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Diffuse Optical Technology: A Portable and Simple Method for Noninvasive Tissue Pathophysiology

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In this article, noninvasive diffuse optical technologies are briefly introduced for the future application for lymphoma diagnosis/treatment monitoring. Diffuse optical technologies measure tumor physiology in deep tissues in vivo, and have demonstrated its efficacy for tumor detection and chemotherapy response monitoring in breast cancer.^{1–8} Light has been used to see tumors in thick human tissues for more than 80 years.⁹ Based on the same fundamental idea that the interaction between the light and tumor provides its pathology related information, biomedical optics technology has advanced to be more quantitative and more accurate so that it can be used for tumor diagnosis and treatment monitoring.

One of the most commonly used optical imaging technologies is bright-field microscopy, which is generally employed to see histologically stained cells in a small piece of excised tissue. Although its role is invaluable in tumor diagnosis, the excised tissues lose significant amount of information that can be only preserved in embedded tissues. Diffuse optical technology, a relatively new technology to clinicians, provides pathophysiological changes in thick in vivo tissues noninvasively.^{3–5,10–12} Diffuse optical technology uses near-infrared (NIR) light and a mathematical model that describes transport of photons in a diffusion regime; photons are modeled to behave as stochastic particles that travel in proportion to a gradient, similar to diffusion of molecules (Fig. 1).¹³ In the NIR, there is a therapeutic window (approximately from 600–1000 nm) where absorption of water and hemoglobin is lower than visual and infrared wavelength range (Fig. 2).^{14,15} As a result, more photons survive to be detected after interacting with the tissues, making the diffuse optics suitable for deep tissue measurement.

When photons travel in thick tissues (> 1–2 mm), they scatter against the tissue components and dominate over absorption. The photons are scattered more often (typically after traveling approximately 20 μm) than absorbed (after approximately 10 cm) in tissues. The scattering reflects size and density of intracellular structures such as nuclei¹⁶ and mitochondria,¹⁷ and extracellular matrix, such as collagen.¹⁸ Dynamic motion of scatters, such as red blood cells, are also measured by a blood flow index using diffuse correlation spectroscopy (DCS).¹⁴

Most tissue components have their unique absorption profile in the NIR, and their concentration or molecular binding state can be quantified when the effect of multiscattering is cancelled using the mathematical diffusion model and modulated light either in time, frequency, or spatial domain.^{19–21} The scattering in thick tissues is measured first using a photon migration model, a diffusion approximation to the radiative transfer equation, and the Mie theory (Fig. 3).^{22,23} Then, the power-law fit scattering spectrum is subtracted from the overall light measurement, which leaves only an absorption spectrum.^{6,19} Most frequently obtained physiologic information from the tissue absorption spectrum are tissue oxygenation and concentrations of oxy-, deoxy- and total hemoglobin, lipid, and water. Also, the molecular binding state of water and deep tissue temperature are measured using quantitative water absorption spectra.^{5,6,19} In breast cancer clinical studies, the tumor tissues have been detected with high sensitivity (98%) and specificity (90%) by measuring total hemoglobin concentration ratio of tumor to normal tissues.¹⁰ Optically measured tissue bound water index (BWI) showed a high correlation ($R = -0.96$, $P = .002$) with histopathologically assessed tumor grades.⁵ Diffuse optical spectroscopy (DOS) can also predict pathologic response to neoadjuvant chemotherapy (NAC) in a few days, even on day 1 into the therapy by measuring tissue physiologic changes noninvasively.^{24,25} A recent publication also suggested that the combination of DOS measured deep tissue temperature and tissue oxygenation may provide apoptotic status of cells during neoadjuvant chemotherapy.¹¹ The DOS measured spectra can be mapped into a 2-dimensional spectroscopic image as shown in Fig. 4, and this method was named diffuse optical spectroscopic imaging (DOSI) by the Tromberg group at the University of California, Irvine.¹³

For lymphoma measurement, a hand-held probe with optical fibers coupled to a source and detector can be placed on the lesion area directly. With a hand-held probe, DOS/DCS can detect photons reflected back after traveling a tissue volume at depths up to several centimeters. Thus, with this set-up, DOS/DCS can only measure palpable lymphoma. However, the instrument can be brought into the examination room and does not require special shielding. Furthermore, it is capable of providing tumor pathophysiology in real time so that the physician can use the information during the patient's visit. DOS/DCS is also harmless (no risk of ionizing radiation) and does not need injection of any contrast agents or radioactive material. Instead, it can quantify endogenous biochemical composition, which can consequently provide the pathologic state of the tumor. For example, the diffuse optics measured hemoglobin concentration and blood flow can communicate vascular structure changes that occur in response to chemotherapy or molecularly targeted therapy.^{24,26,27} Alteration of tissue structural composition during the therapy can be monitored by measuring lipid concentration variations using DOS.¹ Water concentration variation may reflect edema, inflammation, or interstitial fluid pressure changes.^{5,28} Tissue water binding state measurement can communicate the invasiveness of the tumor that may appear as an overall extracellular composition change that also alters the association of macromolecules with water.^{5,29} Noninvasive tissue temperature measurement provides enthalpy variation in the tumor due to mitochondrial changes, such as uncoupling of their membranes as a part of apoptotic process.¹¹ Additionally, tissue oxygen measurement communicates if the tumor is under hypoxia, which may predict bad prognosis.³⁰ Lastly, antibodies, drugs, or biologic agents tagged with a US Food and Drug Administration (FDA)-approved NIR dye (such as indocyanine green) could be injected into the body to be measured with diffuse optical technologies to study certain signal pathways in tissues in vivo.

Ongoing clinical studies using diffuse optical technologies include differentiating various types of non-Hodgkin's lymphoma (diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia/small lymphocytic lymphoma) and monitoring tumor response during chemotherapy/molecularly targeted therapy. During the

author's clinical studies using diffuse optical technologies, patients volunteered cheerfully due to its noninvasiveness and simplicity. Although the diffuse optical technologies have just begun to be used for lymphoma measurement, they hold a great potential for providing tumor pathophysiological information conveniently in the examination room, which might help physicians to optimize the therapy for each patient during the visit.

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Fig. 1.

(A) Photons come out from the source on the surface of the skin then undergo scattering and absorption while interacting with the tissues. (B) A simulated photon sensitivity map. The photons survived after going through multiple absorption, and scattering steps in a banana-shaped region are detected, also on the surface of the skin a few centimeters away from the source.

Fig. 2.
Extinction coefficient spectra of major tissue chromophores measured in the near infrared.

Fig. 3. Reduced scattering $\mu_s'(\lambda)$ (*top*) and absorption $\mu_a(\lambda)$ (*bottom*) coefficients spectra from in vivo human tissues. The reduced scattering spectra is fit to a power law according to the Mie theory then subtracted from a reflectance spectrum to obtain the absorption spectrum shown below.

Fig. 4. An example of a diffuse optical spectroscopic imaging (DOSI) image (*left*). TOI stands for tissue optical index, which is a combined optical index of multiplication of deoxy-hemoglobin and water divided by lipid concentrations. The shown image is a spectroscopic map of 50 × 55 mm diameter infiltrating ductal carcinoma tumor in a 43-year-old subject. (*Right*) Near infrared absorption and reduced scattering spectra obtained by DOSI shown for specific regions of the image.