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Diffuse Optical Tomography & Spectroscopy in Breast Cancer Characterization & Therapy Monitoring at UPENN

(Invited Paper)

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***Abstract*—In this paper, I will provide a broad review of breast cancer research conducted at the University of Pennsylvania and collaborative work with other institution. Our group led by Dr. Arjun G. Yodh has been actively exploring functional and physiological information available via the diffuse optical technique and investigate its use in the area of *in vivo* breast cancer detection, diagnosis, and therapy monitoring. In particular, the recent advances in malignant and benign lesion differentiation from 3D diffuse optical tomography, 3D fluorescence diffuse optical tomography using Indocyanine Green injection, and neoadjuvant chemotherapy monitoring with diffuse correlation spectroscopy will be presented.**

I. Introduction

Diffuse optical technique is emerging with potential to be translated to clinic as a complementary imaging modality for existing modalities or a treatment monitoring device for breast cancer management. The technique derive unique functional/physiological information such as oxy- and deoxy-hemoglobins, water and lipid concentrations, tissue scattering and blood flow non-invasively. In addition, the tumor contrast can be enhanced with use of contrast agent injection, as well as future prospect of detecting tumor-specific optical probes. Diffuse optical technique uses non-ionizing radiation which enables frequent application easily, and is based on technology which is inexpensive, easily scalable in terms of time or space (e.g. become portable).

In our laboratory, we have been actively exploring functional and physiological information available via the diffuse optical technique and investigate its use in the area of *in vivo* breast cancer detection, diagnosis, and therapy monitoring. The most recent results from *in vivo* breast imaging and spectroscopy will be presented: (1) Characterization of tumor-to-normal optical contrast from 3D diffuse optical tomography (DOT) guided by MRI/radiology report, (2) 3D Fluorescence DOT with extrinsic contrast agent injection, and (3) Neoadjuvant (i.e. pre-surgical) chemotherapy monitoring with diffuse optical spectroscopy (DOS) and diffuse correlation spectroscopy (DCS). The following sections summarize these results.

II. Differentiation of Benign and Malignant Lesions by DOT [1]

Using a parallel-plane DOT system with an emphasis on high number of source and detector positions for reliable three-dimensional image reconstruction [2], we reconstructed three-dimensional oxy-hemoglobin (HbO_2), deoxy-hemoglobin (Hb) and scattering (μ_s') images of 51 tumors. Total hemoglobin concentration (THC) and blood oxygen saturation (StO_2) were extracted based on the Hb and HbO_2. With guidance of dynamic-contrast enhanced MRI and/or radiology report, we defined the tumor regions in these images. Figure 1 shows representative images of a malignant lesion and a benign lesion. Tumor contrast for each parameter was estimated as ratio between averaged value over tumor region and averaged value over surrounding normal tissue (e.g. $rTHC =< THC(tumor) > / < THC(normal) >$). Optical index ($OI$) was defined as $rTHC \times r\mu_s'(786nm)/rStO_2$. Tumor contrasts ($rTHC, r\mu_s', rStO_2, rHb, rHbO_2$ and OI) among three groups were compared: benign group (N=10), malignant group with no prior biopsy (N=20), and biopsied malignant group (N=21). Malignant cancers showed statistically significant higher total hemoglobin concentration, scattering, and oxy-hemoglobin concentration ($P < 0.05$) compared to normal tissue. Furthermore, malignant lesions exhibited a two-fold average increase in an optical index derived from the endogenous optical parameters. Benign tumors did not show statistical significance in all of the tumor-to-normal ratios. Areas under the ROC curve of $rTHC$, $r\mu_s$, $rHbO_2$ and OI were between 0.90 and 0.99, suggesting a good discriminatory power between malignant and benign lesions.

III. 3D Fluorescence Diffuse Optical Tomography [3]

Injection of optical contrast agent can enhance tumor-to-normal contrast either through absorption or fluorescence, and may provide additional information such as vessel leakiness. In particular, we have reconstructed three-dimensional images of in vivo human breast cancer based on fluorescence diffuse optical tomography (FDOT). In our protocol, the fluorophore

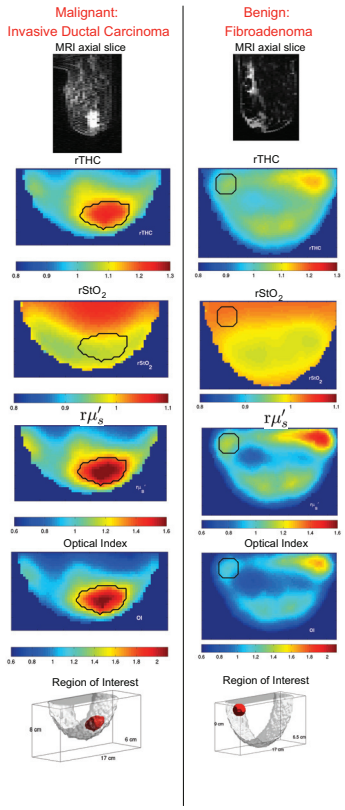

Fig. 1. Malignant vs Benign lesions. MRI axial slice, DOT axial slices of $rTHC, rStO_2, r\mu_s'$, Optical index, and a 3D image of region of interest are shown for malignant (left) and benign lesions (right). The black line indicates the tumor region.

Indocyanine Green (ICG) was injected intravenously. Fluorescence excitation and detection were accomplished in the soft-compression, parallel-plane, transmission geometry using laser sources at 786 nm and spectrally filtered CCD detection. Phantom and in vivo studies confirm the signals are due to ICG fluorescence, rather than tissue autofluorescence and excitation light leakage. Fluorescence images of breast tumors were in good agreement with those of MRI with Gd contrast agent, and with diffuse optical tomography based on endogenous contrast. Tumor-to-normal tissue contrast based on ICG fluorescence was two-to-four-fold higher than contrast based on hemoglobin and scattering parameters (N=3). In Figure 2, one example of FDOT for a 52-year-old post-menopausal female diagnosed with invasive ductal carcinoma is shown. In the region that is confirmed to be the tumor region by the Gd uptake and radiology report, the reconstructed THC, μ_s' and ICG concentrations are higher and StO_2 is somewhat lower than the surrounding tissue. Furthermore, we observed that ICG concentration exhibited up to 4-fold contrast, whereas $rTHC$ and $r\mu_s'$ contrasts were only 1.3 and 1.5. In total the measurements demonstrate that FDOT of breast cancer is feasible and promising.

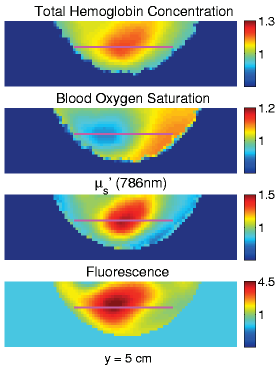

Fig. 2. Image slices of rTHC, $rStO_2$, $r\mu_s'$ and relative Indocyanine Green concentration based on fluorescence are display [3].

IV. Neoadjuvant Chemotherapy Monitoring with Additional Blood Flow Parameter [4]

Recently, the feasibility of applying diffuse optical technique to neoadjuvant chemotherapy monitoring has been demonstrated [5]–[8]. Still, additional parameters sensitive to tumor metabolism and micro-environment would enhance monitoring capability of diffuse optical technique. One of such additional parameters is blood flow accessible by diffuse correlation spectroscopy (DCS) [9]. To explore the potential for early treatment monitoring, we combined diffuse optical spectroscopy and diffuse correlation spectroscopy to measure a breast cancer patient on a daily basis before and within one week after the first chemotherapy cycle [4]. Significant changes in tumor/normal contrast of Hb, HbO_2, lipid concentration and blood flow were observed within the first week as shown in Figure 3.

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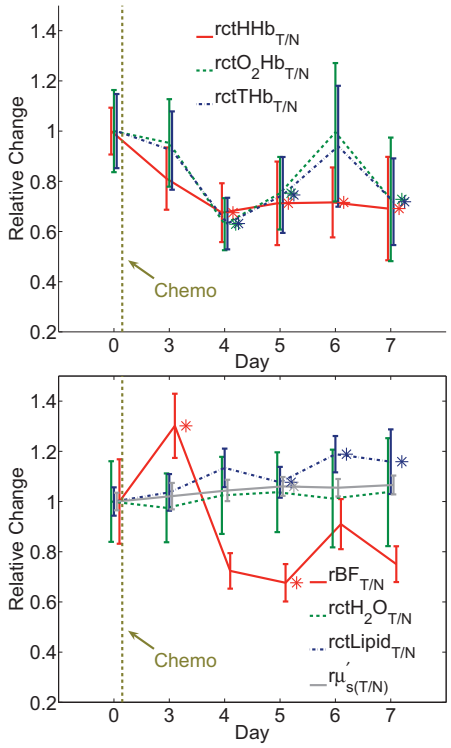

Fig. 3. Daily monitoring of in vivo breast cancer patient undergoing neoadjuvant chemotherapy. Measurements were done before treatment, 3,4,5,6,7 days after the first chemotherapy cycle. Tumor/normal contrast of each time point was normalized with the pre-treatment values. ctHHb: deoxy-hemoglobin concentration, ctO_2Hb: oxy-hemoglobin, ctTHb: total hemoglobin concentration, BF: blood flow, ctH_2O: water concentration, ctLipid: lipid concentration [4].

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