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Imaging Breast Cancer Chemotherapy Response with Light:

Commentary on Soliman et al., p. 2605

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Abstract

Diffuse optical spectroscopy (DOS), which is used to image tumor metabolic response to neoadjuvant chemotherapy (NAC), shows large changes in tumor functional parameters with significant reductions in oxy- and deoxyhemoglobin for responders versus nonresponders. Although investigational, DOS may provide a cost-effective, risk-free method for optimizing NAC drug and dosing strategies for individual patients.

In the current issue of *Clinical Cancer Research*, Soliman and colleagues describe the use of an investigational functional imaging technology, diffuse optical spectroscopy (DOS), for determining the response of breast cancer patients to presurgical neoadjuvant chemotherapy (NAC; ref. 1).

NAC is increasingly prescribed for women with locally advanced or inoperable breast cancers in order to reduce primary tumor size, minimize metastatic impact, and improve breast tissue conservation during surgery. Pathological complete response can be a surrogate for eradicating micrometastases and strongly correlates with survival (2). Thus, there is considerable interest in developing imaging methods to monitor and predict chemotherapy efficacy, both prior to and as early as possible during the course of treatment. These methods would potentially give oncologists new tools for individualized cancer therapy that could be used to optimize the type, dose, and duration of treatment as well as determine the best time for surgery.

DOS is based on advanced near infrared (NIR) photonic technologies. Conventional NIR methods, first introduced for breast cancer detection more than 80 years ago, were not successful because these qualitative approaches did not account for image distortions from multiple light scattering. Unlike X-ray trajectories in soft tissue, NIR photon transport is dominated by intense multiple scattering, which is similar to the problem of seeing an airplane in the middle of a dense cloud. Over the past decade laser-based DOS technology has progressed rapidly, primarily in academic laboratories, and instruments are now available that are capable of separating light absorption from scattering using principles of time and frequency-domain photon migration (3). As a result, it is now possible to image breast tumors with multi-wavelength laser light and form tomographic images of tissue absorbers, e.g., oxyhemoglobin (HbO₂), deoxyhemoglobin (Hb), water, and lipid, as well as cellular-matrix structures, e.g., tissue scatter power (see Fig. 1). These endogenous

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Disclosure of Potential Conflicts of Interest

B.J. Tromberg, A.E. Cerussi, co-inventors of patents related to DOS technology; patents owed by the University of California.

components have been shown to be sensitive to cellular metabolism, angiogenesis, edema, hypoxia, and necrosis; processes that can change significantly with the growth and regression of tumors. DOS is therefore being explored as an approach for breast cancer detection, particularly in mammographically dense subjects, and for providing feedback in NAC (3–8).

Since the first case report of DOS measurements of NAC response in 2004 (4), several groups have shown that quantitative DOS imaging can be used to monitor tumor metabolic changes during treatment (5–8). Although most of these studies have single or small patient numbers, a clear consensus has emerged that diffuse optical methods can provide unique information on treatment efficacy within days and weeks of the first infusion. These studies all employ quantitative optical endpoints that strongly correlate with and, in some cases, predict pathologic response.

In the current issue of *Clinical Cancer Research*, Soliman and colleagues report the first multi-time-point DOS study on a group of 10 patients. Measurements were obtained just prior to treatment and at 1 week, 4 weeks, 8 weeks, and at the conclusion of NAC. One of their goals was to determine the time-dependence of tumor response in order to identify the earliest possible point for separating responders from nonresponders. The mean patient age was 50 years, and mean maximum tumor size was 7.7 ± 2.4 cm. A unique feature of this study was that all patients had aggressive disease and received a variety of neoadjuvant treatment regimens. These regimens were chosen to test the broad applicability of DOS, regardless of tumor cell death mechanism. In addition, the DOS technology employed is a commercial platform (Softscan, ART) that uses four NIR, ultrafast pulsed lasers and is comparable to state-of-the-art systems found in academic laboratories.

A single pathologist interpreted all specimens and categorized five subjects as displaying good response and four subjects as minimal or nonresponders. No subjects had a pathological complete response. When these clinical endpoints were compared with optical endpoints, the responders were clearly separable from nonresponders by treatment week 4. Changes were dramatic, with drops from baseline of 67.6%, 58.9%, 51.2%, and 52.6% in Hb, HbO₂, percent water, and scatter power. Corresponding drops in the four nonresponders were 17.7%, 18.0%, 15.4%, and 12.6%. Differences between responders and nonresponders were statistically significant for all parameters ($P < 0.05$) except for percent water, which approached significance ($P = 0.0598$). These results are comparable to a recent 11-patient study in which separation between responders and nonresponders was achieved within 1 week of therapy (6). A key difference was that all patients in the 11-patient study (6) received identical Adriamycin/Cytosin (AC) treatments, whereas Soliman and colleagues followed 10 patients who had much greater diversity in both disease extent and treatment strategy.

These results provide further support for the idea that quantitative functional imaging endpoints can be used to longitudinally monitor and predict clinical treatment response, regardless of the chemotherapeutic strategy, agent, or dose. Patterns of DOS response include an overall decrease in tumor hemoglobin due to drug-induced alterations in tumor cell metabolism and blood vessel density. More specifically, the oxyhemoglobin decrease reflects a diminished vascular supply, whereas the deoxyhemoglobin drop is representative of a reduction in tumor tissue oxygen consumption that occurs with cell death. Water and scatter power are also sensitive to cell death, and their reduction reflects a progressive loss of cellularity and edema. These changes were clearly observed at week 4, and continued to evolve until the completion of therapy despite the use of a variety of treatment regimens, including the targeted agent trastuzumab (herceptin), cytotoxic compounds, and chemoradiotherapy.

Functional measurements of tumors from contrast-enhanced (CE) MRI (9), magnetic resonance spectroscopy (10), and positron emission tomography (PET; refs. 11, 12) have also been applied to NAC monitoring and have shown substantial improvement over conventional anatomic imaging and clinical palpation. However, these techniques are relatively expensive and comparatively difficult for advanced stage cancer patients, particularly if frequent measurements are desired. In addition, chemotherapies that target and disrupt tumor vasculature may be more challenging to assess using methods that rely on adequate delivery of exogenous contrast, such as CE-MRI and PET.

Although DOS parameters lack the specificity of gene-or protein-based biomarkers, optical imaging measures endogenous biochemical composition that provides information on downstream physiology and metabolism. An important practical advantage of DOS is that it uses risk-free NIR light and can be used frequently in unconventional settings such as a doctor's office or clinic. Validated DOS endpoints for assessing efficacy early in treatment will allow clinicians to tailor therapeutic regimens for maximizing response, minimizing toxicity, and increasing overall survival. This may be particularly important for assessing the effects of targeted compounds, such as anti-angiogenics, in which success may be critically sensitive to the timing of combination strategies with conventional cytotoxic therapies.

Strategies for further improvements in DOS contrast, sensitivity, and specificity are an active area of research. Broadly, these approaches include advanced spectroscopic analysis tools, coregistration with conventional radiologic methods, quantitative image reconstruction, and combining DOS with molecular-targeted exogenous contrast agents. In addition to technical advances, DOS requires further validation and testing in a rigorous multi-center environment in order to determine standard practices and procedures for NAC monitoring. Nevertheless, the report by Soliman and colleagues in the current issue of *Clinical Cancer Research* is an important step in establishing DOS sensitivity to tumor metabolism and highlighting its potential as a functional imaging technology. Because of its low barrier-to-access, DOS can potentially create new opportunities for patients to receive personalized treatment, and for physicians to gain insight into mechanisms of cancer appearance and response to therapy.

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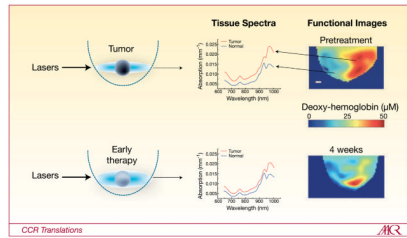


Fig. 1.

DOS reveals patient response to NAC. Ultrafast pulsed or modulated lasers spanning a range of NIR wavelengths are launched into tissue. Multiple light scattering causes the light to spread out (diffuse) in space and time because of the large number of paths that photons can take between the source and detector. Precise measurements of the time for light pulses to propagate through the tissue allow quantitative determination of tissue absorption spectra (middle panels) and scattering spectra (not shown). Elevated tumor levels of oxyhemoglobin, deoxyhemoglobin, and water, and reduced tumor levels of lipid are determined from tissue absorption spectra. When this information is acquired using multiple source and detector combinations, tomographic images of breast tissue biochemical composition (e.g., deoxyhemoglobin) are constructed. Pretreatment tumor and normal tissue deoxyhemoglobin for 10 patients in Soliman et al. (1) averaged $10.23 \pm 2.47 \mu\text{mol/L}$ and $6.41 \pm 1.30 \mu\text{mol/L}$, respectively. After 4 weeks of NAC, 5 responders dropped 67.6% (standard deviation = 20.8), whereas 4 nonresponders had a mean drop of 17.7% (standard deviation = 9.8). Significant differences in functional parameters allow separation of pathologic responders from nonresponders early in treatment. Images reproduced from Soliman et al. with permission (1).