Review Article



# Appropriate margin for lumpectomy excision of invasive breast cancer

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**Abstract:** The management of patients with early-stage breast cancer has evolved over time, with the understanding that tumor biology, and not just disease burden, impact local control. Local control is greatly improved with systemic therapy, providing an opportunity to decrease the morbidity of local therapy in women with invasive breast cancer. In women undergoing breast-conserving therapy, which consists of lumpectomy and whole-breast irradiation, there has been a lack of consensus as to what constitutes a negative margin. Current evidence indicates that wider margins do not reduce local recurrence compared to "no tumor on ink". In this article, we will review the available data on the relationship between margin status and local control for invasive breast cancer, and discuss the impact of molecular subtypes and systemic therapy on local control.

**Keywords:** Margins; local control; invasive breast cancer

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## Introduction

Breast-conserving therapy (BCT), consisting of lumpectomy and whole-breast irradiation, is a preferred treatment option for women with early-stage breast cancer. Six randomized prospective trials, some with follow-up of 20 years or more (1,2) have demonstrated no difference in survival between early-stage breast cancer patients treated with mastectomy compared to breast-conserving surgery and radiotherapy (RT). Over time, rates of local recurrence after BCT have declined steadily and are now considerably less than 10% at ten years of follow-up (3,4). However, the appropriate extent of surgical resection needed to maintain local control following lumpectomy remains a matter of debate, and the lack of consensus regarding what constitutes an adequate negative margin results in multiple trips to the operating room for margin re-excision in a significant number of patients, and unnecessary mastectomies in others (5).

The demonstration in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview that differences in local control between treatments of 10% to 20% at 5 years are associated with significant differences in breast cancer-specific survival at 15 years (6) has focused new attention on the importance of local control. For many years, disease burden as defined by margin status was felt to be the primary determinant of local control. Over time, it has become increasingly clear that both the underlying biology of the tumor and the availability of effective systemic therapy are also critical components of local control. In this article, we will review the available data on the relationship between margin status and local control for invasive cancer, and discuss the impact of molecular subtypes of breast cancer and systemic therapy, including targeted therapy, on local control outcomes.

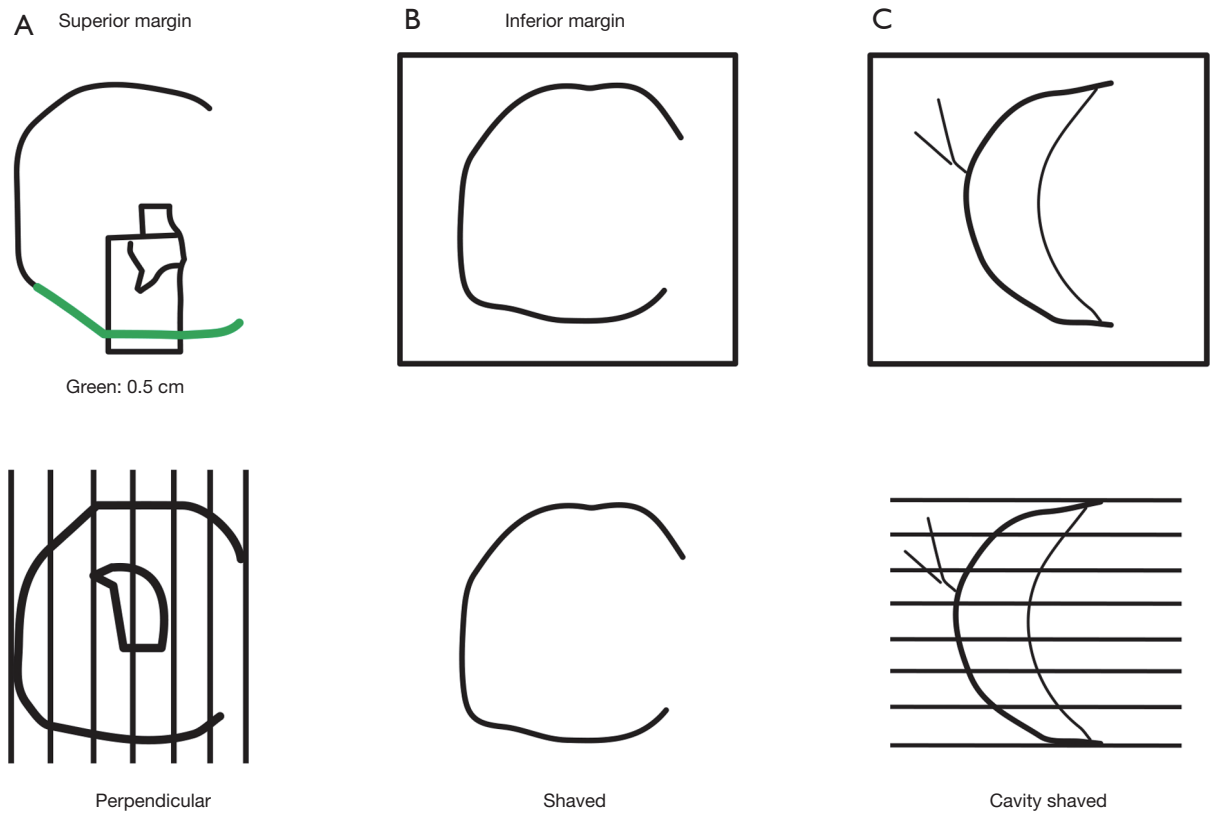


**Figure 1** Margin evaluation methods. (A) Radial (perpendicular) margin evaluation; (B) shaved (en face) margin evaluation; and (C) cavity shaved margin evaluation. With the radial margin technique (A), each margin surface is inked a different color and the distance from the tumor to the ink is reported for each margin. With the en face method (B), the entire surface is shaved and no inking is needed. With the cavity margin evaluation method (C), the primary lumpectomy specimen is not inked. The outer surface of each of the individual margins is inked, and the distance from the tumor to the ink is measured.

## Margin evaluation

There is no standard method of margin evaluation for lumpectomy specimens, nor are there a standard number of histologic sections which are examined from each margin surface. Margins can be evaluated using a radial (perpendicular) method, a shaved (en face) method, or by shaving the walls of the lumpectomy cavity (separate shaved cavity margins) (*Figure 1*). Although each method has its own advantages and disadvantages, the separate shaved cavity margin technique avoids disorientation of the specimen by having the surgeon designate the margin and has been shown by several investigators to reduce the rate of re-excision for close margins when compared to traditional margin assessment (*Table 1*) (7-13). A recent prospective randomized study comparing the cavity shave technique to standard perpendicular margin assessment confirmed a lower rate of positive margins in the cavity-shave group (19% *vs.* 34%, respectively; P=0.01), although the positive margin rate was high in both groups (13).

In addition to the method of margin assessment, other factors related to specimen processing may influence the margin width or the rate of margin positivity. Graham *et al.* compared the measurement of the mean height of the lumpectomy specimen measured by the surgeon in the operating room to the measurement in the pathology lab in 100 consecutive specimens (14) and found that breast specimens lost almost 50% of their height after surgical removal; this "pancake phenomenon" clearly impacts margin assessment. Other factors, such as running ink, imprecise margin orientation, and surface complexity may also compromise margin evaluation. Running of the ink from the irregular fatty specimen surface to the inside of the

**Table 1** Comparison of positive margin rates in patients treated with cavity shaved margins versus routine margin assessment

| Author | Year | n | % positive margin | | P value |
|---|---|---|---|---|---|
| | | | Cavity margins | Routine | |
| Huston *et al.* (7) | 2006 | 171 | 18 | 39 | |
| Jacobson *et al.* (8) | 2008 | 125 | 18 | 66 | |
| Tengher-Barna *et al.* (9) | 2009 | 107 | 13 | 33 | |
| Marudanayagam *et al.* (10) | 2008 | 786 | 5.6 | 12.5 | <0.01 |
| Rizzo *et al.* (11) | 2010 | 320 | 15 | 43 | <0.05 |
| Kobberman *et al.* (12) | 2011 | 138 | 22 | 42 | 0.01 |
| Chagpar *et al.* (13) | 2015 | 235 | 19 | 34 | 0.01 |

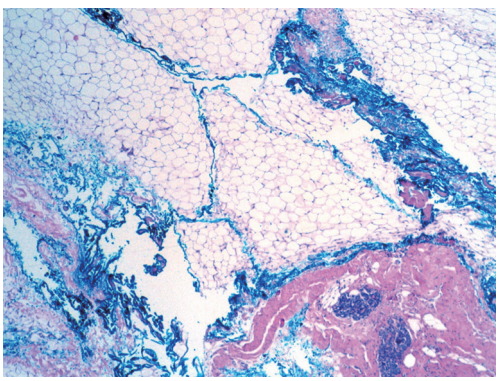

**Figure 2** Problems with radial margin assessment and inking. "Running" of ink (blue) inside a specimen makes identification of the true margin surface difficult.

specimen, and different color inks running into each other, occur frequently, leading to possible over-interpretation and false-positive margins (*Figure 2*).

## The relationship between margin width and local recurrence in invasive cancer

### *What constitutes a "negative" margin?*

Given the lack of standardization in pathology methods, it is not surprising that there has historically been little consensus regarding what constitutes an adequate negative margin. Azu *et al.* (15) surveyed a population-based sample of 318 surgeons identified from breast cancer patients in the Surveillance, Epidemiology, and End Results (SEER) registry. Surgeons were asked "What negative margin width precludes the need for re-excision in a 60-year-old with a 0.8 cm invasive cancer which is estrogen receptor (ER), progesterone receptor (PR), and HER2 negative?" and offered the options of tumor not touching ink, >1–2, >5, or >10 mm. No single answer was selected by more than 50% of respondents. Only 11% endorsed margins of tumor not touching ink, 42% of >1–2 mm, 28% of >5 mm and 19% of >10 mm. Similar variation exists among radiation oncologists. In a survey of 1,133 North American and European radiation oncologists, 45% of those from North America endorsed a margin of tumor not touching ink, while those in Europe favored more widely clear margins, with greater than 5 mm being the most common answer, selected by 29% (16). The net result of the lack of consensus on what constitutes an adequate negative margin is the frequent performance of re-excision to obtain more widely clear margins. Morrow *et al.* (5), reporting on a population-based sample from the SEER registry of 800 women attempting BCT, observed that although the procedure was successful in 88%, 22% underwent a re-excision to obtain wider margins. Other studies report a wide variation in re-excision rates ranging from 6% (10) to 49% (17), with the majority noting re-excision in 15% to 30% of patients (7,18,19).

The prospective randomized trials that established the safety and efficacy of BCT (1,2,20-23) do not provide much guidance on the margin question since only the NSABP B06 trial used a microscopic definition of a negative margin, which was tumor not touching ink (1). Although the other trials are often perceived as requiring more widely clear margins, they relied upon gross margin definitions, making the actual margin width impossible to assess. Similarly, although a trial by Veronesi *et al.*, which randomized patients to quadrantectomy or a more limited tumorectomy, demonstrated a lower rate of local recurrence in the quadrantectomy group (2.2% *vs.* 7.0%), this study also relied on gross margin assessment. The tumorectomy was performed with a gross margin of 1 cm, but in a subset

**Table 2** Local recurrence in randomized trials of breast-conserving surgery versus mastectomy

| Trial | Follow-up (years) | % local recurrence | |
|---|---|---|---|
| | | Mastectomy | Breast-conserving surgery |
| Institute Gustave-Roussy (20) | 15 | 14 | 9 |
| Milan 1 (2) | 20 | 2* | 9 |
| NSABP B06 (1) | 20 | 10 | 14 |
| Danish (21) | 6 | 4 | 3 |

*P<0.0001. NSABP, National Surgical Adjuvant Breast and Bowel Project.

of patients who had microscopic margin evaluation, 16% of those in the tumorectomy group had positive margins (24). The uncertainty over margin status in this trial makes it impossible to conclude that a larger quadrantectomy type procedure is associated with a lower rate of local recurrence than a more limited resection with negative inked margins.

### *A systematic review of margin width and local recurrence*

Houssami *et al.* reported the results of a methodologically rigorous meta-analysis of the relationship between margin width and local recurrence in women with invasive breast cancer. The meta-analysis included 33 studies with 28,162 patients and 1,506 local recurrences with a median follow-up of 79.2 months. The relationship between positive margin status and local recurrences was verified, with an odds ratio (OR) for local recurrence of 2.44 for positive or unknown *vs.* negative margins. No relationship between negative margin width, defined as 1 *vs.* 2 *vs.* 5 mm, and local recurrence was identified (25). Although a non-statistically significant numeric trend for a benefit of more widely clear margins was seen in some models, this did not persist after adjustment for other factors such as age, the use of a radiation boost, or receipt of endocrine therapy. This analysis included information on a large number of factors relevant to local recurrences, such as date of study enrollment, patient age, use of radiation including a boost, and pathologic tumor features such as lymphovascular invasion (LVI), extensive intraductal component (EIC), and tumor grade, and provides the most convincing evidence to date that margins more widely clear than tumor not touching ink do not have a major impact upon local control in the era of modern multidisciplinary therapy.

Although this may seem counterintuitive, it becomes much more logical if one considers that even mastectomy, which provides the widest possible margin, does not entirely eliminate the risk of local recurrence. In the initial randomized trials comparing BCT to mastectomy in which at least grossly negative margins were required, only the Milan study (2), which included T1 cancers treated with radical mastectomy, showed a statistically significant reduction in local recurrence for mastectomy compared to BCT (*Table 2*) (1,2,20,21). This, coupled with the observation from the EBCTCG overview (6) that, even with the addition of postmastectomy RT, the incidence of local recurrence is higher in node-positive women than it is in node-negative women, indicates that local recurrence may be due to either excessive tumor burden or aggressive biology. The failure to observe a decrease in local recurrence with surgical margins more widely clear than tumor on ink suggests that once disease burden is reduced to this level (i.e., no clinically detectable cancer), tumor biology is the main determinant of local control.

## The influence of histology on margin width

Variations in the growth patterns of different histologic types of cancers raise concerns that the same margin width may not be appropriate for all histologic tumor types. Infiltrating lobular cancers are frequently multifocal and grow as single cells in linear strands separated by normal stroma (26), raising the possibility that margins negative only by tumor not touching ink might be associated with a significant residual tumor burden. However, clinical studies do not document a higher rate of local recurrence after BCT for lobular cancers when compared to ductal cancers (27-29), suggesting that if negative margins are obtained, the growth pattern is irrelevant. Galimberti *et al.* (30) analyzed 382 patients with pure infiltrating lobular carcinoma treated with BCT to determine if rates of local control differed among those with margins less than 1 cm compared to 1 cm or greater. The local failure rate was 4.6% for the less than 1 cm margin group compared to 3.7% in the 1 cm or greater group, leading the authors to conclude that more widely negative margins were not necessary for patients with infiltrating lobular carcinoma. Sagara *et al.* evaluated locoregional recurrence in a modern cohort of patients with stage I–III lobular carcinoma. Of 381 patients treated with BCS, in-breast tumor recurrence (IBTR) was significantly increased for patients with positive margins [hazard ratio (HR) =7.5, P=0.01], but it was not

 

increased for patients with margins 1–3 mm (HR =0.57, P=0.60) or margins within 1 mm (HR =0.73, P=0.77) (31). The findings suggest that margins of "no tumor on ink" are adequate in most patients with lobular carcinoma treated with multimodality therapy.

The other group of concern is patients with an EIC in association with their invasive cancer. Early studies performed prior to the routine inking of margins suggested that an EIC was associated with higher rate of local recurrence in patients undergoing BCT (32). Holland *et al.* documented that approximately 30% of patients with EIC positive cancers had prominent intraductal carcinoma more than 2 cm beyond the primary tumor, compared to only 2% of patients with EIC negative tumors (33), indicating that a substantial number of patients with an EIC treated by excision to grossly negative margins have a heavy residual tumor burden. Despite the concern regarding residual disease in EIC positive cancers, additional studies have demonstrated that when patients with an EIC are excised to negative inked margins, rates of local recurrence are not increased compared to patients without an EIC (34,35). Of note, Schnitt *et al.* demonstrated a 5-year IBTR rate of 0% in EIC positive patients with a margin of "no tumor on ink" compared to 50% when margins were more than focally positive (36); these results should be interpreted with caution as the number of EIC positive patients in this study was small (n=30). In patients with pure ductal carcinoma in situ (DCIS), Faverly *et al.* have shown that low- and intermediate-grade tumors often grow with gaps between the DCIS lesions, although these gaps are usually less than 5 mm in size (37), suggesting that margins negative by only tumor not touching ink could be associated with a significant residual tumor burden. The presence of an EIC in association with invasive cancer suggests it may be prudent to consider obtaining a margin of at least 2 mm if large amounts of DCIS are in proximity to the margin. In the case of both infiltrating lobular carcinoma and an EIC, clinical judgment remains important. A single duct of DCIS or microscopic focus of lobular carcinoma in close proximity to the margin is unlikely to be associated with a heavy residual tumor burden, while a large area of tumor immediately adjacent to a margin may be associated with a greater risk of residual disease (38) and should prompt re-excision.

## Other factors influencing local control in invasive cancer

It is important to recognize that a "negative" margin does not indicate that there is no residual tumor in the breast. In a landmark study using serial subgross sectioning to evaluate the remaining breast tissue in 264 mastectomy specimens from patients with clinically unifocal cancers 4 cm or less in size, Holland *et al.* (39) showed that only 39% of cases had no additional tumor beyond the index cancer. In 20% of cases, the additional tumor foci were within 2 cm of the index tumor, and in 41% of cases, the tumor foci were more than 2 cm from the primary tumor. From a practical point of view, a negative margin indicates that the residual tumor burden in the breast is low enough that it is likely to be controlled by RT. The role of RT in maintaining local control is well documented in the EBCTCG overview (6). At five years, the absolute incidence of local recurrence in node-negative women treated with breast-conserving surgery receiving RT was 16% lower than in those not receiving RT, while for node-positive women, a 30% reduction in isolated local recurrence was seen. These reductions in local recurrence at 5 years translate to 15-year survival gains of 5% and 7% in node-negative and node-positive women, respectively. In a prospective randomized trial examining the benefits of boost dose of RT on local control, Bartelink *et al.* demonstrated statistically significant reductions in local recurrence with the addition of a boost in women of all ages (40). While the role of RT in local control has long been recognized, the effect of systemic therapy on local control is less well recognized.

The majority of women with invasive breast cancer now receive some form of adjuvant systemic therapy in addition to surgery and RT. Both endocrine therapy and chemotherapy significantly reduce the likelihood of local recurrence after BCT. In the NSABP B14 trial, in which node-negative, ER positive women were randomized to tamoxifen citrate or placebo, the 10-year rate of in-breast recurrence was reduced from 14.7% in the placebo group to 4.3% in the tamoxifen group (41). In the NSABP B13 trial, node-negative ER negative women were randomized to chemotherapy or a no-treatment control group (41). At eight years, local recurrence was seen in only 2.6% of those receiving chemotherapy compared to 13.4% of controls (P=0.001). In a report of 3,799 node-negative women treated with BCT participating in five NSABP trials of adjuvant systemic therapy, the cumulative incidence of in-breast recurrence at 12 years for those receiving adjuvant therapy was only 6.6% (3). With the increasing use of systemic therapy, rates of locoregional recurrence are declining over time. Bouganim *et al.* performed a meta-analysis of 53 randomized clinical trials with a total of 86,598 patients and demonstrated that between 1990 and

 

2011, the relative frequency of locoregional recurrences was reduced by half, from over 30% to approximately 15% of all recurrences, which was largely related to the use of chemotherapy and/or endocrine therapy (42). Since the time when these trials were conducted, systemic therapy options have improved with the introduction of targeted therapy and better cytotoxic chemotherapy, and this will undoubtedly result in a further decrease in local recurrence rates. For example, in the randomized trials that established the efficacy of adjuvant trastuzumab, the addition of trastuzumab to chemotherapy resulted in a 50% decrease in locoregional recurrence compared to treatment with chemotherapy alone (43). Similar results have been reported in ER positive, node-negative patients when systemic treatment is selected on the basis of the Oncotype DX™ (Genomic Health, Redwood City, CA) recurrence score (RS). Although the RS was developed to predict the risk of systemic recurrence, Mamounas *et al.* (44) demonstrated that in patients treated with placebo, Oncotype DX score also correlated with risk of locoregional failure. The 10-year estimates for locoregional recurrence (LRR) were 18.4% in patients with a high RS compared to 10.8% in those with a low RS (P=0.022). The addition of tamoxifen, which is considered appropriate treatment for those with low RS, reduced the incidence of LRR by more than 50% to 4.3% in the low-risk group. In contrast, a much more modest reduction in LRR from 18.4% to 15.8% was seen with tamoxifen in patients with a high RS. However, when chemotherapy was added, the 10-year LRR decreased to 7.8% in those with a high RS.

The importance of biology and targeted therapy is further supported by the emerging literature on the impact of tumor subtype on local recurrence after BCT or mastectomy. Both Millar *et al.* (45) and Nguyen *et al.* (46) have demonstrated that the rate of local recurrence after BCT varies among the intrinsic subtypes of breast cancer as approximated by ER, PR, and HER2 status. In both studies, the lowest rates of local recurrence at 5 years were seen among the ER positive, PR positive, HER2 negative (Luminal A-like) group, and the highest rates were among the triple-negative (basal-like) and ER negative, HER2 positive patients in the absence of adjuvant trastuzumab. However, ER, PR, and HER2 status are not indicators of the need for more widely clear margins, as chest wall recurrences after mastectomy are also more likely in ER negative patients, regardless of HER2 status, as reported in a retrospective analysis of the Danish Breast Cancer Group randomized trials of mastectomy with or without RT (47). A meta-analysis by Lowery *et al.* (48) evaluated 12,592 patients from 15 studies, of whom 7,174 were treated with BCT and 5,418 with mastectomy. Patients with ER/PR positive tumors had a lower risk of local recurrence than HER2 positive tumors (without trastuzumab) (relative risk 0.34) and triple-negative tumors (relative risk 0.38). Patients with (untreated) HER2 positive tumors had a higher risk of local recurrence than triple-negative tumors (relative risk 1.44). As previously noted, the addition of trastuzumab to chemotherapy has been shown to reduce the risk of local recurrence in HER2 overexpressing patients (43), indicating that targeted therapy is a major contributor to local control. Kiess *et al.* (49) validated a significant decrease in locoregional recurrence in patients treated with BCT by the addition of adjuvant trastuzumab. Among 197 patients who were treated with BCT immediately before and after adjuvant trastuzumab became available, 3-year rates of locoregional recurrence fell from 10% to 1%. Even in patients considered to have aggressive tumor biology, there is no evidence that wider margins result in a lower risk of local recurrence. Pilewskie *et al.* (50) evaluated local recurrence rates in 535 triple-negative breast cancers treated with BCT. Seventy-one had negative margins ≤2 mm, and 464 had negative margins >2 mm. The 5-year incidence of local recurrence was 4.7% with margins ≤2 mm and 3.7% with margins >2 mm, a difference which was not significant after controlling for tumor size and the use of chemotherapy. Moreover, in patients with aggressive tumor biology treated with systemic therapy, mastectomy, which provides the widest surgical margin, does not provide improved local control over BCT. In a study of 646 patients with T1-2N0 triple-negative breast cancer, of whom 81% received adjuvant chemotherapy, the 5-year incidence of LRR was 4.2% for patients undergoing BCT compared to 5.4% for patients treated with mastectomy (51). In aggregate, this information validates the importance of systemic therapy in local control, indicates that factors other than disease burden are key determinants of local control, and provides evidence that margins more widely clear than no tumor on ink are not indicated even for high-risk tumor subtypes.

## Summary and conclusion on invasive cancer: consensus guidelines

The failure of mastectomy, the most widely clear margin which can be obtained in the breast to achieve rates of local control approaching 100%, is clear evidence that disease burden is not the only factor determining local control. Evidence that margins more widely clear than tumor not

 

**Table 3** Society of Surgical Oncology and the American Society for Radiation Oncology consensus guidelines on margins for patients with stage I and II breast cancer treated with breast-conserving surgery and radiation therapy. A positive margin, defined as invasive tumor on ink, confers a two-fold increase in local recurrence

| Clinical question | Recommendation |
|---|---|
| Can the use of radiation boost, systemic therapy, or favorable tumor biology mitigate the two-fold increased risk of IBTR with a positive margin? | This increased risk in IBTR is not nullified by: delivery of a boost, delivery of systemic therapy (endocrine therapy, chemotherapy, biologic therapy), or favorable biology |
| Do margin widths wider than no ink on tumor cells reduce the risk of IBTR? | Negative margins (no ink on tumor) optimize IBTR; wider margin widths do not significantly lower this risk; the routine practice to obtain wider negative margin widths than ink on tumor is not indicated |
| What are the effects of endocrine or biologically targeted therapy or systemic chemotherapy on IBTR? Should a patient who is not receiving any systemic treatment have wider margin widths? | Rates of IBTR are reduced with the use of systemic therapy; in the uncommon circumstance of a patient not receiving adjuvant systemic therapy, there is no evidence suggesting that margins wider than no ink on tumor are needed |
| Should unfavorable biologic subtypes (such as triple-negative breast cancers) require wider margins (than no ink on tumor)? | Margins wider than no ink on tumor are not indicated based on biologic subtype |
| Should margin width be taken into consideration when determining WBRT delivery techniques? | Choice of whole-breast radiation delivery technique, fractionation, and boost dose should not be dependent on margin width |
| Is the presence of LCIS at the margin an indication for re-excision? Do invasive lobular carcinomas require a wider margin (than no ink on tumor)? What is the significance of pleomorphic LCIS at the margin? | Wider negative margins than no ink on tumor are not indicated for invasive lobular cancer; classic LCIS at the margin is not an indication for re-excision; the significance of pleomorphic LCIS at the margin is uncertain |
| Should increased margin widths (wider than no ink on tumor) be considered for young patients (age <40 years)? | Young age (<40 years) is associated with both increased IBTR after BCT as well as increased local relapse on the chest wall after mastectomy and is also more frequently associated with adverse biologic and pathologic features; there is no evidence that increased margin width nullifies the increased risk of IBTR in young patients |
| What is the significance of an EIC in the tumor specimen, and how does this pertain to margin width? | EIC identifies patients who may have a large residual DCIS burden after lumpectomy; there is no evidence of an association between increased risk of IBTR when margins are negative |

A positive margin, defined as invasive tumor on ink, confers a two-fold increase in local recurrence. IBTR, ipsilateral breast tumor recurrence; WBRT, whole-breast radiation therapy; LCIS, lobular carcinoma in situ; BCT, breast-conserving therapy; EIC, extensive intraductal component; DCIS, ductal carcinoma in situ. Data summarized from Moran *et al.* (52).

touching ink decrease local recurrence in patients receiving whole-breast RT is lacking, and the underlying biology of the tumor and the availability of targeted therapy appear to be major determinants of local control.

In recognition of the many factors impacting local control, a multidisciplinary panel was convened in 2013 by the Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) to establish consensus guidelines on margin width for patients with invasive cancer undergoing BCT. The meta-analysis of Houssami *et al.* (25) discussed previously, as well as other published literature, formed the basis for the group's deliberations. The group concluded that while positive margins, defined as ink on invasive tumor or DCIS, were associated with an increased rate of local recurrence, evidence that margins more widely clear than no ink on tumor reduces the risk of local recurrence is lacking, and the routine use of re-excision to more widely clear margins is not indicated. This conclusion applies independent of age, histology, biologic subtype, the presence of an EIC, or the now-uncommon scenario of no planned adjuvant systemic therapy. The consensus statements are summarized in *Table 3* (52). These guidelines have been endorsed by the American Society of Clinical Oncology (ASCO) and the

 

American Society of Breast Surgeons (ASBrS) in addition to the SSO and ASTRO. It is hoped that their adoption will decrease re-excision rates and lower healthcare costs (52). This does not mean that in some circumstances a more widely clear margin is not appropriate; but it does mean that the routine use of unnecessarily large surgical resections or mandatory re-excisions to obtain a more widely clear margin in all patients should be abandoned.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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