

Margin Status Influence on the Outcome of Patients Treated with Breast Conserving Surgery

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Abstract

Background: Breast conserving surgery (BCS) followed by local radiotherapy is the standard treatment for early stage of breast cancer. Margin status may have an important impact on local recurrence and overall survival of patients treated with BCS, but this has not been defined adequately. In this study, we investigated the relationship between microscopic margins and outcome of BCS.

Methods: Three hundred eighty four patients treated with BCS between 1999 and 2010 were included in our study. All surgeries were performed by a single surgical team. Margins were defined as close if surgical margins were less than 2 mm, as free if surgical margins were more than 2 mm and as positive if malignant cells were present in one of the tissue edges. Demographic, clinical, and pathological factors as well as biological markers, recurrence, and survival rates were compared between the close and the free margins groups.

Results: The mean age of patients at the time of diagnosis was 54.2 years. There were 34 (9%) recurrence cases and overall survival was 128.7 months and ten years survival rate was 81%. There was no significant difference between the close and the free margins groups in terms of demographic parameters, tumor characteristics, biological factors (estrogen and progesterone receptor status) and lymphovascular invasion. Also recurrence rate did not differ significantly between these two groups.

Conclusion: Our study indicates that there is no significant difference between the patients with close and the free margins in terms of treatment results. There is no clear consensus in the surgeons' community over the definition of acceptable margin width in BCS, so additional studies are required to find the right answer.

Key words: Breast neoplasm; Breast-conserving surgery; Recurrence; Margin

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Introduction

Breast cancer is the most prevalent and the fifth leading cause of death amongst Iranian women; near 25 percent of breast cancer patients eventually die despite the significant advances in diagnosis and treatment [1]. Breast cancer is the most common fatal cancer among women between the ages of 40 and 55 in the world [2] e.g. 1200 breast cancer patients die every year in Iran [3, 4].

Nowadays, BCS followed by local radiotherapy is the standard treatment for early stage breast cancer. The main objective of BCS is to achieve survival rates equivalent to radical mastectomy. In several clinical trials, disease free survival did not have significant difference between BCS and radical

mastectomy [2, 5]. Also, some recent studies have shown no difference in overall survival of patients treated with classic radical mastectomy and BCS [6-8]. Adequate surgery and postoperative radiotherapy are two important factors to lower the risk of recurrence in BCS and the criteria of clear margins is needed to be strictly defined and histologically proven if post-operative radiotherapy is to achieve its effective function [9, 10].

In patients with positive surgical margins, the risk of local recurrence is 5-25% [11]. A number of studies have shown that the surgical margin status is a major factor [11-13] and even the most important factor [14] for predicting local recurrence. Margin status is also a factor which is under control of

surgeon, so pathological status of surgical margins has a key role in the BCS. However, it remains no agreement on what constitutes an optimal excision margin width, so the patient is left with a small risk of recurrence but a cosmetically acceptable result from BCS. Pathological techniques in assessing margins of breast tissue have had many improvements in the past 10 years and frozen-section or touch-prep methods have been used for intraoperative margin assessment. Intraoperative frozen section allows resection of suspicious or positive margins at the time of lumpectomy and may result in low rates of local recurrence and re-excision [15], but it will often overestimate the involvement of surgical margins so not all of surgeons agree with usefulness of intraoperative frozen section [16].

Factors which predict a higher incidence of positive margins include: Small size of breast, large tumors, previous surgical biopsy for diagnosis and lobular histology [14]. Also lower age at the time of diagnosis and higher number of involved lymph nodes are other risk factors [17, 18]. Most studies have demonstrated that a microscopic tumor-margin width criterion of less than 2 mm is associated with a higher risk of residual disease [14, 19].

The primary aim of this study was to investigate whether the margin status could predict the likelihood of local recurrence and disease free as well as overall survival of patients undergone BCS. We also considered other clinical and pathological factors like tumor size, axillary lymph node involvement and tumor histology; we also evaluated the effect of these factors on local and systemic recurrence of breast cancer.

Materials and Methods

All breast cancer patients who underwent standard techniques BCS by a single surgeon in cancer research center between 1999 and 2010 were retrospectively enrolled in this study. The diagnosis was obtained mainly by core needle biopsy. The patients who had previous primary cancers or presented initially with metastasis or had inflammatory breast carcinoma and also the patients who underwent modified radical mastectomy were excluded from our study. Additional inclusion criteria were a minimum follow up of one year. All patients underwent grossly complete tumor excision with grossly variable amount of surrounding normal tissue and surgical margins of the specimen were also assessed by frozen section during the surgery. Radiation therapy was routinely implemented after surgery.

The breast specimen was examined by a pathologist. Microscopic margins were considered positive if malignant cells were present in any of tissue edges, close if malignant cells were seen within 2 mm or less of the tissue edges and free margin if the space between carcinoma and tissue edges was more than 2 mm. Re-excision was performed in patients with positive margins in frozen section or permanent pathology (17 patients) and in all of these cases the margins proved to be free after pathological evaluation and they were included in the free margins group. Amongst 12 cases of 17 mentioned patients, there were no remnants of malignancies at all. Recurrence was classified as local or systemic. Local recurrence was defined as detection of cancer in the treated breast and axillary lymph nodes. Systemic recurrence was defined as any recurrence away from the breast, axillary or internal mammary node regions.

Finally 384 patients were included in our study and followed up between 1 to 12 years. The mean follow up period was 8.2 years in patients with free margins and 7 years in close margins groups. Clinical and pathological data were obtained from the medical records of the patients by the breast cancer research team. The data consisted of the patients' demographic data, tumor size, number of positive lymph nodes, clinical stage, margin status, biological markers (estrogen receptor, progesterone receptor and HER-2 status), pathological diagnosis, grading and pathological markers including lymphovascular invasion (LVI), time and location of recurrence, date of last follow-up and date of death which was confirmed by the breast cancer research team who have visited the patients on a regular basis.

Statistical analysis was performed using SPSS software (version 16; SPSS Inc. Chicago, IL). Chi-squared analysis was used for categorical variables; also the Mann-Whitney U-test was used for continuous variables. Survival rates were analyzed by the Kaplan-Meier method and Correlation of two factors by Fisher's exact test. P values of 0.05 or less were considered statistically significant.

Results

The final results are summarized in table 1. The mean age of the patients at the time of diagnosis was 54.2 years and all of the patients had undergone BCS. Fifty one (13.3%) patients had close margin and 333 (86.7%) patients had free margin. The mean age of the patients with close margins (51.5 years) and free margins (54.6 years) were not significantly different (P-value=0.1). Chemotherapy was given to 328 (85.4%) patients; 296 patients

(77.1%) were treated with hormonal therapy. The most common pathology was invasive ductal carcinoma (84.7%), followed by invasive lobular carcinoma (5.7%) and ductal carcinoma in situ (3.4%). The mean size of tumor was 3.3 cm overall; there were no significant difference between the mean size of tumor in patients with free margins (3.35 cm) and close margins (2.94 cm) (P-value=0.15).

The mean number of removed axillary lymph nodes was 9.5 (ranging from 1 to 30) and 171 patients (44.5%) had positive lymph nodes. One hundred fifty one (45.8%) patients with free margins and 19 (37.3%) patients with close margins were lymph node positive and there was no significant difference between the two groups (P-value=0.2). The mean number of removed axillary lymph nodes in patients with free margins was 10 while this number in patients with close margins was 8.3 and a significant difference was found between these groups (P-value=0.008).

Amongst the patients, histological grade I was in 30 cases (7.9%), II in 263 cases (68.6%) and III in 91 cases (23.5%). In the free margin group 28 cases (8.4%) had grade I, 228 cases (68.4%) grade II and 77 cases (23.1%) had grade III. In the close margin group 2 cases (4%) had grade I, 35 cases (68.5%) grade II and 14 cases (27.5%) had grade III.

Estrogen receptor was positive in 271 cases (70.6%). There was no significant difference in ER status between the free margin group (70.2%) and the close margin group (72.5%). Progesterone receptor was positive in 260 cases (67.7%). Also, there was no significant difference in PR status between the free margin group (66.3%) and the close margin group (76.4%). HER-2 was positive in 76 (19.7%) patients, of which 64 (19.2%) patients with free margins and 12 (23.5%) patients with close margins. LVI was present in 54 (14%) patients, of which 50 patients were in free margin group and 4 patients were in close margin group and no significant difference existed between these groups.

Overall, there were 34 (9%) recurrences cases. Thirty two (9.6%) patients amongst whom the margin was free had recurrence compared with 2 recurrences out of 51 (3.9%) patients whose margin was close. However, statistically no significant difference was found between the free and close margin groups in terms of recurrence (P-value=0.2). Sixteen recurrences were local and 18 were systemic. Among the free margins group 14 recurrences were local and 18 were systemic but in the close margins group the 2 recurrences were local. In patients who had recurrence, LVI was found in 16 (47%) cases with free margins and 2 (100%) cases with close margins. In both patients with close margins

Table 1. Relationship between variables in two groups with close and free margins

Margin status	Total	Free	Close	P-Value
Number	384	333	51	
Mean age	54.2	54.6	51.5	0.1
Mean tumor size(cm)	3.3	3.35	2.94	0.15
Lymph node positive (%)	171 (44.5)	151 (45.8)	19 (37.3)	0.2
Histology				
Grade I (%)	30 (7.9)	28 (8.4)	2 (4)	
Grade II (%)	263 (68.6)	228 (68.4)	35 (68.5)	
Grade III (%)	91 (23.5)	77 (23.1)	14 (27.5)	
Clinical stage				
0(%)	1(0.3)	1 (0.3)	0	
1(%)	80(20.8)	66 (19.7)	14 (27.4)	
2(%)	232(60.4)	202 (60)	30(59)	
3(%)	71(18.5)	64 (19.1)	7(13.6)	
Biological markers				
Estrogen (%)	271 (70.6)	234 (70.2)	37 (72.5)	1
Progesterone (%)	260 (67.7)	221 (66.3)	39 (76.4)	0.2
HER-2(%)	76 (19.7)	64 (19.2)	12 (23.5)	0.2
LVI (%)	54 (14)	50 (13)	4 (7.8)	0.3
Recurrence (%)	34 (9)	32 (9.6)	2 (3.9)	0.2
Local	16	14	2	
Systemic	18	18	0	
Mean follow up duration	8 years	8.2 years	7 years	
10 year survival rate		81%	100%	
Overall survival	128.7 months			

the recurrence happened after three years and it was local and the final pathology was ductal carcinoma in situ.

Significant difference was present in PR positive group in patients who had recurrence with free margins (42.4%) and close margins (50%) (P-value=0.015). There was also significant difference detected in estrogen receptor positivity in patients who had recurrence with free margins (17cases) and close margins (1 case) (P-value=0.02). Also, recurrence in patients with LVI was observed in 17 cases with free margins and 1 case with close margins and significant difference was found between these two groups (P-value=0.01). The clinical stage in patients with recurrence and free margins were as follows: stage zero 3%, stage one 15.2%, stage two 68.7% and stage three 12.1%. Both patients with close margins were in stage one.

The mean follow up duration was 8.2 years in patients with free margins and 7 years in patients with close margins. Mortality occurred in 40 patients (10.4%). Overall survival was 128.7 months and after 12 years of follow up ten years survival rate was calculated 81%.

Discussion

Two major surgical approaches can be implemented to treat breast cancer: mastectomy and BCS. The risk of local recurrence is between 9% [20] and 18% [21] and it is thought to be higher in BCS [22, 23]; margin status may have an effect on local recurrence [24], however there is controversy in the literature as to whether margin width can have significantly influence over the rate of local recurrence [25].

In this study, results show that significant difference does not exist between the close and the free margins groups in terms of demographic parameters, tumor characteristics, biological factors (estrogen and progesterone receptor status) and LVI. Also, recurrence rate did not depend on the margin status.

The rate of recurrence in our patients was 9% which was like the previous studies with the same subject [14, 20]. The long term results of previous prospective randomized trials of BCS in free margin of resection have demonstrated 8 year recurrence rate was 9-10% [26, 27]. The rate of recurrence in the free margins group in our study was also 9.6%. The long term outcome of patients with close margins has been a matter of uncertainty. This may be due to significant variation in the perception of "negative" and "close" margins amongst physicians and institutional policies which require a change from "no

tumor cells on the ink" to "distance more than 5 mm" in order to consider a margin negative [28]. In this study, a close margin was defined as tumoral cells less than or equal to 2 mm from the inked margins, but not transected by the inked margins.

Our results suggest that local recurrence rate, disease free, and long term survival of patients with close and free margins do not differ significantly. Hardy K et al. investigated 3017 patients with breast cancer who were treated with BCS between 1995 and 2004. Fifty local recurrences were seen in approximately 60 months, concluding that the probability of recurrence was not reduced with clear margins wider than 2 mm [29]. In a study by Zavagno et al it was shown that no correlation was between the rate of recurrence and tumor margin distance [30].

Surgical margins status can affect local recurrence in breast cancer patients, but its impact on overall survival has not been clearly established. Luini and colleagues studied the results of breast cancer patients who undergone BCS with close margins, concluding that there is no general consensus on the definition of clear surgical margins subsequently when there are tumoral cells present near the surgical margins, making decision about performing re-excision is difficult [31]. Park et al. demonstrated that local recurrence did not increase significantly in patients with close margins (less than 1 mm) and they suggested these patients as appropriate candidates for BCS, but these results could not be used in patients with extensive margins involvement (more than 4 microscopic fields), in which re-excision should be performed in these cases [32]. Ten years survival rate was 81% and five years survival rate was calculated to be 92.1%, proving higher than the previous study of Dr. Akbari and colleagues [33, 34].

Conclusion

Overall, our study indicates that there is no statistically significant difference in the treatment results of patients with close and negative margins. There is no clear consensus in the surgical community over the definition of an acceptable margin width in BCS, consequently additional studies are required to identify the exact answer to this issue.

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Conflict of Interest

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

Authors' Contribution

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

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