EDITORIAL

The Controversy Regarding Margin Width in Breast Cancer: Enough is Enough

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In contemporary practice, there is no debate that appropriately selected patients with early stage invasive breast cancer can be managed with breast-conserving therapy (BCT) to include a segmental mastectomy with a negative margin followed by radiation. This is supported by multiple randomized trials demonstrating equivalent survival after BCT or mastectomy published over two decades ago. Since the publication of these trials showing the efficacy of BCT, the definition of a negative margin has been the subject of frequent debate. One of these trials, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial, defined a negative margin as “no ink on tumor.” Other trials required complete resection of the tumor but did not specify a required margin width or did not evaluate microscopic margins. Therefore, despite the acceptance of BCT as the preferred approach for management of patients with early stage breast cancer, the optimal margin width required on a segmental resection has been open to interpretation. This has resulted in substantial variability in treatment often leading to recommendations for reexcision for “wider” negative margins.¹ After all, everyone knows that more is better, right? In the current issue of *Annals of Surgical Oncology*, Moran et al.² provide a consensus guideline on margins developed by the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO). This guideline, based on results of a systematic review of 33 studies, suggests that “no ink on tumor” be the standard for an adequate margin in patients with invasive cancer

undergoing breast conserving surgery. In order for this “less is better” concept to be implemented into practice on Monday morning, it is helpful to review the goals of BCT and to understand how contemporary practice involves many different multidisciplinary considerations.

The goals of BCT are to remove the primary tumor, minimize the risk of local recurrence, and achieve optimal cosmesis. Clearly margin width factors into the equation and surgeons understand the need to remove the tumor with a negative margin. This is drilled into us early in our training, and the first question that we are often asked after surgery is, “Did you get it all?” When excising the primary tumor, one must consider the tumor to breast size ratio and include enough normal breast parenchyma around the tumor such that a negative margin will be achieved without removing more volume of normal breast tissue than necessary. This can present a challenge in that tumors often form unusual shapes and have extensions of invasive or in situ carcinoma that go beyond the obvious palpable or radiographically evident lesion. The reality is that when we remove the tumor, this is done with an estimation of margins grossly and we cannot precisely determine the margin width (1, 2 mm, etc.) until the pathologist performs microscopic assessment. If margin assessment is performed intraoperatively with specimen imaging and immediate pathologic analysis, reexcision of any margins thought to be close or positive can be performed at the time of the initial operation without the need for a return to the operating room at a later date.³ This approach requires close coordination between surgery, pathology, and diagnostic radiology and may not be possible to implement in all practice settings.

More often, margin assessment is determined by the final pathologic evaluation performed in the days after surgery. The surgeon plays a significant role in this evaluation because careful orientation of the specimen will prevent inking of areas that are not true margins or tracking

of ink down crevices, which can result in uncertainty about the margin status. Specimen radiographs should be compared with preoperative imaging to evaluate the completeness of excision. This can be especially helpful in cases with an extensive intraductal component or those with invasive lobular histology where it can be challenging to determine whether “no ink on tumor” is synonymous with a negative margin. Here again, careful collaboration with the pathologist and breast imager can eliminate some of the variability that leads to positive margins and the need for reoperation.

The pathology report generally includes information about the distance from the tumor to the inked margin at multiple areas (superior, inferior, medial, lateral, anterior, and posterior); not just the measurement at one margin. In most cases, the margin width varies at the multiple surfaces. The margin may be wider than “no ink on tumor” at multiple surfaces, but when there is a negative but close margin (<1 , <2 mm), this raises concern for increased risk for local failure. Local recurrence is known to increase the risk for death due to breast cancer, and avoiding local recurrence is a primary concern of the surgeon.⁴

The meta-analysis by Houssami et al.⁵ provides the basis for the SSO/ASTRO guidelines. The authors reviewed 33 studies reporting on over 32,000 subjects and had available margin data on 28,162 subjects that they included in their models. These studies were largely retrospective with a median prevalence of local recurrence of 5.3 % (interquartile range 2.3–7.6 %). They noted that positive and close margins significantly increased the odds of local recurrence compared to negative margins. They did not find, however, that the odds for local recurrence decreased as the distance of a negative margin increased. In some ways, this analysis is an oversimplification. Studies included in the meta-analysis did not categorize the margins as >0 mm but <1 mm, or ≥ 1 mm but <2 mm. Rather, the studies simply categorized margins as negative and used various definitions to define negative (1, 2, or 5 mm). Therefore, these studies included patients with wider margins than the threshold distance (i.e., if negative is defined as ≥ 1 mm, patients with 1 mm or 1 cm margins from the tumor will both be classified as negative). This complicates the analysis in that it would be harder to see a benefit across studies for a wider margin.

Although obtaining a negative margin is important, as suggested above, there are additional multidisciplinary considerations affecting outcomes in patients undergoing BCT. Communication between the surgeon and the radiation oncologist is important in achieving optimal outcomes, both oncologic and aesthetic, in patients undergoing BCT. There is significant variability across studies with respect to the total dose for whole-breast irradiation and with respect to the use of a boost dose. This may be due to

institutional protocols but is likely also affected by margin status. Reducing the need for reexcision by accepting a negative margin as “no ink on tumor” could lead to the decision to increase the radiation dose or, more frequently, use a boost. This additional radiation may have a greater negative impact on cosmesis than simply excising more tissue.⁶ Therefore, communication between the surgeon and radiation oncologist regarding the impact of additional surgery and radiation on the risk of local recurrence and the aesthetic outcome is critical. Sometimes there is a trade-off with respect to radiation dose and the margin width. The breast size, expected volume of residual disease, and additional tissue to be excised, as well as the impact of radiation, should all be factored into decisions regarding further surgical intervention or reexcision.

It is reassuring to note that the local failure rates currently reported in patients undergoing BCT are substantially lower than those reported in the randomized trials performed two decades ago.⁷ This is the result of improvements in patient selection, pathologic processing, surgical techniques, and radiation technology, as well as better understanding of molecular subtypes and targeted therapy. The use of endocrine therapy reduces local failure in patients with hormone receptor-positive breast cancer, and chemotherapy reduces local failure among all breast cancer subtypes. The impact of *HER2*-directed therapies on reduction in local failure is currently being realized, and in the neoadjuvant setting, a pathologic complete response in patients with *HER2*-positive breast cancer is associated with decreased locoregional recurrence in addition to improvements in overall and disease-free survival.⁸ The one subtype that continues to experience higher local failure rates are those patients with triple receptor-negative breast cancer. There are no data that more aggressive surgery benefits patients with triple receptor-negative disease, either with wider margins in BCT or with mastectomy. Ongoing work to identify appropriate targets in this heterogeneous disease provides the greatest hope to improve outcomes for both local and distant tumor control.

The SSO/ASTRO consensus guidelines of using “no ink on tumor” to define a negative margin are based on the absence of data showing benefit for wider margins in BCT; however, there is also an absence of data showing that there is not a benefit. Although we don’t want to advocate for a margin threshold that requires multiple patients to undergo reexcision when only one may benefit, we also do not want to suggest that some patients may not benefit from additional surgery. Instead, we would suggest that each case should be evaluated in a multidisciplinary fashion, considering all important clinical, pathologic, and treatment variables, not just the measurement of the margin. With this approach, every patient will benefit, and we can agree when enough is enough.

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