

**INVITED PERSPECTIVE FOR:**

**“Near-infrared diffuse optical imaging for early prediction of breast cancer response to neoadjuvant chemotherapy: a comparative study using FDG-PET/CT”**

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In recent years, neoadjuvant chemotherapy (NAC) prior to 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 prior to 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 pathological 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 biological 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.

Based on changes in tumor volume, conventional cancer imaging (X-ray mammography, ultrasound and MRI) has been used to assess response to NAC. Usually at least three cycles of treatment is 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 Ueda, et al, show that maximum standardized uptake values ( $SUV_{max}$ ) of FDG-PET/CT can predict pCR after the second cycle of NAC with the areas under the curve (AUC) of 0.9. However, the major weaknesses of using this functional imaging biomarker, is that it is influenced by the histological 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 to 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. So is moderate-cost, with the ability to capture biophysical changes in tissue occurring in the vascular as well as intra- and extra-cellular matrix compartments. 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 multi-center trial of the technology, sponsored by the American College of Radiology Imaging Network, ACRIN 6691[4-6]. In studies published to date, DOSI changes in tumor total hemoglobin ( $Hb_T$ ), blood oxygen saturation ( $StO_2$ ) and water

content ( $H_2O$ ), appear to be present after the first cycle of NAC, before morphological (size) alterations occur that can be detected by structural imaging. [4-6]

The DOSI imaging system used in the Ueda et al study has significant technical limitations as compared to other systems used in clinical trials. The technology of time-resolved spectroscopic (TRS) analysis with a time-correlated single-photon counting (TCSPC), 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 was 3 cm. [7] While this sub-surface scanning system successfully assessed the tumor response to NAC, the measurement volume is clearly dominated by immediately sub-surface tissues (depth~1.5cm) , and so the accuracy of the assessment is highly dependent upon the depth and the size of the tumor. In addition, the limited spectral range of just a 64nm wavelength spread from data at just three wavelengths (760, 800 834nm), 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. Whereas this type of DOSI is most sensitive to lesions near the surface of the skin, the tomographic version of DOSI have been demonstrated [8] that it can successfully characterize lesions throughout the entire breast volume. Instead of using the fixed source-detector separation to characterize the sub-surface 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 CW measurements at 9 wavelengths has 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 shown the AUC to differentiate pCR from non-pCR patients is 1.0, based on the percentage change in tumor to hemoglobin within the first cycle of treatment. In addition, this study shown the first clinical evidence that tumor total hemoglobin estimated from DOST 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. [5]

While optical imaging can be a non-invasive and relatively cost-effective modality for longitudinal monitoring of tumor response to NAC, it may 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 study showed that the prediction accuracy of a combined optical and FDG-PET/CT was 93.7%, while that of FDG-PET/CT and DOSI alone are 82.6% and 56.6%, respectively. However in contrast, our earlier study that combined the results of the ***pretreatment*** tomographic DOSI and DCE-MRI also indicated that the accuracy for predicting pCR could be improved to 100%, from that of 89% (of DOSI) or 82% (of DCE-MRI),

respectively, using a system with more wavelengths and significantly better depth of penetration through the breast. [9]

It worth pointing out that 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, by 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, by using a validated imaging surrogate as an outcome measure.

## DISCLOSURE

No potential conflict interest relevant to this article.

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