

## Evaluation of 2014 margin guidelines on re-excision and recurrence rates after breast conserving surgery: A multi-institution retrospective study

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### ABSTRACT

**Introduction:** A 2014 consensus statement from the Society of Surgical Oncology and American Society for Radiation Oncology supported “no ink on tumor” as an adequate margin for breast conserving therapy (BCT). This study evaluates this statement in a multi-institution cohort.

**Methods:** A retrospective review of BCT cases at 3 comprehensive cancer centers was performed. Women age >18 receiving BCT for T1-2 breast cancer from 2008–2012 were included. Pre-2014, all sites considered 2 mm adequate. Estimated re-excision rates using the 2014 guidelines were calculated and factors predictive of re-excision were analyzed.

**Results:** 542 patients (545 lumpectomies) were eligible. Using a  $\geq 2$  mm margin standard, 32.8% of patients underwent re-excision compared to 14.1% after 2014 ( $p < 0.0001$ ). Tumor size ( $p = 0.003$ ), grade ( $p = 0.015$ ), and lymphovascular invasion ( $p = 0.021$ ) were predictive of re-excision. Patients with additional intraoperative margins excised were less likely to require reoperation ( $p = 0.002$ ). Local recurrence was unaffected by re-excision after mean followup of 66 months.

**Conclusions:** The 2014 margin guidelines markedly reduce re-excision rates. There is no difference in local recurrence for patients after re-excision for a close margin versus without. Powered.

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### 1. Introduction

Current surgical options for the treatment of breast cancer include mastectomy and breast conserving surgery (BCS). Recent data show that approximately 50% of newly diagnosed patients will be treated with BCS [2]. A 1990 consensus statement from the National Institutes of Health advocated breast conserving therapy (BCT), defined as breast conserving surgery plus adjuvant radiation, as the preferred approach for patients presenting with stage I or II breast cancers [3,4]. The National Accreditation Program for Breast

Centers has a target goal of at least 50% of eligible patients with early stage breast cancer undergoing BCT as a standard for clinical management [5].

The cornerstone of BCS is the ability to resect the primary tumor with a negative margin while maintaining enough breast parenchyma for an optimal cosmetic outcome. One pitfall of BCS, and perhaps a factor in patients' surgical decision making, is the potential need for re-excision (rates between 20 and 60%) for positive or close margins [6–11]. Re-excision remains a particularly vexing problem for both clinicians and patients undertaking BCT. There are both psychological and financial burdens to patients associated with the need for re-operation following initial BCS.

Various methodologies of specimen examination have been employed to attempt to decrease the rate of positive margins. Routine utilization of some type of intraoperative margin

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assessment (including specimen radiograph, gross margin analysis, or intraoperative frozen section) has been shown to decrease re-excision rates [12]. However, there is yet to be a national standardized practice of evaluating resected specimens at the time of initial operation. Routine cavity shaved margins has also been studied as way to decrease re-excision rates but this practice has not been shown to alter re-excision rates [10].

The issue has also been complicated by the evolving definition of a “negative” margin, and what margin width is sufficient to avoid re-excision. The 2014 consensus statement from the Society of Surgical Oncology and American Society for Radiation Oncology supported the use of “no ink on tumor” as a negative margin for BCT for patients with stage I or II invasive breast cancers [13]. This is less stringent than commonly used institutionally-driven standards, which often range between 2 and 5 mm of margin width.

Multiple single institution studies have reported a decrease in re-excision when applying the 2014 consensus guidelines to clinical practice in this select group of patients with invasive breast cancer [14,15]. The purpose of this study is to evaluate the effect of the new margin guideline on surgical practice and outcomes in a contemporary cohort with modern surgical and pathologic technologies. In an attempt to minimize systematic and regional bias, this multi-institution study spanned various geographic regions, institutions of varying sizes, and a large number of surgeons with a breast focused practice. We sought to assess the impact of these guidelines on re-excision rates as well as the effect on recurrence at median five year follow-up.

## 2. Methods

A multi-institutional retrospective review was performed at three comprehensive cancer centers: Moffitt Cancer Center (Tampa, FL), The University of Texas MD Anderson Cancer Center (Houston, TX) and the University of North Carolina (Chapel Hill, NC). Institutional Review Board approval was obtained at all participating sites. Based on contractual data agreement among the participating institutions, all of the submitted data was de-identified and pooled prior to analysis.

Cases were identified by institutional database query and further data was obtained by detailed chart review. All patients were women over the age of 18 who underwent BCS for T1-2 invasive breast cancer between 2008 and 2012. In order to be included, patients were diagnosed by core needle biopsy and then treated with BCS. Patients with microinvasion were excluded; however extensive DCIS present in association with invasive disease was included. Specimen radiograph was utilized by the surgeons during the procedure to assure removal of the target lesion. The decision to take directed additional margins was at the discretion of each individual surgeon. Cases of pure ductal carcinoma in situ (DCIS) were excluded [16]. Patients were also excluded if the diagnosis was made by excisional biopsy, if the initial operation was performed at an outside institution, if they had less than 60 days of follow-up. Patients receiving neoadjuvant chemotherapy were also excluded as preoperative systemic treatment has been shown to substantially decrease the need for re-excision [17].

Clinical, pathologic, and follow-up data were collected in keeping with the ASCO-CAP guidelines, a tumor was considered to be estrogen receptor (ER) or progesterone receptor (PR) positive if staining was present in at least 1% of the tumor nuclei [18]. Histologically positive margins had ink on tumor whereas close margins were defined as <2 mm from the inked margin. A combination of perpendicular and parallel sections were employed among the pathology labs when handling gross specimens. Re-excision rates were calculated and Fishers exact test was used to correlate patient and tumor characteristics with the need for re-excision. Continuous

variables were also evaluated against the need for re-excision using Wilcoxon rank sum test. Statistics were completed with SAS® 9.4 software (Copyright © 2013 SAS Institute Inc. Cary NC USA).

## 3. Results

A retrospective database review identified 542 patients undergoing 545 breast conserving surgeries meeting inclusion criteria. Across all three institutions, the dataset includes the work of 25 surgeons and 19 pathologists. All surgeons at all 3 institutions were either breast surgical oncologists or surgical oncologists with a breast-focused practice.

Patient characteristics are summarized in Table 1. All of the patients were female, with a median age of 61 years (range 26–88); a great majority of patients had invasive ductal histology (79.0%). Other histologies included invasive lobular (9.0%) and mixed ductal/lobular cancers (8.6%). Three and a half percent of patients had other or unknown histology. Eighty-nine percent of cases were ER positive. DCIS was associated with the invasive cancer in 63.1% (344/545) of the surgical specimens. The median follow-up time was 66 months (4–116 months).

Re-excision was performed in 179 of 545 cases, resulting in a re-excision rate of 32.8% [Fig. 1]. Of these patients, 72 (13.2%) had reoperation for positive margins while 107 (19.6%) were taken back to the operating room for a close margin. The majority of reoperations were a margin re-excision (149/179, 83.2%) while only 30 patients (16.8%) underwent completion mastectomy as their second operation. When comparing re-excision rates between institutions, two were statistically similar; 35.8% and 36.2% ( $p = 1.00$ ). However, the third institution had a significantly decreased rate of re-excision at 18.1% ( $p = 0.0028$  and  $p = 0.0027$ , respectively). There were 2 (0.4%) cases of positive margins that were not re-excised and 66 (12.1%) cases of close margins not re-excised. The decision to forego re-excision in these cases was at the discretion of the surgeon and the patient.

When the patients with positive margins were taken back for re-excision, 60/72 (83.3%) did not have any additional disease on final pathology. Four patients had residual invasive ductal cancer, 5 had additional DCIS and 3 had both invasive and in situ disease. Of those with close margins, 74/107 (69.2%) had no additional disease. Among the 33 patients with disease identified in the re-excision specimen, 11 had invasive cancer, 20 had DCIS, and 2 had both invasive and in situ components. All achieved a negative margin after re-excision.

The majority of patients (472/545, 86.6%) received multimodal adjuvant treatment. Excluding the 30 patients that had completion

**Table 1**  
Patient characteristics.

Characteristics	Data	
Age (years)	Median (range)	61 (26–88)
Tumor Size (cm)	Median (range)	1.4 (0–8)
Nodal Status	N0	79.1%(431/545)
	N1	17.6% (96/545)
	N2	1.8% (10/545)
	N3	0.4% (2/545)
ER positive		89.5% (491/545)
PR positive		78.4% (427/545)
Radiation		91.3% (470/515)
	whole breast	80.0% (412/515)
	partial breast	10.9% (56/515)
Endocrine Tx		81.1% (442/545)
Chemotherapy		45.0% (245/545)
Recurrence		6.8% (37/545)
	Local	4.4% (24/545)
	Distant	3.1% (17/545)

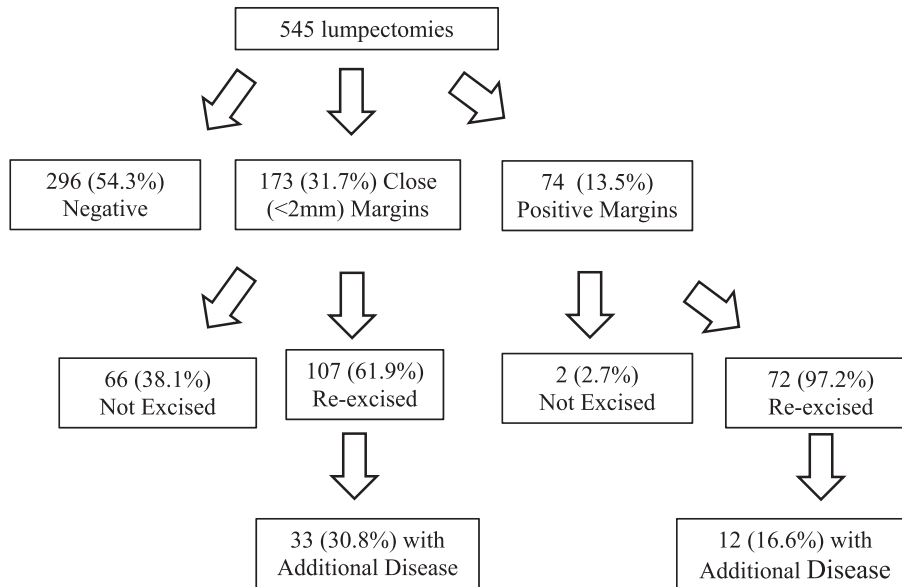


Fig. 1. Flowchart of breast lumpectomy procedures and pathology findings (N = 545).

mastectomy, radiation was completed in 470 patients (91.3%), with 412 (80.0%) undergoing whole breast radiation and 56 (10.9%) receiving partial breast irradiation. There were 245 patients (45.0%) who received adjuvant chemotherapy and 442 (81.1%) who received adjuvant endocrine therapy. Considering that 57 patients were ER negative, only 89.5% (488/545) were eligible for endocrine treatment.

At follow-up, 37 patients experienced disease recurrence, including 24 with ipsilateral breast tumor recurrence; four patients had concurrent local and distant metastases (Table 1). The total recurrence rate for this cohort, including local and distant presentations, was 6.8% with the median time to recurrence being 38 months (range 2–95 months). Among the re-excised subgroup, 4 of 72 (5.6%) patients who had re-excision for a positive margin experienced local recurrence. In the group undergoing re-excision for a close margin, 5 of 107 (4.7%) had local recurrence. Finally, among patients with a close margin who did not undergo re-excision ( $n = 66$ ), 4 had local recurrences (6.1%). The remaining 11 patients had negative margins at initial resection (3.0%). Recurrence rates among these groups were not statistically different ( $p = 0.68$ ). Of note, median follow-up time for patients with close margins not undergoing re-excision was 67 months (range 8–110 months). The majority of patients (61.1%) had greater than 5 year follow up (Table 2).

When clinical and pathologic variables were correlated to the need for re-excision, tumor size as a continuous variable ( $p = 0.003$ ), T category ( $p = 0.005$ ), grade ( $p = 0.015$ ), presence of associated DCIS ( $p = 0.046$ ) and lymphovascular invasion ( $p = 0.021$ ) were associated with higher rates of re-excision. Of note, histologic subtype and hormone receptor status were not predictive of re-excision. An increased number of close margins at initial resection was predictive of re-excision ( $p = 0.010$ ). Similarly, the

presence of DCIS at the close margin, as opposed to invasive cancer, correlated to re-excision ( $p = 0.018$ ). With respect to directed excision margins at the initial operations, those with additional margins taken were less likely to need re-excision ( $p = 0.002$ ).

#### 4. Discussion

The patient population in this multi-institutional cohort is representative of a contemporary U.S. early-stage breast cancer cohort; the geographic, surgical, and pathologic heterogeneity of the study population was intentional to minimize the effects of a single-institution or single surgeon practice. Consistent with a population based evaluation of the effect of the guidelines, as well as several smaller retrospective series, we demonstrated a significant reduction in reoperation after institution of the guidelines, even across multiple institutions with over a dozen practicing breast cancer specialists [19] (Morrow) Consistent with SEER data from 2008 to 2011, which reports a median age of 61 for breast cancer diagnosis, our cohort also had a median age of 61 and is predominantly invasive ductal cancers that are ER-positive [20].

Had the 2014 consensus guidelines been in effect for our patient population, the rate of re-excision would have been significantly decreased, reducing the rate of reoperation from 32.8% to 14.1%. The elimination of re-excision for the close margin group would have spared 60% of the patients who underwent another operation. This is similar to the findings from Merrill et al. who reported the need for reoperation was decreased by 50% in their patient cohort. However, in that cohort, half of the patients who underwent re-excision had residual tumor in the specimen [14]. In our cohort, only 30.8% (33/107) patients that had re-excision for a margin of 2 mm or less had additional disease. Given that this study represents the experience of many physicians across several large institutions, it is unclear what practices contribute to the difference among re-excision pathology findings between the two studies. In particular, circumferential cavity shave margins is not a standard practice at any of the participating institutions, however, a prospective clinical trial published in 2015 demonstrated a 50% reduction in reoperation rates with no negative effect on cosmesis [21]. Performance of cavity shave margins at the discretion of individual surgeons as a routine practice may contribute not only to

Table 2  
Duration of patient follow up.

Duration of Follow Up	Number of Patients	Percentage
<12 months	28	5.1%
12–60 months	184	33.7%
>60 months	333	61.1%

the reoperation rate, but also the difference in pathologic findings at re-excision across studies and institutions.

Of particular interest, given the recent guidelines, is the fact that our cohort had a group of 66 patients with close margins who did not undergo re-excision; thus their management was the same as if they were treated with the current 2014 guidelines. This group did not have a significantly different rate of local recurrence despite possibly having some microscopic residual disease. With a median follow-up time of 67 months, this further supports the safety of the current guideline.

In this contemporary cohort, the role of adjuvant therapy for the treatment of early stage breast cancer has evolved. Systemic therapy is known to impact the rate of ipsilateral breast tumor recurrence in addition to margin clearance. Whole breast radiation techniques have also been refined to decrease rates of in breast tumor recurrence (IBTR). In the EORTC boost vs no boost trial, the addition of boost dose radiation substantially decreased ipsilateral breast tumor recurrence [22]. Similarly the increasing use of endocrine therapy and targeted chemotherapy such as trastuzumab have contributed to decreased rates of local failure [23]. It is important to note that this cohort demonstrated a high rate of recommendation for endocrine therapy (89.5% of eligible patients) as well as high rates of utilization of radiation therapy (91.3%) which may account in part for the overall low local recurrence rate (4.5%). All of these components are routinely included in modern multidisciplinary treatment, and contributed to improved outcomes.

It is interesting to note that the presence of DCIS at the pathologically close margin (as opposed to invasive cancer) correlated to an increased likelihood of re-excision ( $p = 0.018$ ). Although this cohort predates the recent SSO-ASTRO-ASCO DCIS guidelines published in 2016, clinical practice mirrors these recommendations [17]. However, the recommendation of the panel for margin width for DCIS in association with an invasive cancer was to apply the 'no tumor on ink' guideline for invasive cancer as these lesions natural history typically mirrors that of invasive cancer more closely.

This study has limitations, including its retrospective nature. Any study analyzing margin width is inherently limited by the fact that pathologic margin assessment is an inexact science. Due to time and volume constraints, pathologists are only able to sample a small fraction of the surgical specimen for microscopic evaluation and therefore substantial sampling error is possible [24]. Information was not gathered on why re-excision was or was not offered, especially for those with positive or close margins. Margin width is often not reported in the pathology report, particularly if negative and not close. This is a relatively small sample size, and given the favorable disease free and overall survival rates in breast cancer it can be difficult to demonstrate significant differences.

Moving forward, the 2014 guideline offers a new paradigm for BCT with de-escalating surgical treatment in early stage breast cancer [25]. Margin width alone is not enough to make the judgment for re-excision, and the entire clinical and pathologic picture must be considered in the context of multidisciplinary teams [24]. A recent population based review showed that from 2013 to 2015 surgery after initial lumpectomy decreased by 16% and this led to a significant decrease in both unilateral and bilateral mastectomy [19]. In the years since the guideline was adopted, one institution in this study (Moffitt Cancer Center) has seen a 30% reduction in margin re-excision, similar to what was projected in this retrospective data.

## 5. Conclusions

As of 2018, NCCN guidelines now include the 2014 SSO-ASTRO guidelines for margin width in patients with invasive breast

cancer undergoing breast conserving surgery, further validating its widespread use [27]. This change in clinical practice will markedly reduce the need for re-excision without increasing local recurrence. Potential benefits include improved cosmesis and decreased cost to the healthcare system. Over time, the guidelines may even help to increase breast conservation rates in appropriate patients, as mastectomy will not be needed to achieve margin clearance in patients with close margins and an unfavorable breast to tumor ratio. Above all, oncologic outcomes do not appear to be compromised with the adoption of this practice.

## Declaration of competing interest

The authors whose names are listed have NO conflict of interest.

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