

# Society of Surgical Oncology–American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer

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## ABSTRACT

**Purpose.** Controversy exists regarding the optimal margin width in breast-conserving surgery for invasive breast cancer.

**Methods.** A multidisciplinary consensus panel used a meta-analysis of margin width and ipsilateral breast tumor recurrence (IBTR) from a systematic review of 33 studies including 28,162 patients as the primary evidence base for consensus.

**Results.** Positive margins (ink on invasive carcinoma or ductal carcinoma in situ) are associated with a two-fold

increase in the risk of IBTR compared with negative margins. This increased risk is not mitigated by favorable biology, endocrine therapy, or a radiation boost. More widely clear margins than no ink on tumor do not significantly decrease the rate of IBTR compared with no ink on tumor. There is no evidence that more widely clear margins reduce IBTR for young patients or for those with unfavorable biology, lobular cancers, or cancers with an extensive intraductal component.

**Conclusion.** The use of no ink on tumor as the standard for an adequate margin in invasive cancer in the era of multidisciplinary therapy is associated with low rates of IBTR and has the potential to decrease re-excision rates, improve cosmetic outcomes, and decrease health care costs.

**Electronic supplementary material** The online version of this article (doi:10.1245/s10434-014-3481-4) contains supplementary material, which is available to authorized users.

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First Received: 16 September 2013;  
Published Online: 10 February 2014

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Multiple randomized phase III trials with mature follow-up have conclusively demonstrated 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 radiation therapy (WBRT), is equivalent to mastectomy for the treatment of stages I and II invasive breast cancer (BC).<sup>1,2</sup> Of these trials, only one, National Surgical Adjuvant Breast and Bowel Project (NSABP) B06, required a microscopically clear margin, defined as no ink on tumor<sup>2</sup>; all others required

**TABLE 1** Summary of clinical practice guideline recommendations

Clinical question	Recommendation	Level of evidence
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?	Positive margins, defined as ink on invasive cancer or DCIS, are associated with at least a two-fold increase in IBTR. 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	Meta-analysis and secondary data from prospective trials and retrospective studies
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
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?	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
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
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 margin width	Retrospective studies
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
Should increased margin widths (wider than no ink on tumor) be considered for patients of young age (<40 years)?	Young age ( $\leq 40$ 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
What is the significance of an EIC in the tumor specimen, and how does this pertain to margin width?	An 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	Retrospective studies

*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

complete gross removal of the tumor but did not specify a microscopic margin width. Although BCT has been standard practice for more than 20 years, there is still no consensus on what constitutes an optimal negative margin width.<sup>3,4</sup> As a consequence, approximately one in four 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.<sup>5,6</sup> These additional surgical procedures have the potential for added discomfort, surgical complications, compromise in cosmetic outcome for patients, additional unnecessary emotional stress for patients and families, and increased health care costs, and have been associated with patient preference for conversion

to bilateral mastectomy.<sup>7</sup> In the past 30 years since the randomized trials that established the equivalence of BCT and mastectomy, the landscape of BC management has changed dramatically. Breast imaging has improved, and adjuvant systemic therapy is now commonly used, even for small, node-negative BCs, resulting in a decline in rates of ipsilateral breast tumor recurrence (IBTR).<sup>8</sup>

In view of these changes, the Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) convened a multidisciplinary expert panel (ie, Margins Panel [MP]) 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 that might impact this,

**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 MD Anderson Cancer Center
Jay R. Harris, MD	ASTRO	Harvard Medical School
Janet Horton, MD	ASTRO	Duke University
Gary Freedman, MD	ASTRO	University of Pennsylvania
Stuart J. Schnitt, MD	CAP	Harvard Medical School
Peggy L. Johnson	Patient Advocate	Advocate in Science, Susan G. Komen
Armando E. Giuliano, MD	SSO	Cedars-Sinai Medical Center
Seema A. Khan, MD	SSO	Northwestern University

SSO Society of Surgical Oncology, ASTRO American Society for Radiation Oncology, ASBS American Society of Breast Surgeons, ASCO American Society of Clinical Oncology, CAP College of American Pathologists

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 MP 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 standards of the Institute of Medicine (IOM).<sup>9</sup> 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 that could not be addressed 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 SSO Executive Council and ASTRO 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 Web site.

### Literature Review and Meta-Analysis

The systematic review methods were adapted from Preferred Reporting Items for Systematic Reviews and Meta-

Analyses recommendations, IOM standards for systematic reviews and meta-analyses, and previously published methods.<sup>10–12</sup> A comprehensive literature search of MEDLINE and evidence-based medicine was conducted of articles published from 1965 to January 2013 and combined with data from a previously published systematic review that included 21 studies from 1965 to 2010.<sup>12</sup> These new analyses are referred to as the margins meta-analysis and are part of the work led by Houssami et al.,<sup>13</sup> published in full elsewhere. All studies eligible for inclusion in the margins meta-analysis were reviewed and underwent data extraction by two independent investigators as previously described.<sup>12</sup> A study-level analysis was conducted, 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 BC (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<sup>13</sup> and are included in the Appendix (online).

### Study Quality and Limitations of the Literature

All publications that met the inclusion criteria were retrospective in nature, with the exception of two studies.<sup>14,15</sup>

Therefore, the majority of studies included in the meta-analysis provided observational-level data, and the analysis was conducted at the study level because of a 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.<sup>13</sup>

#### Management of Conflicts of Interest for the MP

At the time of the initial telephone planning conference, the MP candidates declared and discussed their potential conflicts. Written disclosures were subsequently obtained at the consensus meeting. The 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 whom 1,506 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.<sup>13</sup> provide additional details of the included studies and full results of the meta-analysis. A synoptic overview of the results is shown in Table 4. In model one, 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, because the data reported in some studies did not allow separation of these two categories. In model two, only studies providing information on specific margin widths were included; margin status was fitted as three 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 the report by Houssami et al.<sup>13</sup>

#### Guideline Recommendations

##### Positive Margins

A positive margin, defined as ink on invasive cancer or ductal carcinoma in situ (DCIS), is associated with at least a two-fold increase in IBTR. This increased risk in IBTR is not nullified by: delivery of a boost dose of radiation, delivery of systemic therapy (endocrine therapy, chemotherapy, or biologic therapy), or favorable biology.

**TABLE 3** Summary of study characteristics

Study characteristics	No. of Studies	Median (interquartile range)
Number of patients per study	33	701 (79–3,899)
Prevalence of IBTR (%)	33	5.3 (2.3–7.6)
Follow-up time (months) <sup>a</sup>	33	79.2 (48.0–160)
Time to IBTR (months) <sup>a</sup>	14	53.5 (47.0–60.0)
Patient and tumor characteristics		
Age (years) <sup>a</sup>	32	53.4 (45.0–60.6)
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) <sup>a</sup>	8	1.6 (1.5–2.1)
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		
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 <sup>b</sup>
Receipt of radiation boost (%)	30	96 (73.1–100)
WBRT dose (Gy) <sup>a</sup>	26	47.2 (45.0–50.0)
Radiation boost dose (Gy) <sup>a</sup>	12	10.0 (10.0–13.1)

Including patient, tumor, and treatment variables included in the margins meta-analysis<sup>13</sup>

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

<sup>a</sup> Denotes median (of the median or mean values across studies)

<sup>b</sup> Inclusion criteria for meta-analysis required WBRT

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

**TABLE 4** Summary of selected results of margins meta-analysis<sup>13</sup>

Relationship between IBTR and margin status					
	No. of studies	No. of participants	Adjusted OR of IBTR <sup>a</sup>	95% CI	<i>P</i> (association)
Margin category (model one)		28,162			<0.001
Close/positive	33	6,178	1.96	1.72–2.24	
Negative	33	21,984	1.0	—	
Margin category (model two)		13,081			<0.001
Positive	19	1,641	2.44	1.97–3.03	
Close	19	2,407	1.74	1.42–2.15	
Negative	19	9,033	1.0	—	—
Threshold distance (model two) <sup>b</sup>					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	—
Impact of margin width on IBTR adjusted for individual covariates and follow-up					
Covariate	No. of studies	Threshold distance negative margin: adjusted OR (mm)			<i>P</i> (association)
		1	2	5	
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

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

<sup>a</sup> Adjusted for study-specific median length of follow-up

<sup>b</sup> 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, 2, and 5 mm<sup>3</sup>). *P* (trend) = 0.58

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 with negative margins after adjustment for length of follow-up. For 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).<sup>13</sup> Other published literature supports the observation that the risk of IBTR with a positive margin is at least two-fold greater than that seen with negative margins.<sup>16,17</sup> Although various other treatment modalities, including use of a boost dose of radiation and adjuvant systemic 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 of patients who had a boost. Other studies support

this finding. For example, a European Organisation 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* < 0.001).<sup>18</sup> 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).<sup>19</sup> These data suggest 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.

Similarly, despite the well-recognized benefit of systemic therapy in reducing IBTR, as discussed in detail below,<sup>20</sup> 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 (and

adjusted for follow-up), the adjusted OR for positive margins (vs. negative) remained significantly higher at 2.53 ( $P < 0.001$ ).

Lastly, based on the results of the margins meta-analysis<sup>13</sup> 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 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 (vs. 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.

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#### Negative Margin Widths

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.

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As discussed above, 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 margin is controversial. To address this question, the MP considered what is known about the microscopic distribution of tumor in the breast in clinically and mammographically unicentric BC, whether the standardization and reproducibility of pathologic processing of lumpectomy specimens allows meaningful differentiation of margin widths of 1 or 2 mm, and the impact of changes in BC management on the relevance of older studies examining margin width to practice today.

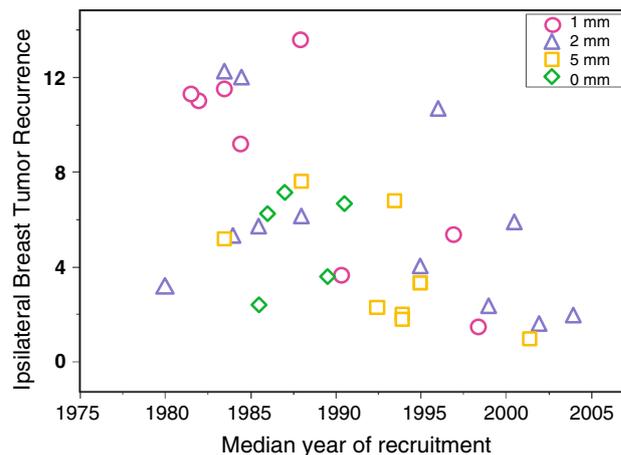
Holland et al.<sup>21</sup> in a meticulous study of mastectomy specimens, demonstrated that clinically unicentric T1–T2 BCs are frequently associated with subclinical foci of invasive cancer and/or DCIS in the surrounding breast tissue and that these may be present at large distances from the primary tumor site. 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, >3, 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 after breast-conserving surgery or 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 because of 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.<sup>22</sup> 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 two 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. Although the shaved margin method permits examination of a greater surface area of the specimen margin than 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.<sup>23</sup> 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.<sup>24</sup> 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.<sup>5</sup> 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, 2, 5 mm<sup>3</sup>) and IBTR was evaluated, as shown in Table 4 (19 studies; 13,081 patients; 753 IBTRs; 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 vs. any), did not change these results. Although 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 because of the heterogeneity among studies in the definitions of close and positive; 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 BC 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. Because 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 Fig. 1, the crude incidence of IBTR declined over time, and although this was observed for all margin widths, the decline appeared 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.<sup>20</sup> The widespread use of systemic therapy today, even for patients with small, node-negative BC, increased the confidence of the MP 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



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

prevalence of IBTR for all studies in the meta-analysis was only 5.3 %. Although the ORs in Table 4 numerically suggest that 5-mm margins offer an advantage compared with margins of 1–2 mm, these differences lack statistical significance despite the use of two 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 ORs (Table 4). 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. 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 two (Table 4), because only a small number of studies with these margin definitions were available for review. The MP considered the long-term results of the NSABP B06 randomized trial,<sup>2</sup> 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 among margins of 1, 2, and 5 mm<sup>3</sup>, and the benefits of a boost dose of radiation on local control discussed below led the MP to believe that the totality of evidence did not support a distinction between margins of no ink on tumor and margins of 1 mm.

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### 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.

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The use of systemic therapy in the treatment of early-stage BC 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 received chemotherapy (melphalan and fluorouracil [FU]). Within the irradiated cohort, node-positive patients demonstrated roughly half the rate of IBTR compared with node-negative patients (5 vs. 12 %) 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 vs. not for ER-positive, node-negative disease), the rate of IBTR was 11.6 % in the control group compared with 5.0 % in the tamoxifen group ( $P < 0.001$ )<sup>8</sup>; in NSABP B13 (chemotherapy vs. not for node-negative disease), the IBTR rate was 15.3 % in the control and 5.4 % in the treated patients ( $P < 0.001$ )<sup>8</sup>; in NSABP B19 (methotrexate and FU vs. cyclophosphamide, methotrexate, and FU in ER-negative, node-negative patients), the IBTR rates were 8.2 and 4.8 % ( $P < 0.03$ ).<sup>25</sup> 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 with those who did.<sup>26</sup> 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 BC subtypes. For women with ER-positive BC 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.<sup>1</sup> The introduction of aromatase inhibitor therapy instead of, or in addition to, tamoxifen in postmenopausal women has led to a consistent reduction in the rates of IBTR across essentially all trials reported, with an average reduction in the HR of approximately 0.67.<sup>27</sup> The addition of taxanes to

anthracycline-based regimens is also accompanied by a relative reduction in the rate of IBTR.<sup>20</sup> Finally, the addition of trastuzumab to cytotoxic regimens for patients with human epidermal growth factor receptor 2 (HER2)-positive BC 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 Herceptin Adjuvant (HERA) trial.<sup>28,29</sup> 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 patients with BC today, reduces the overall risk of IBTR. It also strengthened the confidence of the MP that millimeter increments in margin widths are unlikely to affect 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 is no evidence to suggest that obtaining wider margins beyond no ink on tumor will result in any further reduction of IBTR.

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### Biologic Subtypes

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

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An improved understanding of biologic subtypes of BC has led to great improvements in systemic therapy that have, in turn, decreased IBTR. Several large studies have examined IBTR rates with BCT in relation to molecular markers. In one of the largest studies, Arvold et al.<sup>30</sup> reviewed 1,434 patients who underwent BCT and found that those patients with triple-negative BC (TNBC) and HER2-positive tumors had a significantly higher risk of IBTR compared with patients with other subtypes. 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.<sup>31</sup> 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. Interestingly, they found no increased IBTR among TNBCs with nonbasal tumor markers.<sup>31</sup> Mazouni et al.<sup>32</sup> reported on 1,194 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 disease and TNBC than for luminal A and luminal B tumors,

suggesting that surgeons felt less comfortable with BCT for more aggressive tumor subtypes, despite a lack of data. Haffty et al.<sup>33</sup> as well as Freedman et al.<sup>34</sup> also found no significant differences in IBTR among patients treated with BCT when comparing TNBC with non-TNBC. A recent study by Gangi et al.<sup>35</sup> examined outcome among 1,851 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 with 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 disease and TNBC are more difficult to resect. Pilewski et al.<sup>36</sup> 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  $\leq 2$  mm and those with margins  $> 2$  mm (7.3 vs. 5.1 %). 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 or mastectomy and found no difference based on surgical procedure, suggesting that these local recurrences are more likely a result of aggressive biology, not residual tumor at the surgical site, which could be improved with wider lumpectomy margins.<sup>29,37–39</sup> 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.<sup>29</sup> In summary, the MP 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 over no ink on tumor for any BC subtype.

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#### Radiation Therapy Delivery

The choice of WBRT delivery technique, fractionation, and boost dose should not be dependent on margin width.

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WBRT options have expanded significantly in the last decade. Delivery techniques such as prone positioning and intensity-modulated radiotherapy have been designed to limit treatment-related toxicity by decreasing heart/lung volumes and improving homogeneity across the whole-

breast radiation field, respectively.<sup>40–43</sup> Additionally, attempts have been made to decrease the burden of the protracted treatments inherent to conventionally fractionated WBRT through use 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.<sup>44,45</sup> In general, the studies evaluating these approaches did not specify particular surgical margin widths and required only complete microscopic excision of tumor.<sup>40–43,45</sup> The large United Kingdom Standardization of Breast Radiotherapy (START) trial did mandate a  $\geq 1$ -mm margin, but comparable long-term results were reported in the similar Canadian hypofractionation trial that excluded only those with involved margins.<sup>45–47</sup> Although neither of these trials was 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, although acceptable, rates of late radiation toxicity.<sup>18,48,49</sup> 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 in several single-institution series.<sup>50–52</sup> 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 MP felt that interpretation of these and other retrospective data evaluating both radiation dose and surgical margins was complicated by the heterogeneity of total radiation doses and techniques, and a lack of control cohorts with comparable margin 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.<sup>51</sup> The other studies simply noted no clear relationship between local control and margin width or radiation dose.<sup>50,52</sup>

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.

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#### Invasive lobular carcinoma (ILC) and lobular carcinoma in situ (LCIS):

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

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ILCs comprise 5–15 % of all BCs. Several large retrospective studies demonstrate that when negative margins are obtained, the risk of IBTR is not significantly different between ILC and invasive ductal carcinoma.<sup>53–55</sup> Wider margins do not yield lower IBTR rates. In a retrospective study of 382 patients comparing margins >1 cm with smaller margins, no differences in local recurrence rates were observed.<sup>56</sup> Additionally, most classical ILCs 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 MP 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 impact IBTR. In a retrospective study, the 10-year cumulative incidence rate of IBTR in patients with BC was not significantly different in patients with or without LCIS unless tamoxifen was withheld.<sup>57</sup> 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.<sup>58,59</sup> 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,<sup>60</sup> the MP did not feel that a recommendation regarding pleomorphic LCIS at the margin could be made at this time.

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#### Young age

Young age ( $\leq 40$  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.

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Young patient age, usually defined as <40 years, has been associated with an increased risk of IBTR after BCT compared with 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  $\geq 50$  years in the node-negative subgroup.<sup>1</sup> 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  $\geq 50$  years, respectively. An increased risk for BC 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.<sup>61,62</sup>

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,<sup>63</sup> and the increased risk of both recurrence and BC death is not improved with mastectomy compared with BCT.<sup>62,64</sup> 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 BC, *BRCA1* and *BRCA2* mutation–associated cancers, and BCs associated with adverse gene expression profiles,<sup>65,66</sup> 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 subtype.<sup>66</sup> Young age may be a less important factor for IBTR when controlling for adverse gene-expression profile<sup>30,67</sup> or may not be important at all in 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.<sup>68</sup>

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, 2, or 5 mm<sup>3</sup> ( $P$  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 with older women. In addition, there are data demonstrating equivalent risks for recurrence and BC death in young women irrespective of treatment with BCT or mastectomy.<sup>62,64</sup>

Thus, the MP concluded that although the adverse pathologic and biologic factors associated with young age are mitigated to some extent by 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.

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#### Extensive Intraductal Component (EIC)

An 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 and EIC when margins are negative.

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EIC is a pathologic description of invasive ductal carcinoma that has a prominent intraductal component within the tumor and adjacent normal tissue. The basis of 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 (approximately 25 %) and within breast tissue beyond the edges of the invasive cancer.<sup>69</sup> These EIC-positive cancers often recurred within or at the edge of the boost volume and were more commonly seen in young patients ( $\leq 35$  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.<sup>70</sup> Pathologic examination of a cohort of mastectomy specimens revealed that 33 % of EIC-positive cancers had prominent DCIS (six or more low-power fields of DCIS) at  $\geq 2$  cm from the edge of the index cancer compared with only 2 % of EIC-negative cancers.<sup>71</sup> 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.<sup>72</sup> 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 it was 50 % when there was more than focal positivity.<sup>72</sup> On the basis of this information, the MP did not feel that the available evidence supports the routine use of margins wider than no ink on tumor. However, in view of the potential for substantial 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.<sup>69,72</sup> 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.

**ACKNOWLEDGMENT** The authors thank David Euhus, MD (Society of Surgical Oncology [SSO]), Beryl McCormick, MD (American Society for Radiation Oncology [ASTRO]), Benjamin Smith, MD (ASTRO), Kimberly Van Zee, MD (SSO), and Lee Wilkie, MD (SSO) for critical review of the manuscript, and Shan-san Wu for editorial assistance.

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