

# Implications of New Lumpectomy Margin Guidelines for Breast-Conserving Surgery: Changes in Reexcision Rates and Predicted Rates of Residual Tumor

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## ABSTRACT

**Background.** The 2014 guidelines endorsed by Society of Surgical Oncology, the American Society of Breast Surgeons, and the American Society for Radiation Oncology advocate “no ink on tumor” as the new margin requirement for breast-conserving therapy (BCT). We used our lumpectomy margins database from 2004 to 2006 to predict the effect of these new guidelines on BCT.

**Methods.** Patients with neoadjuvant therapy, pure ductal carcinoma-in situ, or incomplete margin data were excluded. We applied new (“no ink on tumor”) and old ( $\geq 2$  mm) margin guidelines and compared rates of positive margins, reexcision, and rates of residual disease found at reexcision.

**Results.** A total of 437 lumpectomy surgeries met the eligibility criteria. Eighty-six percent had invasive ductal carcinoma, 12 % invasive lobular carcinoma, and 2 % invasive ductal carcinoma and invasive lobular carcinoma. Using a  $\geq 2$  mm margin standard, 36 % of lumpectomies had positive margins compared to 18 % using new guidelines ( $p < 0.0001$ ). Seventy-seven percent of patients with “ink on tumor” had residual disease found at reexcision. Fifty percent of subjects with margins  $< 2$  mm had residual disease ( $p = 0.0013$ ) but would not have undergone reexcision under the new guidelines. With margins of  $\geq 2$  mm, residual tumor was seen in the shaved margins of 14 % of lumpectomies. Residual tumor was more common in reexcisions for ductal carcinoma-in situ  $< 2$  mm from a

margin than for invasive cancer (53 vs. 40 %), although this was not statistically significant.

**Conclusions.** Use of new lumpectomy margin guidelines would have reduced reoperation for BCT by half in our patient cohort. However, residual disease was present in many patients who would not have been reexcised with the new guidelines. Long-term follow-up of local recurrence rates is needed to determine if this increase in residual disease is clinically significant.

Breast-conserving therapy (BCT) is the standard of care for early stage invasive breast carcinoma. There is no difference in overall survival, disease-free survival, or distant disease-free survival between patients undergoing mastectomy or patients undergoing BCT with radiotherapy, but BCT patients have 8–14 % rates of in-breast recurrence at 20 years follow-up.<sup>1–4</sup> A meta-analysis by Clarke and colleagues concluded that for every four patients with an ipsilateral breast tumor recurrence (IBTR), there is one cancer-related mortality over 15 years, illustrating the importance of preventing IBTR.<sup>5</sup>

The strongest predictor of IBTR is positive surgical margins.<sup>6,7</sup> Until recently, there has been no consensus for optimal negative margin width for BCT.<sup>8,9</sup> Many surgeons considered a margin of 2 mm of normal tissue to be negative. Using these standards, historical positive margin rates have been 18–50 %, with similar rates of second surgeries to obtain clear margins.<sup>10–13</sup> The need for reexcision causes discomfort and negative cosmetic, financial, and emotional consequences for patients.

Given the high reexcision rates and no clear guidelines for margin width, the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO)

convened in March 2014 to reassess the association between margin width and IBTR. The consensus panel utilized a meta-analysis from a systematic review of 33 studies of patients with early-stage breast cancer (stage I–II disease) who underwent lumpectomy plus adjuvant whole-breast radiotherapy (WBRT) from 1965 to 2013. Studies of patients with pure ductal carcinoma-in situ (DCIS) and those receiving neoadjuvant therapy were excluded. They concluded that “no ink on tumor” should be the new margin standard, as there was no increased survival benefit seen with wider margins. Tumor was defined as either invasive carcinoma or DCIS. This remained true even when examining high-risk subgroups of patients, such as those with unfavorable biology, age <40 years, invasive lobular cancers, or cancers with an extensive intraductal component.<sup>14,15</sup>

These new guidelines have the potential to significantly decrease rates of positive margins and reexcisions and reduce the overall cost of BCT. We applied these new guidelines to our lumpectomy margins database to predict the effect that these new guidelines will have on rates of positive margins, reexcisions, and extent of residual tumor in the lumpectomy cavity.

## METHODS

Institutional review board-approved retrospective analysis identified all consecutive patients undergoing BCT for primary invasive breast cancer between January 1, 2004, and December 31, 2006, at the Massachusetts General Hospital, Boston. Surgery was performed by four dedicated breast surgeons (B.L.S., K.S.H., M.A.G., M.C.S.) The decision to resect one or more shaved cavity margin (SCM) and the thickness of the shaves were at the discretion of the surgeon, without guidance from intraoperative imaging or analysis of frozen sections.

This study excluded excisional biopsy samples and included only patients who had oriented lumpectomy specimens, oriented SCMs, and invasive carcinoma. We excluded patients undergoing neoadjuvant therapy and patients with pure DCIS or incomplete margin data (on the lumpectomy or the SCMs).

Lumpectomy specimens were marked with sutures that allowed spatial orientation and then inked with multiple colors by the pathologist and sectioned. Representative tissue, including the closest margins, was submitted for histologic evaluation. Most SCMs were entirely submitted. The presence and extent of tumor and margin distance was recorded for each SCM.

Age, family history, *BRCA* status, primary tumor histopathology (histology, size, grade, and presence of extensive DCIS, defined as DCIS within and beyond the tumor), lymphovascular invasion, estrogen receptor status,

and human epidermal growth factor receptor 2 (HER2) status, lymph node status, overall margin status, need for reexcision, adjuvant therapy, and length of follow-up were recorded for each patient.

Overall margin status was determined for all tumors, with margin status reflecting assessment of the outermost edge of tissue excised. For patients undergoing lumpectomy alone, margin status was determined from the detailed pathology report on the lumpectomy itself. For tumors with lumpectomy and select SCM, both the lumpectomy margins and SCM margins were taken into account. For lumpectomies with complete SCMs (4–6 shaves), the SCM margin status was used to determine overall margin status of the specimen.

Rates of positive margins and reexcision were calculated using our institution’s old margin guidelines of  $\geq 2$  mm. We then applied the new “no ink on tumor” guidelines to calculate the predicted rate of positive margins and reexcisions using these new guidelines. It was also noted whether positive margins consisted of invasive cancer, DCIS, or both. Rates of residual tumor (DCIS or invasive cancer) found at reexcision for “ink on tumor” versus tumor <2 mm from the margin (but “not on ink”) were determined. Given the heterogeneity of language used by multiple pathologists and absence of standard national guidelines for margin assessment, it was difficult to quantify the amount of residual tumor found at reexcision. We therefore described it as being present as a single or small focus, or as being more extensive on the basis of the description in the pathology reports (extensive, scattered, multiple foci of tumor, foci of tumor larger than 2 mm, or present in more than one block).

Lumpectomies with margins  $\geq 2$  mm on the main lumpectomy specimen that also had complete SCMs taken were used to assess residual disease when a  $\geq 2$  mm margin standard was applied. For these lumpectomies, tumor present in the shaved margins was equivalent to residual disease that would have been found on a reexcision and was scored as residual disease in our analysis.

Pearson’s Chi square test was used to test for categorical variables. Statistical analyses were performed by STATA 13.0 (StataCorp, College Station, TX), and *p* values of  $\leq 0.05$  were considered statistically significant.

## RESULTS

A total of 766 consecutive lumpectomies from 2004 to 2006 were analyzed. A total of 193 patients were excluded for a diagnosis of pure DCIS; 99 were excluded because their shaved margins were not oriented, and 38 were excluded because they received neoadjuvant chemotherapy. Our final cohort included 437 cancers from 432 patients.

Median patient age was 55 years (range 29–91 years), and most were postmenopausal (63 %,  $n = 273$ ). A total of 378 patients (86 %) had invasive ductal carcinoma as their primary pathology, 12 % had invasive lobular carcinoma, and 1.6 % had mixed invasive ductal carcinoma and invasive lobular carcinoma. A total of 91 % of patients with clear margins underwent radiotherapy, either whole breast or partial breast radiotherapy, with some elderly patients receiving endocrine therapy alone. A total of 76 % of patients received endocrine therapy and 43 % underwent adjuvant chemotherapy. At 89 months median follow-up the rate of IBTR was 3.5 % (Table 1).

Using a margin standard that required  $\geq 2$  mm of tumor-free tissue at the edge of the specimen, 36 % of lumpectomies had positive margins. Thirty-two percent of patients underwent a second surgery to achieve negative margins; of these, 84 % had a reexcision, while 16 % opted for mastectomy. Nineteen patients with positive margins did not undergo reexcision for the following reasons: margin was managed with radiotherapy, positive margin was posterior and fascia was taken, positive margin was anterior and just beneath the skin, and patient choice due to age.

Using the new margin guidelines of “no ink on tumor,” only 18 % of lumpectomies would be considered to have positive margins, compared to 36 % using the  $\geq 2$  mm margin standard ( $p < 0.0001$ ). This represents a 50 % decrease in positive margins and reexcisions.

We then evaluated the frequency of residual disease on reexcisions performed for close or positive margins of various widths (Fig. 1). Among lumpectomies with “ink on tumor,” 77 % had residual disease found at reexcision. The majority, 52.5 %, of residual disease was pure DCIS. Twenty-two percent had residual invasive carcinoma, and the remaining 25 % had both DCIS and invasive carcinoma. In 32 % there was only a small focus of residual disease (DCIS or invasive) found at reexcision. The remaining residual disease was described as more extensive.

In lumpectomies reexcised for margins  $< 2$  mm (but “not on ink”), 50 % had residual disease that would not have been reexcised using new guidelines. Pure DCIS comprised the majority of residual disease (68 %), while 16 % had residual invasive carcinoma and 16 % had residual invasive carcinoma and DCIS. In 33 % there was only a small focus of residual disease, while the rest of the residual disease was described as more extensive.

In order to determine the extent of residual tumor when margins of  $\geq 2$  mm are used, we used shaved cavity margin (SCM) data. A total of 292 of 437 lumpectomies had complete (4–6 shaves) SCMs taken after the main lumpectomy specimen was excised. These cases allowed us to compare the margin width on the

**TABLE 1** Characteristics of patients in the ASTRO/SSO cohort versus the MGH cohort

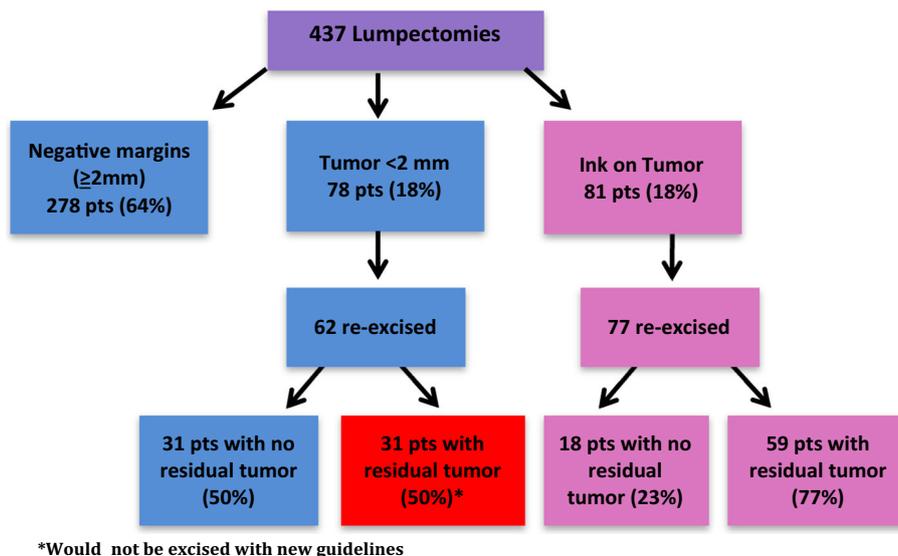
Characteristic	ASTRO/SSO ( $n = 28,162$ )	MGH ( $n = 437$ )
Age, years (range)	53.3 (47.0–60.6)	55 (29–91)
Histologic subtype		
IDC	Not reported	86 %
ILC	Not reported	12 %
IDC + ILC	Not reported	2 %
Node positive	25.8 %	23 %
Tumor size, cm (range)	1.6 (1.2–2.1)	1.3 (0–11)
High grade (III)	28.3 %	29 %
Estrogen receptor status		
Positive	45.5 %	82 %
Negative	20.5 %	18 %
Unknown	28.4 %	0 %
Progesterone receptor status		
Positive	40.6 %	78 %
Negative	22 %	22 %
Unknown	38.3 %	0 %
Extensive intraductal component	9.6 %	39 %
Lymphovascular invasion	17.1 %	27 %
Radiotherapy	100 %	91 %
WBRT	100 %	82 %
Partial breast irradiation	0 %	9 %
Endocrine therapy	38 %	76 %
Chemotherapy	25.6 %	43 %
IBTR	5.3 %	3.4 %
Follow-up, mo	79.2	89

ASTRO American Society for Therapeutic Radiology and Oncology, MGH Massachusetts General Hospital, SSO Society of Surgical Oncology, IDC invasive ductal carcinoma, ILC invasive lobular carcinoma, WBRT whole-breast radiotherapy, IBTR ipsilateral breast tumor recurrence

main lumpectomy specimen with the extent of residual tumor found in the shaved margins specimens. In these patients, rates of residual disease for “ink on tumor” and  $< 2$  mm were similar to the entire cohort, at 69 and 37 %, respectively. For lumpectomies with margins  $\geq 2$  mm, the rate of residual tumor found in shaved margins was only 14 %.

Residual tumor was more common in reexcisions for DCIS  $< 2$  mm from a margin than in those for invasive cancer  $< 2$  mm from a margin (53 vs. 40 %), although this was not statistically significant. Tumors with extensive DCIS were more likely to have residual disease at reexcision for (70 vs. 53 %) but this did not reach statistical significance. Hormone receptor status and lymph node status did not influence rates of residual disease.

**FIG. 1** Schematic of lumpectomy margin status based on margin width



## DISCUSSION

A 2014 SSO/ASTRO endorsed meta-analysis advocated “no ink on tumor” as an adequate margin width for BCT for invasive breast cancers.<sup>14,15</sup> This conclusion was reached after meta-analysis of 33 studies and remained true even for patients with unfavorable biology, age <40 years, invasive lobular cancers, or cancers with an extensive intraductal component.<sup>14</sup>

Our study used our lumpectomy database, including data from shaved margins specimens and reexcisions, to assess potential results of applying these new guidelines. Our cohort is similar to that in the SSO/ASTRO meta-analysis with respect to median patient age and lymph node status. However, our cohort had a higher rate of lymphovascular invasion (27 vs. 17 %) and extensive intraductal component (39 vs. 10 %), possibly reflecting differences in patient population or pathology analysis of specimens and potentially increasing rates of positive margins in our cohort. Our cohort also had a slightly lower IBTR (3.4 vs. 5.3 %), potentially as a result of higher rates of systemic therapy utilization in our patients compared to those in the SSO/ASTRO meta-analysis. The meta-analysis included patients treated over a longer time period (1965–2013), including years when systemic therapy was used less frequently.

We found that new “no ink on tumor” lumpectomy margin guidelines would have reduced the reoperation rate in our cohort by half. Potential benefits of fewer reoperations include reduction in patient pain and stress, decreased recovery times, improved cosmetic outcomes, and reduction in the overall cost of BCT. However, our data showed that use of the new “no ink on tumor” guidelines would have significantly increased the frequency of leaving

residual tumor behind, from 14 % with a  $\geq 2$  mm margin requirement to 50 % with a “no ink on tumor” requirement.

A randomized trial evaluating outcomes of performing SCMs for lumpectomies reported a 12 % rate of residual disease in SCMs when margins on the main specimen were negative.<sup>16</sup> Our 14 % rate of residual tumor for negative margins is similar; however, the other study considered a negative margin to be “no tumor on ink” for invasive cancer and <1 mm for DCIS, and did not examine specific margin widths.

Our data set allows us to quantify rates of residual disease but does not allow us to determine the clinical significance of this residual tumor, as patients in our cohort routinely underwent reexcision to achieve margins  $\geq 2$  mm before proceeding to radiotherapy. The retrospective SSO/ASTRO meta-analysis concluded that these rates of residual tumor would likely be managed successfully with modern radiotherapy and systemic therapy, although this has not yet been examined in a prospective fashion. Our data suggest that careful monitoring of local recurrence rates using new guidelines will be important.

Our data do allow us to provide some useful information about residual tumor after lumpectomy surgery with different margin widths. In lumpectomies with positive margins by the new guidelines (“ink on tumor”), 77 % had residual disease at reexcision, with about half of this residual disease being DCIS. For those with negative margins using the new guidelines (<2 mm, but not on ink), the rate of residual disease was 50 %, with about two thirds of this residual disease pure DCIS. Post-lumpectomy treatments aimed at effective management of residual DCIS will be critical with use of new margin guidelines.

Current concerns about leaving residual disease in the breast after lumpectomy are not new. In 1985 Holland et al. studied unicentric breast cancers and frequently found subclinical foci of invasive cancer and/or DCIS more than 2 cm away from the main tumor.<sup>17</sup> Despite these satellite foci, local recurrence rates after standard BCT have been low. Some of these satellite lesions may now be identified preoperatively with improved breast imaging, but these more distant subclinical foci would not be found even with margins  $\geq 2$  mm.

Our cohort's 50 % rate of residual tumor adjacent to the tumor bed using a "no ink on tumor" standard has implications for several aspects of BCT. First, our data may help explain why a radiation boost to the tumor bed reduces local failure rates. All meta-analysis patients underwent WBRT and the majority received a boost. Randomized trials have shown lower local recurrence rates in breast cancer patients who receive a 16 Gy boost to the tumor bed, although overall survival is unaffected.<sup>18–20</sup> Bartelink et al. reported 20-year follow-up in 2015.<sup>21</sup> This study defined a negative margin as "no ink on tumor" and had local recurrence rates after 20 years of 16.4 % in the no-boost group and 12.0 % in the boost group. A central pathology review for one third of study patients showed no significant effect on local recurrence based on margin width (negative, close, or positive) for either invasive tumor or DCIS.<sup>21</sup>

It is important to point out that the SSO/ASTRO "no ink on tumor" guidelines apply only to patients receiving whole-breast irradiation and were not intended for patients who will not receive radiotherapy. Our series' 50 % rate of residual tumor when a "no ink on tumor" margin standard was applied supports this approach. Prior trials of lumpectomy without radiotherapy for DCIS required 3–10 mm negative margins.<sup>22–24</sup> Our data suggest that such wide margins do indeed reduce the extent of residual disease. The CALGB 9343 trial of lumpectomy without radiotherapy in elderly women with favorable estrogen receptor-positive tumors used a "no ink on tumor" margin standard but did not report recurrence rates by margin width.<sup>25</sup>

The prospective trial of hypofractionated ("Canadian") whole-breast irradiation used a "no ink on tumor" standard and found no difference in local recurrence rates, disease-free survival, or overall survival with hypofractionated versus standard WBRT, both without a boost.<sup>26</sup> In this trial, the risk of local recurrence at 10 years was 6.7 % among women assigned to standard irradiation and 6.2 % among women assigned to hypofractionated radiotherapy. The implication of higher volumes of residual disease in patients undergoing accelerated partial breast irradiation is unknown.

Our data confirm that the new SSO/ASTRO "no ink on tumor" margin guidelines could significantly reduce reexcision rates in patients undergoing breast-conserving surgery. However, these guidelines will leave more tumor behind than with the previous  $\geq 2$  mm margin guidelines. In-breast recurrence rates have been extremely low with  $\geq 2$  mm margin guidelines, but at the cost of high rates of reexcision. Potentially, modern radiotherapy and systemic therapies will permit less stringent margin requirements, reducing reexcision rates without increasing local recurrence. Ongoing monitoring of local recurrence rates using the new guidelines will be important to confirm the efficacy of this approach and to identify subsets of patients who require different margin standards.

**DISCLOSURE** The authors declare no conflict of interest.

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