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## Breast Cancer Recurrence Survival among Iranian Patients; A 17-Year Retrospective Cohort Study

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## ABSTRACT

**Background:** Nowadays breast cancer (BC) is the most common cancer in women. More than 1.5 million cases are detected yearly. Survival of patients is dependent on several factors. Metastasis and cancer recurrence of different types and in different locations have various outcome.

**Methods:** This is a retrospective cohort study to describe survival of patients after diagnosis of breast cancer based on receptor subtypes and sites of metastasis among Iranian population. A total number of 2051 females with breast cancer were evaluated and among these, 138 patients with recurrent BC were investigated.

**Results:** The 1-year survival of local, bone, visceral and brain metastasis were 64.99%, 63%, 32.83%, and 21.57%, respectively. Based on sites of metastasis, bone and local metastasis showed the best survival while brain and visceral metastasis had the worst survival and prognosis.

**Conclusion:** Our study showed that HER2 enriched positive BCs had the worst survival, this may be due to Trastuzumab uncovered insurance till 10 years ago in our country. Also, drugs related to luminal A and B which are used to improve their survival and hormonal therapy could be associated with their better prognosis in comparison to triple negative receptor subtype. But this study showed that triple negative BC had better survival.

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## INTRODUCTION

Nowadays breast cancer (BC) is the most common cancer in women.<sup>1</sup> More than 1.5 million cases are detected yearly.<sup>2</sup>

BC has been known as a heterogeneous disease which might have various clinical outcomes.<sup>3</sup> Medical therapies can be preventive in earlier stages.<sup>4</sup>

in spite of all kinds of therapies still patients with breast cancer are at high risk of relapse after 5 years.<sup>5</sup>

Adjuvant chemotherapy can decrease the risk of recurrence during first 5 years following to diagnosis.<sup>6</sup> Prognostic factors which can almost anticipate the chance of early recurrence of breast cancer are limited.<sup>7</sup> As a result of several studies the most important breast cancer prognostic factors are tumor size and number of involved lymph nodes.<sup>8</sup>

Size of the tumor, histological grade, HER2 receptors and the estrogen progesterone levels are known factors that have also value for prognosis of patients with risk of breast cancer recurrence.<sup>9</sup>

Moreover, studies suggested that extended tamoxifen therapy (extra 5 years) in women with breast cancers at premature stages can lower the risk of late recurrence.<sup>10, 11</sup>

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Although so many trials had been performed on factors which might be capable of displaying prognosis of BC and its recurrence, all the known markers used currently or recently introduced cannot precisely address the timing of metastatic recurrence.<sup>12</sup>

We are focusing on understanding the breast cancer recurrence and survival among Iranian population. Describing survival of patients after diagnosis of breast cancer based on receptor subtypes and sites of metastasis which provide trustworthy information to categorize breast cancer severity according to receptor subtypes and sites of metastasis. To achieve this goal, we analyzed data acquired from previous studies and develop a horizon through controlling the risk of recurrence.

## METHODS

In this Retrospective Cohort Study, A total number of 2051 female patients with breast cancer who were referred to Hazrat-E-Rasul Akram hospital and Khatam-Ol-Anbia hospital were followed from October 2003-2020.

Among these patients, 138 cases with recurrent breast cancer were included and non-recurrent patients were excluded. Each patient is followed every 6 months in order to update the medical record for at least 5 years. Patients who were male, had lost data or those who had insufficient follow up period also were excluded. Patient's information was extracted from their clinical records in Rasul Akram and Khatam-Ol-Anbia hospitals. Variables include demographic data ; age at the diagnosis of breast cancer, number of pregnancies, number of abortions, family history of breast cancer, marital status, breast feeding duration, and taking oral contraceptives also pathology and surgical findings such as type of tumor pathology, tumor size, number of total lymph nodes, status of sentinel node, perineural or vascular invasion, calcification, necrosis, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), percentage of KI67 antigen, status of receiving neoadjuvant therapy, and surgery procedure are recorded. Likewise, overall and disease-free survival (DFS) status, recurrence location is investigated at the end of the follow up.

Three types of tumor pathology were reported as invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), ductal carcinoma in situ (DCIS). Three surgical procedures were as follow; breast conserving, modified radical mastectomy (MRM) and subcutaneous mastectomy with reconstruction. DFS (disease-free survival) in this study was the time interval between the diagnosis of breast cancer and its recurrence. Also, recurrence site was categorized based on their importance local, bone, visceral and brain

recurrence. The Kaplan-Meier survival estimate, survival rate and Log-rank test were performed and reported. This study was done based on declaration of Helsinki, and all the patients filled and signed the consent form to participate in this study and this trial has been approved by the ethical committee of Iran University of Medical Sciences (IUMS). All of the collected data were analyzed by STATA version 13 and level of significance was considered <0.05. Descriptive analysis was presented as mean ( $\pm$ SD) for quantitative variables, frequency and percentage for categorical variables.

## RESULTS

The mean age of patients was  $47.95 \pm 12.01$  years at diagnosis and according to the history of patients there was a positive family history for breast cancer in 36 patients (26.1%). 26 patients (18.8%) mentioned no history of breast feeding and 13 (9.4%) patients were married but had no child and 12 (8.7%) were not married. Demographic data, tumor details and recurrence information were shown in Tables 1-3.

Breast tumor features in different patients analyzed based on pathology report. Mean size of tumors among all eligible cases was  $3.06 \pm 1.70$  centimeters. Total number of resected lymph nodes in all cases was  $10.33 \pm 6.49$  and among these resected lymph nodes  $6.97 \pm 5.69$  were involved by difference breast cancers.

**Table 1.** Baseline characteristics of 138 patients with recurrent breast cancer

Variable	
<b>Quantitative</b>	Mean $\pm$ SD
Age at Diagnosis	47.95 $\pm$ 12.01 years old
Pregnancy Times	2.86 $\pm$ 1.42
Abortion Times	1.34 $\pm$ 0.48
<b>Qualitative</b>	Number (%)
Family History Positive	36 (26.1%)
<b>Marital Status</b>	
	12 (8.7%)
	13 (9.4%)
	113 (81.9%)
<b>Breast Feeding</b>	
	26 (18.8%)
	8 (5.8%)
	16 (11.6%)
	39 (28.3%)
	49 (35.5%)
<b>Oral Contraceptive</b>	
	113 (81.9%)
	6 (4.3%)
	7 (5.1%)
	12 (8.7%)

**Table 2.** Breast tumors details based on pathology report in patients with recurrence

Variable		Variable	
Quantitative	Mean±SD	Multicentric	11 (8%)
Tumor size Centimeter	3.06±1.70	Neoadjuvant	22 (15.9%)
Total lymph nodes Numbers	10.33±6.49	ER Positive	87 (63%)
Positive lymph nodes Numbers	6.97±5.69	PR Positive	84 (60.9%)
Qualitative	Number (%)	HER2 Positive	28 (20.3%)
Pathology		KI67 Percent	29.17±20.04
Invasive DC	98 (71%)	Grade	
Invasive LC	26 (18.8%)	1	5 (3.6%)
Mixed Invasive DCIS	2 (1.4%)	2	56 (40.6%)
DCIS	11 (8%)	3	77 (55.8%)
DCIS + LCIS	1 (0.7%)	Stage	
Sentinel node		2A	31 (22.5%)
Not Done	36 (26.1%)	2B	17 (12.3%)
Done & Positive	57 (41.3%)	3A	27 (19.5%)
Done & Free	45 (32.6%)	3B	4 (2.9%)
Perineural invasion Positive	29 (21%)	3C	24 (17.4%)
Vascular invasion Positive	66 (47.8%)	4	35 (25.4%)
Calcification Positive	26 (18.8%)	Type	
Necrosis Positive	40 (29%)	Luminal A	79 (57.2%)
Surgery type		Luminal B	11 (8%)
Breast Conserving	83 (60.1%)	Triple Negative	31 (22.5%)
Subcutaneous Mastectomy with Repair	9 (6.6%)	HER2 Enrich	17 (12.3%)
Mastectomy	46 (33.3%)		

Invasive DC; invasive ductal carcinoma, Invasive LC; invasive lobular carcinoma, DCIS; ductal carcinoma in situ, DCIS+LCIS; ductal carcinoma in situ and lobular carcinoma in situ ER; estrogen receptor, PR; progesterone receptor, HER2 human epidermal growth factor receptor 2.

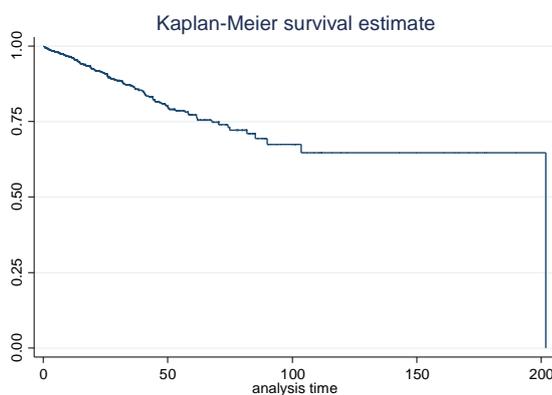
**Table 3.** Death, & Location of recurrent breast cancer

Site	
Local (Breast/Skin)	32 (27.6%)
Bone	20 (17.2%)
Visceral (lung/liver)	50 (43.1%)
Brain	14 (12.1%)
Death	54 (39.1%)

Analysis of Stage of tumor in patients showed that 35 (25.4%) patients had stage 4 of breast cancer while 4 (2.9%) had stage 3B of breast cancer and 12.3% had stage 2B. Sixty five percent of patients were Luminal A or B, 31 (22.5%) patients triple negative receptor and 17 (12.3%) patients were HER2 enrich.

Based on site of metastasis 32 (27.6%) of patients had local cutaneous metastasis, 50 (43.1%) patients had visceral metastasis, 20 (17.2%)

Patients with bone metastasis and 14 (12.1%) patients with brain metastasis According to the follow up of patients, mortality was 39.1% (54 cases) among

**Figure 1.** Total disease-free survival of the recurrence patients

X axis is duration of evaluation in weeks

Y axis shows the survival rate of patients



recurrent patients and As the Graph 1a shows, the 1-, 3- and 5-year disease-free survival were 96.13%, 86.51% and 77.10% respectively (Graph 1a).

Due to 4 types of recurrence that categorized, the log rank was calculated and there was a high significant difference in recurrence events after the surgery in 4 groups. Luminal B and HER2 Enriched were the subtypes of breast cancer with the lower and the highest recurrence probability after the surgery among all four subtypes, respectively. The equity of survival function was investigated using log-rank test ( $P=0.0022$ ) (Figure 3).

The 1-year survival of local, bone, visceral and brain metastasis in patients were 64.99%, 63%, 32.83%, and 21.57% respectively. Based on survival analysis of metastasis in 4 recurrence groups, there was significant difference among groups in the period of metastasis till death ( $P=0.0022$ ) (Figure 2).

Disease-free survival analysis was done and log rank test showed a significant difference in 4 groups based on recurrence type. ( $P=0.0110$ ) (Figure 4).

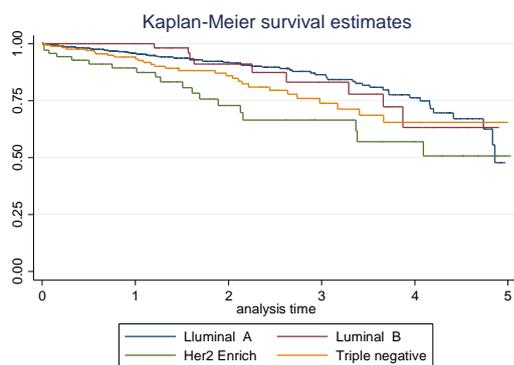
The mean of surgery time to recurrence diagnosis was higher in skin/breast (local) metastasis in comparison of other groups. However, the recurrence

time to death was lower in the visceral metastasis eventually (Table 4).

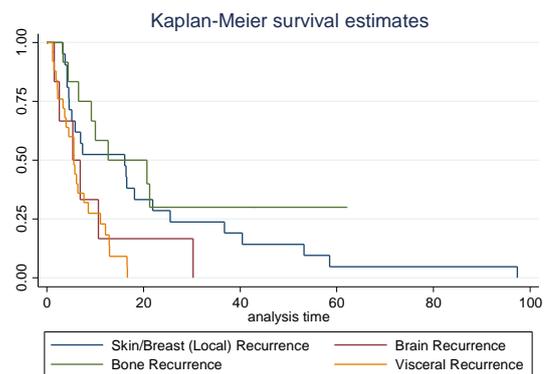
The Duration of liver and lung metastasis from the first surgery was  $24.9\pm 3.51$  and  $32.58\pm 6.25$  months respectively (95%CI: 17.96,31.83 months for liver recurrence and 20.23,44.9 months for lung recurrence). Also, the time to death from liver and lung recurrence diagnosis were  $10.65\pm 3.38$  and  $5.76\pm 0.85$  months respectively (95%CI: 3.91,17.39 months for liver recurrence and 4.06,7.45 months for lung recurrence).

## DISCUSSION

Several studies considered different variables as prognostic factors for breast cancer survival and recurrence. Gluck *et al.*,<sup>14</sup> Devita *et al.*,<sup>15</sup> and Kuru *et al.*,<sup>16</sup> demonstrated that lymph node involvement, primary tumor size and stage of malignancy in addition to older age ( $>50$  years), number of positive lymph nodes ( $>0$ ), SBR grade ( $>1$ ), negative HR status and treatment with adjuvant chemotherapy, estrogen, progesterone and HER2 receptors, pathology, invasion, calcification, grade, receptor type are inextricably intertwined with survival or recurrence of patients with breast cancer.<sup>17, 18, 19</sup>



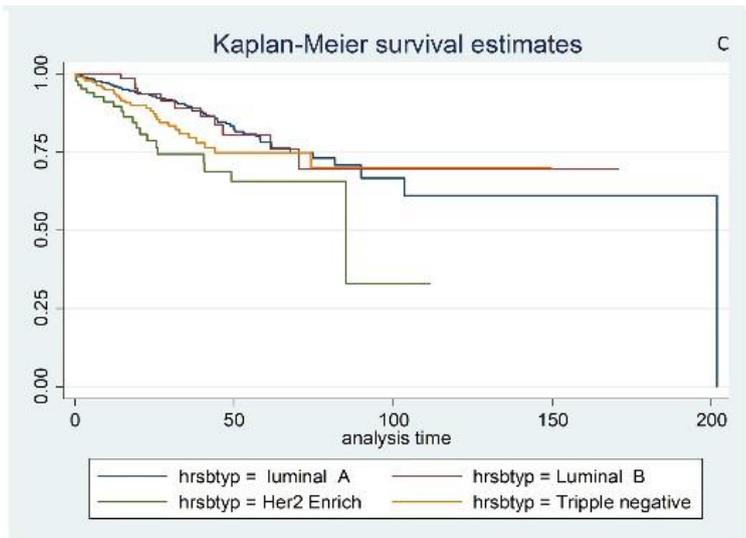
**Figure 2.** Survival probability in the first 5-year after surgery based on hormone receptor subtypes (4 subtypes), (Event: recurrence). X axis is indicative of years and Y axis is the survival rate



**Figure 3.** Survival from metastasis until death in recurrence patients. X axis is indicative of weeks and Y axis is the survival rate

**Table 4.** Mean duration between surgery to recurrence and recurrence to death

Group	Mean time (Months)		Standard error of mean (Months)		95% CI (low- High)	
	Surgery to Recurrence	Recurrence to Death	Surgery to Recurrence	Recurrence to Death	Surgery to Recurrence	Recurrence to Death
Skin/breast (Local)	31.571	21.444	4.477	5.252	(22.722-40.419)	(10.947-31.941)
Brain	22.872	9.538	6.222	4.354	(10.577-35.167)	(0.837-18.240)
Bone	26.150	11.008	5.561	2.424	(15.160-37.140)	(6.163-15.853)
Visceral	27.976	8.967	3.274	2.255	(21.505-34.446)	(4.460-13.475)



**Figure 4.** Disease-free survival based on hormone receptor. Y axis shows survival and X axis shows duration (months)

Our study confirms that prognosis and survival of patients can be different according to receptor subtypes, molecular subtypes and baseline characteristics, which is compatible with previous related studies.<sup>19</sup>

One of the main concerns in prognosis and survival of patients with breast cancer is DFI which is considered as an effective factor on survival of patients. The longer DFS the longer survival in patients with breast cancer even after recurrence.<sup>20</sup> Thus, disease free survival as a prognostic factor for recurrence of breast cancer could be evaluated through different aspects for instance, in our study we assessed disease free survival based on hormone receptors which showed that during first 5 years of evaluation and follow up HER2 enrich receptor positive patients had the worst outcome and also they had low disease free survival and the Luminal B and triple negative breast cancer subtypes had greater disease free survival. the worst prognosis of HER2 enrich receptor breast cancers could be correlated with the fact that most of the patients with HER2 enrich receptor subtype who survived in our study received monoclonal antibodies and new found drugs but on the other hand vast majority of patients included in our trial have not been treated with HER2 receptor drugs recently found, thus survival of triple negative patients was more than HER2 enrich receptor subtype. This finding will be altered by the consumption of new drugs in our patients and moreover results will be similar as new released studies that consider best prognosis of breast cancer attributed to HER2 enrich receptor subtypes. Survival of patients following to metastasis averagely lasts more than 24 months in our study which is associated with triple negative treatment and HER2 enrich treatment.

In accordance with site of metastasis many studies evaluated 5 years interval of patient's survival and

several studies demonstrated that bone metastasis regardless of its prevalence has the best prognosis among all sites of metastasis.<sup>27, 28, 29</sup> In our study Follow up of patients in 3 different intervals 0-5, 5-10 and 10-15 months from the diagnosis reveals that survival among patients with bone metastasis was exactly higher than others, whereas visceral metastasis had the higher mortality. Thus, Site of metastasis is another concerning factor which can play an important role in survival and prognosis of patients with breast cancer recurrence.<sup>30</sup>

Akbari *et al.*,<sup>29</sup> depicted that visceral metastasis has poor prognosis in comparison to local or other particular sites of metastasis. It also showed that bone metastasis had more mortality than loco-regional metastasis. In our study, visceral metastasis similarly has the worst prognosis and the lowest survival however there are different results in various articles performed on this subject which could possibly be related to the sample size and group of patients that have been analyzed,<sup>26</sup> regarding bone metastasis; our trial demonstrated that bone metastasis has better prognosis almost among other subtypes and in fact it has best survival following to local metastasis which could show the contrast between our study and other studies. Sta *et al.*,<sup>20</sup> showed that factors mentioned above as prognostic factors or related factors to recurrent and survival of patients with breast cancer are also correlated with metastasis of breast cancer. It concludes that based on receptor type of different breast cancers "Visceral metastasis was found to be significantly dependent ( $P=0.05$ ) on 8 variables: age, menopausal, status, stage, primary tumor size, lymph node involvement, estrogen and progesterone receptor status and pattern. this study supports our findings regarding prognosis of patients with visceral metastasis which is considered as a poor prognostic category in patients with breast cancer. But on the



other hand, we consider bone metastasis with better prognosis and survival in comparison to visceral and brain metastasis.

A study performed by Rosa Mendosa,<sup>24</sup> calculated the average survival of patients with metastatic breast cancer as 12 to 24 months and moreover late recurrence has been experienced more than early recurrence in patients. Interestingly we assessed Mean duration between surgery to recurrence and recurrence to death among patients and it demonstrated that breast cancers with brain metastasis had  $22.872 \pm 6.222$  months' duration between initial surgery and recurrence and also  $9.538 \pm 4.354$  months' duration between recurrence and death apart from that visceral metastasis duration between surgery and recurrence was  $27.976 \pm 3.274$  and the duration between recurrence and death was  $8.967 \pm 2.255$  so these two sites of metastasis are considered as the worst metastatic breast cancer. Skin or local metastasis significantly had better outcome and the duration between surgery and recurrence was  $31.571 \pm 4.477$  and the duration between recurrence and death was  $21.444 \pm 5.252$ .

Strength of this trial is the extended analysis on different aspects of breast cancer; disease free survival for each receptor subtype and Survival from metastasis till death in patients with recurrence breast cancer are precisely assessed. There are few studies which evaluate the same elements of breast cancers. Mean duration between surgery to recurrence and recurrence to death provided a great horizon through

understanding of different manners of subtypes and sites of recurrence.

## CONCLUSION

This study performed on breast cancer recurrence and its survival among Iranian population. According to the outcome based on receptor subtypes; totally after 5 years evaluation of each patient in our study it showed that HER2 enrich positive breast cancers had the worst survival and on the other hand triple negative receptor breast cancers showed the best survival while other studies demonstrated outcome completely opposite to our finding. this contrast is due to discovery of Herceptin drugs for HER2 enriched receptor breast cancers which ameliorates their prognosis and survival, also drugs related to luminal A and luminal B which are a huge step to improve their survival and hormonal therapy could be associated with their better prognosis in comparison to triple negative receptor subtype. Since our patients from 17 years ago till recent years did not consume Herceptin drugs difference among our findings and other studies could be related to release of this category of drugs. Based on sites of metastasis bone and local metastasis among our patients showed the best survival while brain and visceral metastasis had the worst survival and prognosis.

## CONFLICTS OF INTEREST

None.

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