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Original Research Article

Risk factors for loco-regional recurrence after breast conserving surgery: impact of young age and surgical margin status in breast cancer patients

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ABSTRACT

Background: Breast cancer is a common malignant tumor and treatment predominantly consists of surgery. Modern society has increased the demands of women to have higher requirements for breast appearance and quality of life. Therefore, exploring effective measures to control or reduce the rate of loco-regional recurrence (LRR) after breast conserving surgery (BCS) is the main focus of this study.
Methods: This cohort included 743 consecutive patients with invasive breast cancer, treated with BCS in 2 centers in Tehran, Iran between 2005 and 2010. The primary endpoint was the rate of loco-regional recurrence in a 5-year follow- up period. Authors also investigated the factors that could predict LRR after BCS.
Results: The prevalence of LRR after BCS was 7.6% in a median follow-up of 56.9 months. The Median time to local recurrence was 20.45 months. A correlation between follow-up outcome and age; histologic sub-type; surgical margin; number of positive nodes; complete pathologic response to neo-adjuvant chemotherapy; chemotherapy and hormone therapy was recognized. Surgical margin status, hormone therapy, histologic sub-type, age and Ki67 were shown to be significant risk factors for LRR in univariate analysis whereas surgical margin status emerged as an independent risk factor in multivariate analysis.
Conclusions: Increased LRR was observed among those with higher ki67, aged under35, not receiving hormone therapy and with a surgical margin less than 2mm. These factors appeared to be risk factors for LRR after BCS, while, histologic grade, axillary nodal status, tumor size and biologic sub-type did not predict LRR after BCS.

Keywords: Breast conserving surgery, Loco regional recurrence, Surgical margin status, Young age breast cancer

INTRODUCTION

As a common malignant tumor, the treatment of breast cancer predominantly consists of surgery followed by postoperative radiotherapy and chemotherapy. In recent years, breast-conserving surgery has become the first option for breast cancer patients, especially for those in the early stages of the cancer. Relevant results in recent years have shown that the tumor metastasis rate and survival rate of breast cancer patients treated with breast conserving surgery were equivalent to those treated with total mastectomy.[1-4] Moreover, the quality of life of patients treated with breast conserving surgery was better and the rate of loco-regional recurrence (LRR) was

higher among them.[5,6] In most series, LRR occurs in approximately 4% to 20% of cases.[7,8] It is an important clinical outcome, leading to significant morbidity. LRR is associated with an increased risk of distant relapse, and in patients undergoing BCS, a positive surgical margin increases the likelihood of a distant relapse.[9] It has been recognized as an aggressive tumor biology and is associated with an increased risk of breast cancer metastasis and death.[10]

Clarke et al found that 75% of LRRs occur within the first 5 years and the lack of LRR within this time period was a predictor of 15-year breast cancer mortality.[11] Therefore, the pattern of recurrence risk and prognostic factors for the development of subsequent breast cancer recurrences after breast conserving surgery can provide valuable information for informed clinical decision-making and patient centered follow-up.

Using a population-based cohort of women with follow-up data of five years after treatment for primary invasive breast cancer, authors aimed to: firstly, analyze the occurrence and timing of LRR after BCS, and secondly identify prognostic factors for LRR after BCS.

METHODS

Patient selection

The cohort included 743 consecutive patients with invasive breast cancer, treated with BCS in 2 large referral breast cancer centers in Tehran, Iran, between 2005 and 2010. Clinico-pathologic parameters for all patients were collected including tumor size, nodal involvement, estrogen receptor (ER) and progesterone receptor (PR) status, HER2/neu status by immunohistochemical staining and/or fluorescent in situ hybridization, and histologic grade (Table 1). This study was approved by the institutional review boards of the participating centers.

Follow-up and end points

Patients were seen in follow-up approximately 1–1.5 months after radiotherapy and every 6 months thereafter, typically with annual breast imaging. The duration of follow-up was calculated from the date of diagnosis to the last confirmed date of disease-free status.

The follow-up was terminated as long as local recurrence or distant metastasis occurred. The primary endpoint was the rate of LRR after BCS. Authors also investigated the factors that could predict LRR after BCS.

Classification of groups

Authors employed ER and PR status, along with HER2/neu (HER2) amplification and histologic grade to approximate breast cancer (BC) biologic subtypes: ER-positive or PR-positive, HER2-negative (Luminal); ER-positive or PR-positive, and HER2-positive (luminal-HER2); ER-negative, PR-negative, and HER2-positive (HER2); ER-negative, PR-negative, and HER2-negative (triple-negative breast cancer (TNBC).

ER and PR status were determined by immunohistochemical (IHC) staining. Samples were considered HER2 positive if they were scored 3 by IHC, or 2 by IHC with evidence of amplification by fluorescent in situ hybridization (FISH).

In addition, patients were classified into two age groups (less than 40: young age group, over 40: old age group). According to the number of involved lymph nodes (LN) they were categorized as follows: no LN involvement (N0); 1–3 involved LNs (N1); 4–9 (N2); or>9 (N3). Histologic sub type was determined, IDC, ILC, and others considering the report of surgical pathology.

Statistical analysis

Descriptive statistics were used to assess baseline differences between strata as defined by age groups, biologic subtype, nodal status, intrinsic sub type, surgical margin, grade, and tumor size.

The Chi-squared statistic was used to evaluate categorical variables, and the Kruskal–Wallis test was used for continuous variables. Cox proportional hazards analyses were used to estimate clinico-pathologic associations with the primary endpoint.

The Cox model was represented by hazard ratios with 95% confidence intervals and related P value. If $P<0.05$, the difference was statistically significant. All analyses were performed using IBM SPSS 20. All reported P values are two sided. The content of the follow-up included the patients' LRR and distant metastasis.

RESULTS

Patient characteristics

In total 743 breast cancer patients were initially recruited in this study, however, patients diagnosed with inflammatory breast cancer or sarcoma, and in situ breast cancers were excluded.

Table 1: Loco-regional recurrence after breast conserving surgery by surgical margin status.

	Without local recurrence	With local recurrence	p-value
>2 mm free margin	617 (96.6%)	22 (3.4%)	<0.001
0-2 mm free margin	21 (51.2%)	20 (48.8%)	
Involved margin	6 (37.5%)	10 (62.5%)	

Table 2: Patient and tumor characteristics.

	N (%)
No. of patients	696
Median age (years)	45.6±9.9
Tumor histology	
Ductal	583 (83.8)
Lobular	19 (2.7)
Others	94 (13.5)
Intrinsic subtypes	
Luminal	434 (62.4)
Luminal HER-positive	78 (11.2)
HER2, no luminal	58 (8.3)
Triple negative	126(18.1)
Clinical T stage	
T1	131 (18.8)
T2	468 (67.2)

Therefore, a total of 696 patients were included in the analysis. All the patients included, underwent BCS and surgery to the axilla (axillary dissection, sentinel node biopsy, or sample±axillary dissection).

Table 2 summarizes the characteristics of the study population. The median age at diagnosis was 45.6 years (range 27-76). The majority of patients had primary tumors 2-5 cm (67.2%), grade II disease (70.6%) and no nodal involvement (59.2%). The median follow-up was 56.9 months. There were 55 (7.6%) LRR events. The median time to local recurrence was 20.45 months. When assessing LRR by BCS in patients with surgical margins of 0-2mm versus those with greater than 2mm, those with margins greater than 2mm had a significantly better local control compared with those with less than 2mm or tumoral involved margins (Table 1).

Table 3: Baseline demographic information for all patients by follow-up outcome.

	Disease free No. (%)	Loco-regional recurrence No. (%)	Distant metastasis No. (%)	p-value
Age at diagnosis				
Younger than 40	203 (86.8)	24 (10.2)	8 (3.4)	0.013
Older than 40	389 (84.2)	31 (6.7)	43 (9.3)	
Histologic type				
Invasive ductal	499 (85.2)	40 (6.9)	44 (7.5)	0.002
Invasive lobular	18 (94.7)	0	1 (5.3)	
Other	75 (79.8)	15 (15.9)	6 (6.4)	
Histological grade				
1	37 (97.4)	1 (2.6)	0	0.21
2	417 (84.9)	42 (8.1)	34 (6.9)	
3	137 (82.5)	12 (7.2)	17 (10.2)	
Maximum invasive tumor size (mm)				
<20	116 (88.5)	13 (10)	3 (2.3)	0.9
20-50	397 (84.8)	35 (7.5)	37 (7.9)	
>50	50 (79.4)	5 (7.9)	8 (12.7)	
Number of positive nodes				
0	174 (85.7)	19 (9.4)	12 (5.9)	0.006
1-3	232 (87.5)	19 (7.2)	14 (5.3)	
4-9	156 (82.1)	17 (8.9)	17 (8.9)	
>10	30 (78.9)	0	8 (21.1)	
ER status				
Positive	437 (85.9)	37 (7.3)	36 (7.1)	0.69
Negative	155 (82.9)	18 (9.6)	15 (8)	
HER2 status				
Positive	113 (92.6)	6 (4.9)	3 (2.5)	0.17
Negative	117 (86)	8 (5.8)	12 (8.8)	
Chemotherapy treatment period				
Neo adjuvant	51 (73.9)	5 (7.2)	14 (20.2)	0.001
Adjuvant	487 (86.8)	43 (7.7)	32 (5.7)	
Not applicable	45 (81.8)	7 (10.6)	5 (7.6)	
Adjuvant trastuzumab				
Yes	43 (82.7)	4 (7.7)	5 (9.6)	0.87
No	549 (85.2)	51 (7.9)	46 (7.1)	
Adjuvant radiotherapy				
Yes	548 (85)	54 (8.4)	45 (7)	0.23
No	27 (87.1)	0	4 (12.9)	
Adjuvant hormone treatment				
Yes	393 (88.1)	25 (5.6)	30 (6.7)	0.004
No	199 (79.6)	30 (12)	21 (8.4)	

Table 4: Loco-regional recurrence interval flexible parametric survival model univariable analysis results for all patients, enrolment in cancer institute, Tehran, 2005.

Covariate	HR	95%CI	p-value
Age at diagnosis, y,			
>30	1 (Ref. cat.)		
<30	2.82	1.01-7.82	0.047
Pathology			
IDC	1 (Ref. cat.)		
Other	2.22	1.18-4.18	0.01
Maximum overall (invasive and in situ) tumor size			
<20	1 (Ref. cat.)		
20-50	0.95	0.48-1.87	0.88
>50	1.11	0.38-3.18	0.85
N stage			
N0	1 (Ref. cat.)		
N1	0.76	0.39-1.49	0.43
N2	1.02	0.52-2.04	0.93
Histological grade			
1	1 (Ref. cat.)		
2	3.20	0.44-23.35	0.25
3	3.13	0.41-24.11	0.27
Surgical margins, mm			
>2mm	1 (Ref. cat.)		
0-2mm	1.84	0.98-3.49	0.05
Involved	5.31	2.31-12.21	<0.01
ER status			
Negative	1 (Ref. cat.)		
Positive	0.85	0.46-1.55	0.59
HER2 status			
Negative	1 (Ref. cat.)		
Positive	1.13	0.38-3.37	0.83
Ki67 (continuous)	1.03	1.01-1.06	0.04
Intrinsic subtype			
luminal	1 (Ref. cat.)		
luminal HER+	0.95	0.37-2.45	0.92
HER+	0.51	0.12-2.11	0.35
Triple negative	1.53	0.80-2.93	0.20
Adjuvant hormone therapy			
No/unknown	1 (Ref. cat.)		
Yes	0.42	0.24-0.73	0.002
Anti HER2 therapy			
No/unknown	1 (Ref. cat.)		
Yes	1.12	0.40-3.11	0.83
Chemotherapy			
No/unknown	1 (Ref. cat.)		
Yes	0.63	0.28-1.40	0.26
Neoadjuvant chemotherapy			
No	1 (Ref. cat.)		
Yes	0.96	0.34-2.69	0.94
Complete pathologic response			
No	1 (Ref. cat.)		
Yes	0.78	0.19-3.20	0.73

CI indicates confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor.

51 (7.3%) of the patients had distant metastasis during follow up. The most common site of metastasis was bone (82.2%), followed by liver (19.7%) and lung (16.2%). A correlation between follow-up outcome and age (P val=0.013); histologic sub-type (P val=0.002); surgical margin (P val<0.001); number of positive nodes (P val=0.006); complete pathologic response to neo-adjuvant chemotherapy (if applicable) (P val<0.001); chemotherapy (P val=0.001) and hormone therapy (P val=0.004)) was recognized (Table 3). Disease characteristics differed significantly as a function of age with regard to tumor size (p>0.001), number of involved

lymph nodes (p>0.001), tumor grade (p>0.001), receipt of chemotherapy (p>0.001), endocrine therapy (P<0.001) and disease outcome (p=0.006). When compared to older patients, those in the youngest quartile were more likely to have larger tumors, of higher grade, with more involved lymph nodes, and were more likely to receive both endocrine therapy and chemotherapy.

When stratified by nodal involvement, the subgroups exhibited significant baseline differences with regard to tumor size (p>0.001) and receipt of radiotherapy (p=0.007) or chemotherapy (p=0.003). As compared to patients with no or limited nodal disease, those with N2 or N3 presentations were more likely to have larger tumors. The risk of LRR at 5 years was 7.1% for those with luminal disease, 6.4% for luminal-HER2, 5.2 % for HER2, and 10.3 % for TNBC.

In order to find out the risk factors of LRR after breast conserving surgery in this study, the patients' age, tumor size, surgical margin, histologic sub type, grade, ER, HER-2 status, ki67, postoperative radiotherapy, chemotherapy, anti HER2 therapy, hormone therapy, lymph node status and intrinsic subtype were included into single factor variable. Table 4 shows the univariate analysis of prognostic factors. Nodal involvement, histologic sub type, chemotherapy and hormone therapy were significantly associated with 5-year follow-up outcome of the disease, while, age below 30, surgical margin status, histologic sub type of tumor, hormone therapy and ki67 predicted LRR. In the multivariate analysis, surgical margin status remained a statistically significant prognostic factor for LRR.

DISCUSSION

In recent years, breast-conserving surgery has become the first option for patients who have breast cancer, especially for early stage breast cancer patients. Several studies have indicated that there was no significant difference in the rate of distant metastasis and survival of breast-conserving surgery when compared with mastectomy.[9,12] Moreover, Modern society has increased the demands and needs of women to have ever higher requirements for breast appearance and quality of life. Therefore, exploring effective measures to control or reduce the rate of recurrence have become the main focus of this study. Authors investigated the LRR rate and identified prognostic factors for LRRs after BCS during a follow-up of five years using data from 743 women treated for primary invasive breast cancer. Failure of treatment occurred in 14.9% in present cohort. The data showed that the 5-year metastasis rate was 7.3% and LRR was recognized in 7.6% of the patients. It was reported by Xia et al. that the recurrence rate after BCS was 10.78%, metastasis rate was 8.82% and survival rate after 5 years was 96.08%. They also concluded that the independent risk factors affecting the recurrence of breast were volume of tumor over 2 cm, margin invasion positive, HER-2 receptor positive, estrogen receptor positive, lymph node metastasis and tumor stage III.[13] Behm et al's 5 large follow-up series of 2,300 patients found a LRR of 4.3% during a mean follow-up period of 7.9 years.[8] Another retrospective analysis of 533 patients had a LRR of 7% over a follow up period of 8 years.[14]

Recent studies indicated that the clinical factors related to recurrence rate and metastasis rate of breast surgery includes surgical indications, age of patients, size of patient's tumor, lymph node metastasis, whether patients had a margin of infiltration, HER-2 receptor, estrogen receptor and other factors.[7] The results of this analysis indicated a correlation between 5 year disease outcome and age, histologic sub type, nodal involvement, surgical margin, chemo therapy, endocrine therapy, anti HER2 therapy and complete pathologic response to neo-adjuvant chemotherapy.

There are reports predicting the risk factors of local recurrence after BCS. Advanced age, lymph node metastasis, and HER-2 receptor positivity were recognized as the risk factors for local recurrence.[5,8,10,15-18] Cox proportional hazards regression analysis in this study displayed that the independent risk factors affecting the recurrence of breast cancer after BCS were surgical margin, hormone therapy, histologic subtype, age below 30 years and ki67. The current Association of Breast Surgery guidelines state that the target local-recurrence rate after surgery should be <3% and not >5% at 5 years.[19] This study has demonstrated that LRR rate in younger patients (<30years) treated by BCS (18.2%, P val=0.07) would not fulfill this criterion (HR, 2.81; 95% CI 1.01-7.82). There are reports indicating, differences in LRR between BCS and mastectomy in young women.[5,9,12] Results of a large cohort with extensive follow-up demonstrated that younger age is independently associated with adverse risk of LRR.[20]

The choice between mastectomy and breast-conserving surgery (BCS) in young women is not often a straight forward decision for clinician and/or patient.[21] BCS is associated with better quality of life but higher LRR, although a meta-analysis of mostly registry and database studies in patients <40 years suggests equivalent disease-free and overall survival,(22) whereas very young age (<35 years) has been considered a relative contraindication to BCS.[6,23]

An interesting finding from this study is the effect of margin on LRR. Positive margins were associated with significantly higher LRR. In this analysis, a positive margin was defined according to ASCO guidance as tumor at the margin.[24] Although pathologic report of no ink on tumor is accepted as a safe margin, authors observed an increased risk of LRR in margins less than 2 mm (HR=1.84). Taken together with the lack of evidence that oncological surgical type influences distant-relapse it could be argued that completeness of excision is more important than the extent of surgery.[24] After BCS with positive margins, residual cancer is detected in

approximately 50% of re-excisions. (25,26) Several studies indicate that positive margin is an important predictor of LRR, independent of tumor factors and adjuvant therapies.[25,27-29]

In regard to radiotherapy, patients treated with BCS, who were not documented to have adjuvant radiotherapy surprisingly did not have higher LRR (P val=0.08), implying that maybe authors had data missing because of patients having radiotherapy elsewhere. However, the clinical implication authors would indicate is that, at least in this study, the provision of radiotherapy appears to be less important than attention to surgical margins in terms of its effect on LRR.

Interestingly, maximum tumor size was not a significant risk factor affecting LRR, indicating that whereas overall tumor size influences surgical decision making, invasive tumor size does not predict LRR after BCS. Authors have not demonstrated an impact of tumor grade, axillary nodal status and intrinsic subtype on local recurrence in this analysis either. This was possibly because of reduced power due to short follow up periods.

The association between intrinsic subtype and five-year risk of LRR has been investigated in several cohorts. There are reports that detected biologic subtype as the main risk factor for LRR following BCS.[30] Some studies observed that HER2+and/or Basal subtype tumors have a significantly higher risk of local failure than LumA tumors, whereas others found no such association.[31,32] Authors found a significant correlation between HER2 positivity, Ki67 and disease outcome. Similar to prior reports, a higher rate of LRR in triple-negative subtypes was observed.[20] The distribution of intrinsic sub type between young and old age groups did not differ significantly. However; cox proportional hazards regression model in this study did not detect intrinsic subtype to be a risk factor for LRR after BCS. In addition to age and margin status, factors recognized to influence local recurrence after BCS in this study included, histologic sub-type, lack of hormone therapy and Ki67.

A limitation of this study is that as this was not a Randomized Clinical Trial, any differences or lack of differences in LRR could be the result of confounding. However, authors have accounted as far as possible for biases and this is a large retrospective cohort representative of cancer treatment in Iran. As a retrospective study, another limitation to present study is that data collection was limited to what was available and documented in cancer center and hospital charts.

CONCLUSION

In conclusion, the 5-year outcomes of a multi-institutional cohort of BCS patients demonstrated salient risk factors for LRR that should be considered in the adjuvant setting, including age, surgical margin, hormone therapy, Ki67 and histologic sub-type. In light of these observations, and coupled with advances in BCS, authors should select suitable operation modes strictly according to the clinical indication. Present data suggests that valid strategies to reduce local recurrence might include avoidance of a positive margin after BCS, and in young patients bellow the age of 35 with a high Ki67 and ER negative, mastectomy may be considered.

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