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Original article

Rates of residual disease with close but negative margins in breast cancer surgery

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ABSTRACT

Objectives: A recent multidisciplinary consensus defined an adequate breast cancer margin as no ink on tumor. The purpose of this study was to analyze rates of residual disease at re-excision by margin width.
Materials and methods: A prospective database at a single institution was reviewed from 2000 to 2012. Institutional protocol had been to perform re-excision surgery when margins were <2 millimeters (mm).
Results: There were 2520 procedures. Re-excision surgery was performed for 12% of breast conserving therapy (BCT) procedures and 2% of mastectomies; residual disease was present in 38% and 26%, respectively. The rates of residual disease for all patients with positive, 0.1–0.9 mm, and 1.0–1.9 mm margins were 40%, 38%, and 33%, respectively. Age, race, menopause status, width of closest final margin, tumor histology, hormone receptor status, triple-negative disease and presence of lymphovascular invasion (LVI) were not significantly associated with the presence of residual disease. The presence of multiple margins <2 mm trended toward significance ($p = 0.06$).
Median follow-up was 43 months. The five-year local recurrence rates (5-year LR) were 1.1% for mastectomy patients and 1.9% for BCT patients.
Conclusions: Breast cancer patients with margins of excision <2 mm have a substantial risk of residual disease but the rates far exceed LR rates. These findings suggest that using residual disease rates to determine the appropriate margin width is not reliable, but also serve as a note of caution to track LR rates as institutions conform to new national guidelines for margin management.

Introduction

The definition for adequate margin width for breast cancer surgery has long been controversial. A recent survey of surgeons found a wide variation in what margin width was thought to be adequate ranging from no tumor touching ink to >1 centimeter (cm) [1]. A similar study of radiation oncologists had a more narrow range of no tumor touching ink to >2 mm, but no particular margin width was favored by greater than 50% of survey respondents in either study [1,2]. Previous studies have identified a positive margin as a risk factor for residual disease [3–8], though a 2010 meta-analysis of 21 retrospective studies encompassing 14,571 early stage breast cancer patients treated with BCT showed no significant association between local recurrence rate and margins >1 mm versus (vs.) >2 mm vs. >5 mm [8]. It is difficult to isolate the influence of margin width on local therapy success since many other patient and disease factors are associated with the presence of residual disease and local recurrence (LR) such as age, tumor size, tumor histology, hormone receptor status, multifocal disease, extensive in-situ component and axillary lymph node metastases [4,5,7,9–12].

In 2014, after convening another meta-analysis of 33 studies [13], the Society of Surgical Oncology and the American Society for Radiation Oncology developed consensus guidelines on margins for breast-conserving surgery for patients undergoing whole-breast irradiation for stages I and II invasive breast cancer [14]. These

Abbreviations: mm, millimeters; BCT, breast conserving therapy; 5-yr LR, five year local recurrence; cm, centimeter; vs., versus; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; ER, estrogen receptor; LVI, lympovascular invasion; CI, confidence interval; HR, hazard ratio.

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guidelines were also endorsed by the American Society of Clinical Oncology [15]. According to the guidelines, a positive margin is the presence of ink on invasive carcinoma or ductal carcinoma in situ and re-excision was not recommended for patients with no ink on tumor. There remains some controversy, however, as the meta-analysis that served as the primary evidence for the guideline panel demonstrated that positive margins were associated with an odds-ratio (OR) for LR of 2.44 ($p < 0.001$), but "close margins" versus negative margins was also associated with significant increase in LR risk (OR 1.74, $p < 0.001$) [13]. When the model was limited to only those studies that quantified "close" margins with measurements, there was little to no statistical evidence that the odds of LR decreased as the distance for declaring negative margins increased, adjusting for follow-up time. The guideline panel concluded that the finding of increased risk of LR with "close" margins in the model was not reliable. Many surgeons and pathologists remain concerned about the possibility of leaving residual disease when margins are close and that LR rates could increase.

While the presence of residual disease does not necessarily produce a LR, logic suggests that those patients with residual disease at the end of their breast cancer surgery would be at higher risk for LR than those without residual disease. Therefore knowledge of whether patients with "close" but negative margins have a substantial risk of residual disease can help inform us as institutions implement the new guidelines on margin management in BCT. In addition, if one could combine margin width with other clinical and pathologic factors to refine which patients are at higher or lower risk of residual disease, one could make more individualized judgments about re-excision. Previously, our institutional guideline was to perform re-excision surgery for breast cancer margins <2 mm. This gives us the opportunity to examine the rates of residual disease for a population that will no longer undergo re-excision if the new guidelines are adopted, at least for those patients undergoing BCT with planned whole-breast radiation. Thus, the purpose of this study was to determine the rates of residual disease at re-excision based on original width of margin. Although the new guidelines deal only with BCT and invasive cancer, we elected to examine the broad population of patients with invasive and in-situ carcinoma and those undergoing mastectomy as well as BCT in order to have a comprehensive view of this issue.

Materials and methods

Institutional review board approval was obtained. A prospective breast cancer database was reviewed including all BCT and mastectomy patients from January 2000 through May 2012. Patients with invasive breast cancer or ductal carcinoma in situ (DCIS) were included. Patients undergoing neoadjuvant therapy were also included. An extensive in-situ component was defined as an invasive tumor with ≥25% DCIS. Re-excision surgery was defined as a separate operation for margins found to be inadequate on final histology. Institutional protocol was to perform re-excision surgery for patients with either invasive cancer or DCIS within 2 mm of one or more margin for either BCT or mastectomy. Exceptions were made for patients who have undergone a mastectomy with a posterior margin that is negative by at least 1 mm for DCIS. The methods for intraoperative handling and pathology processing of specimens with respect to margins were previously described [16]. In brief, all patients have specimens oriented by the surgeon and six standardized ink colors applied by the pathologist for both BCT and mastectomy specimens. Each specimen is subjected to intraoperative sectioning and gross examination with selective frozen section analysis with intraoperative re-excision for any margin deemed inadequate. Patients are routinely presented at a multidisciplinary management conference and undergo consultation with radiation and medical oncology to educate them on and offer appropriate adjuvant therapy. All patients ≤70 years of age with invasive cancer have radiation therapy recommended, and those patients >70 years of age have radiation therapy discussed and offered. All estrogren receptor (ER) and/or progesterone receptor (PR) positive patients have hormonal therapy recommended. Follow up information is obtained through a tumor registry via mailings and phone interviews.

Statistical analysis was performed with SAS version 9 (SAS Institute). Chi-square tests were used for categorical variables. Wilcoxon rank sum test were used for continuous variables. Time to event endpoints were estimated using Kaplan–Meier curves and compared between groups using Cox proportional hazards regression. All p-values were two-sided and considered statistically significant if <0.05.

Results

There were 2520 procedures performed on 2377 patients, for which BCT was performed in 1588 cases (63%). The mean tumor size was 1.3 ± 0.9 cm for BCT, 1.4 ± 0.9 cm for BCT requiring re-excision and 2.6 ± 2.3 for BCT requiring conversion to mastectomy. For mastectomy, the mean tumor size was 2.4 ± 2.3 cm versus 4.6 ± 5.5 cm for mastectomy requiring re-excision. In total, 204 procedures (8%) resulted in re-excision at a second operation for inadequate margins, including 185 (12%) patients undergoing BCT and 19 (2%) patients undergoing mastectomy. Twenty seven of the 1588 BCT cases (2%) were converted to mastectomy. Positive margins on final histology were present in 3% of all procedures while an additional 3% had margins 0.1–0.99 mm and 2% had margins 1.0–1.99 mm.

Among patients who underwent re-excision, the mean age was 64 years (range 31–94 years), 194/204 (95%) were white and 161/204 (79%) were postmenopausal. Thirty of 204 patients (15%) had only DCIS at their first surgery and the remaining 174 (85%) had invasive breast cancer. Four patients (2%) had neoadjuvant therapy prior to their surgical procedure. Residual disease was present in 5/19 patients (26%) who underwent re-excision after mastectomy and in 70/185 (38%) of BCT patients who underwent re-excision: 50/158 of those who completed BCT (32%) and 20/27 of those who were converted to mastectomy (74%). Overall, 75/204 patients (37%) who underwent re-excision had residual disease (Fig. 1). Forty-four of the 75 (59%) patients had quantitative data on the degree of residual disease ranging from foci to 28 mm with 27/44 (61%) patients with ≤5 mm residual disease, 6/44 (14%) with 5–10 mm residual disease and 11/44 (25%) with >10 mm residual disease.

Age, race, menopausal status, width of closest final margin, tumor histology, ER status, triple-negative disease and presence of LVI were not associated with the presence of residual disease on re-excision (Table 1). Patients with DCIS had a 39% rate of residual disease at re-excision, while those with invasive cancer had a rate of 36%. Patients with invasive lobular carcinoma had a 52% rate of residual disease versus 35% rate for patients with IDC, and 13% rate for patients with other carcinoma subtypes such as colloid and tubular carcinoma. Nonetheless, histologic type was not a significant predictor of recurrent disease ($p = 0.26$).

When separating patients into those whose final margin was positive, those whose closest final margin was 0.1–0.9 mm in width, and those whose closest final margin was 1.0–1.9 mm in width, there was no significant difference in the rate of residual disease present at re-excision ($p = 0.78$). The rates of residual disease for all patients with positive, 0.1–0.9 mm, and 1.0–1.9 mm margins were 40%, 38% and 33%, respectively. Among BCT patients, the rates of residual disease by margin width were 39% for positive