A variety of patient, treatment, and pathologic factors are associated with an increased risk of ipsilateral breast tumor recurrence (local recurrence) after breast conservation therapy for invasive breast cancer. Arguably, the most important of these has been the status of the microscopic margins of excision of the resected breast specimen. Among patients treated with breast-conserving surgery and radiation therapy, positive margins (ie, invasive carcinoma or ductal carcinoma in situ [DCIS] touching an inked tissue edge) are associated with a 2-fold increase in the risk of local recurrence when compared with negative margins. Therefore, obtaining negative margins prior to radiation therapy is the primary goal of breast-conserving surgery, and minimizing the microscopic residual tumor burden through removal of larger amounts of normal breast tissue has traditionally been considered a major factor for optimizing local control.

Although it has been more than 20 years since 6 randomized clinical trials reported that treatment with breast-conserving surgery and radiation therapy results in equivalent survival to mastectomy for women with early-stage breast cancer, there is still no universal agreement on what constitutes an adequate negative margin for patients being managed with the breast-conserving approach. Surveys of surgeons and radiation oncologists have demonstrated that there is no single threshold margin width identified as adequate by more than 50% of respondents. When 318 surgeons were presented with a scenario involving a patient with a T1 invasive breast cancer with planned radiation therapy following lumpectomy, 11% indicated that tumor not touching ink was an adequate negative margin, 42% favored a margin of at least 1 to 2 mm, 28% favored a margin of 5 mm or more, and 19% preferred a margin of more than 10 mm.

In a survey of 730 surgeons in Canada, 40% considered a margin negative for invasive breast cancer if there was no tumor at ink, 14% required at least a 1-mm margin, 29% at least a 2-mm margin, and 18% at least a 5-mm margin. A similar pattern was seen for patients with DCIS. Finally, in a survey of 702 North American radiation oncologists, 45.9% considered a margin negative when there was no tumor at the inked 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. Lack of consistency among clinicians in defining an adequate negative margin has led to wide variation in the rate of re-excision following lumpectomy. In a study that included 54 surgeons, rates of re-excision ranged from 0% to 70%.

In current clinical practice, 10-year local recurrence rates after breast-conserving surgery and radiation therapy are low, ranging from 5% to 10%. For the most common subgroup of breast cancer patients, that is, those with estrogen receptor (ER)–positive tumors, local recurrence rates are typically less than 5%. This improvement in local control can be attributed to a variety of factors, including better preoperative imaging, more detailed pathologic evaluation of specimens, and, perhaps most importantly, the use of effective systemic therapy that not only reduces the risk of recurrence but also affects the biology of the residual disease.
issues in margin assessment, the panel questioned whether margins of ink not touching tumor and 1 mm were meaningfully different.

Multiple other NSABP studies using this margin definition have reported 10-year rates of local recurrence of less than 5% and 8% in patients with ER-positive and ER-negative cancers, respectively, who receive systemic therapy.

The SSO-ASTRO consensus guideline reinforces the importance of obtaining negative margins, defined as no ink on invasive cancer or DCIS, to optimize local control. In support of this contention, although preoperative magnetic resonance imaging has demonstrated additional tumor foci in the breast not found by mammogram in 16% of breast cancer patients, an individual patient–level meta-analysis including 3180 patients demonstrated no decrease in the local recurrence rate following breast-conserving treatment in women who had undergone magnetic resonance imaging compared with those who had not.

In addition, in the American College of Surgeons Oncology Group Z0011 trial, women undergoing breast-conserving surgery and whole breast irradiation who had metastases in 1 or 2 sentinel lymph nodes were randomized to either axillary dissection or no further axillary treatment. More than 95% of patients in this trial received systemic therapy (hormonal therapy, chemotherapy, or both). Although additional lymph node metastases were found in 27% of patients in the axillary dissection group, only 0.9% of patients in the sentinel node-only group experienced a first recurrence in the axilla. Data such as these support the contention that surgical removal of all subclinical disease may not be required to achieve low local recurrence rates in either the breast or the axilla in the current era of multimodality treatment, which includes effective systemic therapy.

The lack of agreement regarding what constitutes an adequate negative margin, the common use of re-excision to optimize negative margin widths in patients undergoing breast-conserving therapy (particularly in those patients already with no ink on tumor), the recognition of the direct impact of contemporary systemic therapies in reducing local recurrence rates, and a better understanding of tumor biology led the Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) to convene a multidisciplinary panel of experts to develop consensus guidelines regarding margins for patients with stage I and II breast carcinoma in the setting of breast conservation therapy. The panel commissioned a systematic review and meta-analysis of the literature as the primary evidence base for the guideline, but also considered outcomes from relevant randomized clinical trials and other published literature in developing consensus. The panel met in July 2013 with support provided by Susan G. Komen. The consensus guidelines were published earlier this year in the *Annals of Surgical Oncology*, the *International Journal of Radiation Oncology, Biology, Physics*, and the *Journal of Clinical Oncology*, and have been endorsed by the SSO, ASTRO, the American Society of Breast Surgeons, and the American Society of Clinical Oncology. Several editorials and commentaries about this consensus guideline have also been published.

It is important to note that this guideline applies only to patients with early-stage invasive breast cancer treated with breast-conserving surgery followed by whole breast irradiation, and is not applicable for patients with pure DCIS or for patients with invasive cancer intending to undergo partial breast radiation, lumpectomy without radiation, or neoadjuvant chemotherapy.

The SSO-ASTRO consensus guideline reinforces the importance of obtaining negative margins, defined as no ink on invasive cancer or DCIS, to optimize local control. This has been recognized as important for many years, and the panel found that the increased risk of local recurrence associated with positive margins is not negated by treatment modifications such as a boost dose of radiation or systemic therapy or by favorable biology. The most important and potentially practice-changing conclusion of the panel was that although negative margins (no ink on tumor) minimize the risk of local recurrence, the routine practice of obtaining wider negative margin widths than no ink on tumor does not appear to further reduce local recurrence rates. This conclusion was largely based on the findings in the meta-analysis noted above that indicated that margins of 1, 2, or 5 mm were not associated with significantly different risks of local recurrence. 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 former margin definition and because the statistical modeling was constrained by variability in negative margin definitions. To address this issue, the panel considered both the overall conclusions of the meta-analysis and the long-term results of the NSABP B-06 randomized trial, which defined a negative margin as no ink on tumor, began accrual in 1976, and reported a 5% rate of local recurrence in patients receiving systemic therapy after 12 years of follow-up.

Multiple other NSABP studies using this margin definition have reported 10-year rates of local recurrence of less than 5% and 8% in patients with ER-positive and ER-negative cancers, respectively, who receive systemic therapy. Finally, given the variability, technical limitations, and sampling issues in margin assessment, the panel questioned whether margins of ink not touching tumor and 1 mm were meaningfully different.
It is important to note that although consensus guidelines such as this one are intended to help standardize practice, they are not a substitute for clinical judgment. In fact, although the guideline states that the routine practice of obtaining margins wider than no ink on tumor is not indicated, the panel recognized that there are selected circumstances under which wider negative margins may be appropriate. Certain clinical situations indicative of a higher risk for a large residual tumor burden after lumpectomy, such as in a young patient with an invasive breast cancer that has an extensive intraductal component and tumor within less than 1 mm of the margin across a broad front, do warrant the use of re-excision. Thus, the intent of the guideline is 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 (eg, 2, 5, or 10 mm) intended to diminish local recurrence in the breast conservation therapy setting may not be evidence based. Rather, the consensus provides the prospect for liberation from rules mandating re-excisions based merely on margin widths alone, and suggests reserving re-excisions for individuals likely to be at high risk for local recurrence when all relevant risk factors are considered together.

What effect should the SSO-ASTRO consensus guideline on margins have on the practice of breast pathology? Should pathologists now simply report lumpectomy margins as positive when there is invasive cancer or DCIS at an inked tissue edge and report all other margins as negative without further qualification? As noted above, there may be selected clinical situations in which re-excision is warranted for margins that are negative. Therefore, pathologists should continue to report margin status according to the recommendations of the College of American Pathologists: a margin should be reported as positive when there is ink touching invasive cancer or DCIS, and the anatomic location of the positive margin should be specified in oriented specimens. For negative margins (ie, ink not touching invasive cancer or DCIS), the distance of invasive cancer and/or DCIS from the margin(s) should be reported. In the current era, when the pathology report is a communication not only between the pathologist and the treating clinicians but also with the patient and the patient’s family, it is preferable to avoid the use of subjective terms to describe margins, such as “close,” which may be perceived as suboptimal or an indicator of an inadequate resection. It is also helpful to provide some quantitative information regarding the extent of tumor in proximity to the margin(s), although this is not currently a required data element in the College of American Pathologists protocol. Though ultimately the clinicians caring for the patients need to interpret the reported margin status in the context of the other pathologic features of the tumor, the imaging studies, and the clinical circumstances to decide on the necessity of further surgery, providing the above-stated details when describing margins gives important information that can greatly facilitate the decision-making process for determining the need for re-excision.

In our view and that of others, the SSO-ASTRO consensus guideline recommendation indicating that it is not necessary to routinely obtain negative lumpectomy margins wider than no ink on tumor has the potential to standardize practice and reduce the number of re-excisions in women who pursue breast conservation therapy for early-stage invasive breast cancer. Pathologists can assist in this endeavor to diminish routine re-excisions by familiarizing themselves with the margins consensus guideline and avoiding subjective terms to categorize margin status, instead providing as many objective details as possible. These details will, in turn, provide critical information for treating clinicians, and, together with other clinical and pathologic risk factors, will allow for a more individualized approach to determining the need for re-excision. To this end, reductions in re-excision rates should reduce the emotional distress, morbidity, and costs associated with additional surgery and may improve cosmetic outcomes following breast conservation therapy as well as reduce the likelihood of mastectomy in these patients.

References


Author notes

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