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SPECIAL ARTICLE

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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A B S T R A C T

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 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.

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INTRODUCTION

Mature phase III trials have conclusively demonstrated the equivalence of 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), to mastectomy for the treatment of stages I and II invasive breast cancer (BC).[1,2] Of these trials, only National Surgical Adjuvant Breast and Bowel Project (NSABP) B06 required a microscopically clear margin, defined as no ink on tumor[2]; all others required only gross total resection. Despite the lengthy track record of BCT, there is still no consensus on what constitutes an optimal negative margin width.[3,4] As a consequence, approximately one in four women attempting BCT undergo a re-excision, often performed to obtain more widely clear margins than no ink on tumor.[5,6] Re-excisions have the potential for added discomfort, surgical complications, compromise in cosmesis, additional stress for patients and families, and increased health care costs and have been associated with conversion to bilateral mastectomy.[7] Since BCT was established more

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 ≥ 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 margin 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?	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?	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 young patients (age < 40 years)?	Young age (≤ 40 years) is associated with both increased IBTR after BCT as well as increased local relapse on the chest wall after mastectomy and is also more frequently associated with adverse biologic and pathologic features; there is no evidence that increased margin width nullifies the increased risk of IBTR in young patients	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?	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

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

than two decades ago, the landscape of BC management has evolved dramatically, with advances in imaging and adjuvant treatments, resulting in a decline in ipsilateral breast tumor recurrence (IBTR) rates.[8]

In view of these changes, the Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) convened a multidisciplinary margins panel (MP) to evaluate IBTR in relation to margin width; the primary question addressed was: "What margin width minimizes the risk of IBTR in patients with invasive cancer receiving WBRT?" The guideline developed from this consensus panel is intended to assist treating physicians and patients in the clinical decision-making process. The key findings of the guideline are summarized in Table 1.

METHODS

The process for guideline development followed, to the extent possible, the standards of the Institute of Medicine (IOM)[9] and was funded by a Susan G. Komen grant. The experts on the MP (Table 2) commissioned a systematic review/meta-analysis, which served as the primary evidence base, with additional topic-specific literature reviews conducted by participants for questions not addressed in the meta-analysis. The MP convened in July 2013; the resulting manuscript was approved by all participants and externally reviewed, and feedback was incorporated. The final manuscript was approved by the SSO Executive Council and ASTRO Board of Directors and endorsed by the American Society of Breast Surgeons. Patient-related guideline information and a question-answer sounding board will be available on the Komen Web site.

Meta-Analysis

The methodology for the systematic review/meta-analysis has been published in its entirety elsewhere.[10,11] A detailed summary providing definitions, data extracted, statistical models, and so on is provided in the Appendix (online only). Briefly, using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and IOM guidelines,[10,12,13] MEDLINE and evidence-based medicine were searched inclusive of 1965 to 2012 for eligible studies. The results were combined with a previously published meta-analysis.[10] Two independent investigators performed the review and data extraction.[10] All reported odds ratios (ORs) were adjusted for study-specific median follow-up time (to account for the inherent increased risk of IBTR with longer follow-up) and are reported relative to negative margins (OR, 1.0).

Inclusion/Exclusion Criteria

Studies of patients with stage I/II BC (no neoadjuvant chemotherapy) treated with local excision and WBRT and reporting IBTR in relation to microscopic margin widths, with a minimum follow-up of 4 years (because of the increased incidence of IBTR over time) were eligible (Appendix, online only).[11]

Study Quality/Literature Limitations

All publications in the meta-analysis (except for two) were retrospective[14,15] and provided observational data at the study level. The characteristics/quality assessment of the studies included have been reported elsewhere.[11]

Table 2. Expert Panel Members

Panel Member	Society	Affiliation
Monica Morrow, MD (cochair)	SSO	Memorial Sloan-Kettering Cancer Center
Meena S. Moran, MD (cochair)	ASTRO	Yale University
Nehmat Houssami, MBBS, 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

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

Conflicts of Interest Management

The MP candidates declared and discussed potential conflicts of interest before convening; written disclosures were obtained at the consensus meeting. The cochairs deemed no MP members had conflicts that could influence the process/development of specific recommendations.

RESULTS

The meta-analysis included 33 studies, 28,162 patients, and 1,506 IBTRs. At a median follow-up of 79.2 months (ie, 6.6 years), the median prevalence of IBTR was 5.3% (interquartile range, 2.3% to 7.6%). Table 3 provides a summary of the study/patient characteristics; Table 4 provides a synoptic overview of the results.[11] All models and all reported ORs were adjusted for study-specific follow-up.[11]

GUIDELINE RECOMMENDATIONS

Positive Margins

A positive margin, defined as ink on invasive cancer or ductal carcinoma in situ (DCIS), is associated with ≥ 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. There is no debate that a positive margin, defined as the presence of ink from the specimen surface on tumor cells (invasive or DCIS), implies a potentially incomplete resection and is associated with a higher risk of IBTR. As shown in Table 4, for close/positive margins, the OR for IBTR was 1.96 (95% CI, 1.72 to 2.24). In a subset analysis (n = 19 studies; n = 13,081 patients) separating negative, close, and positive margins, the OR for positive margins was 2.44 (95% CI, 1.97 to 3.03).[11] Other literature supports this ≥ two-fold increased IBTR risk for positive margins.[16,17] Although various treatment modalities (ie, radiation boost, endocrine therapy/chemotherapy/biologically targeted therapy) all reduce IBTR risk, adjustment for the use of these treatment modalities did not nullify the increased IBTR risk with positive margins in the meta-analysis. The risk of IBTR with positive margins remained elevated despite receipt of a boost (n = 18 studies; OR, 2.45; $P < .001$).[11] Similarly, in a European Organisation for Research and Treatment of Cancer (EORTC) trial, which established the benefit of a boost in reducing IBTR rates,[18] a subset analysis was conducted of 251 patients with positive margins receiving a boost, and an unacceptably high IBTR incidence was reported (10 Gy, 17.5%; 95% CI, 10.4% to 24.6%).[19] These data suggest that although a boost partially mitigates the effect of positive margins, the absolute risk of IBTR still remains higher than in patients with negative margins receiving a boost. Similarly, systemic therapy does not negate the risks associated with positive margins. In a subset analysis (n = 16 studies) adjusting for endocrine therapy receipt, the OR for positive margins remained significantly elevated at 2.53 ($P < .001$), despite endocrine therapy use.[11]

Lastly, the panel concluded that patients with positive margins, despite favorable tumor biology (ie, strongly estrogen receptor [ER] positive), remain at higher risk for IBTR than similar patients with negative margins. In a subset analysis adjusted for ER status (n = 15 studies), the OR for IBTR among ER-positive patients with positive margins remained significantly elevated (OR, 2.66; $P < .001$).[11] The impact of a boost, systemic therapy, and biologic subtype on margin width is discussed further in our report.

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. To address the question of optimal negative margin width, the MP considered data on the microscopic distribution of clinically and mammographically unicentric BC. Holland et al[20] demonstrated that clinically and radiographically unicentric T1 to T2 tumors are frequently associated with subclinical foci of tumor cells at distances remote from the primary tumor, independent of tumor size, with 42% of patients with T1 disease having tumor foci > 2 cm away and 10% having foci > 4 cm away. Thus, a negative margin does not guarantee the absence of residual tumor in the breast, and the high frequency of remote tumor foci may, in part, explain why millimeter increments in margin width have no significant impact on IBTR risk.

There are technical limitations confounding the meaningful differentiation of 1 to 2 mm of margin width that affect the relationship between margin width and IBTR. For example, margins are artifactually narrower ex vivo, when specimens become flattened from lack of

Table 3. Summary of Study Characteristics*

Characteristics	No. of Studies	Median	Range
Study			
No. of patients per study	33	701	79-3,899†
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			
Age, years‡	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‡	8	1.6	1.5-2.1
High grade (III), %	17	28.3	20.6-30.6
Unknown		2.9	0.8-21.5
ER status, %	24		
Positive		45.5	38.4-56.3
Negative		20.5	16.6-26.3
Unknown		28.4	14.2-42.0
PR 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			
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	45.0-50.0
Radiation boost dose, Gy‡	12	10.0	10.0-13.1

Abbreviations: EIC, extensive intraductal component; ER, estrogen receptor; IBTR, ipsilateral breast tumor recurrence; LVI, lymphovascular invasion; PR, progesterone receptor; WBRT, whole-breast radiation therapy.

*Including patient, tumor, and treatment variables included in the margins meta-analysis.[11]

†Interquartile range.

‡Denotes median (of the median or mean values across studies).

§Inclusion criteria for meta-analysis included WBRT.

surrounding supportive tissue, a phenomenon exaggerated by compression for specimen radiography.[21] Additionally, surface ink can track into deeper portions of the specimen, posing significant challenges in determining true margin location. Finally, tumor-to-ink distance on any single slide may not be representative of the entire specimen; a so-called adequate margin on one section may become positive if additional or deeper sections are examined. Two common methods for margin evaluation include sectioning perpendicular to ink (to determine tumor-to-ink width) or en-face examination of shaved margins (where any residual tumor in the shaved specimen is considered a positive margin). Although an advantage of the shaved method is greater surface-area examination, a known disadvantage is the higher frequency of margins categorized as positive that are, in comparison, negative by the inked method, which may in turn result in unnecessary re-excision or even mastectomy.[22] Specimen sampling is also highly variable, and even total sequential embedding results in only a small proportion (< 1%) of the specimen margins being examined.[23] Together, these studies highlight the substantial variability in margin assessment irrespective of the technique used.

Despite variability in margin assessment, great emphasis has been placed on achieving specific negative margin widths. Examination of the relationship between specific margin widths (1, 2, 5 mm) and IBTR (n = 19 studies; n = 13,081 patients; n = 753 IBTRs; median follow-up, 8.7 years) failed to identify an association with margin distance ($P = .90$), nor any statistical evidence for a trend suggesting a decreased rate of IBTR with increased negative margin widths (P trend = .58). Adjusting for covariates (age, study recruitment year, use of endocrine therapy, use of a radiation boost, use of re-excision, ER status, and first *v* any IBTR) did not alter these findings (Table 4). Although comparison of the numeric ORs in Table 4 suggests a potential benefit of larger margins, these differences lack statistical significance. Given the robust sample sizes and the use of two different statistical tests, it is unlikely that the meta-analysis lacks the power to detect clinically meaningful differences in IBTR. Furthermore, with an overall median IBTR rate of 5.3% across all 33 studies, the possible absolute reduction in IBTR with the OR of 0.77 seen with 5-mm margins is approximately 1% to 2%. More importantly, after adjusting for treatment (ie, endocrine or/and boost), this difference in the OR is virtually eliminated (Table 4). Although the analysis using study-specified margin definitions (model one, close, positive, negative) did reveal a significant increase in the odds of IBTR with close (OR, 1.74; 95% CI, 1.42 to 2.15) or positive (OR, 2.44; 95% CI, 1.97 to 3.03) versus negative margins ($P < .001$), the MP felt that because of the heterogeneity between study definitions of close versus positive margins, the analysis of specific quantitative margin widths (model two, 1, 2, 5 mm) superseded this finding. Additionally, the MP acknowledged significant changes in BC management not reflected in older studies included in this meta-analysis. Only 26% and 38% of included patients received chemotherapy and endocrine therapy, respectively, despite a median tumor size of 1.6 cm and a nodal positivity rate of 26%.[11] The crude rate of IBTR declined over time for all margin widths, but the decline was most pronounced for margins < 5 mm (Fig 1). Systemic therapy is well documented to decrease IBTR, and its widespread use today, even for patients with small node-negative cancers, increased the confidence of the MP that wider margins were unlikely to reduce IBTR in a clinically meaningful way.

It was not possible to compare rates of IBTR between margins of no ink on tumor and margins of ≥ 1 mm in model two (Table 4), because few studies provided this information. The MP considered the long-term results of the NSABP B06 trial,[2] which, defining negative margins as no ink on tumor, reported a 12-year IBTR of only 5% in node-positive patients receiving systemic therapy. Additionally, the variability in margin assessment discussed here, the lack of evidence of a significant difference in rates of IBTR among 1-, 2-, and 5-mm margins, and the benefits of adjuvant treatments (ie, systemic or boost) with regard to IBTR led the MP to believe that the totality of evidence did not support distinguishing between margins of no ink on tumor and margins of 1 mm. Thus, although larger margin widths (than no ink on tumor) may have resulted in small reductions in IBTR years ago, there are no data suggesting their importance with contemporary multimodality treatment.

Table 4. Summary of Selected Results of Margins Meta-Analysis[11]

Margin Status	No. of Studies	No. of Participants	Adjusted OR of IBTR*	95% CI	*P* (association)
	Relationship Between IBTR and Margin Status				
Margin category (model one)		28,162			< .001
Close/positive	33	6,178	1.96	1.72 to 2.24	
Negative	33	21,984	1.0	—	
Margin category (model two)		13,081			< .001
Positive	19	1,641	2.44	1.97 to 3.03	
Close	19	2,407	1.74	1.42 to 2.15	
Negative	19	9,033	1.0	—	—
Threshold distance (model two), mm†					.90
1	6	2,376	1.0	—	—
2	10	8,350	0.91	0.46 to 1.80	—
5	3	2,355	0.77	0.32 to 1.87	—

Covariate	No. of Studies	Threshold Distance for Negative Margin: Adjusted OR (mm) 1	2	5	*P* (association)
	Impact of Margin Width on IBTR Adjusted for Individual Covariates and Follow-Up*				
Age	18	1.0	0.53	0.77	.53
Endocrine therapy	16	1.0	0.95	0.90	.95
Radiation boost	18	1.0	0.86	0.92	.86

Abbreviations: IBTR, ipsilateral breast tumor recurrence; OR, odds ratio.
*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, 2, and 5 mm). *P* trend = .58.

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. Systemic therapies (endocrine therapy, chemotherapy, targeted therapy) intended to reduce distant disease and improve survival outcomes have well-established effects in decreasing IBTR. In NSABP B06, node-positive women who received chemotherapy and WBRT had significantly less IBTR than node-negative patients receiving only WBRT (12 years, 5% *v* 12%).[2] Subsequent improvements in survival with new agents have been accompanied by additional decreases in IBTR.[8,24] Furthermore, pooled data from NSABP neoadjuvant trials have demonstrated that women who achieved a pathologic complete response, which predicts for improved distant disease and BC survival outcomes, also experienced significantly reductions in IBTR compared with partial responders (hazard ratio, 1.55; 95% CI, 1.01 to 2.59).[25]

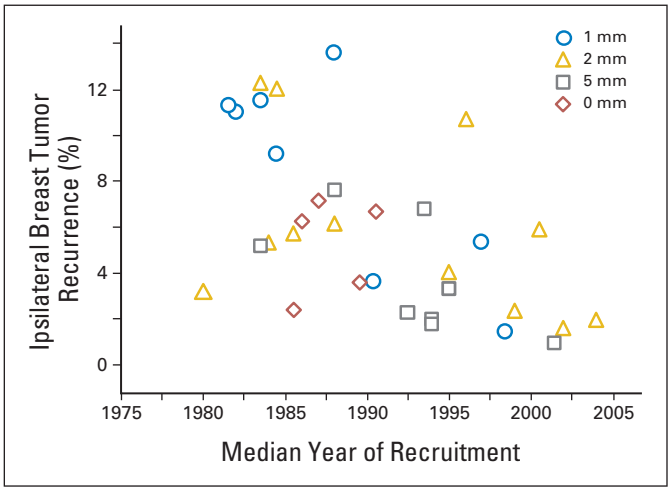

Fig 1. Scatter plot of unadjusted rates of ipsilateral breast tumor recurrence by median year of study recruitment.

Improvements in BC subtype–specific targeted therapy should also continue to decrease IBTR risk. For example, the Oxford overview demonstrated a decrease in 10-year IBTR rates from 18.6% to 8.7% with tamoxifen.[1] Introduction of aromatase inhibitors has led to a further reduction in IBTR risk,[26] as has the use of trastuzumab for human epidermal growth factor receptor 2 (HER2) –positive patients[27,28] and the incorporation of taxanes.[29] These contemporary trials establish the principle that as systemic treatments improve, so does their impact on diminishing IBTR.

These studies provide evidence that systemic therapies, used for the vast majority of patients with BC in the current era, clearly reduce the risk of IBTR, which further 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 has been obtained. The MP agreed, although the evidence was less robust, that in the rare circumstance when a patient does not receive any form of systemic treatment, there are no data suggesting wider margins beyond no ink on tumor would result in any further reduction of IBTR.

Biologic Subtypes

Margins wider than no ink on tumor are not indicated based on biologic subtype. An improved understanding of BC subtypes has led to improvements in systemic therapy that have, in turn, decreased IBTR. Several large studies have examined IBTR rates with BCT in

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relation to molecular markers. One study reported significantly higher risk of IBTR in triple-negative BC (TNBC) and HER2-positive disease (relative to luminal A/B); however, these results were from an era predating trastuzumab, which is known to reduce IBTR in HER2-positive patients.[30] Voduc et al[31] similarly reported increased IBTR in HER2-positive and basal tumors but no increased IBTR among nonbasal TNBCs. Mazouni et al[32] found no significant differences in IBTR by subtype, but mastectomy was more commonly performed for HER2-positive disease and TNBC than for luminal tumors, suggesting discomfort among surgeons with BCT for more aggressive subtypes. Others have also reported no significant differences in IBTR among patients with TNBC versus non-TNBC receiving BCT.[33,34] In an era when trastuzumab was used routinely for HER2-positive patients, a large study[35] found no significant difference in IBTR among patients with TNBC compared with other BC subtypes.

Intuitively, wider margins might be thought necessary to control more aggressive subtypes; however, there are no data to support this concept. A study assessing the impact of margin width on IBTR in TNBC found that incidence of IBTR did not differ significantly with margins ≤ 2 mm or > 2 mm (4.7% *v* 3.7%).[36] Support of this concept comes from three retrospective studies examining the incidence of local failure in TNBC after BCT or mastectomy and finding no differences based on surgical procedure, suggesting local recurrences are more likely a result of aggressive biology and less likely to be affected by removal of additional breast tissue around the tumor site.[28,37-39] In summary, the MP concluded that although there is evidence that IBTR risk varies by subtype, 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.

Radiation Delivery

The choice of WBRT delivery technique, fractionation, and boost dose should not be dependent on margin width. Improvements in WBRT techniques in the last decade have focused on limiting treatment-related toxicity (ie, heart, lung, skin).[40-43] In general, the studies evaluating these approaches did not specify particular margin widths and required only complete microscopic excision of tumor.[40-44] Additionally, attempts to decrease the 5-week treatment time inherent to conventionally fractionated WBRT have been explored. Two large randomized hypofractionation trials reported comparable long-term efficacy and toxicity data with shorter WBRT schemas.[44,45] One of these trials mandated a $\geq$ 1-mm margin, and the other only excluded patients with involved margins; however, their long-term outcomes were comparable.[44,46,47] Although neither of these trials was designed to address a possible interaction between margin width and fractionation schemas, there is no evidence to suggest that margin width should dictate patient selection for hypofractionated regimens.

As discussed earlier, a boost to the tumor bed after WBRT significantly reduces IBTR risk.[18,48,49] The randomized trials establishing the benefit of a boost largely defined negative margins as no ink on tumor. Tailoring of the boost dose (ie, increasing boost dose with decreasing margin width) has been explored in several institutional series, with conflicting results.[50-52] One study demonstrated an increased IBTR rate in patients with close/positive margins despite dose escalation,[51] whereas others noted no clear relationship between IBTR risk, margin width, and dose.[50,52] The MP felt that interpretation of these data evaluating dose escalation and margins was complicated by the heterogeneity of the total dose delivered, the techniques used, and a lack of control cohorts with comparable margin widths. Therefore, the panel concluded that there was no clear evidence that escalating the radiation dose reduces IBTR for narrower margin widths.

In summary, margin width should not determine radiation delivery technique or fractionation, or vice versa. In patients with negative margins (no ink on tumor), the use and dose of a boost should be based on a priori estimation of IBTR risk and should not be determined, in isolation, by the width of the surgical margin.

Invasive Lobular Carcinoma and Lobular Carcinoma in Situ

Wider negative margins than no ink on tumor are not indicated for invasive lobular carcinoma. Classic lobular carcinoma in situ (LCIS) at the margin is not an indication for re-excision. The significance of pleomorphic LCIS at the margin is uncertain. Invasive lobular carcinomas (ILCs) comprise 5% to 15% of all BCs. The risk of IBTR is not significantly different between ILC and invasive ductal carcinoma.[53-55] Wider margins for ILC do not yield lower IBTR rates. In a study comparing margins ≥ 1 to < 1 cm in patients with ILC, no difference in the rate of IBTR was seen.[56] Additionally, most classical ILCs have a luminal A phenotype (ER positive), and these patients will experience the previously discussed benefit of endocrine therapy in IBTR. Thus, the MP concluded that ILC histology should not alter margin recommendations.

In contrast to clear evidence demonstrating that DCIS at the margin increases IBTR, the presence of LCIS at the margin does not seem to affect IBTR. One study found no difference in IBTR with or without LCIS unless tamoxifen was withheld.[57] Other large studies failed to show an association between LCIS at the resection margin and IBTR risk.[58,59] Concern has been raised regarding the impact of the pleomorphic variant of LCIS (with morphologic features akin to high-grade DCIS) at the margin on IBTR risk. Given the limited data available to address this question,[60] the MP did not feel that a recommendation regarding pleomorphic LCIS at the margin could be made at this time.

Young Patient 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 pathologic and biologic features. There is no evidence that increased margin width nullifies the increased risk of IBTR in young patients. Young age, usually defined as age $<$ 40 years, has been associated with increased IBTR risk after BCT, compared with the risk among older women. In the Oxford meta-analysis of breast-conserving surgery, an inverse relationship between rate of any first recurrence and age was demonstrated for both node-negative and node-positive subgroups.[1] Other studies have also confirmed higher IBTR or local recurrence risk, distant recurrence, and BC-specific mortality in young women,[61-63] and these outcomes are not improved with mastectomy.[4,61,63]

These worse outcomes likely result from the presence of adverse pathologic and biologic features (ie, higher grade, ER/progesterone receptor negativity, lymphovascular invasion, *BRCA1*/*BRCA2* mutations, adverse gene-expression profile)[64,65] occurring in younger compared with older women. Young age may be a less important factor for

IBTR after controlling for gene-expression profile[30,66] or may not be relevant in predicting outcomes in an era of modern systemic therapy and anti-HER2–directed therapy.[67]

There was no evidence in our meta-analysis suggesting younger patients benefit from larger margin widths than no ink on tumor. In a subset analysis (n = 18 studies) adjusting for age, with negative margin widths defined as 1, 2, or 5 mm, the OR for IBTR did not differ significantly when wider negative margin widths were obtained (*P* association = .86; *P* trend = .58). This is consistent with the finding that mastectomy, which theoretically provides the largest margin width obtainable, is also associated with an increased risk of local recurrence in younger (*v* older) women.

Thus, the MP concluded that although the adverse pathologic and biologic features associated with young age are mitigated to some extent by negative margins, use of systemic therapy and a 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.

Extensive Intraductal Component

An extensive intraductal component (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. EIC, initially described in the 1970s when margins were not routinely assessed, indicates a prominent intraductal component within and around an invasive ductal carcinoma. The basis of the definition stemmed from a high rate of IBTR in patients undergoing BCT when a prominent (approximately 25%) DCIS burden was noted within and beyond the edges of the primary invasive tumor.[68] EIC-positive cancers recurred within or around the boost volume and were more commonly seen in younger patients.

Subsequently, when inking of margins and re-excisions for positive/close margins were routinely performed, patients with EIC-positive cancers (but not EIC-negative cancers) were frequently found to have considerable residual DCIS in the re-excision specimens.[69] Examination of mastectomy specimens revealed that a significantly greater proportion of EIC-positive cancers than EIC-negative cancers had additional DCIS foci at ≥ 2 cm from the index cancer,[70] suggesting that EIC-positive cancers may have extensive multifocal DCIS involvement with increased IBTR risk if not adequately resected.

Later investigations found the 5-year IBTR was 0% for EIC-positive cancers when no tumor cells were at the inked margin or when the margin was defined as close, but it was 50% with greater than focal margin positivity,[71] highlighting the importance of no ink on tumor in EIC-positive patients. On the basis of these data, the MP did not feel that the routine use of margins wider than no ink on tumor was supported. However, in view of the potential for substantial residual DCIS in EIC-positive patients, consideration should be given to obtaining postoperative mammography to identify residual calcifications warranting re-excision. Additionally, when an EIC is present, young age and multiple close margins are associated with an increased IBTR risk and can be used to select patients who may benefit from re-excision.[68,71]

DISCUSSION

There are limitations to this guideline. It applies to patients with invasive BC treated with WBRT. The findings cannot be extrapolated to patients with pure DCIS, those receiving neoadjuvant chemotherapy or accelerated partial breast irradiation, or to those not receiving radiotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

American Society for Radiation Oncology Disclaimer

Guidelines present scientific, health, and safety information and may to some extent reflect scientific or medical opinion. They are made available for educational and informational purposes only. Any commercial use of any content in this guideline without the prior written consent is strictly prohibited. Adherence to this guideline will not ensure successful treatment in every situation. Furthermore, this guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all circumstances presented by the individual patient. In addition, this guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials, given that clinical studies are designed to evaluate or validate innovative approaches in a disease for which improved staging and treatment are needed or are being explored. This guideline was prepared on the basis of information available at the time the panel was conducting its research and discussions on this topic.

Summary of Methodologic Specifics for the Margins of the Meta-Analysis

Definitions of Margins

Positive margins. The presence of (invasive or in situ) cancer at the transected or inked margin.

Negative margins. Absence of tumor within a specified distance (mm) of the resection margin.

Close margin. Presence of tumor within a certain distance but not at the resection margin.

Study Eligibility Criteria

Inclusion. Study had to report data allowing calculation of the proportion of local recurrence (LR) in relation to margin status and the threshold width or distance used to declare a negative margin; participants had early-stage invasive breast cancer (clinical or pathologic stage I or II in at least 90% of the study cohort); treatment in all patients had to consist of breast-conserving therapy (breast-conserving surgery, whole-breast radiation therapy); study had to report quantitatively defined microscopic margins where negative margins, and relatively positive and/or close margins, were defined in terms of a threshold distance or width from the cut edge of the specimen (with noted exception); studies that did not declare a quantified distance for negative margins but provided information allowing for classification of negative margins as >0 mm were allowed (however, these studies were not included in trend analysis for negative margin distance; study had to provide age data; and study had a minimum median/mean follow-up time of 4 years.

Exclusion. Where $\geq$ two articles reported the same cohort, the most recent study (that provided margin-specific LR data) was preferentially used to minimize duplicate data; and studies reporting LR without quantifying margins, studies in which all participants had the same margin status, studies that used nonstandard or unclear margin definitions, and studies limited to small subgroups were excluded.

Statistical Analysis

Model one. Included all 33 studies, combining positive/close (because some studies did not distinguish between these categories or did not report LR data separately for positive and close) versus negative. Margin status was fitted as a dichotomous variable (positive/close *v* negative); distance was fitted as a categorical variable (>0 *v* 1 *v* 2 *v* 5 mm), using 1 mm as the referent category. Each model was refitted to test for trend.

Model two. Only studies providing specific margin width information were included. Margin status was fitted as three categories (positive, close, negative), and margin distance was analyzed as a categorical variable.

Other Statistical Considerations

Covariates reported in less than half of studies were not considered reliable for modeling. Patients with unknown margin status were not included in the analysis. Ipsilateral breast tumor recurrence (IBTR) was classified into two categories: one, IBTR (first), defined for studies reporting IBTR as the first site of relapse (including studies where LR may have occurred alone or simultaneously with regional and/or distant relapse); and two, IBTR (any), defined for studies reporting LR occurring at any time (including LR as the first site of relapse or concurrent with or after regional or distant relapse, or LR not further specified).

Extracted Variables (descriptive and quantitative data)

Margin definition and categories. Local relapse definition and outcomes data; duration of (and losses to) follow-up; years of study recruitment; study design; age; stage (distribution, node status, aggregate tumor size); surgery (including re-excision); radiation details (whole-breast radiation therapy dose, boost [proportion given boost and dose], total dose to tumor bed, node irradiation); systemic therapy (endocrine, chemotherapy, hormone receptor status); tumor grade; lymphovascular invasion; and extensive intraductal component.

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