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Breast cancer: Assessing response to neoadjuvant chemotherapy by using usguided near-infrared tomography

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## Assessing Response to Neoadjuvant Chemotherapy by Using US-guided Near-Infrared Tomography

In patients with higher than stage-two breast cancer who need chemotherapy in the course of treatment, the benefit of receiving neoadjuvant chemotherapy (NAC) before surgery is well established. The goal of NAC is to achieve pathologic complete response (pCR), which is proven to be associated with favorable prognosis. Many cytotoxic chemotherapeutic agents and targeted agents can be used to treat breast cancer, and with the promising research in this field, more agents may gradually become available. One great advantage of NAC is to allow *in vivo* assessment of tumor response for timely adjustment of regimens, not only to avoid unnecessary toxicity but also to allow the effective regimen to work sooner. Therefore, it will be very helpful to find reliable early response indicator that can guide the change of regimens. The clinical exam and standard clinical breast imaging modalities--mammography, US, and magnetic resonance imaging (MRI)--are relying on the change of tumor size, and they cannot provide a reliable early response indicator before tumor shrinkage occurs. Many MRI-based studies have tried to investigate whether other parameters, e.g. vascular parameters measured by dynamic contrast enhanced MRI (DCE-MRI), proliferation marker measured by MR spectroscopy (MRS), or cellular density marker measured by diffusion weighted imaging (DWI), can be used as early marker for predicting final response, yet with inconclusive findings.

Over the last 2 decades, a substantial research effort has been devoted to develop optical imaging technology for the breast, aiming to provide an alternative or complementary imaging modality. The advantage over existing modalities include no radiation, not limited by breast density, relatively low-cost, and portable as a bedside device that can be applied to image the patient frequently. Among all optical imaging systems, the ultrasound (US)-guided diffuse optical tomography (DOT) developed by Dr. Zhu's group is a unique system that can provide anatomic information as well as tomographic optical images, not limited by the depth of the lesion. The system has been successfully applied in a large clinical study to test its diagnostic performance in differentiating between malignant lesions (early Tis-T1 stage and more advanced T2-T4 stage) and benign lesions (proliferating and non-proliferating), and yield very interesting results. The maximum total hemoglobin (tHb) within the lesion was measured. It was found that by choosing a tHb cutoff value of 82  $\mu\text{mol/L}$ , the sensitivity and specificity were 92% and 93%, respectively, for Tis-T1 tumors; and 75% and 93%, respectively, for T2-T4 tumors. For more advanced tumors, although the sensitivity is not high; yet when complementary optical imaging is used to rule out possible malignancy, a high specificity that can aid in avoiding unnecessary biopsy is the most important.

In the present article, Zhu and colleagues used a refined system with 4 wavelengths (740-, 780-, 808-, and 830-nm) to measure oxygenated Hb (oxyHb), deoxygenated Hb (de-oxyHb), and tHb in tumors undergoing NAC at different times before and after 1, 2, and 3 cycles of treatment.

Several articles published earlier have demonstrated the potential role of optical imaging to distinguish good from poor responders, but all of them were pilot studies only analyzing a very small number of subjects.(1-6) The present study enrolled a total of 35 patients, with 32 complete

datasets available for analysis. Only Hb parameters (including tHb, oxyHb, and de-oxyHb) were considered. The maximum value within the tumor was measured, and the averaged value from volumetric zone exceeding 50% of the maximum value was calculated. The baseline values and the percent changes at different cycles during the treatment were used to differentiate tumors showing a good vs. a poor response. With the improved NAC regimens, most tumors will respond to some extent, and the traditional way of separating them into responders and non-responders may not be applicable any more. Although pathologic complete response (pCR) is known to be associated with favorable prognosis, yet tumors that show a very close to complete response are also known to have a good prognosis, and in this study they are combined as a good response group. The authors used the Miller-Payne grade system based on cellularity of the residual disease to separate tumors into two response groups, MP1-3: <90% change in cellularity, and MP4-5: >90% change in cellularity and pCR. The results showed a significantly higher tHb in MP4-5 group than in MP1-3 group, suggesting that tumors with a higher vascularity (more hemoglobin) have a better response- presumably through a better delivery of therapeutic agents into the tumors. Compared to the baseline value, the percentage changes in tHb after 1 cycle, 2 cycles, and 3 cycles were all greater in the MP4-5 group than in the MP1-3 groups. Since the system has an integrated US, the tumor size measured by US was also used to differentiate between the two response groups. Of the 32 patients, the US tumor size could only be measured in 21 patients, and the size difference between these two groups was not significant after 1 or 2 cycles, then it became significant after 3 cycles of treatment. The results suggest that US may not be applied to evaluate tumor sizes in some cases, also that the early size change cannot be used to predict final treatment outcome. MRI is known as the best imaging modality for evaluating the extent of residual disease, but since most patients only had one MRI done after completing NAC

treatment, it is not possible to compare the predictive value of MRI size with other parameters measured by the US-DOT system.

Although Zhu and colleagues present very encouraging results, processing optical imaging data to generate tHb maps requires sophisticated experience and, thus, is operator dependent. The region of interest (ROI) used in the reconstruction was based on the segmentation of the lesion seen on the pretreatment US examination, and the same ROI was used for processing all data sets obtained at different treatment cycles while the tumor was shrinking. The reason for using the same ROI throughout the treatment period was not explained. A possible reason was to minimize variations coming from the use of different ROI's. However, it is necessary to evaluate how the reconstructed parameter is dependent on the choice of ROI, particularly when the tumor is shrinking substantially. For those cases whose tumor size cannot be measured on US, tumor size determined on MRI was used in the reconstruction. In general, it will be interesting for authors to investigate how the obtained results are dependent on the data processing methods, as done by Jiang and colleagues,(4) as well as the dependence on the operators who perform the optical imaging acquisition and the data analysis. For this imaging system to become clinically feasible, a more automated procedure that minimizes operator variations needs to be developed. In a recently published optical imaging study by Ueda and colleagues,(7) they analyzed 41 NAC patients and reported that none of the Hb parameters (tHb, oxyHb, de-oxyHb) measured at baseline before treatment showed a significant difference between the pCR and non-pCR groups, and that only the oxygen saturation showed a significant difference (higher in pCR than in non-pCR, also explained by delivery of therapeutic agents, less in hypoxic tumors). Many reasons may account for different findings that were reported in different studies, but overall, the

variation of optical imaging parameters measured by different imaging systems using different data analysis procedures may be a main reason and that needs to be further investigated.

One great advantage of optical imaging in NAC management is the capability for frequent measurements, even within hours or days after administration of agents to assess the flare response. In a recent study published by Roblyer and colleagues,(6) the authors reported a statistically significant increase, flare, of oxyHb measured on day 1 after the first infusion in partial responders (n = 11) and pCR patients (n = 8), whereas non-responders (n = 5) showed no flare and a subsequent decrease in oxyHb on day 1. Whether the initial flare on day 1 can serve as a reliable indicator of response, at least for partial response, needs to be further evaluated. If it is proven true, optical imaging can provide very unique information that cannot be measured by any other breast imaging modality, and that will have a high impact in improving the management for NAC patients- with the ultimate goal of reaching pCR with the least toxicity.

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