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ASO PERSPECTIVES

Moving Forward with Omission of Breast Cancer Surgery Following Neoadjuvant Systemic Therapy

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It is hard to imagine how a surgical procedure could benefit patients with a pathologic complete response (pCR) in the breast and the lymph nodes when all disease has already been eradicated by neoadjuvant systemic therapy (NST). The main obstacle facing the field is how to accurately predict which patients will have eradication of disease without performing the actual surgical procedure. We have come to a time when we now know that a population of patients with invasive breast cancer will have a 50% or more chance of having a pCR in the breast and nodes following NST.[1] Clearly, we also know that these same patients with triple-negative or human epidermal growth factor receptor 2 (HER2)-positive disease derive a disease-free and overall survival benefit with the use of these targeted systemic therapies. The use of subtype-specific NST in these cases serves many roles, including reducing the extent of therapeutic surgery, and may also even allow for some carefully selected patients to someday avoid surgery entirely.[2–6]

The concept of attempting to omit surgical therapy among patients with invasive breast cancer who have had a clinical complete response is not new.[1] Many of the early groundbreaking studies in the field were initiated for locally advanced breast cancer to avoid radical breast surgery after NST among patients who are going to receive radiotherapy. The fundamental question being asked at that time before selective and targeted therapies were developed, tested, and standardized was: Does surgery add anything to local control or disease-free and overall survival in these types of patients? That was a time before improved regimens were available, and investigators wanted to ensure that performing radical surgical procedures was not futile in controlling disease and thus potentially only palliative. Subsequent studies looking at patients who appeared to have a complete clinical response and omitting breast surgery in earlier disease were hindered by limited use of rudimentary breast imaging techniques and before our understanding of the molecular subtypes most likely to be associated with an exceptional response.[1] Even with improved modern breast imaging, current breast imaging technologies lack diagnostic accuracy in selecting patients for omission of a surgical procedure that would otherwise provide no benefit if the NST had eradicated the disease.

Conceptual introduction, testing, and implementation of new mechanisms to limit surgery have often taken several decades, with refinements coming only much later secondary to the introduction of improved technologies. Historically, breast-conserving therapy was conceptually and initially introduced about 100 years ago, but several key single-center retrospective and prospective larger trials first had to be performed in order to implement the procedures with relative success.[7] It is fascinating to note that the six landmark randomized trials demonstrating the efficacy of breast-conserving therapy versus more radical surgery begun and were completed even before the introduction of modern breast imaging to select the optimal patients for this surgical procedure and before the standardized routine techniques used to assess margin status.[7] These examples better help us to gage how far we have

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come and to generate a greater appreciation of where the future may take us toward elimination of breast cancer surgery in optimally selected patients.

Up to about 35 years ago, almost all patients went to the operating room for a lump, bump, or otherwise for diagnosis of cancer or benign disease. Essentially all diagnostic biopsies were surgical until image-guided stereotactic needle biopsy was introduced to select patients who need to undergo therapeutic surgery (as opposed to the then-standard "diagnostic" breast surgery) for malignant disease.[8] Utilizing the same conceptual framework, several studies have recently been undertaken and published testing the hypothesis that image-guided biopsy can accurately identify patients with a pCR and subsequently where surgery might be safely tested and omitted on clinical trials.[9–16] As neoadjuvant systemic therapy may eradicate disease preferentially in the invasive versus in situ component or result in a more scattered pattern of disease eradication in luminal breast cancers, it was not clear whether image-guided vacuum-assisted core biopsy (VACB) could accurately predict residual disease after NST.[17,18] Published false-negative results on utilizing VACB following NST to detect a pCR/residual disease have been variable, ranging from 5% in the MD Anderson Cancer Center study[12] to 37% in the Netherlands Cancer Institute study[14] and 40% in the Seoul National University College of Medicine study.[13] The success of this procedure is highly dependent on super selection of appropriate patients and meticulous standardized techniques. False-negative rates have been shown to decrease to the 0–5% range with better selection of patients with triple-negative or HER2-positive unicentric disease initially T1 or T2 in size, ensuring appropriate imaging directed biopsy with representative tissue sampling, use of multimodality breast imaging, consistent minimum numbers of core biopsy sampling with clip removal, standardized histopathologic processing and examination of tissue, and larger-gauge VACB use.[13,16,19]

In one of the most recent studies in this field, the multinational exceptional responder investigator group introduced the concept of intelligent VACB to identify exceptional responders with a pCR to NST.[20] The investigators called this technique "intelligent" because, like artificial intelligence, it utilizes a multivariable risk model using machine learning techniques to analyze conventional biopsy results alongside patient, imaging, and tumor information. In the most recent analysis published by the German group in the *Journal of Clinical Oncology*, Pfob et al. trained, tested, and validated a machine learning algorithm using patient, imaging, tumor, and biopsy variables to detect residual cancer after NST (ypT1or in situ or ypN1) before surgery.[21] In that study, they utilized data from 318 women with cT1–3, cN0 or1, HER2-positive, triple-negative, or high-proliferative luminal B-like breast cancer who underwent VACB before surgery (ClinicalTrials.gov identifier NCT02948764, RESPONDER trial). To train and test the algorithm, they used an externally validated dataset from an independent trial (ClinicalTrials.gov identifier NCT02575612). They compared findings with the histopathologic evaluation of the surgical specimen, with the main outcomes being the false-negative rate (FNR) and specificity. Using this approach, the intelligent VACB showed an FNR of 0.0–5.2% and a specificity of 37.5–40.0%, with an area under the curve of 0.91–0.92 to detect residual cancer in the breast and lymph nodes after NST. While a very low FNR is key to the success of eliminating surgery after NST, the authors note that the rate of identified patients without residual cancer is also important. Moving forward, they expect that the specificity of intelligent VACB of only 40% can be improved with more experience in performing and evaluating these types of biopsies after NST. In this study, it is important to note that about 53% of the VACB in the external validation set were deemed to be unrepresentative of the lesion by the biopsying physician and approximately 24% to be unrepresentative by the pathologist reviewing the case. Nevertheless, using the intelligent VACB technique, residual cancer after NST was shown to be reliably excluded.

The MD Anderson multicenter trial for eliminating breast cancer surgery in exceptional responders to neoadjuvant systemic therapy based on image-guided VACB demonstration of a pCR enrolled its first patient in 2017 and has reached accrual (ClinicalTrials.gov identifier NCT02945579).

Patients on this study had initial T1/T2 N0/1 unicentric triple-negative or HER2-positive disease. Following NST, the residual lesion had to be less than 2 cm and a minimum of 12 9G image-guided VACB were needed to be obtained with removal of the clip and placement of another clip for identification of the area if residual disease was found and for radiation planning. The tissue was meticulously processed and histologically analyzed using standardized protocols. Patients with residual disease had standard surgery followed by radiotherapy, and those with a pCR did not have breast surgery. Although still early, there have not been any local regional or distant recurrences in patients on the study, and planned first protocol directed analyses/publication of the trial results are projected in the next few months. Many clinicians and patients have also asked: Why not omit radiation in patients with a documented pCR? That is, keep the standard surgery but deescalate the radiotherapy. This hypothesis is also now being investigated at MD Anderson in a separate clinical trial cohort of patients.

The ultimate form of breast conservation is exclusion of any breast surgery following NST, and this field is advancing rapidly. It is expected that newer targeted and immunooncology-based systemic therapies will further increase the pCR rates in breast cancer and other solid organ malignancies. Similarly with respect to the development and testing of breast conservation surgery and sentinel node biopsy/targeted axillary dissection, there will be a need for several other prospective clinical trials in this arena to demonstrate the safety and efficacy of eliminating breast surgery for patients with invasive breast cancer following NST.

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