1.129304	0.599	0.7176197-1.777165
Nodal ratio			
<0.25	1		
>0.25	2.026603	0.002	.28655-3.192351

*, Lymph vascular invasion; **, ER and PR and her2 receptor are positive; ***, ER and PR are positive and her2 is negative; ****, ER and PR and her2 are negative; *****, ER and PR are negative and her2 is positive; ******, disease free survival; 1, breast conserving surgery 2, modified radical mastectomy.

Table 2. Prognostics Factors for Survival in Recurrent Breast Cancer Patients (Multivariate Cox Regression Analysis)

Factors	Haz.Ratio	p>z	95%con.interval
Age			
<40	1		
>=40	0.0058437	0.253	8.70e-7-3924609
Stage			
1			
2	3.420663	0.819	0.00909-128716.9
3	2.88E-12		
Tumor size			
<2cm	1		
2-5cm	0.0855957	0.652	1.99e-06-3690.573
>5cm	0.7908029	0.94	0.0016913-369.7621
Lymph node			
negative	1		
Positive<4 node	4.58E+11	0	1.26e+09-1.67e+14
Positive>=4node	3.63E+13	0	7.44e+10-1.78e+16
DFI			
<2year	1		
>=2year	0.8660959	0.909	0.743554-10.08834
Surgery			
BCS	1		
MRM	0.319669	0.13	0.0037-2.2762072
Place			
Loco regional	1		
Bon	4.17E+11	0	2.73e+10-6.37e+12
Visceral	3.93E+11	0	
Receptors			
Luminal A	1		
Luminal B	4.127313	0.363	0.1949789-87.36695
Triple negative	2.197177	0.686	0.484883-99.56191
Her2 nreach	6.559239	0.24	0.2442123-151.3785
LVI			
negative	1		
positive	0.148506	0.194	0.0083319-2.646926
Nodal Ratio			
<0.25	1		
>=0.25	0.100675	0.089	0.000503-2.013802

This study was performed on 442 patients with breast cancer recurrence. The mean age of recurrent people was 50 years (24-90 years) and the mean survival was 1.6 years after recurrence (5 days -13 years). 219 patients (70.42 %) survived for two years, 75 patients (12.22%) survived between 2-5 years, and 17 patients (5.47%) survived more than 5 years; in 131 patients, the survival was unknown.

The average follow-up period of patients was 45 months (38 months, 10 months), of which 155 died during this period.

47.96% of the distant metastasis included 41% bone metastasis, 22.16% lung metastasis, 14.22% liver metastasis, 16.5% brain metastasis, 47.0% spleen metastasis and 4.7% other cases, 93 patients (43.86%) had loco-regional recurrence. The mean survival after loco-regional recurrence was 24 months, while it lasted

Table 3. Life Table

interval	Beq. Total	Deaths	Lost	Survival	Std. Error	95% con.int.
o-2 year	278	119	75	0.5052	0.0322	0.4404 -0.5664
2-5 year	84	33	36	0.2526	0.035	0.1870-0.3232
>5 year	15	3	12	0.1684	0.0461	0.0901-0.2675

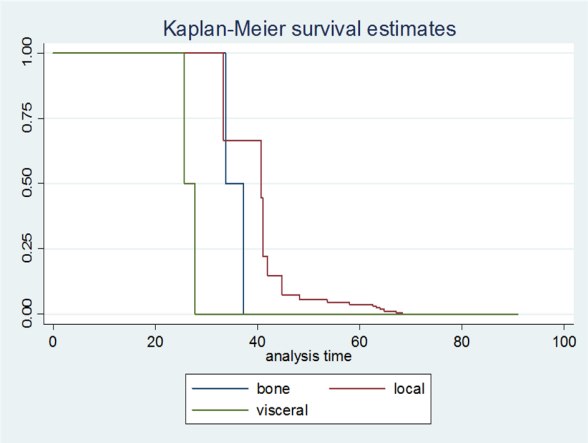

Figure 1. Kaplan – Meier Curve in Survival Estimates According to Place Recurrence

for 22 months in bone recurrence and 15.6 months in visceral recurrence. The mean survival after recurrence in a variety of biomarkers including luminal A and B was 20 months while it lasted for 14 months in patients with triple negative, 24 months in HER2 +. Table 1 prognostic factors for survival in recurrent breast cancer patients (Univariate cox regression analysis)

Factors such as age, stage of disease, primary grade of tumor, lympho-vascular invasion, the primary tumor size, lymph node metastasis, DFI (disease free survival), adjuvant therapy (chemotherapy and radiotherapy), the location of recurrence (visceral, bone, loco-regional) and nodal ratio analysis were evaluated using univariate and multivariate analyses. The result of this analysis is shown inTable 2:Prognostics factors for survival in recurrent breast cancer patients (Multivariate cox regression analysis).

the univariate analysis of Cox regression model has shown the most important factors with a negative impact on survival in metastatic patients including age more than 40 years (p = 0.041), lymph node involvement (p = 0.000), visceral recurrence (p = 0.000) compared to the bone recurrence and loco-regional recurrence while the DFI <2 years (p = 0.018) and (p = 0.002) nodal ratio> 0.25. Yet, in the multivariate analysis of the most important factors included visceral recurrence (p = 0.000), status of lymph node involvement (p = 0.000) while nodal ratio in the multivariate analysis showed no effect on survival after recurrence.

Discussion

Several studies have shown that the age of diagnosis is a major contributor to survival, which means that patients over 50 years of age have a worse prognosis (Khanfir et

al., 2013). In our study, based on univariate analysis, the age of more than 40 years had a negative effect on survival after recurrence. The importance of DFI (disease free survival), i.e. the period without disease after breast cancer treatment to the recurrence, is known to be a major contributor to recurrence. It has been proven in numerous studies that patients with a long DFI have better prognosis (Blanco et al., 1990; Bastholt et al., 1996; Dhodapkar et al., 1996; Cardoso et al., 2002). In this study, the effect of DFI on survival after recurrence was also observed in the univariate analysis. DFI <2 years had a negative effect on survival after recurrence.

In our study on univariate and multivariate analysis, the location of metastasis has the most important effect on survival prediction, thus, visceral metastasis has a more negative effect on survival while bone metastasis has worse prognosis compared to loco-regional recurrence. This result is also evident in previous studies reporting that prognosis of patients with visceral metastasis has been proven to be worse than those with bone metastasis (Vogel et al., 1992; Bastholt et al., 1996; Venturini et al., 1996; Chang et al., 2003; Truong et al., 2005).

Another important and different outcome of this study was the effect of lymph node involvement on survival after recurrence. Several studies have been conducted on the negative effects of nodal ratio on breast cancer patients concerning their increased risk of metastasis reporting that those with a nodal ratio of> 0.25 had worse prognosis. This ratio enjoyed a more prognostic value than just the number of lymph nodes (Veronesi et al., 1993). In a study conducted by Dr. Tazhibi and his colleagues in Iran, in patients with metastatic breast cancer and NR> 0.25 the risk of subsequent metastasis increased and patients survive for a less period of time (Tausch et al., 2012).

However, in our study, lymph node involvement, regardless of its number, had a negative effect on survival after recurrence, and nodal ratio was not effective in multivariate analysis. In fact, patients with less than 4 lymph nodes or with more involvement received equal negative effects on their survival after recurrence, (compared to the patients with negative lymph nodes). Although the number of lymph nodes in these patients influenced their increased risk of recurrence, lymph node involvement regardless of its number reduces survival after recurrence.

Also, in this study, the primary surgical method (mastectomy or breast preservation surgery) has not been shown to have an effect on survival. The effect of primary adjuvant treatments (radiotherapy and chemotherapy) has not been proven on survival, which may be due to the fact that about 80% of patients received chemotherapy and radiotherapy. This effect was not measurable in two groups. One of the limitations in this study was the lack of evaluation for the effects of radiotherapy, chemotherapy and hormone therapy in patients after recurrence, mostly due to lack of data in this area.

The status of hormone receptors (estrogen, progesterone, HER2 receptor, triple negative) has been shown in several studies reporting that the patients with luminal A and B have a better prognosis than the patients with triple negative(Hess et al., 2003; Tazhibi et al., 2013). In a series of studies of the patients with HER2 + after recurrence, it was reported that they had better prognosis than other biomarkers (Bertucci et al., 2008; Sparano et al., 2012; Weide et al., 2014). However, in this study, the effect of biological factors on survival evaluation after recurrence has not been proven in the multivariate and univariate analyses. Patients with HER2 positive had a prolonged mean survival after recurrence, so that the mean survival after recurrence in the patients with luminal A and B was 20 months while the triple negatives were 15 months. Yet, the patients with HER2 positive had a survival of 24 months, which could be due to the effect of anti her2 treatment. Several studies have highlighted the effect of this treatment on increasing the survival of HER2 positive patients while suggesting that the treatment with trastuzumab as a humanized monoclonal antibody targeting HER2 receptor, also increases DFS, OVERAL SURVIVAL both in the adjuvant and metastatic phases(Verma et al., 2012; Cadoo et al., 2013).

This study did not evaluate the effect of metastatic adjuvant therapy and surgical treatment of breast tumor in patients with metastatic in primary breast cancer. In fact, we examined the effect of some factors on the survival of metastatic breast cancer patients. Further investigation in this field are still needed.

Statement conflict of Interest

The authors of this study receive research support from the Vice chancellor for research of the Shahid Beheshti University of Medical Sciences. The terms of this arrangement have been reviewed and approved by the University of Shahid Beheshti at Tehran in accordance with its policy on objectivity in research.

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