Published in final edited form as:

J Surg Res. 2014 July ; 190(1): 164–169. doi:10.1016/j.jss.2014.03.049.

Margin index: a useful tool for the breast surgeon?

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Abstract

Background—In breast conservation surgery (BCS) for breast cancer, the appropriate surgical margin is controversial. Margin index, a mathematical relationship between tumor size and closest margin, has been shown to be predictive of the probability of residual cancer following BCS for early stage breast cancer. We applied this tool to the same population of patients at our institution to evaluate its ability to predict residual disease after BCS.

Methods—We retrospectively reviewed a prospectively maintained database of women undergoing BCS between 1980-2010 at the University of Pennsylvania. 246 women underwent re-excision due to close margins. Average margin index between groups with and without residual disease in the re-excision specimen was compared using Student's t-test. A receiver operating curve (ROC) was created using logistic regression to assess the overall diagnostic ability of the margin index on the presence or absence of residual disease.

Results—Of patients who underwent re-excision, 29% of patients had residual disease. We analyzed several cutoff values for margin index, but none proved to be significant predictors of

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Contributions:

Dr. Edwards: data collection, analysis and interpretation, writing

Dr. Gao: statistical analysis

Dr. Freedman: conception and design, critical revision

Dr. Margenthaler: conception and design, analysis and interpretation, critical revision

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Disclosures

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

residual disease. Average margin index was significantly higher for patients without residual disease compared to patients with residual invasive cancer but not for patients with residual DCIS.

Conclusions—In women undergoing BCS for early-stage breast cancer at our institution, margin index was not predictive of the presence of residual cancer on re-excision. We hypothesize that the predictive ability of margin index is likely limited by several factors including presence of DCIS and the location and extent of the close margin.

Keywords

breast cancer; breast-conserving surgery; surgical margins; radiation therapy; lumpectomy

Introduction

As surgical treatment for breast cancer, breast conservation surgery (BCS) has equivalent survival to mastectomy when followed by radiation therapy^{1, 2, 3, 4, 5, 6}. BCS involves removal of the breast tumor with a surrounding margin of normal tissue, however, the appropriate margin width is controversial. Studies comparing BCS to mastectomy have been variable in their definition of margin width for BCS, from the absence of tumor cells at the inked margin to removal of the entire quadrant of the breast in which the tumor is located^{2, 3, 4, 5, 6}.

While positive margins in BCS correlate with increased risk of local recurrence, it is unclear whether the width of a negative margin impacts local recurrence^{7, 8, 9}. Some studies have shown a harmful impact of close (< 2 mm) margins on tumor recurrence in the same breast as compared to patients with margins ≥ 2 mm suggesting that there may be an optimal “negative” margin¹⁰.

At present, about 40% of American surgeons regularly perform re-excision surgery in the case of a margin less than 1-2 mm around a small (T1) breast cancer^{11, 12}. Margin index, defined as the mathematical relationship between the size of the tumor and the closest margin (see Fig. 1), was shown to be predictive of the probability of residual disease following surgery with close margins for women with Stage I-II breast cancer within one large academic center¹³.

Specifically, all patients with a margin index greater than 5 in this study had a very low risk (3.2%) of residual disease in the re-excision specimen. Given these findings, it was suggested that margin index could be used to help determine the need for additional surgery with close margins. With this helpful predictor, re-excision for patients with a margin index >5 could be avoided, thus decreasing potentially unnecessary surgery.

We applied this predictive tool retrospectively to breast cancer patients at our institution who underwent BCS to determine its ability to predict residual disease in a re-excision specimen.

Methods

Institutional review board approval was obtained before commencement of this retrospective study. Clinical and pathologic data from all patients undergoing BCS and radiation for stage

I or II breast cancer between 1980 and 2010 at the Hospital of the University of Pennsylvania were prospectively recorded in a database. We retrospectively reviewed this database and identified 246 women who underwent an additional re-excision surgery after initial breast conservation surgery for invasive breast cancer with or without DCIS and close or negative margins prior to radiation. Patients with positive margins were not included. Margins of 2 mm or less were coded in the database as a close margin. The presence or absence of residual disease in the re-excision specimen was obtained from the database for each case.

Tumor size and margins were assessed microscopically by our surgical pathologists. All margins of the specimen are inked (anterior, posterior, superior, inferior, medial, and lateral) before sectioning. Each specimen is serially sectioned in 3 to 5 mm intervals and then stained with hematoxylin and eosin. Pathologic analysis includes assessment of proximity to or involvement of each margin for invasive carcinoma or carcinoma in situ.

When available, the pathology report was examined for the actual margin. Pathology reports were not available for patients who underwent surgery before 2005. This was the majority of patients (194). For these patients, margins coded in the database as “close” were assigned a margin value of 1 mm and patients with margins coded as “negative” were assigned a margin value of 3 mm. These values were chosen because within this database (and in clinical practice at our institutions), a margin less than 2 mm is considered “close.” We therefore assumed that margins coded as “negative” were more than 2 mm, but could have exceeded that value slightly, and margins coded as close were less than 2 mm, but could have been closer. To determine whether assigning these particular values affected the results, data was also analyzed using randomly generated margin values between 0.5 and 1.5 mm for “close” margins, and between 2.0 and 3.0 mm for “negative” margins for all instances where the actual value was unobtainable. Random values were selected for unknown “close” margins from a uniform distribution between 0.5 and 1.5 and for unknown “negative” margins from a uniform distribution between 2.0 and 3.0. A logistic regression was fit to the data. A receiver operating curve (ROC) was then created using the derived margin index and the presence or absence of residual disease in the re-excision specimen. Each ROC curve plots true positive rates (sensitivity) versus false positive rates (1-specificity) across all possible cut-off values and therefore was used to facilitate identifying optimal cut-off values if one exists. The area under ROC curve (AUC) was also calculated as an overall measure of the accuracy of diagnosis. The process was repeated 1,000 times to estimate the average AUC and 95% confidence intervals.

The distributions of clinical characteristics between groups with and without residual disease present in the re-excision specimen were compared by Fisher's exact test.

As previously reported¹³, margin index was calculated as closest margin (mm)/tumor size (mm) $\times$ 100. Margin index was compared for the groups with and without residual disease present in the re-excision specimen. Student's t-test was used for comparisons between groups. Statistical analyses were performed using SAS (SAS Institute, Cary, NC). All analyses were two-sided and $P < 0.05$ was considered statistically significant.

Results

We identified 246 women who underwent re-excision for invasive breast cancer with or without DCIS and close or negative margins prior to radiation. Of the 246 patients, 174 (71%) had no residual disease found on re-excision and 72 (29%) had residual disease. Of patients with residual disease, 30 had invasive cancer and 41 had ductal carcinoma in situ (DCIS). For one patient, the nature of the residual disease on re-excision was unobtainable from available records.

Patient demographic and tumor characteristics are outlined in Table 1. The majority of patients (85.4%) had small (T1) tumors. Most tumors were estrogen and progesterone receptor positive and HER-2/neu receptor negative. Tumor size, grade, and status of estrogen, progesterone, and HER-2/neu receptor were distributed similarly for patients with and without residual disease.

A margin index was calculated for each of the 246 patients included in the study. We analyzed several cutoff values for margin index to calculate the sensitivity and specificity to predict the presence or absence of any residual disease (Table 2). There was no cutoff value with both high sensitivity and high specificity, meaning no margin index value was optimal for predicting the presence of residual disease. Receiver operating curves were then calculated (Figures 2a-2c) for each of three comparisons (no residual disease vs. residual invasive disease, no residual disease vs. residual DCIS, and residual DCIS vs. residual invasive disease). All ROC curves at most had an AUC of 0.655, demonstrating that margin index was not a good predictor for any of these comparisons. Analysis of the data using randomly generated margin values between 0.5 and 1.5 mm for “close” margins, and between 2.0 and 3.0 mm for “negative” margins when the actual value was unknown did not change the result. This data, presented in Table 3, shows that no comparisons and no methods of analysis had an AUC near 1 which would indicate a good predictive ability for margin index. When mean margin index was compared between groups, as shown in Figure 3, there was a trend toward higher margin index for patients without residual disease (mean 12.67) compared to patients with residual disease (12.67 vs 10.29, $p=0.07$). When only patients with residual invasive disease were analyzed, the mean margin index was 8.10 and significantly different from those with no residual disease (12.67 vs 8.10, $p=0.03$). For patients with DCIS only on re-excision, the mean margin index was 12.00 and not statistically different from the group with no residual disease ($p=0.37$).

Conclusions

Given that re-excision surgery following BCS continues to attract much attention and discussion¹⁴, a tool that could accurately predict residual disease following BCS would be very helpful to surgeons performing this procedure. A margin index provides that tool and is quick and easy to calculate.

The concept of margin index was first introduced in a study of 475 patients with early stage breast cancer undergoing re-excision for close margins treated at the Washington University School of Medicine¹³. The authors demonstrated a strong relationship between margin index

and residual disease. However, these findings have not been reproduced in several additional studies utilizing margin index in other patient populations. In a study of 55 patients in an Irish breast care center, margin index was not statistically predictive of the presence of residual cancer and, as in our study, this was true when multiple values were used as a cut off¹⁵. In addition, margin index failed to predict the presence or absence of residual disease on re-excision in a study of 48 patients with DCIS only, also at Washington University¹⁶. An abstract of 41 patients found that margin index was unable to predict residual disease, however, the only cutoff value analyzed was 5¹⁷.

The authors in the Irish study noted that while the original margin index paper reported only a 3% risk of residual disease when the margin index was greater than five, 34.4% of the cases in their study in which margin index was greater than five had residual disease. Similarly, 26.1% of our patients with a margin index greater than 5 had residual disease on the re-excision specimen, therefore demonstrating that a margin index of 5 was not a useful cutoff value to predict residual disease.

The data presented here is the largest analysis of margin index since the original study. We were unable to demonstrate an ability of margin index to predict the presence of residual disease on re-excision of a close or negative margin. It is clear that there is a relationship between the size of the tumor and the width of the margin, but unfortunately margin index in its current form does not appear to be a useful tool for the clinical question of when additional surgery for close margins is needed. Certainly, the predictive ability of margin index is affected by multiple factors, especially in this retrospective study. This study covers patients operated on over a 30 year study period and pathologic techniques and documentation have changed over time. One limitation of the data is that the actual margin was unknown for many cases, although whether the margin was “negative” or “close (less than or equal to 2 mm)” was known. We assigned values of 1 mm for all cases with close margins and 3 mm for all cases with negative margins. In order to correct for possible effects of making these assumptions on the result, we also performed the analysis using randomly generated margin values between 0.5 and 1.5 mm for “close” margins, and between 2.0 and 3.0 mm for “negative” margins when the actual value was unknown. This however, did not change the result, so we do not believe these assumptions influenced the data, and our conclusions remain the same.

A possible limitation of the current margin index is that the margin location is unknown. It is possible that distance to some margins, such as at an anatomic boundary like the posterior fascia, are less prognostic for residual cancer than other breast tissue margin directions. In addition, the current margin index does not account for the amount of the tumor near the margin, which has previously been shown to be prognostic for residual disease and local recurrence¹⁸, but currently only incorporates the overall tumor size in the specimen and closest margin distance.

In our study, the presence of DCIS appears to impact the accuracy of margin index. Our data suggest that the relationship between residual disease and margin index is less strong when the residual disease is DCIS than when the residual disease is invasive cancer. Margin index has previously been shown to not be predictive for patients with DCIS-only disease¹⁶.

Pathologic studies suggest that DCIS, as compared to an invasive tumor, grows within the sometimes structurally complicated framework of the lactiferous ducts, in a radial or pyramidal fashion, unlike the more concentric growth of invasive tumor^{19, 20}. This likely makes it less amenable to a mathematical prediction of its behavior. Perhaps also for this reason, the presence of DCIS has been shown to increase the likelihood of a positive margin^{21, 22}. We suggest that, for margin index to potentially be useful, the presence or absence of DCIS should be investigated as a component of the calculation.

Whether a close margin in BCS is clinically significant in terms of patient outcome, particularly as adjuvant therapy for breast cancer advances, is not yet clear. A meta-analysis of studies of the effect on margin distance on local recurrence showed that a positive margin has prognostic value compared to a negative margin. However, increasing the threshold distance for declaring negative margins is only weakly associated with a reduction in local recurrence, which loses significance when adjusted for adjuvant therapy²³.

Ultimately, in women undergoing BCS and radiation for early stage breast cancer at our institution, margin index was not shown to be predictive of the presence of residual disease in the re-excision specimen. Therefore, in the absence of further evaluation of the impact of the area and extent of close margin and presence of DCIS on the margin index concept, we do not believe that it is a useful tool for the surgeon in its present iteration.

Acknowledgements

The authors wish to thank Ms. Robin Noel for creating the graphic for Figure 1.

The authors wish to acknowledge the support of the Biostatistics Core, Siteman Comprehensive Cancer Center and NCI Cancer Center Support Grant *P30 CA091842*.

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Figure 1.

Concept of margin index. Margin index is calculated as (closest margin in mm/tumor size in mm) * 100. For example, a 2 cm tumor with a 1 mm margin or a 1 cm tumor with a 0.5 mm margin would both have a margin index of 5.

Figure 0002

Figure 0003

Figure 0004

Figure 2.

(a) Receiver operating curve for the dataset (residual cancer on re-excision vs. no disease on re-excision). Area under the curve (AUC) was 0.611, indicating that margin index was not accurate in this dataset. (b) Receiver operating curve for the dataset (in situ cancer on re-excision vs. no disease on re-excision). C index was 0.513, indicating that margin index was not accurate in this dataset. (c) Receiver operating curve for the dataset (residual cancer on re-excision vs. in situ cancer on re-excision). C index was 0.628, indicating that margin index was not accurate in this dataset.

Figure 3.
Bar graph comparison of margin index.

Table 1

Tumor characteristics of 246 women undergoing re-excision surgery after breast-conserving surgery.

	All patients (%)	Patients with residual disease (%)	Patients without residual disease (%)	p value
Age				0.67
< 45	54 (22.0)	18 (25.0)	36 (20.7)	
45-55	68 (27.6)	22 (30.6)	46 (26.4)	
55-65	59 (24.0)	16 (22.2)	43 (24.7)	
> 65	54 (22.0)	13 (18.1)	41 (23.6)	
Unknown	11 (4.5)	3 (4.2)	8 (4.6)	
Tumor size				0.32
T1	210 (85.4)	60 (83.3)	150 (86.2)	
T2	35 (14.2)	11 (15.3)	24 (13.8)	
T3	1 (0.4)	1 (1.4)	0	
Tumor grade				0.20
I	42 (17.1)	15 (20.8)	27 (15.5)	
II	39 (15.9)	7 (9.7)	32 (18.4)	
III	100 (40.7)	27 (37.5)	73 (42.0)	
Unknown	65 (26.4)	23 (31.9)	42 (24.1)	
Estrogen receptor (ER) status				0.78
ER+	150 (61.0)	43 (59.7)	107 (61.5)	
ER-	61 (24.8)	17 (23.6)	44 (25.3)	
Unknown	35 (14.2)	12 (16.7)	23 (13.2)	
Progesterone receptor (PR) status				0.60
PR+	134 (54.5)	37 (51.4)	97 (55.7)	
PR-	76 (30.9)	22 (30.6)	54 (31.0)	
Unknown	36 (14.6)	13 (18.1)	23 (13.2)	
HER2-Neu receptor status				0.63
Amplified	39 (15.9)	9 (12.5)	30 (17.2)	
Non-amplified	110 (44.7)	32 (44.4)	78 (44.8)	
Unknown	97 (39.4)	31 (43.1)	66 (37.9)	

Table 2

Sensitivity and specificity of multiple cutoff values for margin index

Margin index cutoff value	Sensitivity (%)	Specificity (%)
5	20	90
10	54	46
20	88	13

Table 3

Area under the curve for assigned margin values and randomly generated margin values.

Comparison	Assigned margin values		Randomly generated margin values	
	AUC (mean)	95% confidence interval	AUC (mean)	95% confidence interval
No residual disease vs. any residual disease	0.539	0.502 - 0.613	0.558	0.532-0.586
No residual disease vs. residual DCIS	0.513	0.501 - 0.614	0.515	0.501-0.545
No residual disease vs. residual invasive cancer	0.611	0.512 - 0.717	0.642	0.607-0.677
Residual invasive cancer vs. residual DCIS	0.628	0.518 - 0.759	0.655	0.604-0.702