

# Optimal Margin Width in Breast Conservation Therapy: a Review of the Current Guidelines and Literature

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**Abstract** Randomized trials have clearly established breast conservation therapy (BCT) as appropriate treatment for early-stage invasive breast cancer. Current evidence shows that positive margins confer a greater than twofold risk of ipsilateral breast tumor recurrence. Thus, patients who have positive margins after BCT warrant re-excision. With regard to negative margins, however, the optimal negative margin width remains unclear. This article reviews the recent guidelines set forth by the Society of Surgical Oncology and the American Society of Radiation Oncology regarding the margin width in stage I and II invasive breast cancer. We also discuss the controversies related to implementation of these guidelines.

**Keywords** Breast conservation therapy · Margin width · Ipsilateral breast tumor recurrence · Margin re-excision

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## Introduction

Several multicenter randomized controlled trials have validated the equivalence of breast conservation therapy (BCT), defined as surgical excision of the tumor followed by whole breast radiation therapy, and mastectomy for the treatment of early-stage invasive breast cancer [1]. These trials include the NSABP-06 and Milan I–III trials that showed no significant differences in disease-free, distant metastasis-free, or overall survival between the mastectomy and BCT groups [2, 3]. Subsequent trials from Europe further supported these findings [4, 5, 6]. As a result, BCT has been established as treatment for early-stage breast cancer.

Despite data showing that BCT is equivalent to mastectomy in terms of survival outcomes, the question as to what constitutes the optimal negative margin width for surgical excision that minimizes local recurrence has still not been clearly answered. This is an important debate as many women undergo re-excision after BCT for already negative margins [7] and thereby are subjected to the risks of additional surgery, potential for worse cosmesis, and increased health care costs.

To address this question, the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) formed a multidisciplinary panel to conduct a meta-analysis on the margin width and ipsilateral breast tumor recurrence in BCT for patients with stage I and II invasive breast cancer. These guidelines are intended to aid physicians and patients in the clinical decision-making process. Herein, we review the guidelines and highlight continuing areas of controversy in selecting the optimal margin width.

## Results of the Meta-analysis

The SSO/ASTRO panel performed a systematic review of 33 studies that included 28,162 patients with stage I or II invasive

breast cancer diagnosed between 1965 and 2012 [8•]. Following strict inclusion and exclusion criteria, they assessed the odds of local recurrence based on the margin status and width, adjusted for study-specific median follow-up time. The median follow-up was 79.2 months, the median prevalence of ipsilateral breast tumor recurrence was 5.3 % (interquartile range 2.3 to 7.6 %), and median time to ipsilateral breast tumor recurrence was 53.5 months. Patient characteristics from this meta-analysis are presented in Table 1.

Two models were used in defining the margin status. In model 1, margins were a dichotomous variable, defined as positive/close versus negative. The margin width was a categorical variable (0 versus 1 versus 2 versus 5 mm). Results from model 1 revealed an odds ratio (OR) of 1.96 (95 % confidence interval (CI) 1.72 to 2.24) for ipsilateral breast tumor recurrence in patients with close/positive margins. In model 2, the margin status fell into three categories: positive versus close versus negative, while the margin width remained a categorical variable (1 versus 2 versus 5 mm). The OR in model 2 for ipsilateral breast tumor recurrence in patients with a positive margin was 2.44 (95 % CI 1.97 to 3.0). In patients

with negative margins, defined as no ink on tumor, no association was found between a specific margin width and ipsilateral breast tumor recurrence. These results are summarized in Table 2.

The multidisciplinary panel further evaluated the effect of specific covariates on the OR of ipsilateral breast tumor recurrence based on the margin width [8•]. In patients receiving a radiation boost or systemic therapy, the adjusted OR in patients with a positive margin remain elevated at 2.53 and 2.45, respectively, suggesting that the risk of ipsilateral breast tumor recurrence is not nullified by the delivery of a radiation boost or systemic therapy. In a subset analysis adjusting for age, the OR for ipsilateral breast tumor recurrence did not differ significantly with a wider margin width ( $P=0.86$ ). Similarly, ipsilateral breast tumor recurrence in patients with more aggressive biologic subtypes or extensive intraductal component (EIC) was not decreased by wider negative margin widths. Finally, the panel found that wider negative margin widths for patients with invasive lobular cancer did not decrease ipsilateral breast tumor recurrence rates.

**Table 1** Patient characteristics from meta-analysis

Study results	Median	Range
Age in years	53.4	45–60.6
Stage distribution, %		
0	0	0–1.4
1	55	52.5–56.9
2	44.4	39.4–45.9
3	0	0–0.9
Tumor characteristics		
Nodal status, %		
Positive	25.8	17.9–28.8
Negative	70.5	65.5–74.2
Tumor size, cm	1.6	1.5–2.1
Higher grade (grade 3), %	28.3	20.6–30.6
Unknown	2.9	0.8–21.5
Estrogen receptor status, %		
Positive	45.5	38.4–56.3
Negative	20.5	16.6–26.3
Unknown	34	
Progesterone receptor status, %		
Positive	40.6	33.5–47
Negative	22	19.4–28
Unknown	37.4	
Treatment		
Chemotherapy, %	25.6	18.3–38
Endocrine therapy, %	38	19.3–59.5
WBRT, %	100	
Radiation boost, %	96	73.1–100

**SSO/ASTRO Guidelines**

Based on this meta-analysis, the SSO and ASTRO developed guidelines to aid clinical decision-making on surgical margins in patients with stage I or II invasive breast cancer undergoing breast conservation therapy [9••]. These guidelines address whether a specific margin width minimizes the risk of ipsilateral breast cancer recurrence in this patient population.

**Table 2** Results of meta-analysis

	Subjects	Odds of LR (odds ratio)	95 % CI	P value [P for trend]
Model 1 <sup>a</sup>	28,162	–	–	
Margin status				<0.001
Negative	21,984	1.0	–	
Positive/close	6178	1.96	1.72–2.24	
Model 2 <sup>b</sup>	13,081			<0.001
Margin status				
Negative	9033	1.0		
Close	2407	1.74	1.42–2.15	
Positive	1641	2.44	1.97–3.03	
Threshold distance for negative margins				0.90 [0.58]
1 mm	2376	1.0		
2 mm	8350	0.91	0.46–1.80	
5 mm	2355	0.77	0.32–1.87	

<sup>a</sup> Model 1 margin was assessed as positive and/or close versus negative

<sup>b</sup> Model 2 margin was assessed as three categories (positive versus close versus negative)

Specifically, the guidelines indicate that if tumor margins are positive, defined as ink on the tumor, studies have shown a greater than twofold increase in ipsilateral breast tumor recurrence. This increased risk is not affected by receipt of systemic therapy, receipt of a radiation boost, or tumor biology. Thus, re-excision is warranted if pathologic margins are positive.

Regarding negative margins, defined as no ink on tumor, the guidelines maintain that although negative margins overall decrease the risk of ipsilateral breast tumor recurrence, wider margins do not significantly lower this risk. In other words, as long as there is no ink on tumor, obtaining wider negative margins is not necessary. Studies evaluating the effect of a specific margin width on ipsilateral breast tumor recurrence not only failed to show a statistical significance between the two but also did not show a trend between increasing negative margin widths and decreasing ipsilateral breast tumor recurrence rates.

It has already been established that systemic therapies, including endocrine therapy, chemotherapy, or targeted therapies, decrease rates of ipsilateral breast tumor recurrence. In the uncommon scenario in which a patient does not receive any systemic treatment after breast-conserving surgery, the guidelines indicate that margin widths greater than negative margins (no ink on tumor) would not decrease the risk of recurrence.

Negative margins, defined as “no ink on tumor,” are also sufficient regardless of tumor biology. It is known that certain biologic subtypes, such as HER2-positive disease and triple-negative disease, exhibit more aggressive behavior and therefore have higher rates of ipsilateral breast tumor recurrence. While a better understanding of these subtypes has led to improvements in systemic therapy, such as the development of HER2-targeted therapies, which have resulted in decreased recurrence rates, no studies have shown greater negative margin widths to have any effect on ipsilateral breast tumor recurrence rates. This is supported by studies in patients with triple-negative breast cancer that show similar recurrence rates regardless of whether patients undergo breast conservation therapy or mastectomy.

The guidelines also report that determining the radiation delivery technique, including fractionation and use of a radiation boost, should not be based on the margin width. Although a boost to the tumor bed after whole breast radiation therapy has been associated with decreased ipsilateral breast tumor recurrence, margin widths greater than negative margins (no ink on tumor) have not been shown to provide additional benefit. Therefore, the use of a radiation boost should be based on a prior estimation of ipsilateral breast tumor recurrence risk, not based on the margin width.

When considering invasive lobular carcinoma, the guidelines indicate that negative margins are sufficient. In contrast to ductal carcinoma in situ (DCIS), where positive margins increase ipsilateral breast tumor recurrence, lobular carcinoma

in situ (LCIS) at the margin has not been shown to affect ipsilateral breast tumor recurrence rates. Thus, classic LCIS at the tumor margin is not an indication of the need for re-excision. Data on pleomorphic LCIS, however, has been less clear and more limited. Thus, the guidelines are not able to give specific recommendations as to the management of patients with margins positive for pleomorphic LCIS.

In younger patients, defined as age less than 40 years old, there are increased ipsilateral breast tumor recurrence rates whether patients undergo breast conservation therapy or mastectomy. Thus, there is no evidence that wider negative margin widths greater than no ink on tumor decrease the risk of ipsilateral breast tumor recurrence in this population. These outcomes are likely related to more aggressive tumor biology in younger patients, and as stated previously, wider negative margins do not appear to provide any additional benefit over no ink on tumor based on tumor subtype.

In patients with EIC, the guidelines state that there is no increased risk for ipsilateral breast tumor recurrence if margins are negative (no ink on tumor). Patients with EIC have a large intraductal component within and around the invasive ductal carcinoma, and initial studies showed them to have potential for considerable DCIS involvement away from the index cancer. However, further studies indicated that ipsilateral breast tumor recurrence rates were similar for EIC-positive and EIC-negative cancers as long as tumor margins were negative. Thus, the guidelines support that wider negative margins (more than no ink on tumor) for the invasive component are not indicated. Nevertheless, the guidelines recognize that patients with EIC-positive disease have the potential for extensive residual DCIS and, thus, postoperative mammography to assess for residual calcifications, young age, or multiple close margins may identify patients in this population in which re-excision is warranted.

### Controversies Regarding the Optimal Margin Width

The SSO and ASTRO acknowledge limitations to the recently published guidelines. Specifically, they note that the recommendations only apply to patients with invasive breast cancer treated with whole breast radiation and that they cannot be applied to patients receiving neoadjuvant therapy or partial breast irradiation or those not receiving radiotherapy at all.

The American Society of Clinical Oncology (ASCO) reviewed the guidelines set forth by SSO and ASTRO [10]. They concluded that the guidelines were clear, thorough, and based on the most relevant scientific evidence. Thus, they deemed the guidelines acceptable to physicians and patients. Although as a whole ASCO agreed with the recommendations presented in the SSO/ASTRO guidelines, they added

qualifications in certain scenarios. First of all, they reiterated the SSO/ASTRO request that institutions monitor the outcomes of using these guidelines, as margin assessments can be influenced by specimen handling, imaging, and processing. Second, in patients with microcalcifications, ASCO emphasizes the importance of postoperative mammography. Because the implementation of the SSO/ASTRO guidelines will result in decreased re-excision rates, postoperative mammography in patients with microcalcifications is necessary to ensure adequate resection of primary disease prior to radiation. Third, and most importantly, ASCO stresses the weakness of the studies on which the SSO/ASTRO guidelines are based. The majority of these studies are retrospective studies with selection bias, and despite the use of meta-analysis, the intrinsic limitations of these studies still remain [11]; therefore, physicians should allow flexibility in applying these guidelines in clinical practice. In other words, these guidelines should aid clinicians in continuing to make individualized treatment decisions based on each patient's clinicopathologic characteristics, rather than be rigidly followed.

Other studies reiterate that although positive margins clearly warrant re-excision, negative margins should not be considered adequate on their own without taking into account other clinicopathologic factors. These factors include discrepancy between radiographic and pathologic tumor sizes with multiple close margins, scattered foci of DCIS or invasive cancer with multiple close margins, and cautery artifact within ductal tissue at the margin with DCIS or invasive cancer near the margin [12]. Age should also be considered, since many studies are underpowered to assess margins and risk of ipsilateral breast tumor recurrence in young breast cancer patients. Therefore, while guidelines enhance clinical decision-making, the characteristics of each patient should be considered in selecting the best treatment to achieve local control and recurrence-free survival.

Adequate margins for DCIS are another area of controversy. Like invasive breast cancer, it is known that negative margins in DCIS are associated with a reduced risk of ipsilateral breast tumor recurrence. However, the optimal width of the margin has not been defined. In a meta-analysis of 22 studies examining patients with DCIS undergoing lumpectomy and postoperative radiation therapy, Dunne et al. found that 2-mm margins were superior to narrower margins but that margins greater than 2 mm were not associated with decreased risk of ipsilateral breast tumor recurrence [13]. However, another meta-analysis of 21 studies in patients with DCIS undergoing lumpectomy with or without postoperative radiation therapy reported by Wang et al. found that wider margins minimize the risk of ipsilateral breast tumor recurrence. Wang et al. recommended that, within cosmetic constraints, attempts should be made to obtain the widest possible negative margin in patients with DCIS [14].

## Conclusion

Positive margins in BCT are known to confer a greater risk of ipsilateral breast tumor recurrence; therefore, surgical re-excision is indicated. The management is less clear when margins are negative, as it is not known what negative margin width is optimal in decreasing the risk of recurrence. Although the SSO/ASTRO guidelines outline many scenarios in which negative margins (no ink on tumor) are sufficient and re-excision is not warranted, the evidence is based on retrospective data. Furthermore, the SSO/ASTRO guidelines only apply to stage I and II invasive breast cancer patients treated with whole breast radiation, and they cannot be applied to patients receiving neoadjuvant therapy or partial breast irradiation or those not receiving radiotherapy at all. Thus, these guidelines should only be used as an aid in clinical decision-making, and the clinician should still exercise flexibility and take into account all clinicopathologic features for each patient before deciding if the margin width obtained is adequate.

## Compliance with Ethics Guidelines

**Conflict of Interest** Ava Hosseini, Bindupriya Chandrasekaran, Rebecca Aft, and Sarah Blair declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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