Margin Status Following Partial Mastectomy: One Size Does Not Fit All!

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Breast-conserving therapy (BCT), which includes wide local excision of the tumor followed by irradiation, has become a standard treatment option for women with early-stage invasive breast cancer. Long-term survival following BCT has been shown to be equivalent to that seen with mastectomy, while providing an acceptable cosmetic outcome and low morbidity.[1] These results have been corroborated in five major prospective randomized controlled trials in Europe and North America, including the National Cancer Institute (NCI) trial,[2] the European Organisation for Research and Treatment of Cancer (EORTC) 10801 trial,[3] the Danish trial,[4] the French trial,[5] and the Italian trial.[6]

Local recurrence following BCT has been shown to be impacted by a variety of patient and tumor characteristics, including patient age, tumor size, tumor grade, and presence of multifocal or multicentric disease; however, the strongest predictor of local recurrence remains that of surgical margin status.[7,8] Further, Fortin et al demonstrated that local failure is a powerful predictor of mortality: age less than 40 years, tumor size, absence of endocrine therapy, and close surgical margins were the only variables associated with local failure in their multivariate model.[9] Despite these findings, currently there is no consensus regarding the definition of a negative margin, or sufficiently negative margin, following surgical excision of the tumor. In this issue of ONCOLOGY, Revesz and Khan review the literature surrounding this hotly debated topic.[10] They conclude that a randomized, controlled trial is necessary in order to come to a consensus regarding the definition of an adequate margin and the indications for re-excision. We agree that such a trial would be beneficial to address this important issue. However, we also propose that the optimum margin following BCT should depend on the original size of the tumor, not simply on the actual size of the margin itself. We refer to this concept as the "margin index" and propose that it is a better predictor of residual disease than absolute margin size alone.[11] Margin index represents a mathematical calculation [closest margin (mm)/tumor size (mm) ×100] that can reliably estimate the risk of finding residual disease in the breast following BCT for stage I–II invasive breast cancer with or without ductal carcinoma in situ (DCIS).[11] Unlike a nomogram, calculation of the margin index does not require complex mathematical models, computer programs, or access to multiple patient and tumor variables. We found that a margin index cutoff of greater than 5 was optimal for maximizing the sensitivity and specificity in a cohort of 475 patients.[11] In fact, when the margin index was greater than 5, we found that 97% of patients had no residual disease in the re-excision specimen. The index cut-off value can be raised or lowered to alter the sensitivity and specificity. For example, when the margin index was greater than 20, none of our patients had residual disease in the re-excision specimen. Although this concept seems simple, we believe that it represents a mathematical quantification of what all breast cancer surgeons already do intuitively. In other words, we tend to take a little more tissue at the margins as the tumor size increases, to heighten our chances of achieving a clear margin. Revesz and Khan discourage the use of simplistic models that suggest wider margins equate to lower risks of in-breast recurrence.[10] We agree that the solution is not simply bigger overall margins, but we do believe that the tumor size is of paramount importance when determining the optimum margin width. However, we acknowledge that one criticism of the margin index is that it does not account for the multitude of patient and tumor characteristics that have also been shown to be predictive of residual disease following BCT.[12-15] The only factor that reliably predicted the presence or absence of residual disease in the re-excision specimen in our cohort was the derived margin index; no other factor was an independent predictor of residual disease on multivariate
analysis in our study. We were not very surprised by this finding, given the widely variable reports in
the literature regarding the impact of such factors.
We also believe that a randomized trial would allow us to clearly delineate the reliability of the
margin index in predicting residual disease, not only for patients with stage I-II invasive cancers but
also for those with stage 0 DCIS. We recently reported that the margin index is not a reliable method
for the prediction of residual disease after attempted BCT with close margins in patients with DCIS
only.[16] This study was limited by a small sample size (N = 48) and the complexity of accurately
determining DCIS size and margin status retrospectively in pathologic specimens. Given these
limitations, we believe that use of the margin index may prove significant in a larger, prospectively
studied population of patients with DCIS.
The review by Revesz and Khan[10] illustrates the need for better techniques for determining the
optimum margin following attempted BCT. We believe that the margin index is a simple and reliable
method with the potential to increase the accuracy of the planned resection specimen, decrease the
need for re-excision in patients with close margins, obviate multiple surgical resections, and
decrease surgical costs. This requires validation in a prospective, randomized fashion with a uniform
approach toward the pathological evaluation of margins. It may not be a "sexy" trial, but the
thousands of women who undergo re-excision every year should inspire enthusiasm for it.

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