



Surgical Margins in Breast Cancer: Finally Defined?

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Authors' contributions

This work was carried out in collaboration between both authors. Author CFH designed the study, wrote the first draft of the manuscript and managed the literature searches. Author CEML conducted the analysis of the study, its structure and the final corrections. Both authors read and approved the final manuscript.

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ABSTRACT

It is proven that breast conservative surgery plus radiotherapy is safe and has equivalent results when compared to mastectomy. It is known that positive surgical margins increase the risk of local recurrence. The effect of increasing negative margin width after breast-conserving therapy on local recurrence is controversial. There is no consensus on what constitutes adequate negative margins in breast conservative surgery. There is also an evident association between widely negative margins and excessive breast tissue resection, with poor cosmetic outcomes. Besides, reexcisions represent elevated costs and psychological trauma to the patients. Definition of what constitutes an adequate margin for both invasive and noninvasive breast cancer is clearly needed. We review here the evolution of surgical margins concepts in breast cancer and try to establish the ideal and current surgical approach for each patient.

Keywords: Breast cancer; surgical margins; margin status; local recurrence.

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1. INTRODUCTION

Breast cancer is now recognized to be a heterogeneous disease with different behaviors. Both tumor burden and tumor biology contribute to its clinical outcomes. Adequate local control has been shown to confer a survival benefit at long-term follow-up [1]. Multiple randomized phase III trials have conclusively demonstrate that survival after breast-conserving therapy (BCT), defined as surgical excision of the primary tumor and a margin of surrounding normal tissue followed by whole-breast irradiation (WBRT), is equivalent to mastectomy for the treatment of stages I and II invasive breast cancer [2,3]. The goal of breast-conserving surgery (BCS) is to completely excise the tumor with negative margins, avoiding excessive resection of breast tissue and maintaining acceptable cosmesis. Positive margins are definitively associated with increased rates of local recurrence (LR), compared to negative margins, but there is no consensus on what constitutes an adequate negative margin for breast-conserving surgery. This is a problem, because of the high rates of reexcisions to achieve widely clear margins. Approximately one in four women attempting BCT undergo a reexcision, and nearly half of these are performed with the rationale of obtaining more widely clear margins. The additional surgical reoperative lumpectomy procedure or the mastectomy can result in psychological trauma to the patient, delay of adjuvant therapy, worsened cosmesis and increased cost [4].

With improved mammographic screening, pathology margin assessment, radiotherapy use and routine use of adjuvant systemic therapy, LR rates have decreased over the time with current rates of 3% or less at 5 years and less than 8% at 10 years follow-up [5-8].

Margins definitions range from no ink on tumor surface to 1cm or more. Blair et al. sent a survey to nearly 1,000 breast cancer surgeons, and found that 15% defined a negative margin as no tumor on inked margin, 21% accepted a 1 mm margin, 50% accepted a 2 mm margin, 12% accepted a 5 mm margin, and 3% accepted a 1 cm margin [9]. A meta-analysis by Wang et al. found that wider margins minimize the risk of ipsilateral local recurrence, with lowest recurrence rates achieved with a negative margin larger than 10 mm rather than 2 mm. This finding was independent of whether or not the patient received radiation [10]. In another meta-analysis

of 21 retrospective studies which included 14,571 patients, Houssami et al. [11] demonstrated an odds ratio for local recurrence of 2.42 ($P < 0.001$) with positive margins. This meta-analysis did not identify a statistically significant difference in local recurrence associated with margin widths of more than 1 mm, more than 2 mm, or more than 5 mm after adjustment for a radiation boost and endocrine therapy. This suggests that a 2 or 5 mm margin is not necessarily better than a 1mm margin.

When considering optimal margin width, it is useful to remember that a negative margin does not indicate the absence of residual unresected tumor in the breast [12]. It simply suggests that the residual tumor burden is probably low enough to be controlled with radiotherapy (RT). Even the widest margins resulting from mastectomy do not eliminate risk of local recurrence. This indicates that residual disease burden is not totally eliminated by local surgery and that tumor biology, radiation therapy, and systemic therapy really may play an important role in controlling local recurrence [6].

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 study showed that in 1,815 patients who underwent breast conservation, the positive margin rate was 6, 8% and the in-breast tumor recurrence rate was 14.2% over 20 years of follow-up [3]. Several subsequent NSABP trials showed improvement in 10-year local recurrence rates ranging from 3.5% to 6.5% [13]. The likelihood of LR is related to not only surgical margin. Evidence supports the fact that systemic treatments not only reduce the risk of distant metastases but also reduce the risk of local recurrence. In the NSABP B-14 trial, women with node-negative, estrogen-receptor (ER)- positive tumors were randomly assigned to tamoxifen or placebo. The 10-year rate of local recurrence after breast-conserving surgery was reduced from 14.7% in the placebo group to 4.3% in the tamoxifen group [14]. Similarly, in the NSABP B-13 trial, women with node-negative, ER-negative tumors were randomly assigned to methotrexate and fluorouracil or to no treatment. A reduction was noted in the 10-year local recurrence rate from 13.4% in the no-treatment group to 2.6% in the treatment group [15]. In both studies, the NSABP definition of no ink on tumor was used to define a negative margin.

Further, the majority of the studies describing local recurrence rates do not make the distinction between true local recurrences and new

ipsilateral primary tumors. Yi et al. [16] suggested that approximately 50% of ipsilateral breast tumor recurrences (IBTRs) are actually new primary cancers as differentiated by histologic subtype and receptor status and that these new primary tumors therefore would not be expected to be affected by margin width.

The aim of this article is to review the evolution and modifications of surgical margins concepts in breast cancer during the last decades based on recent scientific evidence, and consequently contribute to the best surgical approach for each patient.

2. METHODS

This literature review was done by data base from LILACS, PubMed, BIREME and a search for articles using Google. The search was carried out during February and March of 2014, using the terms surgical margins, breast cancer, margin status, local recurrence. Articles were selected by their title, year of publication and scientific evidence. Fifty-seven articles were preselected by their abstract or full text. Forty-eight articles were used to confection the present study.

3. RESULTS

3.1 Invasive Breast Cancer

A meta-analysis of 33 studies including 28,162 patients with a median follow-up of 6.6 years reported an odds ratio (OR) for IBTR of 1.96 (95% confidence interval [CI] 1.72-2.24) for close or positive margins compared with negative margins after adjustment for length of follow-up. For the 19 studies of 13,081 patients with sufficient detail to separate positive, close and negative margins, the OR for positive versus negative margins was 2.44 (95% CI 1.97-3.03) [17]. In the 18 studies reporting information about the use of a boost, the risk of IBTR in patients with positive margins remained elevated (OR 2.45; $P < 0.001$) after adjustment for study-specific follow-up and for proportion of patients who had a boost. It suggests that although a boost provides a degree of reduction in IBTR when margins are microscopically positive, the absolute benefit is not sufficient to reduce the rate of IBTR to that seen with negative margins and the use of a boost.

To address the question of the importance of margin width, the meta-analysis of Houssami et

al. [17] evaluated the relationship between specific margins widths (1, 2 and 5 mm) and IBTR. In 19 studies, 13,081 patients, 753 IBTRs and median follow-up of 8.7 years, there was no statistically significant evidence that the odds of IBTR were associated with margin distance ($P = 0.90$) (Table 1). The odds of IBTR did not decreased as the distance for declaring negative margins increased ($P = 0.58$ for trend). Moreover, there was no evidence that the distance used to define negative margins significantly contribute to the odds of LR. Overall, data synthesis in 28,162 subjects indicates that the risk of LR is not driven by the distance defining negative margins.

3.2 Ductal Carcinoma *in situ*

Dunne et al. compared the rate of IBTR according margin status in patients with DCIS (positive margins, no cells on ink, 1 mm, 2 mm and ≥ 5 mm). The meta-analysis, with 22 studies and 4,660 patients, found a 64% reduction in the risk of recurrence in patients with a negative margin after BCS compared with positive margins (OR=0.36; 95% CI, 0.27 to 0.47). Compared with a margin of 5 mm or greater, no cells on the ink (OR=2.56; 95% CI, 1.1 to 7.3; $P < 0.05$) and margins of 1 mm (OR=2.89; 95% CI, 1.26 to 8.1; $P < 0.05$) were associated with a significantly higher risk of IBTR. However, when a 5-mm or greater margin was compared with a margin of 2 mm, no significant difference in the risk of IBTR was observed (OR=1.51; 95% CI, 0.51 to 5.04; $P > 0.05$). When specific margin thresholds were examined, a 2-mm margin was found to be superior to a margin less than 2 mm (OR=0.53; 95% CI, 0.26 to 0.96; $P < 0.05$) (Table 2). They concluded that negative surgical margins should be obtained after BCS for DCIS and that a margin threshold of 2 mm seems to be as good as a larger margin when BCS for DCIS is combined with RT [18]. In both Tables 1 and 2 the χ^2 – based Q statistic was used.

4. DISCUSSION

A positive margin is defined as the presence of ink at the surface of the surgical specimen on either invasive tumor cells or ductal carcinoma in situ (DCIS). It implies a potentially incomplete resection that is associated with a significantly higher risk of IBTR.

Houssami et al. [17] conclusively show, as previously mentioned, that positive margins

increase the risk of IBTR for about 2.5 times in comparison to negative margins. Despite the well-recognized benefit of systemic therapy in reducing IBTR, the effects of a positive margin do not appear to be negated by the use of either adjuvant endocrine therapy or chemotherapy. In a subanalysis of 16 studies within the margins meta-analysis that allowed adjustment for the proportion of patients who received endocrine therapy, the adjusted OR for positive margins (vs negative) remained significantly higher at 2.53 ($P < 0.001$). Analysis of 15 studies that included detailed information on ER status found that the adjusted OR for IBTR among patients with ER-positive tumors with positive (vs negative) margins remained significantly elevated at 2.66 ($P < 0.001$) [17].

Similarly, with a median follow-up of 87.5 months, Russo et al. found a 5-year cumulative incidence of LR of 2.3% for negative margins and 6.4% for positive margins ($P = 0.03$) in patients with early-stage breast cancer treated with BCT [19].

Thus, in the presence of positive surgical margins, there is a significant increased risk of IBTR and this risk is not nullified by delivery of a boost dose of radiation, delivery of systemic therapy or favorable biology.

Negative margins, defined as no ink on invasive carcinoma or DCIS, substantially reduce the risk of local recurrence compared with positive margins. However, the amount of normal breast tissue around the tumor that constitutes an optimal negative margins is controversial.

In the Houssami study, only 26 and 38% of patients included in the entire meta-analysis received chemotherapy and endocrine therapy, respectively. The widespread use of systemic therapy today, even for patients with small, node-negative breast cancer, increased the confidence that wider margins were unlikely to enhance local control in a clinically significant way in the current era. Thus, although larger margin widths may have resulted in small reductions in local recurrence in the past, there is no evidence that

they are important in the setting of current multimodality treatment.

McCahill et al. [20] reported that in 2,200 BCS cases, 509 had reexcision, and 48% of these reexcisions were performed in patients with negative margins to obtain a more widely clear margin. Failure to achieve consensus on margin width is a potential cause of unnecessary surgery, leading to worse cosmetic outcome and increased health care costs.

Several large studies have examined IBTR rates with BCT in relation to molecular markers. In one of the largest studies, it was reviewed 1,434 patients who underwent BCT and found that those patients with triple-negative breast cancer (TNBC) and HER2-positive tumors had a significantly higher risk of IBTR compared with patients with other subtypes [5]. However, the study did not include treatment with adjuvant trastuzumab, which lowers IBTR for the HER2-positive group. Another large study by Voduc et al. of nearly 3,000 patients with a median follow-up of 12 years also found increased IBTR among those with HER2-enriched and basal tumors [21]. Morrow et al. evaluated the effect of margin width on local recurrence in TNBC patients treated with BCT and found that wider surgical margins did not improve LR rates in this subgroup of patients. Among 525 patients who completed radiotherapy, the cumulative incidence of LR at 60 months for patients with margins ≤ 2 mm was 4.7% and 3.7% for those with margins > 2 mm ($P = 0.11$) [22]. There were no observed differences in the risk of distant recurrence and death between the margin groups.

In the recent study by Russo et al., the impact on LR of margin widths of ≥ 2 mm to margins < 2 mm in 906 women undergoing BCT between 1998 and 2006, controlling for tumor subtype, was examined. The 5-year rate of LR was 0% for margins < 2 mm and 2.3 % for ≥ 2 mm margins. On multivariate analysis, margin width was not associated with LR, but triple-negative subtype was a highly significant predictor of LR with an adjusted hazard ratio of 3.7 (95 % CI 1.6–8.8; $p = 0.003$) [19].

Table 1. Relationship between IBTR and margin status (invasive breast carcinoma)

	Number of studies	Number of participants	Adjusted OR of IBTR	95% CI	P
Threshold distance					0.90
1 mm	6	2,376	1.0	-	-
2 mm	10	8,350	0.91	0.46-1.80	-
5 mm	3	2,355	0.77	0.32-1.87	-

OR: Odds Ratio, IBTR: Ipsilateral Breast Tumor Recurrence, CI: Confidence Interval

Table 2. Optimum margin threshold for DCIS resection (n=2,514)

Negative Margin Widht	Number of Patients	% of Patients with IBTR	OR (relapse v > 5 mm)	95% CI (relapse v > 5mm)	P
No cells on ink	914	9,4	2,56	1,1-7,3	<0,05
1 mm margin	1,239	10,4	2,89	1,3-8,1	<0,05
2 mm margin	207	5,8	1,51	0,51-5,0	>0,05
≥5 mm margin	154	3,9	1		

DCIS: Ductal Carcinoma in situ; IBTR: Ipsilateral Breast Tumor Recurrence; OR: Odds Ratio

There is no targeted therapy for TNBC, so it could be postulated that more extensive surgery might improve LR for the triple-negative subtype. A mastectomy represents the widest margin that can be obtained in breast cancer surgery, and three studies have examined the effect of surgery type (BCT compared to mastectomy without RT) on LR in TNBCs. Patients treated with mastectomy had larger tumors and higher risk features; however, on multivariate analysis, type of surgery was not a predictor of locoregional recurrence in this patient population [23-25].

Radiotherapy has an important role in the local control in BCT, but margin width should not be used to determine the delivery technique or fractionation for WBRT. In patients with negative margins (no ink on tumor), the use and dose of a tumor bed boost should be based on a priori estimation of local failure and should not be determined, in isolation, by the width of the surgical margin.

Young patient age, usually defined as < 40 years, has been associated with an increased risk of LR after BCT. In the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of breast-conserving surgery with and without radiotherapy, the rate of any first recurrence by age was 5.9% per year for age < 40 years, 2.7% per year for age 40–49 years, and 1–1.9% per year for ≥ 50 years in the node-negative subgroup. Corresponding rates in the node-positive subgroup were 8.3% per year for age < 40 years, 6.5% per year for age 40–49 years, and 4.8–6.5% per year for age ≥ 50 years, respectively. An increased risk for breast cancer mortality was also seen in the subgroup of women age < 40 years [26]. Other studies have confirmed a higher risk for distant recurrence as well as IBTR in young women [27,28]. Young patient age is not associated with an improved outcome with mastectomy. The risk for locoregional recurrence after mastectomy without radiation is also significantly higher in young

women compared with their older counterparts and the increased risk of both recurrence and breast cancer death is not improved with mastectomy compared with BCT [28-30]. The increased IBTR rates in young women likely result from the greater frequency of adverse biologic and pathologic features in this group compared with older women. Young women have more aggressive tumor characteristics, such as high histologic grade, lymphovascular invasion, hormone receptor–negative breast cancer, BRCA1 and BRCA2 mutation–associated cancers, and association with adverse gene expression profiles, compared with their older counterparts [31,32]. There is no evidence that young patients benefit from a greater negative margin width than no ink on tumor. In the meta-analysis of Houssami et al., in 18 studies, the adjusted OR for IBTR with age as covariate did not differ significantly when margin widths were defined as 1, 2 or 5 mm (P = 0,86) [17].

Regarding the presence of some lesion at margin specimen, in contrast to clear evidence demonstrating that DCIS at margin increases IBTR, the presence of lobular carcinoma in situ (LCIS) at the margin does not impact IBTR. Presence of classic LCIS at the margin is not an indication for reexcision, but the real significance of pleomorphic LCIS at the margin is uncertain [33,34].

Therefore, negative margins (no ink on tumor) minimize the risk of IBTR. Wider margin widths do not significantly lower this risk. The routine practice to obtain wider negative margin widths than no ink on tumor is not indicated.

As a consequence of population-based screening and the increased use of surveillance mammography, DCIS now accounts for 20% of newly diagnosed breast cancers [35]. BCS with RT is now considered a standard treatment option in women with localized DCIS. The major determinant of whether a patient is an acceptable candidate for BCT is the likelihood of obtaining a

negative surgical margin, and the main topic of debate now is the size of the negative margin.

Large tumor size alone is not an absolute indication for mastectomy, but mastectomy should be considered in the setting of large tumors, multicentric lesions and in cases of persistent positive margins after attempts at breast conservation in DCIS [36].

The retrospective studies from the Silverstein group demonstrated a strong relationship between margin width and local control. In a group of 260 patients treated with excision and RT, after a median follow-up time of 105 months, local recurrence was observed in 30% of patients with margins of 1 mm or less, 17% of patients with margins of 1 to 9 mm, and only 2% of patients with margins of 10 mm or greater [37]. In contrast, in 418 patients treated at multiple institutions and observed for a median of 9.4 years, Solin et al. [38] observed a 10-year local recurrence rate of 7% for patients with close margins (defined as within 1 to 3 mm) compared with 9% for patients with negative margins (defined as > 3 mm). These results are similar to what is seen in invasive cancer, where a linear relationship between margin width and local control and a threshold margin to achieve optimal local control have not been identified.

The meta-analysis of Dunne et al. demonstrate that a 2 mm margin is superior to a margin less than 2 mm, but not inferior to a ≥ 5 mm margin for DCIS. Likewise, results from a prospective study of a large group of patients with DCIS conducted by the Eastern Cooperative Oncology Group also do not support a causal relationship between margin width and LR [39]. In the National Surgical Adjuvant Breast and Bowel Project B17 and B24 trials that required margins of tumor not touching ink, only 2.8% of 2612 patients with DCIS treated with BCS with and without RT died of breast cancer after 15 years of follow-up [40].

In the position statement on breast cancer lumpectomy margins, the American Society of Breast Surgeons recommend that if margins are negative and ≥ 1 mm, no further surgery must be performed [41].

5. CONCLUSIONS

The association between margins and the risk of LR is largely driven by margin status, and achieving negative margins in BCT contributes to reducing the risk of LR. However, recent studies

have conclusively shown that margin status is not the only risk factor related to IBTR. The adoption of wider margins for declaring negative margins in BCT is unlikely to have a substantial benefit for long-term local control over a minimally defined negative margin [17].

Differences in rates of LR by subtype of breast cancer are similar after BCT and mastectomy. It suggests that larger surgical excisions, whether in form of more widely clean margins or mastectomy, are unlikely to alter aggressive biology [42]. Negative surgical margins do not mean the absence of residual cancer in the breast. It predicts that residual tumor burden is minimal and is likely to be controlled with adjuvant therapies. Histological studies have shown that additional cancer can be found in a substantial proportion of women despite adequate surgical resection [12,43]. Although patients with TNBCs have higher reported rates of LR than other breast cancer subtypes, it does not appear that more extensive surgery improves outcomes.

Oncoplastic breast conserving surgery is emerging and has the potential to improve the aesthetic outcomes of BCS as well as extending the role of BCS in situations previously considered unsuitable for conservation. Oncoplastic techniques offer patients a safe oncological outcome, large resections and low rates of involved margins. Asgeirsson et al. from the European Institute of Oncology have reported long-term results with a 5-year local recurrence rate of 3% [44]. A recent Institute Curie review of 540 oncoplastic conservation procedures between 1986 and 2008 revealed a local recurrence rate of 6.8%. They also noted involved or close margins in 18.9% of patients with 9.4% requiring further surgery as a mastectomy [45]. In a meta-analysis comparing BCT alone to the oncoplastic technique, Losken et al. found that positive margin rate was significantly lower in the oncoplastic group (12% vs 21%; $P < 0,0001$) and that reexcision was more common in BCT alone (14.6% vs 4%; $P < 0,0001$) [46]. Other 2 studies have specifically examined the effect of oncoplastic surgery on surgical margins. Kaur et al. demonstrated, in a prospective trial comparing quadrantectomy alone and resection with oncoplastic reconstruction, larger resection weights with fewer close or positive margins (16.7% vs 43.4%; $P = 0,005$) in the oncoplastic series [47]. Giacalone et al. [48] performed a similar prospective comparative study and found lower

rates of positive involved margins in the oncoplastic group. Thus, oncoplastic resections are generous and allow for wider excisions with subsequently reduction in the risk of positive margins, a basic oncologic principle.

Current data support the definition of a negative margin as no ink on tumor, even in the right breast cancer subsets. In a large number of patients underwent reexcision for close or negative margins to achieve wider negative margins, no residual disease is found. It is clear that adoption of a standard definition of a negative margin is needed. Based on literature reviewed here, the definition of tumor not touching ink is reasonable for invasive breast cancer. For DCIS, due to the discontinuous growth pattern, a slightly wider margin of 2 mm is preferable.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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