

Recurrence and Survival Effect in Breast Conserving Surgery: What are the Predictive and/or Prognostic Factors?

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Abstract

Background: Breast conserving surgery (BCS) is a widely accepted form of operation in patients with early breast cancer. Recurrence remains one of the greatest concerns in breast conserving surgery. It can provoke serious anxiety in the patient and, when treated by mastectomy, negate the objective of conservation.

Methods: In this study we investigated the prognostic value of demographic, clinical and pathological factors and biological markers in breast cancer patients treated with BCS. This study was performed on 258 patients who underwent BCS from 2002 to 2010. All of the surgeries were performed by a single surgical team. Recurrence and its risk factors were evaluated.

Results: The mean age of the patients at the time of diagnosis was 50. The overall 10 year survival was 81%, 5 year survival was 88% and recurrence rate after surgery was 9%. Lymphovascular Invasion (LVI) was observed in 41 (16%) patients and in 11 (48%) patients with recurrence.

Conclusion: Our study confirmed that tumors with estrogen receptor negative and LVI had more recurrence rate but other demographic, clinical and pathological factors and biological markers (progesterone receptor, P53, HER-2) did not have any significant effect on recurrence. We recommend considering LVI and estrogen receptor assay as a prognostic factor in the patients treated with BCS.

Key words: Breast cancer; Breast conserving surgery; Recurrence; Survival; Biological markers

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Introduction

Breast cancer has the second place after skin cancer in Iran in both sexes in terms of prevalence [1]. Breast cancer is the most common malignancy in Iranian women and is the fifth leading cause of death among malignancies. 8090 new cases occur annually and more than 1300 of breast cancer cases die every year [2]. The main treatment of breast cancer is surgery, including breast conserving surgery (BCS) or mastectomy. BCS means resection of tumor with clear margins and acceptable cosmetic outcome.

Lymph node involvement and tumor size are known as the most important clinical prognostic factors in breast cancer [3]. In the past, molecular markers such as p53 have been investigated for determining prognosis but the result of these studies are

sometimes not identical. This may be due to genetic diversity of patients and heterogeneity in malignant tumors [4, 5, 6].

In this study, we evaluated the recurrence and survival of the patients treated with BCS for breast cancer considering demographic, clinical and pathological factors and four biological markers (estrogen receptor, HER-2, P53, progesterone receptor).

Materials and Methods

All of the patients with breast cancer that underwent BCS by a single surgeon in cancer research center from 2002 to 2010 that could be followed and at least one year has elapsed since their operation were retrospectively enrolled.

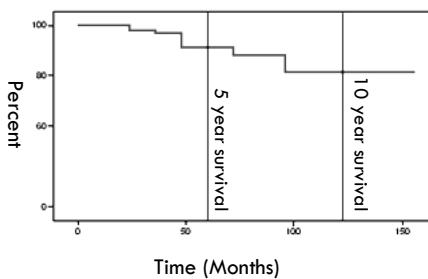


Figure 1. Overall survival in patients treated with BCS

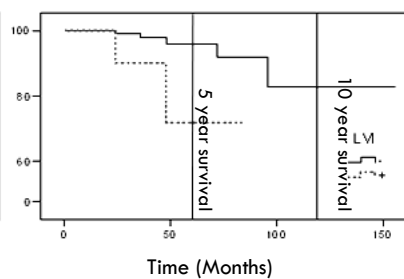


Figure 2. Survival in patients with and without LVI

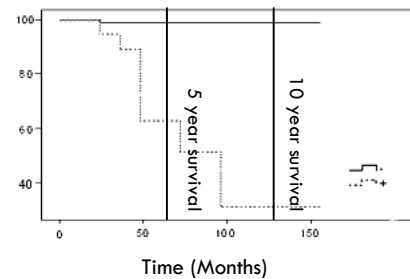


Figure 3. Survival in patients with and without recurrence

The patients who had previous primary cancers or presented with metastasis initially or had inflammatory breast carcinoma and the patients who underwent modified radical mastectomy were excluded from our study. Cancer was diagnosed mainly by core needle biopsy and in a limited number of cases by excisional biopsy. In all of the patients the excision specimen was histologically examined by frozen and permanent section and the surgical margins were free of tumor with the closest margin from the tumor measuring 2 millimeters. Oncoplastic reconstruction was also performed as indicated. All of the patients underwent radiotherapy after the surgery and the patients who did not receive radiotherapy were excluded from the study.

The breast cancer team visited the patients on a regular basis and their clinical and radiologic data were recorded. Surgeries were performed with BCS using standard techniques. Ultimately 258 patients were studied and all variables were entered in the information form. The form included demographic data, primary tumor size, number of axillary lymph nodes removed, number of positive lymph nodes, clinical stage, p53, HER-2, estrogen receptor, progesterone receptor, pathological diagnosis and grading and pathological markers including lymphovascular invasion (LVI), time and location of recurrence, date of last follow-up and date of death.

Statistical analysis was done by using SPSS software (release 18 SPSS Inc., Chicago, IL, USA). Quantitative variables with normal distribution and non-normal distribution were compared in order by using T-test and Mann-Whitney test. Survival rates were analyzed by the Kaplan-Meier method. Nominal variables were compared in form of frequency tables using chi square test or Fisher's exact test. For all statistical tests, P-values <0.05 were considered significant.

Results

The mean age of patients at diagnosis time was 49.8 years. Among the subjects who mentioned their

education, 22.3 % was illiterate, 12.6% had elementary education, 44.6% had high school diploma and 20.4% had a university degree. Chemotherapy in 230 patients (92%) and hormone therapy in 215 patients (86%) were performed. The mean tumor size was 2.7 centimeters and the mean number of removed axillary lymph nodes was 9 (ranging from 0 to 30). One hundred one patients (39.1%) had positive lymph nodes. The tumor's staging was: stage 0 in 5 patients (2%), stage 1 in 78 patients (31.5%), stage 2 in 122 patients (49.2%) and stage 3 in 43 patients (17.3%). The most common type of cancer was invasive ductal carcinoma with 199 cases (79.6%) and then ductal carcinoma in situ (6.8%) and invasive lobular carcinoma (5.2%). LVI was present in 41 patients (16%).

Recurrence after surgery was observed in 23 patients (9%). Local recurrence and systemic metastasis were seen in 55% and 45% of the cases and death occurred in 10 patients (3.9%). Overall survival in patients treated with breast conserving surgery was 133.8 months and after 10 years of follow up the survival rate was calculated 81% (Figure 1). The mean age at the time of diagnosis in patients with tumor recurrence and without tumor recurrence was 50.3 and 49.7 years with no significant difference (P-value = 0.8). Also significant difference in mean tumor size between patients with and without recurrence did not exist (P-value = 0.07). In those with recurrence, the mean number of dissected axillary lymph nodes was 11/6 and in those without recurrence it was 9.3 and significant difference in the mean number of dissected lymph nodes existed between patients with and without recurrence (P-value = 0.03). However, in patients with recurrence, the mean number of positive lymph nodes did not have a significant difference with those without recurrence (4.3 versus 3.9).

Table 1. Relationship between variables in two groups with and without recurrence

	Recurrence					P value
	Negative n=235		Positive n=23			
Age of Diagnosis (Y)	49.96		50.05		0.973	
	Total No.	Percent	Number	Percent	Number	
Education						
Illiterate	n=58	22.5	53	21.7	5	-
Elementary school	n=32	11.5	27	21.7	5	-
High school	n=115	46.4	109	26.1	6	-
University degree	n=53	19.6	46	30.4	7	-
Pathology						
Cancer Type						
DCIS	n=17	7.5	16	4.4	1	0.011
IDC	n=186	79.9	171	65.2	15	0.000
IDC+DCIS	n=10	3.7	8	8.7	2	0.080
IDC+ILC	n=4	1.4	3	4.4	1	-
ILC	n=13	5.2	11	8.7	2	0.027
Page't's disease	n=1	0.5	1	-	-	-
Phyllodes tumor	n=1	0.5	1	-	-	-
LCIS+ILC	n=3	0.9	2	4.4	1	-
SCC	n=1	0.5	1	-	-	-
Grading						
0	n=6	2.8	6	-	-	
1	n=35	15.1	33	8.7	2	
2	n=137	57.8	126	47.8	11	
3	n=63	24.3	53	43.5	10	
LVI	n=41	12.8	30	47.8	11	0.001
T						
1	n=106	45.9	101	22.7	5	
2	n=112	45.0	99	59.1	13	
3	n=23	8.6	19	18.2	4	
4	n=1	0.5	1	-	-	
LN Positive	n=96	41.2	84	54.5	12	0.231
Biologic Markers						
HER-2	n=95	36.6	86	39.1	9	0.571
P53	n=92	41.9	83	40.9	9	0.542
PR	n=169	69.6	158	47.8	11	0.090
ER	n=174	72.2	164	43.5	10	0.010
Stage						
0	n=5	2.2	5	-	-	-
1	n=78	32.5	74	17.4	4	-
2	n=122	48.7	111	47.8	11	-
3	n=43	15.8	36	30.4	7	-
4	n=4	1.3	3	4.3	1	-
Death	n=10	0.4	1	39.1	9	0.050
Survival						
OS (month)	149.804		84.416			
DFS rate (%)						
1 year	99		77			
2 year	99		59			
3 year	99		32			
4 year	99		23			
5 year	99		23			

LVI was observed in 48% of patients with recurrence and 12.8% of patients without recurrence. As it is shown in figure 2, five year survival rate was significantly lower in patients with LVI (92% versus 72%). Also, overall survival was significantly lower in the patients with LVI (64.8 months versus 137 months). LVI was present in 66.7 % of patients with recurrence and positive lymph nodes, 26.7% of patients without recurrence with positive lymph nodes, 20% of patients with recurrence with negative lymph nodes and 6.5% of patients without recurrence with negative lymph nodes. In patients with recurrence, LVI was significantly positive in lymph node positive cases.

Estrogen receptor, progesterone receptor, P53 and HER-2 were positive in 10 (43.5%), 11 (47.8%), 9 (41%) and 9 (39.1%) patients with recurrence. In contrast, in patients without recurrence these markers were positive in 164 (69.8%), 158 (67.2%), 83 (41.9%) and 86 (36.6%) of subjects. Significant difference existed in estrogen receptor status between the patients with and without recurrence (P -value = 0.01) and estrogen receptor was significantly negative in the patients with recurrence but in other cases there was no difference between the two groups (P -value > 0.05).

Mortality occurred in 10 patients (3.9%). Overall survival was 133.8 months and after 12 years of follow up ten years survival rate was calculated 81%. Overall survival in patients with recurrence was 84.4 months whereas in those without recurrence it was estimated to be 149.8 months (P -value < 0.001). After 12 years of follow up the 10 year survival rate was calculated 31% in the patients with recurrence and 99% in the patients without recurrence. Also, overall survival in patients with positive lymph nodes was 116.2 months while in those with negative lymph nodes it was estimated 134.8 months. After 10 years of follow up survival rates in patients with positive lymph node and negative lymph node was calculated 88% and 81%.

As it is seen in Table 1, estrogen receptor was significantly negative in patients with positive lymph nodes who had recurrence (P -value = 0.03). In those with negative lymph nodes, there was no significant difference in estrogen receptor status between the patients with and without recurrence.

Discussion

This study indicates that among the various markers investigated, estrogen receptor positive tumors were significantly less common in the patients with recurrence who underwent BCS. Age at diagnosis time, tumor characteristics (size, pathology,

tumor grading) and other positive biological markers (progesterone receptor, HER-2, P53) had no effect on recurrence.

In our study, the mean age of patients at the time of diagnosis for breast cancer was 49.8 years which is similar to previous studies in Iran [7, 8].

Also The 10-year overall survival rate after surgery using BCS was calculated 81% and there was no significant difference in survival rate between node negative and node positive patients. In previous studies the 10-year overall survival rate in BCS patients has been 78% which is similar to our study [2].

In various studies, the local recurrence rate after BCS has been 6% to 43% and it decreases about 70 % with radiotherapy [9]. Local recurrence is a predictive factor for systemic metastasis [10, 11] and great efforts has been done to find factors predictive of local recurrence.

Increased tumor size, axillary lymph node involvement, multi focal tumors, tumors with positive margins, positive family history of breast cancer and BRCA1 and BRCA2 mutations have been proposed to be predictive factors for recurrence after breast cancer surgery [5]. Type of cancer and its grade, presence of tumor emboli, endolymphatic invasion, negative estrogen receptor, increased expression of HER-2 [12] and positive P53 [5] are all variables that have been associated with risk of local recurrence.

Previous clinical data suggest that increased expression of HER-2 increases cellular resistance to radiation and thus increases recurrence rate after BCS [13]. Hafty and his colleagues in a case - control study showed that in the group with recurrence compared with the control group increased HER-2 expression was a predictive factor of breast cancer recurrence [12]. However, larger cohort studies do not confirm these findings [14]. In another study by Lopez-Guerrero and his colleagues HER-2 status did not have an impact on survival rate of the patients with recurrence (contrary to the patients without recurrence). In our study, HER-2 had no effect on recurrence too [15].

In a study by Fisher and colleagues in patients with negative lymph nodes, estrogen receptor positivity has been associated with better prognosis, while progesterone receptor did not have significant effect on prognosis [16]. This finding is contrary to our study in which the estrogen receptor impact on prognosis was significant in lymph node positive patients but it was not significant in other cases. Other studies shown that the effect of hormone receptors on the prognosis may be less in the long

term. In a study conducted by Hilsenbeck and colleagues it was shown that in the first three years after diagnosis, estrogen receptor positivity impact on prognosis is significant but after three years this effect is not present [17]. However, estrogen or progesterone receptor positive tumors will respond better to treatment with antiestrogen drugs like Tamoxifen. A large study conducted in 37000 women in 1998 indicated that Tamoxifen treatment in estrogen receptor positive patients will decrease recurrence and mortality rate 47% and 26% [18].

In the previous studies, LVI was associated with higher recurrence rate in lymph nodes [19]. Our study showed that LVI is significantly higher in the patients with recurrence. Five year survival rate and overall survival was significantly lower in patients with LVI. However, in patients with recurrence LVI was present only in lymph node positive cases. In other studies it is shown that LVI is an independent prognostic factor in lymph node-positive breast cancer [20]. This means LVI can be used as an independent prognostic factor in the patients treated with BCS [21, 22].

Our study limitation was the modest sample size of 260 patients. The retrospective nature of this study was also a shortcoming.

Conclusion

Our study confirmed that tumors with estrogen receptor negative and LVI in BCS cases had more recurrence rate but other demographic, clinical and pathological factors and biological markers (progesterone receptor, P53, HER-2) did not have any significant effect on recurrence. We recommend considering LVI and estrogen receptor assay as a prognostic factor in the patients treated with BCS.

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Conflict of Interest

The authors declare that they have no conflict of interest in this article.

Authors' Contribution

AME conceived, designed the study, interpreted the results, draft the manuscript and carried out the data analyses. HA, AA, ZH, HSF, AM contributed to data gathering, participated in writing and revising the manuscript, while MM revised and approved the final manuscript. All authors read and improved the final manuscript.

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