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SSO-ASTRO Consensus Guideline on Margins for Breast-Conserving Surgery with Whole Breast Irradiation in Stage I and II Invasive Breast Cancer

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Summary

Changes in the management of breast cancer over time have led to decreased rates of IBTR. The 2013 SSO/ASTRO guidelines on margins in breast-conserving surgery for invasive cancer are summarized in this document.

Keywords

margins; ipsilateral breast tumor recurrence; breast-conserving surgery; guidelines

Multiple randomized phase III trials with mature follow-up have conclusively demonstrated that survival after breast-conservation therapy (BCT), defined as surgical excision of the primary tumor and a margin of surrounding normal tissue followed by whole-breast radiation therapy (WBRT), is equivalent to mastectomy for the treatment of stage 1 and 2 invasive breast cancer.^{1,2} Of these trials, only one, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B06, required a microscopically clear margin, defined as no ink on tumor²; all other trials required complete gross removal of the tumor but did not specify a microscopic margin width. While BCT has been standard practice for over 20 years, there is still no consensus on what constitutes an optimal negative margin width.^{3,4} As a consequence, approximately 1 in 4 women attempting BCT undergo a re-excision, and nearly half of these are performed with the rationale of obtaining *more widely* clear margins in women whose margins are negative, as defined by no ink on tumor.^{5,6} These additional surgical procedures have the potential for added discomfort, surgical complications, compromise in cosmetic outcome for patients, and additional unnecessary emotional stress for patients and families; increase healthcare costs; and have been associated with patient preference for conversion to bilateral mastectomy.⁷ In the past 30 years since the randomized trials that established the equivalence of BCT and mastectomy, the landscape of breast cancer management has changed dramatically. Breast imaging has improved, and adjuvant systemic therapy is now commonly used, even for small, node-negative breast cancers, resulting in a decline in rates of ipsilateral breast tumor recurrence (IBTR).⁸

In view of these changes, the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) convened a multidisciplinary expert panel (Margins panel) in 2013 for the purpose of examining the relationship between margin width and IBTR. The primary clinical question was: What margin width minimizes the risk of IBTR? Specific clinical circumstances which might impact upon this, such as tumor histology, patient age, use of systemic therapy, and technique of radiation delivery were also examined. The project was funded by a grant from Susan G. Komen. The guideline developed from this consensus panel is intended to assist treating physicians and patients in the clinical decision-making process. As with any guideline, the monitoring of outcomes at the institutional level is encouraged. The key findings of the guideline are summarized in Table 1.

METHODS

The Margins panel comprised a multidisciplinary group of experts designated by their respective organizations, an expert methodologist who led the evidence review, and a patient representative (Table 2). The process for development of this guideline followed, to the extent possible, the Institute of Medicine's standards.⁹ The panel commissioned a systematic review and meta-analysis of the literature as the primary evidence base for the guideline. Additional literature reviews for specific clinical questions, which could not be address in the meta-analysis, were performed by designated panel members. The panelists met in July 2013 and all of the recommendations in this guideline were unanimously adopted. The guideline manuscript was approved by all panel members and sent to external reviewers for feedback which was incorporated into the final document. The content of the manuscript was approved by the Society of Surgical Oncology (SSO) Executive Council and the American Society for Therapeutic Radiology and Oncology (ASTRO) Board of Directors and the guideline recommendations have been endorsed by the American Society of Breast Surgeons Board of Directors. Patient-related information regarding the guideline, and a question-answer sounding board will be made available for patients on the Susan G. Komen website.

Literature Review and Meta-analysis

The systematic review methods were adapted from Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) recommendations, Institute of Medicine (IOM) standards for systematic reviews and meta-analysis, and previously published methods.^{10–12} A comprehensive literature search of MEDLINE and Evidence Based Medicine (EBM) was conducted from 1965 to January 2013 and combined with data from a previously published systematic review which included 21 studies from 1965–2010.¹² These new analyses are referred to as the margins meta-analysis and are part of the work led by Houssami et al and published in full elsewhere.¹³ All studies eligible for inclusion in the margins meta-analysis were reviewed and underwent data extraction by 2 independent investigators as previously described.¹² A study-level analysis was conducted and was adjusted for study-specific median follow-up time (to account for the inherent increased risk of IBTR with longer follow-up) as well as covariates.

Inclusion/Exclusion criteria

Studies eligible for inclusion had to allow calculation of the *proportion* of IBTR in relation to margin widths and had to meet the following criteria: (1) Early-stage invasive breast cancer (stages I and II); patients treated with neoadjuvant chemotherapy or with pure ductal carcinoma in situ were not included; (2) Treatment consisted of BCT (all patients receiving adjuvant WBRT); (3) Microscopic margins had to be reported quantitatively with defined threshold distances/widths; (4) Age data had to be present; and (5) A *minimum* median/mean follow-up time of 4 years was required. Details of the data collected can be found in the complete publication of the meta-analysis.¹³

Study quality and limitations of the literature

All publications that met the inclusion criteria were retrospective in nature with the exception of 2.^{14,15} Therefore, the majority of studies included in the meta-analysis provided observational level data, and the analysis was conducted at the study level due to lack of availability of patient level data from the retrospective studies. The characteristics and quality assessment of the studies included in the meta-analysis are reported elsewhere.¹³

Management of Conflicts of Interest (COI) for the Margins Panel—At the time of the initial telephone planning conference, the proposed panel members declared and discussed their potential conflicts. Written disclosures were subsequently obtained at the consensus conference. Both co-chairs reviewed each conflict of interest (COI) form and determined that there were no individuals on the panel for whom a COI could influence the development or process of specific recommendations for this guideline.

RESULTS

The margins meta-analysis was based on 33 eligible studies published between 1965 and 2013. The analysis included 28,162 patients, of which 1,506 patients had an IBTR. The median follow-up was 79.2 months, and the median prevalence of IBTR was 5.3% (interquartile range, 2.3–7.6%). Patients with “unknown” margin status were not included in the analysis. Table 3 summarizes the characteristics of the studies, and the patient, tumor, and treatment variables included in this analysis. Houssami et al provide additional details of the included studies and full results of the meta-analysis.¹³ A synoptic overview of the results is shown in Table 4. In Model 1, margin status in all studies included in the analysis was fitted as a dichotomous variable (negative vs close/positive), with close and positive margins combined since the data reported in some studies did not allow separation of these 2 categories. In Model 2, only studies providing information on specific margin widths were included; margin status was fitted as 3 categories (positive, close, negative), and margin distance was analyzed as a categorical variable. All models were adjusted for study-specific follow-up. Details of the models and methodology are available in Houssami et al.¹³

Guideline Recommendations

1. Positive Margins

A positive margin, defined as ink on invasive cancer or ductal carcinoma in situ (DCIS), is associated with at least a 2-fold increase in IBTR. This increased risk in IBTR is not nullified by:

- a) Delivery of a boost dose of radiation
- b) Delivery of systemic therapy (endocrine, chemotherapy, or biologic), or
- c) Favorable biology

A positive margin is defined as the presence of ink at the surface of the surgical specimen on either invasive tumor cells or DCIS, and implies a potentially incomplete resection that is associated with a significantly higher risk of IBTR. There is no debate regarding this

concept. As shown in Table 4, the margins 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 to negative margins after adjustment for length of follow-up. From the 19 studies of 13,081 patients with sufficient detail to separate negative, close, and positive margins, the OR for positive versus negative margins was 2.44 (95% CI, 1.97–3.03).¹³ Other published literature supports the observation that the risk of IBTR with a positive margin is at least 2-fold greater than that seen with negative margins.^{16,17} While various other treatment modalities, including utilization of a boost dose of radiation and adjuvant system therapy with endocrine therapy, chemotherapy, or biologically targeted agents, have all demonstrated a favorable impact on IBTR (see below), adjustment for the covariates of endocrine therapy or use of a boost dose of radiation did not nullify the increased risk of IBTR seen with a positive margin in the meta-analysis. 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 who had a boost. Other studies support this finding. For example, the European Organization for Research and Treatment of Cancer (EORTC) trial demonstrated that an additional boost dose of 16 Gy targeting the tumor bed after microscopically complete removal of the tumor and WBRT significantly reduced the rate of IBTR. The overall cumulative incidence of IBTR at 10 years was 10.2% (95% CI, 8.7–11.8%) without a boost and 6.2% (95% CI, 4.9–7.5%) with a boost ($p < 0.0001$).¹⁸ In the small subset of 251 patients who had positive margins and received a boost, the cumulative incidence of IBTR at 10 years was 17.5% (95% CI, 10.4–24.6%) with 10 Gy and 10.8% (95% CI, 5.2–16.4%) with 26 Gy ($p > 0.10$).¹⁹ These data suggest that while 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.

Similarly, despite the well-recognized benefit of systemic therapy in reducing IBTR that is discussed in detail below²⁰, the effects of a positive margin do not appear to be negated by the use of either adjuvant endocrine therapy or chemotherapy. In sub-analysis of 16 studies within the margins meta-analysis that allowed adjustment for the proportion of patients who received endocrine therapy (and adjusted for follow-up), the adjusted OR for positive margins (versus negative) remained significantly higher at 2.53 ($p < 0.001$).

Lastly, based on the results of the margins meta-analysis¹³ and other retrospective series, the panel concluded that patients with positive margins who have favorable tumor biology, such as those with tumors that are strongly estrogen receptor (ER) positive, remain at a higher risk for IBTR than similar patients with negative margins despite good biologic features. From the model of 19 studies reporting margin widths in the meta-analysis, adjusted 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 (versus negative) margins remained significantly elevated at 2.66 ($p < 0.001$). The impact of a boost dose of radiation, the use of systemic therapy, and biologic subtype on margin width is discussed further below.

2. Negative Margin Widths

Negative margins (no ink on tumor) minimize the risk of IBTR. Wider margins 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 discussed above, negative margins, defined as no ink on invasive carcinoma or DCIS, substantially reduce the risk of local recurrence compared to a positive margin. However, the amount of normal breast tissue around the tumor that constitutes an optimal negative margin is controversial. In order to address this question, the panel considered what is known about the microscopic distribution of tumor in the breast in clinically and mammographically unicentric breast cancer, whether the standardization and reproducibility of pathologic processing of lumpectomy specimens allows meaningful differentiation of margin widths of 1 or 2 millimeters, and the impact of changes in breast cancer management on the relevance of older studies examining margin width to practice today.

Holland et al, in a meticulous study of mastectomy specimens, demonstrated that clinically unicentric T1-T2 breast cancers are frequently associated with subclinical foci of invasive cancer and/or DCIS in the surrounding breast tissue, and that these may be present at large distances from the primary tumor site.²¹ Although the cases examined in this study preceded the mammographic era, the frequency of additional foci was independent of tumor size. For example, even among T1 lesions, 42%, 17%, and 10% of patients had additional foci of invasive cancer and/or DCIS > 2 cm, > 3 cm, and > 4 cm from the index tumor, respectively. The frequent presence of foci of invasive carcinoma and DCIS at considerable distances from the index lesion may at least partially explain why increasing the width of lumpectomy margins in millimeter intervals has no significant impact on the risk of local recurrence following breast-conserving surgery and WBRT.

There are also technical limitations to lumpectomy margin evaluation that confound the interpretation of data relating margin width to risk of local recurrence. Once a lumpectomy specimen is removed from the breast, there is flattening due to lack of support from the surrounding tissue. This is further exaggerated by compression in specimens submitted for specimen radiography. These factors result in artifactually narrower margins than existed in vivo.²² Furthermore, ink applied to the surface of the specimen often tracks into deeper portions of the specimen which, in turn, can pose significant challenges for the pathologist to microscopically determine the location of the true margin. In addition, there is no standard method for margin evaluation, and this process is highly prone to sampling error. The 2 major options for lumpectomy margin evaluation include sectioning the specimen perpendicular to the inked margin (in which case the precise distance to the margin can be determined), and shaving the specimen margins and examining them en-face (in which case, any residual tumor in the shaved specimen is considered a positive margin). Some surgeons submit separate margins obtained from the walls of the biopsy cavity after the lumpectomy specimen is removed; these can be examined by either the inked or the shaved method. While the shaved margin method permits examination of a greater surface area of the specimen margin that can be examined by the inked method, the use of shaved margins

results in the categorization of many margins as positive that are, in fact, negative by the inked margin method—this, in turn, may result in unnecessary re-excision or even mastectomy.²³ Sampling of lumpectomy specimens is also highly variable and ranges from submission of a limited number of sections to total, sequential embedding of the entire specimen. However, even the process of total, sequential embedding results in the examination of only a very small proportion ($< 1\%$) of lumpectomy specimen margins.²⁴ Finally, the presence of tumor at a certain distance from the inked margin on any single slide may not represent the true state of that margin three-dimensionally; a margin that appears “adequate” on one given section may actually be positive if additional sections are examined and even if deeper sections are cut from the same tissue block. As a group, these studies indicate that there is a great degree of variability in margin assessment and that regardless of the technique of margin evaluation employed, a “negative margin” does not guarantee the absence of residual tumor in the breast.

In spite of the variability in margin assessment discussed above, great attention has been paid to achieving specific negative margin widths in the belief that this reduces the risk of IBTR, and re-excision is frequently performed for margins in which there is no ink on tumor.⁵ To address the question of the importance of margin width, we evaluated the results of one model of the meta-analysis in which the relationship between specific margin widths (1 mm, 2 mm, 5 mm) and IBTR was evaluated, as shown in Table 4 (19 studies; 13,081 patients; 753 IBTR; median follow-up, 8.7 years). After adjustment for study-specific length of follow-up, there was no statistically significant evidence that the odds of IBTR were associated with margin distance ($p = 0.90$), nor was there statistical evidence for a trend that the odds of IBTR decreased as the distance for declaring negative margins increased ($p = 0.58$ for trend). Adjusting for covariates, including age, median year of study recruitment, use of endocrine therapy, use of a radiation boost, use of re-excision, ER status, and type of IBTR (first versus any) did not change these results. While an analysis of these data using study-specified margin definitions of negative, close, and positive did reveal a significant increase in the odds of IBTR with close (OR 1.74; 95% CI, 1.42–2.15) or positive margins (OR 2.44; 95% CI, 1.97–3.03) versus negative margins ($p < 0.001$), the panel felt that the analysis of specific margin widths superseded this finding due to the heterogeneity among studies in the definitions of close and positive since margins defined as “positive” in one study could be classified as “close” or even “negative” in other studies included in this analysis. Additionally, the panel recognized that there have been significant changes in breast cancer management that are not reflected in the relatively older studies included in this meta-analysis comparing negative versus close versus positive margins. Only 26% and 38% of patients included in the entire meta-analysis received chemotherapy and endocrine therapy, respectively, in spite of a median tumor size of 1.6 cm and a 26% incidence of nodal positivity. Since the incidence of local recurrence increases with time, a median follow-up of at least 4 years was one of the criteria for inclusion in the meta-analysis, and inclusion of studies with a longer follow-up period was felt to be important for an accurate assessment of the risk of local recurrence. As noted in Figure 1, the crude incidence of IBTR declined over time, and although this was observed for all margin widths, the decline appears more pronounced in those with margins less than 5 mm. As discussed in detail below, the benefits of adjuvant systemic therapy in reducing IBTR are well

documented.²⁰ The widespread use of systemic therapy today, even for small node-negative breast cancer patients, increased the panel's confidence that wider margins were unlikely to enhance local control in a clinically significant way in the current era. Additionally, although the median year of study recruitment of studies included in the meta-analysis was 1990, the median prevalence of IBTR for all studies in the meta-analysis was only 5.3%. Although the odds ratios in Table 4 numerically suggest that 5 mm margins offer an advantage compared to margins of 1 to 2 mm, these differences lack statistical significance despite the use of 2 different statistical tests and robust sample sizes, making it unlikely that the meta-analysis lacks the power to detect clinically meaningful differences in IBTR based on margin width. Furthermore, with the overall rate of IBTR of 5.3%, the absolute benefit in possible decreased IBTR with an OR of 0.77 is on the order of 1–2%. More importantly, adjustments for covariates, which are a standard part of practice today, such as the use of endocrine therapy and the use of a boost dose of radiation, virtually eliminate the numeric differences in the odds ratios (Table 4). Thus, while 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. It was not possible to compare rates of IBTR between margins of no ink on tumor and margins of 1 mm or more in Model 2 (Table 4) since only a small number of studies with these margin definitions were available for review. The panel considered the long-term results of the NSABP B06 randomized trial² which defined a negative margin as no ink on tumor, began accrual in 1976, and reported a 5% rate of IBTR after 12 years of follow-up in patients receiving systemic therapy. Additionally, the variability in margin assessment discussed above, the lack of evidence of a significant difference in rates of IBTR between margins of 1 mm, 2 mm, and 5 mm, as well as the benefits of a boost dose of RT on local control discussed below, led the panel to believe that the totality of the evidence did not support a distinction between margins of no ink on tumor and margins of 1 mm.

3. Systemic Therapy

The 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.

The use of systemic therapy in the treatment of early-stage breast cancer has changed dramatically over the past 30 years; throughout this period, consistent evidence has accumulated that successful systemic therapy improves local control. In the NSABP B06 trial, only women with node-positive disease were given chemotherapy (melphalan and 5-fluorouracil). Within the radiated cohort, node-positive patients demonstrated roughly half the rate of IBTR compared to node-negative patients (5% versus 12%)² at 12 years, an advantage attributable to the use of chemotherapy. This positive impact of systemic therapy on local control has continued with improvements in systemic therapy. As illustrated in subsequent analyses of NSABP trials of systemic therapy, each improvement that led to improved survival was accompanied by a decline in IBTR. In NSABP B14 (tamoxifen versus not for ER positive, node-negative disease) the rate of IBTR was 11.6% in the control group compared to 5.0% in the tamoxifen group ($p < 0.0001$)⁸; in NSABP B13

(chemotherapy versus not for node-negative disease), IBTR rate was 15.3% in the control and 5.4% in the treated patients ($p < 0.001$)⁸, and in NSABP B19 (methotrexate and 5-FU [MF] versus cyclophosphamide, methotrexate, and 5-fluorouracil [CMF] in ER negative node-negative patients), the IBTR rates were 8.2% and 4.8% ($p < 0.03$).²⁵ The 1990s saw the introduction of taxanes into adjuvant and neoadjuvant regimens, and pooled data from NSABP trials B18 (anthracycline-based chemotherapy) and B27 (inclusion of docetaxel) demonstrated that women who did not achieve a pathologic complete response (pCR) in the breast had an increased hazard ratio (HR) for local-regional recurrence (1.55, 95% CI, 1.01, 2.59) compared to those who did.²⁶ Thus, achieving a pCR, which heralds a much-reduced risk of distant disease and breast cancer death, also results in a significantly reduced risk of IBTR.

The adjuvant systemic therapy of today is substantially improved over that of 20 years ago, and is likely to continue to improve, with better targeting of specific breast cancer subtypes. For women with ER positive breast cancer undergoing BCT, the 10-year rates of IBTR in the Early Breast Cancer Trialists' Group overview were 18.6% when tamoxifen was not used, and 8.7% with tamoxifen.¹ The introduction of aromatase inhibitor therapy instead of, or in addition to, tamoxifen in postmenopausal women has led to a consistent reduction of the rates of IBTR across essentially all trials reported, with an average reduction in the HR of approximately 0.67.²⁷ The addition of taxanes to anthracycline-based regimens is also accompanied by a relative reduction in the rate of IBTR.²⁰ Finally, the addition of trastuzumab to cytotoxic regimens for HER2 positive breast cancer patients leads to a further reduction in the crude hazard of IBTR, with HRs of 0.47 and 0.66 in the pooled United States trials and European HERA trial^{28,29}. These data from large randomized clinical trials establish the principle that systemic therapy advances that lead to improved survival and decreased risk of distant disease also contribute to improved local control, and suggest that as systemic therapy continues to improve, so will its impact on diminishing IBTR.

The panel agreed that the evidence indicates clearly that systemic therapy, used for the vast majority of breast cancer patients today, reduces the overall risk of IBTR. It also strengthened their confidence that millimeter increments in margin widths are unlikely to impact on IBTR once a margin of no ink on tumor cells has been obtained. Although the evidence base was less robust, the panel agreed that in the rare circumstance when a patient does not receive any form of systemic treatment, there was no evidence to suggest that obtaining wider margins beyond no ink on tumor would result in any further reduction of IBTR.

4. Biologic Subtypes

Margins wider than no ink on tumor are not indicated based on biologic subtype.

An improved understanding of biologic subtypes of breast cancer has led to great improvements in systemic therapy that have, in turn, decreased IBTR. Several large studies have examined IBTR rates with BCT related to molecular markers. In one of the largest studies, Arvold et al reviewed 1434 patients who underwent BCT and found that the patients

with triple negative breast cancer (TNBC) and HER2 positive tumors had a significantly higher risk of IBTR compared to those with other subtypes.³⁰ However, the study did not include treatment with adjuvant trastuzumab, which lowers IBTR for the HER2 positive group. Another large study by Voduc et al³¹ of nearly 3000 patients with a median follow-up of 12 years also found increased IBTR among patients with HER2-enriched and basal tumors. Interestingly, they found no increased IBTR among TNBC with non-basal tumor markers.³¹ Mazouni et al reported on 1194 patients and found no statistically significant differences in IBTR on the basis of subtype. They did, however, note that mastectomy was more commonly performed for HER2 positive and TNBC than for the luminal A and luminal B tumors, suggesting that surgeons felt less comfortable with BCT for the more aggressive tumor subtypes despite a lack of data.³² Haffty et al as well as Freedman et al also found no significant differences in IBTR for patients treated with BCT when comparing TNBC to non-TNBC.^{33,34} A recent study by Gangi et al³⁵ examined outcome among 1851 consecutive patients treated between 2000 and 2012 during which trastuzumab was routinely used for HER2 positive patients. There was no significant difference in IBTR among patients with TNBC compared to those with the other subtypes of tumors.

Intuitively, it might be thought that wider margins are necessary to control the more aggressive tumor types. However, there is no reason to believe that HER2 positive and TNBC are more difficult to resect. Pilewskie et al examined the impact of margin width on local recurrence in 535 patients with TNBC. At 60 months, the incidence of IBTR did not differ significantly between patients with margins ≤ 2 mm and those with margins > 2 mm (7.3% versus 5.1%).³⁶ Alternatively, local failure occurs as a marker of aggressive biology, as is seen after mastectomy. Three retrospective studies have examined the incidence of local failure in TNBC after BCT and mastectomy and found no difference based on surgical procedure, suggesting that these local recurrences are more likely a result of aggressive biology, and not residual tumor at the surgical site, which could be improved with wider lumpectomy margins.^{29,37–39} This theory is supported by the approximately 40% decline in IBTR seen in patients with HER2 positive tumors receiving adjuvant systemic trastuzumab and other HER2-targeted agents.²⁹ In summary, the panel concluded that although there is evidence that the risk of IBTR varies by subtype based on the results of many studies, patients with aggressive tumors remain at equally increased risk for local failure irrespective of treatment with mastectomy or BCT, indicating there is no justification for more widely clear margins than no ink on tumor for any breast cancer subtype.

5. Radiation Therapy Delivery

The choice of whole breast radiation delivery technique, fractionation, and boost dose should not be dependent on the margin width.

WBRT options have expanded significantly in the last decade. Delivery techniques such as prone positioning and 3D conformal field-in-field techniques have been designed to limit treatment-related toxicity by decreasing heart/lung volumes and improving homogeneity across the whole breast radiation field, respectively.^{40–43} Additionally, attempts have been made to decrease the burden of the protracted treatments inherent to conventionally fractionated WBRT through utilization of accelerated, hypofractionated, whole-breast

schemas. Two large randomized trials have now reported comparable long-term efficacy and toxicity data with this approach, establishing it as an acceptable alternative.^{44,45} In general, the studies evaluating these approaches did not specify particular surgical margin widths and required only complete microscopic excision of tumor.^{40–43,45} The large United Kingdom Standardization of Breast Radiotherapy (START) trials did mandate a 1 mm margin, but comparable long-term results were reported in the similar Canadian hypofractionation trial that excluded only those with involved margins.^{45–47} Though none of these trials were designed to address a possible interaction between margin width and the specifics of radiation delivery, there is no evidence to suggest that margin width should dictate patient selection for these therapies.

As discussed earlier, a radiation boost to the tumor bed after WBRT has been shown to significantly reduce the risk of IBTR at a cost of increased, though acceptable, rates of late radiation toxicity.^{18,48,49} In the randomized trials establishing the benefit of a boost, negative surgical margins were largely defined as no ink on tumor.

Further tailoring of the boost dose has been explored both in several single-institution series.^{50–52} In each of these studies, margin width was used as an indicator of potential residual tumor burden, and boost doses were increased with decreasing margin width. The panel felt that interpretation of these and other retrospective data evaluating both radiation dose and surgical margins was complicated by heterogeneity of total radiation doses and techniques, and a lack of control cohorts with comparable margins widths and uniform doses. Therefore, the panel concluded that there was no clear reduction in IBTR as a result of escalating the radiation dose when margin widths are smaller. In one report, an increased rate of IBTR was noted in patients with close or positive margins despite the dose escalation strategy.⁵¹ The other studies simply noted no clear relationship between local control and margin width or radiation dose.^{50,52}

In summary, margin width should not be used to determine the delivery technique or fractionation for WBRT or vice versa. Furthermore, 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 risk and should not be determined, in isolation, by the width of the surgical margin.

6. Invasive lobular carcinoma and lobular carcinoma in situ (LCIS)

Wider negative margins than no ink on tumor are not indicated for invasive lobular carcinoma. Classic LCIS at the margin is not an indication for re-excision. The significance of pleomorphic LCIS at the margin is uncertain.

Invasive lobular carcinomas comprise 5–15% of all breast cancer. Several large retrospective studies demonstrate that when negative margins are obtained, the risk of IBTR is not significantly different between invasive lobular carcinoma and invasive ductal carcinoma.^{53–55} Wider margins do not yield lower IBTR rates. In a retrospective study of 382 patients comparing margins greater than 1 cm to smaller margins, no differences in local recurrence rates were observed.⁵⁶ Additionally, most classical invasive lobular carcinomas

have a luminal A phenotype and are ER positive, so the benefits of endocrine therapy on local control, discussed previously, will be seen in this population. Thus, the panel concluded that the general recommendations regarding margin width should not be altered for invasive lobular histology.

In contrast to clear evidence demonstrating that DCIS at the margin increases IBTR, the presence of LCIS at the margin does not appear to impact IBTR. In a retrospective study, the 10-year cumulative incidence rate of IBTR in breast cancer patients was not significantly different in patients with or without LCIS unless tamoxifen was withheld.⁵⁷ In other large studies, the presence of LCIS within the specimen or at the resection margin did not appear to affect the risk of local recurrence.^{58,59} There is concern that the pleomorphic variant of LCIS, which has some features more akin to high-grade DCIS than to classical LCIS, may carry an increased risk of recurrence when at the margin. Given the limitation of only small retrospective studies with a very limited number of events available to address this question,⁶⁰ the panel did not feel that a recommendation regarding pleomorphic LCIS at the margin could be made at this time.

7. Young age

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.

Young patient age, usually defined as less than 40 years, has been associated with an increased risk of IBTR after BCT compared to that seen in older women. In the Early Breast Cancer Trialists' Collaborative Group 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.¹ 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. Other studies have confirmed a higher risk for distant recurrence as well as IBTR in young women.^{61,62}

Young patient age is not associated with an improved outcome with mastectomy. The risk for local-regional recurrence after mastectomy without radiation is also significantly higher in young women compared to their older counterparts,⁶³ and the increased risk of both recurrence and breast cancer death is not improved with mastectomy compared to BCT.^{62,64} The increased IBTR rates in young women are likely due to the greater frequency of adverse biologic and pathologic features in this group compared to 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 breast cancers associated with adverse gene expression profiles^{65,66} compared with their older counterparts. In one study, very young patients with tumors classified as luminal B, HER2, and triple negative subtypes were at increased risk of IBTR

when compared with older patients, but no significant effect of age was seen in the subgroup with the most favorable luminal A subtype⁶⁶. Young age may be a less important factor for IBTR when controlling for adverse gene expression profile^{30,67}, or may be not important at all for predicting recurrence and survival in an era of modern systemic therapy and anti-HER2 directed therapy, as suggested in one recent study of young women with HER2 overexpressing cancers.⁶⁸

There was no evidence in the margins meta-analysis that once a negative margin has been achieved, young patients benefit from a greater negative margin width than no ink on tumor. In 18 studies in the meta-analysis, the adjusted OR for IBTR with age as a covariate did not differ significantly when negative margin widths were defined as 1 mm, 2 mm or 5 mm (p for association, 0.86; p for trend, 0.58). This is consistent with the finding that mastectomy, which theoretically, should provide the largest margin width that can be obtained, is also associated with an increased risk of local recurrence in younger, compared to older women. In addition, there are data demonstrating equivalent risks for recurrence and breast cancer death in young women irrespective of treatment with BCT or mastectomy.^{62,64}

Thus, the panel concluded that while the adverse biologic and pathologic factors associated with young age are to some extent mitigated with excision to negative margins, use of systemic therapies, use of a radiation boost, and possible exclusion of young BRCA mutation carriers from a BCT approach, there is no evidence supporting obtaining wider negative margins beyond no ink on tumor solely on the basis of young patient age.

8. Extensive Intraductal Component (EIC)

An EIC identifies cases that may have a large residual DCIS burden after lumpectomy. There is no evidence of an association between increased risk of IBTR and EIC when margins are negative.

EIC is a pathologic description of invasive ductal carcinoma that has a prominent intraductal component within the tumor and adjacent normal tissue. The basis for the definition of EIC was the observation in the 1970s at the Harvard Joint Center for Radiation Therapy, at a time when margins of resection were not routinely assessed, that a high rate of IBTR was observed in patients undergoing BCT when a prominent DCIS burden was noted within the confines of the invasive cancer (~25%) and within breast tissue beyond the edges of the invasive cancer.⁶⁹ These EIC positive cancers often recurred within or at the edge of the boost volume and were more commonly seen in young patients (< 35 years of age). Furthermore, IBTR was more common in young EIC positive patients than in older EIC positive patients.

In subsequent years, when margins of resection were inked and re-excisions were performed for positive or close margins, patients with EIC positive cancers (but not EIC negative cancers) were frequently found to have considerable residual DCIS in the re-excision specimens.⁷⁰ Pathologic examination of a cohort of mastectomy specimens revealed that 33% of EIC positive cancers had prominent DCIS (6 or more low power fields of DCIS) at 2 cm or greater from the edge of the index cancer compared with only 2% of EIC- cancers.⁷¹

In aggregate, these studies indicated that an EIC denotes a cancer that may have extensive multifocal DCIS involvement and an increased rate of IBTR if not adequately resected.

Later, additional studies revealed that patients with EIC positive tumors did not have an increase in IBTR unless tumor cells were present at the inked margin.⁷² In a cohort of EIC positive patients, IBTR was 0% at 5 years when there were no tumor cells at the inked margin or when the margin was defined as “close,” but was 50% when there was more than focal positivity.⁷² Based on this information, the panel did not feel that the available evidence supports the routine use of margins wider than no ink on tumor. However, given the potential for considerable residual DCIS in EIC positive patients, consideration should be given to obtaining postoperative mammographic imaging, to assist in identifying residual tumor bed calcifications warranting re-excision. Additionally, when an EIC is present, young age and multiple close margins are associated with an increased risk of IBTR and can be used to select patients who might benefit from re-excision.^{69,72} Post excision mammography is a useful adjunct to margin status to assess the completeness of excision of lesions with calcifications even when an EIC is not present.

Limitations

This guideline addresses outcomes for patients with invasive breast cancer undergoing whole breast irradiation. The findings should not be extrapolated to patients with pure DCIS. The discontinuous growth pattern of low and intermediate grade DCIS and management without systemic therapy in the majority of cases necessitate a separate examination of optimal margins in DCIS. Similarly, whether this guideline applies to patients treated with accelerated partial breast irradiation is unknown. Additionally, we excluded patients treated with neoadjuvant therapy. The “buckshot” pattern of response to neoadjuvant therapy raises concerns that margins of no ink on tumor may be associated with a significant residual tumor burden and should be a subject for future study.

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FIG. 1.
Scatter plot of unadjusted rates of ipsilateral breast tumor recurrence by median year of study recruitment.

TABLE 1

Summary of clinical practice guideline recommendations

Clinical Question	Recommendation	Level of Evidence
1) What is the absolute increase in risk of IBTR with a positive margin? Can the use of radiation boost, systemic therapy, or favorable tumor biology mitigate this increased risk?	A positive margin, defined as ink on invasive cancer or DCIS, is associated with at least a 2-fold increase in IBTR. This increased risk in IBTR is not nullified by: a) Delivery of a boost b) Delivery of systemic therapy (endocrine, chemotherapy, biologic therapy), or c) Favorable biology	Meta-analysis, secondary data from prospective trials and retrospective studies
2) Do margin widths wider than no ink on tumor cells reduce the risk of IBTR?	Negative margins (no ink on tumor) optimize IBTR. Wider margins widths do not significantly lower this risk. The routine practice to obtain wider negative margin widths than ink on tumor is not indicated.	Meta-analysis and retrospective studies
3) What are the effects of endocrine or biologically targeted, or systemic chemotherapy on IBTR? Should a patient who is not receiving any systemic treatment have wider margin widths?	The 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.	Multiple randomized trials and meta- analysis
4) 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.	Multiple retrospective studies
5) Should margin width be taken into consideration when determining WBRT delivery techniques?	The choice of whole breast radiation delivery technique, fractionation, and boost dose should not be dependent on the margin width.	Retrospective studies
6) 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.	Retrospective studies
7) Should increased margin widths (wider than no ink on tumor) be considered for patients of young 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.	Secondary data from prospective randomized trials and retrospective studies
8) What is the significance of an EIC in the tumor specimen and how does this pertain to margin width?	An EIC identifies cases that 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.	Retrospective studies

Abbreviations: IBTR, ipsilateral breast tumor recurrence; DCIS, ductal carcinoma in situ; WBRT, whole breast radiation therapy; LCIS, lobular carcinoma in situ; BCT, breast-conserving therapy; EIC, extensive intraductal component

TABLE 2

Expert Panel Members

Panel Member	Society	University/Institution
Monica Morrow, MD (Co-chair)	SSO	Memorial Sloan-Kettering Cancer Center
Meena S. Moran, MD (Co-chair)	ASTRO	Yale University
Nehmat Houssami, MD, PhD (Systematic Review Methods)	(School of Public Health)	University of Sydney
Suzanne Klimberg, MD	ASBS	University of Arkansas
Mariana Chavez MacGregor, MD	ASCO	University of Texas M.D. Anderson Cancer Center
Jay Harris, MD	ASTRO	Harvard Medical School
Janet Horton, MD	ASTRO	Duke University
Gary Freedman, MD	ASTRO	University of Pennsylvania
Stuart Schnitt, MD	CAP	Harvard Medical School
Peggy Johnson	Patient Advocate	Advocate in Science, Susan G. Komen
Armando Giuliano, MD	SSO	Cedars Sinai Medical Center
Seema A Khan, MD	SSO	Northwestern University

Abbreviations: SSO, Society of Surgical Oncology; ASTRO, American Society for Therapeutic Radiology and Oncology; ASBS, American Society of Breast Surgeons; ASCO, American Society of Clinical Oncology, CAP, College of American Pathologists

TABLE 3

Summary of study characteristics, including patient, tumor, and treatment variables included in the margins meta-analysis¹¹

Study Characteristics	Number of Studies	Median (Interquartile Range)
Number of patients per study	33	701 (79-3899)
Prevalence of IBTR	33	5.3% (2.3%-7.6%)
Follow-up time (months) *	33	79.2 (48.0–160)
Time to IBTR (months) *	14	53.5 (47.0–60.0)
Patient and Tumor Characteristics	Number of Studies	Median (Range)
Age (years) *	32	53.4 years (45.0–60.6 years)
Stage distribution (%)	11	
0		0 (0–1.4%)
I		55.0% (52.5%-56.9%)
II		44.4% (39.4%-45.9%)
III		0% (0%-0.9%)
Nodal status (%)	30	
Positive		25.8% (17.9%-28.8%)
Negative		70.5% (65.5–74.2%)
Tumor size (cm) *	8	1.6 cm (1.5–2.1 cm)
High grade (III) (%)	17	28.3% (20.6–30.6%)
Unknown		2.9% (0.8–21.5%)
Estrogen receptor status (%)	24	
Positive		45.5% (38.4–56.3%)
Negative		20.5% (16.6–26.3%)
Unknown		28.4% (14.2–42.0%)
Progesterone receptor status (%)	10	
Positive		40.6% (33.5–47.0%)
Negative		22.0% (19.4–28.0%)
Unknown		38.4% (23.8–44.7%)
EIC (present) (%)	16	9.6% (7.5–15.7%)
LVI (present) (%)	16	17.1% (12.0–30.3%)
Treatment Characteristics	Number Studies	Median (Range)
Receipt of chemotherapy (%)	26	25.6% (18.3–38.0%)
Receipt of endocrine therapy (%)	27	38.0% (19.3–59.5%)
Receipt of WBRT (%)	33	100% ¥
Receipt of radiation boost (%)	30	96% (73.1–100%)
WBRT dose (Gy) *	26	47.2 Gy (45.0–50.0 Gy)
Radiation boost dose (Gy) *	12	10.0 Gy (10.0–13.1 Gy)

Abbreviations: IBTR, ipsilateral breast tumor recurrence; EIC, extensive intraductal component; LVI, lymphovascular invasion; WBRT, whole breast radiation therapy

* Denotes median (of the median or mean values across studies)

‡ Inclusion criteria for meta-analysis required WBRT

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TABLE 4 Summary of selected results of margins meta-analysis¹¹

Relationship Between IBTR and Margin Status					
	N Studies	N Subjects	Adjusted OR of IBTR *	95% CI	p-value (association)
Margin category (Model 1)		28,162			< 0 . 001
Close/Positive	33	6178	1.96	1.72–2.24	
Negative	33	21984	1.0	-	
Margin category (Model 2)		13,081			< 0 . 0 0 1
Positive	19	1641	2.44	1.97–3.03	
Close	19	2407	1.74	1.42–2.15	
Negative	19	9033	1.0	-	-
Threshold distance (Model 2) ** p-value (trend) = 0.58					0.90
1 mm	6	2376	1.0	-	-
2 mm	10	8350	0.91	0.46–1.80	-
5 mm	3	2355	0.77	0.32–1.87	-
Impact of Margin Width on IBTR Adjusted for Individual Covariates and Follow-up *					
Covariate	No. of studies	Threshold Distance Negative Margin: Adjusted OR			p-value (association)
		1 mm	2 mm	5 mm	
Age	18	1.0	0.53	0.77	0.53
Endocrine therapy	16	1.0	0.95	0.90	0.95
Radiation boost	18	1.0	0.86	0.92	0.86

Abbreviations: OR, odds ratio; IBTR, ipsilateral breast tumor recurrence; CI, confidence interval

* Adjusted for study-specific median length of follow-up.

** Threshold distance was also tested for significance for trend (reflects whether there was statistical evidence of a decrease in the odds of IBTR as the threshold margin distance increased from 1 mm, 2 mm, and 5 mm). P-value (trend) = 0.58; p-value (association) = 0.90