SPECIAL SERIES: LOCOREGIONAL MANAGEMENT OF BREAST CANCER

Lumpectomy Margins for Invasive Breast Cancer and Ductal Carcinoma in Situ: Current Guideline Recommendations, Their Implications, and Impact

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A variety of patient, treatment, and pathologic factors have been reported to be associated with an increased risk of ipsilateral breast tumor recurrence after breast conservation therapy (BCT) for invasive breast cancer and for ductal carcinoma in situ (DCIS). Perhaps the most important of these factors is the status of the microscopic margins of excision of the lumpectomy specimen. It is well documented that for patients with either invasive breast cancer or DCIS treated with BCT (which is classically defined as lumpectomy and whole-breast irradiation [WBI]), positive microscopic margins are associated with a 2-fold or greater increase in local recurrence risk when compared with negative margins.[1,2] Therefore, obtaining tumor-free margins before WBI is of utmost importance in the BCT setting.

Until recently, there has been no general agreement among surgeons or radiation oncologists as to what constitutes an adequate negative lumpectomy margin in the breast conservation setting. Several survey studies of surgeons and radiation oncologists have highlighted substantial discordance in defining a threshold margin width for both invasive cancers and DCIS. In one of these surveys, 318 surgeons were asked to indicate their preferred margin width for a patient with a T1 invasive breast cancer in whom radiation treatment is planned after lumpectomy. In that survey, 11% of the surgeons stated that no tumor on ink would be considered adequate for a negative margin, whereas 42% preferred a margin of at least 1-2 mm, 28% preferred a margin of $\geq$ 5 mm, and 19% favored a margin of $>$ 10 mm.[3] In another survey, 730 surgeons in Canada were asked about their preferred margin width for an invasive breast cancer. In that survey, 40% considered no tumor on ink a negative margin for invasive breast cancer, 14% required a margin of at least 1 mm, 29% required a minimum 2-mm margin, and 18% required a 5-mm margin. Similar margin widths were favored in patients with DCIS.[4] Finally, a survey of 702 radiation oncologists from North America found that 45.9% regarded no tumor on ink as a negative margin; margin widths of 1, 2, 3, 5, and 10 mm were considered negative by 7.4%, 21.8%, 10%, 10%, and 4.9% of respondents, respectively.[5]

This inconsistent definition of a negative margin among clinicians has led to wide variations in the rates of re-excision after lumpectomy. In a study of 54 surgeons, the re-excision rates ranged from 0%-70%.[6] Moreover, approximately half of these re-excisions were performed in patients with negative margins (no ink on tumor), with the apparent belief that a wider negative margin would further decrease the rate of local recurrence. Reducing the re-excision rate is an important clinical goal, because re-excisions have the potential to increase patient anxiety, increase morbidity, adversely affect cosmesis, result in patients opting for mastectomy, and increase costs to the health care system. Furthermore, in patients with invasive breast cancer, re-excisions can delay the initiation of systemic therapy and radiation therapy.

The lack of agreement on the definition of an adequate negative margin, the frequent use of re-excision (including in patients who already have negative margins), the declining rates of local recurrence, the recognition of the impact of systemic therapy on reducing local recurrence, and a better understanding of tumor biology led the Society of Surgical Oncology (SSO) and American Society of Therapeutic Radiology and Oncology (ASTRO) to initiate a 2-part venture to develop consensus guidelines for defining margins in the BCT setting for invasive breast cancer and for DCIS. The SSO-ASTRO invasive cancer margin guideline was published in 2014,[7-9] followed in 2016 by the SSO-ASTRO-ASCO consensus guideline on DCIS margins.[10-12] The purpose of this article is to review these consensus guidelines and to examine their implications and their impact on clinical practice.

LUMPECTOMY MARGINS FOR INVASIVE BREAST CANCER

Currently, for patients with invasive breast cancer, local recurrence rates at 10 years of follow-up after

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BCT are low (5%-10%). For low-risk patients with estrogen receptor (ER)–positive tumors, treated with lumpectomy, radiation therapy, and hormonal therapy, local recurrence rates are usually < 5%.[13] These low rates of local recurrence compared with those experienced in the earlier years of BCT are likely due to a number of factors, including improved imaging, more sophisticated and detailed breast specimen processing and evaluation, and perhaps most importantly the development and increased use of effective systemic agents that have resulted in both reducing the risk of distant relapse and reducing the risk of local recurrence.[14-16]

In addition, with improved knowledge and understanding of the biology of breast cancer, there has also been increased evidence suggesting that residual tumor burden may not be the strongest predictor of local recurrence, and removal of all subclinical disease may not be essential for maximizing local control. Supporting this concept is a patient-level meta-analysis of data from 3,180 patients, which revealed that although preoperative magnetic resonance imaging (MRI) demonstrated mammographically occult additional tumor foci in 16% of patients, local recurrence rates after BCT did not differ between those patients who had a presurgical MRI and those who did not.[17,18] Additional data to support this concept come from the American College of Surgeons Oncology Group Z0011 trial (ClinicalTrials.gov identifier: NCT00003855), where women with 1 or 2 positive sentinel nodes undergoing lumpectomy were randomly assigned to either axillary dissection or no further axillary treatment; all went on to receive WBI. Notably, 95% of patients in that trial received systemic therapy (endocrine therapy, chemotherapy, or both). Although additional lymph node metastases were found in 27% of patients in the axillary dissection group, first recurrence in the axilla was observed in only 0.9% of patients in the sentinel node–only group.[19] These data support the concept that complete surgical resection of all subclinical disease may not be required to achieve acceptable locoregional control in the current era of multimodality treatment using the combination of surgery, radiation therapy, and systemic therapy.

The inconsistent definition and wide variability in what constitutes an adequate negative margin, the high rates of re-excision to achieve negative margins in patients undergoing BCT (particularly in those patients already with no ink on tumor), the wide use of systemic therapies and their impact on local recurrence rates, and improvements in our understanding of tumor biology led SSO and ASTRO to convene a multidisciplinary panel of experts to develop a consensus guideline regarding margins in the setting of BCT for patients with stage I and II invasive breast cancers. Initially, the panel commissioned a systematic review and meta-analysis of the literature to serve as the primary evidence base for the guideline[20] but also considered outcomes from relevant randomized clinical trials and other published literature in developing the consensus statement.

The SSO-ASTRO invasive cancer margin consensus guideline was published in 2014[7-9] and was endorsed by the SSO, ASTRO, the American Society of Breast Surgeons (ASBS), ASCO, and subsequently by the St Gallen Consensus Conference (2015). In addition, these guideline recommendations were incorporated into the National Comprehensive Cancer Network (NCCN) clinical practice guidelines beginning in 2016 and have been discussed in numerous editorials and commentaries.[21-25] It is important to note that this guideline applies only to patients with early-stage *invasive* breast cancer (with or without the presence of associated DCIS) treated with lumpectomy followed by WBI and does not apply to patients with pure DCIS or to patients with invasive cancer planning to undergo accelerated partial breast irradiation, breast-conserving surgery alone without radiation, or patients treated in the setting of neoadjuvant chemotherapy.

The SSO-ASTRO invasive cancer consensus guideline reinforces the importance of obtaining negative margins, defined as no ink on invasive cancer or associated DCIS (if present), to optimize local control. The panel found that the higher risk of local recurrence observed in patients with positive margins was not offset by administration of a radiation boost, systemic therapy, or favorable biology. The most critical and practice-influencing conclusion of the panel was that although a negative margin defined as ink on tumor minimizes the risk of local recurrence, the routine practice of obtaining negative margin widths wider than no ink on tumor does not appear to further reduce local recurrence rates. This conclusion was primarily based on the findings in the meta-analysis cited earlier that demonstrated margins of 1 mm, 2 mm, or 5 mm were not associated with significantly different local recurrence rates.[20] However, that study was unable to adequately investigate margins of no ink on tumor compared with 1-mm margins because of the small number of studies using the 1-mm margin definition and the fact that the statistical modeling was constrained by variability in negative margin definitions. To address this issue, the panel considered the overall conclusions of the meta-analysis in combination with the long-term results of the NSABP B-06 randomized trial, which defined a negative margin as no ink on tumor. This trial, which started accrual in 1976, reported a local recurrence of 5% in patients who received systemic therapy after 12 years of follow-up.[26] A number of NSABP studies using this margin definition have reported 10-year rates of local recurrence of < 5% and 8% in patients with ER-positive and -negative cancers, respectively, who receive systemic therapy.[13] Finally, the consensus panel recognized that the assessment of microscopic margins of breast lumpectomy specimens is limited by a variety of technical, methodologic, and interpretive problems. These include specimen flattening, which results in artifactual

reduction of margin widths (a problem exacerbated by compression for specimen radiography); difficulties with specimen orientation and in distinguishing the boundaries between margins when applying ink; variation in extent and rigor of margin evaluation; and difficulties in the identification of the true margin of excision in cases in which there is tracking of ink into the specimen.[27-30] Given these limitations in margin evaluation, the panel questioned whether a margin of ink not touching tumor versus 1 mm was a reproducible or clinically meaningful difference.[31]

LUMPECTOMY MARGINS FOR DCIS

Similar to the decrease in local recurrence rates experienced with invasive breast cancer, the rate of local recurrence for patients with DCIS has declined over time, due in part to improvements in preoperative imaging and the use of more comprehensive pathologic examination of excised specimens. The similar argument regarding lack of uniform definition of an optimal adequate margin width for patients with DCIS has resulted in re-excision rates ranging from 20%-40%.[32,33] The SSO-ASTRO consensus panel recognized that the invasive margins guideline[7-9] is not directly applicable to patients with DCIS for a variety of reasons, including differences in the patterns of involvement of breast tissue between invasive cancers and DCIS and the less frequent use of adjuvant systemic therapy (ie, endocrine therapy) in patients with DCIS. These factors led to the SSO-ASTRO-ASCO consensus margin guideline for patients with DCIS treated with lumpectomy and WBI, which was published in 2016.[10-12] Similar to the SSO-ASTRO margin guideline for invasive breast cancer, the DCIS guideline recommendations were largely based on the results of a meta-analysis demonstrating that for patients with DCIS treated with lumpectomy and WBI, margins of at least 2 mm were associated with a reduced risk of local recurrence compared with narrower margins and that wider margins did not significantly improve the risk of local recurrence.[2] Thus, the SSO-ASTRO-ASCO guideline states that for patients with DCIS treated with lumpectomy and WBI, the routine practice of obtaining negative margin widths $>$ 2 mm is not supported by the evidence. After review of additional published literature, the panel recommended that the DCIS guideline be used for patients with DCIS with associated microinvasive carcinoma, because the pattern of tumor involvement of the breast in patients with DCIS with microinvasion is more similar to pure DCIS than to invasive breast cancer.[10-12] For patients with DCIS margins $<$ 2 mm, clinical judgment must be used in determining whether the patient would benefit from a re-excision, and the decision making should incorporate factors such as amount of DCIS that is $<$ 2 mm from ink, patient age/life expectancy, comorbidities, cosmetic impact of re-excision, presence of residual microcalcifications, and location of the close margin. This DCIS margin guideline has been endorsed by SSO, ASTRO, ASBS, and ASCO and, beginning in 2017, was included in the St Gallen Consensus Guideline and incorporated into the NCCN clinical practice guidelines.

The SSO-ASTRO-ASCO guideline panel also considered the optimal margin width for patients with DCIS treated with lumpectomy without radiation therapy. The results of 5 randomized clinical trials as well as a meta-analysis by the Early Breast Cancer Trialists Collaborative Group have shown that lumpectomy alone is associated with a consistently higher risk of local recurrence than lumpectomy with WBI, even in low-risk DCIS subgroups.[34-39] However, the optimal margin width in patients treated with lumpectomy without radiation therapy remains unknown, and there are conflicting data on this subject.[40-42]

The panel, therefore, stated that given the consensus guideline threshold for DCIS margins treated with lumpectomy and WBI is 2 mm, the margin width for patients with DCIS treated with lumpectomy without WBI should be at least 2 mm, recognizing that although there are some data to suggest more widely clear margins may be beneficial,[42] these data were inconsistent. For example, several prospective DCIS studies incorporated wider margin widths into their protocols when omitting WBI after lumpectomy. ECOG 5194 (ClinicalTrials.gov identifier: NCT00002934) and RTOG 9804 (ClinicalTrials.gov identifier: NCT00003857) both recommended margins of at least 3 mm for patients not receiving WBI,[39,40] and a prospective, single-arm trial of wide excision alone required negative margins of $>$ 1cm for enrollment.[41] Nevertheless, despite the wider negative margin widths in these trials, local recurrence rates without WBI were high, and no association between margin width and local relapse was established. Thus, the consensus panel believed that although it may be reasonable to obtain negative margins $>$ 2 mm for DCIS treated without WBI, there were insufficient data to make a definitive recommendation for routinely obtaining margin widths $>$ 2 mm in this setting.[10-12]

INVASIVE CANCER AND DCIS MARGIN GUIDELINES: IMPLICATIONS AND IMPACT

Consensus guidelines are intended to help decrease variability and provide guidance in standardizing practice, but they are not meant to be a substitute for clinical judgment.[21-24] For example, the SSO-ASTRO invasive cancer margin guideline panel acknowledged that there are circumstances under which wider negative margins than no ink on tumor may be appropriate, such as in clinical scenarios that predict for a larger residual tumor burden after lumpectomy. One example of such a scenario is a young patient with an invasive breast cancer that has an extensive intraductal component and a close margin of $<$ 1 mm across a broad front. In such a case, clinical judgment may dictate that a re-excision is warranted, despite a negative margin of no ink on tumor. Thus, the intent of the guideline was to convey the view of the panelists that in the

context of current clinical practice, where the vast majority of patients typically receive some form of systemic treatment, the frequent practice of routine re-excisions for arbitrary margin widths (2 mm, 5 mm, 10 mm, etc) intended to diminish local recurrence after BCT is not evidence based.[7-9] Similarly, for treatment of patients with DCIS, the SSO-ASTRO-ASCO margin guideline panel acknowledged that there are situations in which margins < 2 mm may acceptable for patients with DCIS who undergo excision and in whom radiation therapy is planned (eg, those in which the margin < 2 mm is the superficial margin abutting skin or the deep margin abutting pectoral fascia, or in whom wider margins may result in a poor cosmetic outcome).[10-12]

The invasive cancer and DCIS margin consensus guideline recommendations provide the opportunity to dispense with mandatory rules regarding re-excisions on the basis of margin widths alone. The guidelines suggest reserving re-excisions for situations where patients may be at higher risk of local recurrence after all relevant risk factors and treatment-related factors are considered together. Reductions in re-excision rates should reduce the emotional distress and anxiety in the patient, decrease the morbidity and costs associated with additional surgery, improve cosmetic outcomes after BCT, and reduce the likelihood of mastectomy in these patients.[24,43]

The acknowledgment, acceptability, and appropriate use of these margin guidelines has been demonstrated by 2 survey studies of the ASBS (conducted first for margins in invasive cancer and then for margins in DCIS).[44,45] In addition, there is evidence that the 2014 SSO-ASTRO invasive cancer margin guideline has contributed to a change in practice. A recent meta-analysis that included 7 studies (5 single-institution studies, 1 population-based study, and 1 national registry study) showed that among patients undergoing lumpectomy there has been a 35% reduction in the odds of reoperation and a reduction of the rate of re-excision from 22% to 14% since publication of the guideline.[46] In addition, 1 study demonstrated both significant cost savings and improvement in quality-of-life scores for patients undergoing lumpectomy after publication of the guideline when compared with those treated before guideline publication.[47] It should be noted, however, that these studies are unable to demonstrate a direct cause-and-effect relationship between the guideline publication and these outcomes. Although it may be possible that other factors such as changes in surgical technique (ie, use of shave margins) may be contributing to the diminishing reoperation rates,[48,49] regardless of the explanation, on the basis of available data and the increasingly widespread acceptance of these guidelines, it is reasonable to conclude these consensus definitions for margins will continue to increase patient satisfaction after BCT and result in improvements in operative and financial outcomes.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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