Should Intraoperative Frozen Section Evaluation of Breast Lumpectomy Margins Become Routine Practice?

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In this issue of the Journal, Jorns et al¹ report that intraoperative frozen section examination of breast lumpectomy margins was associated with a substantial reduction in the rate of reexcision. In their retrospective study, at some time after the initial lumpectomy a reexcision was performed in 48.9% of patients who did not have frozen section margin evaluation compared with only 14.9% of those in whom frozen section evaluation of the margins was performed. Further, these investigators developed a technique to overcome the methodological difficulties of attempting to cut frozen sections of fatty tissue such as margins of breast specimens. So if it is now technically feasible to obtain adequate frozen sections from lumpectomy margins and if intraoperative frozen section evaluations of these margins can reduce the need for a subsequent reexcision by almost 70%, should pathologists the world over be gearing up to routinely freeze margins of breast lumpectomy specimens? To answer this question, we must first review some fundamental data on lumpectomy margins and their association with local recurrence, and put these data into current clinical context.

Various patient factors, treatment factors, and pathologic factors have been reported to be associated with an increased risk of recurrence in the ipsilateral breast (local recurrence) after breast-conserving treatment for invasive breast cancer and ductal carcinoma in situ (DCIS). Arguably the most important of these is the status of the microscopic margins of excision of the resected breast specimen. Positive margins (ie, invasive carcinoma or DCIS at an inked tissue edge) have consistently been associated with a higher risk of local recurrence than negative margins.² Therefore, obtaining negative margins is the primary goal of breast-conserving surgery. Unfortunately, there is far from universal agreement as to what constitutes an adequate negative margin. In fact, results of surveys of surgeons and radiation oncologists have demonstrated that no single margin width is considered 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 after lumpectomy, 11% indicated that tumor not touching ink was an adequate negative margin, 42% favored a margin of 1 to 2 mm, 28% favored a margin of 5 mm or more, and 19% preferred a margin of more than 10 mm.³ 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 a 1-mm margin, 29% a 2-mm margin, and 18% a 5-mm margin. A similar pattern was seen among patients with DCIS.⁴ 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; margins of 1 mm, 2 mm, 3 mm, 5 mm, and 10 mm were considered negative by 7.4%, 21.8%, 10%, 10% and 4.9% of respondents, respectively.⁵

Lack of agreement among clinicians as to what constitutes an adequate negative margin has led to wide variation in the rate of reexcision after lumpectomy. In a recent study that included 54 surgeons, rates of reexcision ranged from 0% to 70%.⁶ Further, approximately half of all reexcisions are performed in patients with negative margins in the belief that a wider negative margin will further decrease the rate of local recurrence. The effect of frozen section examination on reducing reexcision rates will be highly dependent on the baseline rate of reexcision (ie, the benefit will be greater when the baseline reexcision rate is high, as in the study of Jorns et al¹ in which the baseline rate of reexcision was almost 50%) and
whether reexcision is routinely performed to achieve some arbitrary negative margin width beyond tumor at the inked tissue edge, as seen in the study of Jorns et al.\textsuperscript{1}

However, do millimeters really matter when it comes to lumpectomy margins? The results from retrospective studies have not consistently demonstrated that increasing margin widths in millimeter intervals in the 1-mm to 5-mm range results in a significant reduction in the risk of local recurrence among patients with invasive breast cancer treated with breast-conserving surgery and radiation therapy. Moreover, a metaanalysis of 21 retrospective studies that examined the influence of margin width on local recurrence in more than 14,500 patients failed to identify a statistically significant difference in local recurrence rates associated with margin widths of more than 1 mm, more than 2 mm, or more than 5 mm after adjustment was made for the use of a radiation boost or adjuvant systemic therapy.\textsuperscript{2}

It should not be surprising that it has been difficult to demonstrate that millimeters matter with regard to negative margin width, given the sampling issues and technical limitations involved in evaluating breast specimen margins and given what is known about the distribution of tumor in the breast in patients with invasive breast cancer and DCIS. For example, Holland et al.,\textsuperscript{7} using a combined radiographic-pathologic technique to evaluate mastectomy specimens, showed that among patients with clinically unicentric T1-2 breast cancers, 43% had tumor foci more than 2 cm from the primary site. Further, in many cases of DCIS (particularly non–high grade lesions), the ducal segment is discontinuously involved, creating “skip areas” or gaps of histologically normal tissue between foci of DCIS (multifocal disease).\textsuperscript{8} Therefore, it is not possible to determine whether the absence of DCIS at an inked margin indicates that the resection has extended beyond the edge of the DCIS (a truly negative margin) or if the histologically normal tissue at the margin simply represents a “skip area,” in which case considerable residual DCIS in the breast may be seen.

The aforementioned data indicate that negative lumpectomy margins of any width do not guarantee the absence of residual disease in the breast in patients with either invasive breast cancer or DCIS. However, it has never been the goal of lumpectomy to surgically remove all tumor in the breast in patients with invasive breast cancer or DCIS who will be treated with radiation therapy. Rather, the objective is to remove the index lesion with sufficient surrounding tissue such that the residual tumor burden is low enough to be controlled with radiation while preserving cosmesis. Jorns et al\textsuperscript{1} do not specify how many reexcisions were performed in their frozen section group for positive margins and how many were done for margins that were negative but considered to be too close by the surgeon. In the former circumstance, the need for further surgery is inarguable; in the latter, the decision about whether to reexcise should be more nuanced. In addition to the lack of evidence supporting the need for more widely clear margins discussed herein, it is important to recognize that local recurrence rates after lumpectomy and radiation therapy today are considerably lower than they were in the early days of breast-conserving therapy. At most institutions, 10-year local recurrence rates after lumpectomy and radiation therapy are currently in the 5% to 10% range, and for the most common subgroup of patients with estrogen receptor (ER)–positive tumors, local recurrence rates are less than 5%.\textsuperscript{9} This improvement in local control can be attributed to various 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 distant relapse but also substantially reduces the risk of local recurrence. For example, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial in which women with ER-positive, node-negative breast cancer were randomized to tamoxifen or placebo treatment groups, the 10-year rate of local recurrence after breast-conserving surgery was reduced from 14.7% in the placebo group to 4.3% in the tamoxifen group.\textsuperscript{10} Similarly, in the NSABP B-13 trial, in which women with ER-negative, node-negative tumors were randomized to methotrexate and 5-floururacil or no chemotherapy, the addition of chemotherapy resulted in a reduction in the 10-year local recurrence rate from 13.4% to 2.6%.\textsuperscript{11} In both studies, the same NSABP definition of a negative margin was used (ie, tumor not touching ink).

Further, as we gain a better understanding of breast cancer biology, it has become evident that residual tumor burden is not the strongest predictor of local recurrence and that removal of all subclinical disease is not essential to achieve high rates of local control. In support of this contention, although preoperative magnetic resonance imaging (MRI) has demonstrated additional tumor foci in the breast not found on mammography in 16% of patients with breast cancer,\textsuperscript{12} retrospective studies have not shown a decrease in the local recurrence rate after breast-conserving treatment in women who undergo MRI compared with those who do not.\textsuperscript{13-15} In addition, in the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, women undergoing breast-conserving surgery, sentinel lymph node biopsy, 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.\textsuperscript{16} Data such as these support the contention that it is
not necessary to surgically remove all subclinical disease to achieve low local recurrence rates in either the breast or axilla in the current era of multimodal treatment that includes effective systemic therapy.

We agree completely with Jorns et al\(^1\) that too many patients currently undergo reexcision after lumpectomy.\(^{17}\) However, we believe that it is more prudent for clinicians and pathologists to change the way they think about the relationship between margin width and risk of local recurrence based on available evidence than to implement the routine use of frozen sections to evaluate lumpectomy margins. Such a change will not only decrease the costs and morbidity associated with reoperation but will also improve the cosmetic outcome of breast-conserving therapy because the removal of a large amount of breast tissue is the major predictor of a poor cosmetic result.\(^{18}\) In fact, a change in thinking about the relationship between residual disease and risk of recurrence in the axilla based on the results of the ACOSOG Z0011 trial has already led to many institutions abandoning the use of intraoperative examination of sentinel lymph nodes for patients who would have met the eligibility criteria for that trial.\(^{19}\)

At a time when recommendations for systemic therapy are becoming increasingly individualized because of a growing understanding of breast cancer biology, it seems illogical to take a “one size fits all” approach to margins of breast lumpectomy specimens by performing routine intraoperative margin evaluation and immediately reexcising margins that do not meet some arbitrary minimum width beyond no tumor at the inked tissue edge. As noted before, the available evidence suggests that surgical eradication of all residual microscopic disease is not necessary for obtaining high levels of local tumor control in the current era of multimodal therapy. In current clinical practice, the NSABP negative margin definition of “tumor not touching ink” is likely to be an adequate negative margin in lumpectomy specimens before radiation therapy in most patients.\(^{20}\) The identification of the subset of patients likely to have a larger residual tumor burden after lumpectomy to a margin of no tumor on ink (such as those with an invasive cancer with an “extensive intraductal component” and perhaps some patients with invasive lobular carcinoma) requires careful permanent section evaluation of the lumpectomy specimen to assess both the histologic features of the tumor and the extent of disease in proximity to the margins. To make a more individualized decision about the benefit of reexcision in a particular case, this information should be integrated with other data, such as findings on imaging studies, axillary lymph node status, plans for systemic therapy based on receptor status (supplemented in some cases by results of molecular tests such as the OncotypeDX assay [Genomic Health, Redwood City, CA]), patient factors (such as age and comorbidities), and patient preferences. Ultimately, patient outcomes will be optimized by considering the full spectrum of factors that predict tumor burden and impact on local recurrence. Much of this information, however, is not available at the time of initial surgical resection of the primary tumor.

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References


