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Optimal Selection of Breast Cancer Patients for Elimination of Surgery Following Neoadjuvant Systemic Therapy

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Reply

This is an exciting time in the management of invasive breast cancer and the logical next step as we continue to reduce and refine the extent of surgical procedures toward the paradigm of elimination of surgery among patients who demonstrate exceptional response and no evidence of histopathological disease following neoadjuvant systemic therapy. The key here is the optimal, accurate, and safe selection of patients who have had a complete pathologic response. If there is no detectable residual disease among patients who will be receiving radiotherapy, the benefit of surgery would appear to be very low and potentially unnecessary. This new field requires meticulous and precise image-guided biopsy of the tumor bed that was performed in the MD Anderson feasibility trial.¹ In the University of Heidelberg analysis,² the only way that the investigators were able to improve the negative predictive value and false-negative rates was to go back retrospectively to examine the biopsy specimens for histologic evidence of the representativeness of the sampling by determining the presence of therapy changes including stromal fibrosis and associated

inflammation. Overall, no evidence of the target lesion on histopathologic review was seen in 24% of cases in the Heidelberg series. Another significant issue in the Heidelberg series was that the imaging for the final biopsy following systemic therapy was performed only by ultrasound guidance in the surgical suite, and there was no clear delineation of residual disease extent by imaging (including residual calcifications) before the final biopsy. This is not optimal given that mammography and magnetic resonance imaging (MRI) may be appropriate methods for sampling of the tumor bed in the radiologic suite, if ultrasound significantly underestimates the residual tumor extent. Using the MD Anderson approach to optimize selection with extensive image guided biopsy, 100% of the cases demonstrated residual carcinoma, atypia, the clip, and or therapy changes consistent with representative sampling of the tumor bed. In fact, both false-negative cases utilizing vacuum-assisted core biopsy in our study clearly demonstrated therapy-related changes in the biopsy specimens, but these cases were unique in that they only had 4 or 6 core biopsies taken while the median for the rest of the study was 12. This led to our conclusions that to safely test the elimination of surgery in our ongoing trial, we insisted upon a minimum of 12 cores of the residual region of prior carcinoma in and around the area of the marker clip.³

We agree that potential inclusion of HER2-negative/estrogen receptor (ER)-positive cases in further feasibility biopsy trials and elimination of surgery studies are indicated as patients in the subtypes might also be candidates. The decision to not include these cases in our initial and subsequent studies was made after retrospective review of all HER2-negative/ER-positive cases from our database, even when only including cases with extremely high Ki-67 and lower ER-expression, revealed that approximately 5% of these tumors had a pathologic complete response for invasive and in situ disease. Thus, only 1 in 20 cases might become eligible for no surgery. Additional information related to parameters associated with these tumor subtypes will be derived from the recently opened US multi-center cooperative group NRG BR005 biopsy feasibility study.⁴

The current MD Anderson trial, “Eliminating breast cancer surgery in exceptional responders with neoadjuvant systemic therapy,” is in fact a phase 2 prospective clinical trial and not randomized. We agree that well-designed future studies will establish greater confidence and scientific merit when additional phase 2 and randomized trials are performed in this groundbreaking new arena for breast cancer patients. In the interim, a good place to move the needle toward safe, minimally invasive surgery, is with well-designed phase 2 prospective clinical trials utilizing evidence-based data from preliminary feasibility studies where there is meticulous collaboration among key multidisciplinary specialties.

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