A Comparison of Near-Infrared Diffuse Optical Imaging and 18F-FDG PET/CT for the Early Prediction of Breast Cancer Response to Neoadjuvant Chemotherapy

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In recent years, neoadjuvant chemotherapy (NAC) before surgery has become the standard of care for patients who present with advanced breast cancers or multiple lesions, in order to control distant metastases as well as reduce breast tumor size before surgery (*1*). The remaining medical oncology challenge is that most patients (>80%) have a positive response to NAC, yet many of these women (~40%–70%) fail to reach a complete pathologic response (pCR) and, therefore, do not realize the gains in disease-free survival experienced by pCR (*1*). Thus, imaging breast cancers during the course of NAC offers scientific and clinical value in terms of understanding the biologic changes that occur in complete versus incomplete responses. It also affords the opportunity to develop image-based prognostic biomarkers that could lead to superior individualized treatment and patient care.

On the basis of changes in tumor volume, conventional cancer imaging (x-ray mammography, ultrasound, and MRI) has been used to assess response to NAC. Usually at least 3 cycles of treatment are required before reaching the determination (*2*). Functional imaging techniques such as dynamic contrast-enhanced MRI (*3*) and PET (*1*) have been used to monitor cancer response to NAC. The results of the study by Ueda et al. (*4*) in this issue of *The Journal of Nuclear Medicine* show that the SUV$_{max}$ of 18F-FDG PET/CT can predict pCR after the second cycle of NAC, with an area under the curve of 0.9. However, the major weaknesses of using this functional imaging biomarker is that it is influenced by the histologic subtype, and so it is dependent on the type of NAC used. In addition, the concerns about contrast agent use and subsequent cost (*1*) reduce the potential routine clinical adoption of these approaches.

When compared with other clinical imaging modalities, near-infrared diffuse optical spectroscopic imaging (DOSI) has substantial advantages for efficient and effective longitudinal monitoring because it does not involve contrast injection. An additional advantage is the ability of DOSI to capture biophysical changes in tissue occurring in the vascular as well as intra- and extra-cellular matrix compartments, with moderate cost. During the past decade, DOSI has progressed from relatively simple laboratory instruments to complex clinical systems capable of imaging the breast during individual-investigator, single-institution clinical trials and the first multicenter trial of the technology, sponsored by the American College of Radiology Imaging Network (ACRIN 6691) (*5–7*). In studies published to date, DOSI changes in tumor total hemoglobin, blood oxygen saturation, and water content appear to be present after the first cycle of NAC, before morphologic (size) alterations occur that can be detected by structural imaging (*5–7*).

The DOSI imaging system used in the study by Ueda et al. has significant technical limitations as compared with other systems used in clinical trials. The technology of time-resolved spectroscopic analysis with a time-correlated single-photon counting does provide one of the largest dynamic ranges possible for absorption and scattering distribution in tissue. Yet the source and detector separation determines the tissue depth of accurate assessment of the tumor optical property, and in this case tissue depth was 3 cm (*8*). Although this subsurface scanning system successfully assessed the tumor response to NAC, the measurement volume is clearly dominated by immediately subsurface tissues (depth, ~1.5 cm), and so the accuracy of the assessment is highly dependent on the depth and the size of the tumor. In addition, the limited spectral range of just a 64-nm wavelength spread from data at just 3 wavelengths (760, 800, and 834 nm) reduces the assessment accuracy due to the crosstalk of the chromospheres. As the authors point out in the "Discussion" section, "The entire tumor blood volume cannot be observed using this approach," which may be the key factor that only an accuracy of 56.6% has been achieved. Although this type of DOSI is most sensitive to lesions near the surface of the skin, the tomographic version of DOSI has demonstrated (*9*) that it can successfully characterize lesions throughout the entire breast volume. Instead of using the fixed source-detector separation to characterize the subsurface breast vasculature, the tomographic system uses 16 fiber bundles around the breast, so it can assess a cross section of the breast vasculature changes. In addition, the enhanced spectral coverage through the frequency domain and continuous wave measurements at 9 wavelengths have demonstrated the better quantification accuracy of water content and decreased the spectral coupling

between estimates of different tissue constituents. A clinical study using the tomographic DOSI showed that the AUC to differentiate pCR from non-pCR patients was 1.0, based on the percentage change in tumor to hemoglobin within the first cycle of treatment. In addition, this study showed the first clinical evidence that tumor total hemoglobin estimated from diffuse optical spectroscopic images differentiates women with locally advanced breast cancer who have a pCR with NAC from those who do not with predictive significance based on image data acquired before the initiation of therapy (6).

Although optical imaging can be a noninvasive and relatively cost-effective modality for longitudinal monitoring of tumor response to NAC, it may be more efficient and accurate to combine the results with other existing clinical modalities to maximize prediction accuracy of the tumor response to NAC before and in the early stage of treatment. The Ueda et al. (5) study showed that the prediction accuracy of combined optical and ^{18}F-FDG PET/CT imaging was 93.7%, whereas that of ^{18}F-FDG PET/CT and DOSI alone were 82.6% and 56.6%, respectively. However, in contrast, our earlier study that combined the results of the pretreatment tomographic DOSI and dynamic contrast-enhanced MRI also indicated that the accuracy for predicting pCR could be improved to 100%, from that of 89% (of DOSI) or 82% (of dynamic contrast-enhanced MRI), respectively, using a system with more wavelengths and significantly better depth of penetration through the breast (10).

Beyond the value to clinical care assessment, the combined-modality imaging approaches with higher specificity to tumor response should be considered as a way to dramatically accelerate trials that seek to optimize NAC combination regimes, using imaging endpoints to more quickly assess outcome in randomized clinical trials. This could reduce the number of patients required and the length of time needed to follow them, using a validated imaging surrogate as an outcome measure.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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