Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Association for Academic Surgery

Margin index: a useful tool for the breast surgeon?

Claire Edwards, MD,[a,*] Feng Gao, PhD,[b] Gary M. Freedman, MD,[c] Julie A. Margenthaler, MD,[d] and Carla Fisher, MD[e]

[a] Department of Surgery, George Washington University Medical Center, Washington, District of Columbia
[b] Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri
[c] Division of Radiation Oncology, Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania
[d] Department of Surgery, Washington University School of Medicine, St. Louis, Missouri
[e] Division of Surgical Oncology, Rena Rowan Breast Center, Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

ARTICLE INFO

Article history:
Received 3 January 2014
Received in revised form
20 February 2014
Accepted 14 March 2014
Available online 21 March 2014

Keywords:
Breast cancer
Breast-conserving surgery
Surgical margins
Radiation therapy
Lumpectomy

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 after 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 and 2010 at the University of Pennsylvania. A total of 246 women underwent re-excision because of close margins. Average margin index between groups with and without residual disease in the re-excision specimen was compared using the Student *t*-test. A receiver operating curve 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 residual disease. Average margin index was significantly higher for patients without residual disease compared with patients with residual invasive cancer but not for patients with residual ductal carcinoma *in situ*.

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 a margin index is likely limited by several factors including the presence of ductal carcinoma *in situ* and the location and extent of the close margin.

1. Introduction

As surgical treatment for breast cancer, breast conservation surgery (BCS) has equivalent survival to mastectomy when followed by radiation therapy [1–6]. 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

* *Corresponding author*. Department of Surgery, George Washington University Medical Center, 2150 Pennsylvania Avenue NW, Suite 6B, Washington, DC 20037. Tel.: +1 202 741 3159; fax: +1 202 741 3209.
E-mail address: cedwards@mfa.gwu.edu (C. Edwards).

0022-4804/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jss.2014.03.049

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 [2–6].

Although positive margins in BCS correlate with an increased risk of local recurrence, it is unclear whether the width of a negative margin impacts local recurrence [7–9]. Some studies have shown a harmful impact of close (<2 mm) margins on tumor recurrence in the same breast compared with patients with margins ≥2 mm suggesting that there may be an optimal "negative" margin [10].

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 after surgery with close margins for women with stage I–II breast cancer within one large academic center [13]. Specifically, all patients with a margin index >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 patients with breast cancer at our institution who underwent BCS to determine its ability to predict residual disease in a re-excision specimen.

2. Methods

Institutional review board approval was obtained before the 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 BCS for invasive breast cancer with or without ductal carcinoma *in situ* (DCIS) and close or negative margins before radiation. Patients with positive margins were not included. Margins ≤2 mm 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.

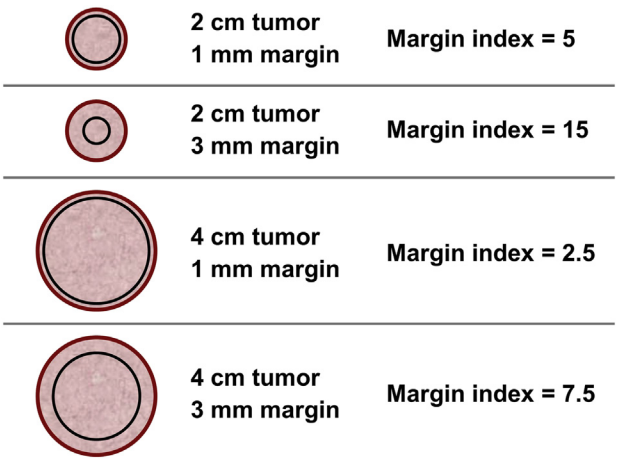

Fig. 1 – Concept of margin index. Margin index is calculated as follows: (closest margin [in millimeters]/tumor size [in millimeters]) × 100. For example, a 2-cm tumor with a 1-mm margin or a 1-cm tumor with a 0.5-mm margin would both have a margin index of 5. (Color version of figure is available online.)

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 the assessment of proximity to or the 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 <2 mm is considered close. We therefore assumed that margins coded as negative were >2 mm, but could have exceeded that value slightly, and margins coded as close were <2 mm, but could have been closer. To determine whether assigning these particular values affected the results, data were 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 cutoff values and therefore was used to facilitate identifying optimal cutoff values if one exists. The area under the ROC curve (AUC) was also calculated as an overall measure of the accuracy of diagnosis. The process was repeated 1000 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 the Fisher exact test.

As previously reported [13], margin index was calculated as follows: (closest margin [in millimeters]/tumor size [in millimeters]) × 100. Margin index was compared for the groups with and without residual disease present in the re-excision specimen. The Student *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.