Diffuse Optical Tomography Imaging System for Monitoring Breast Tumor Response to Neoadjuvant Chemotherapy

Jacqueline Gunther¹, Molly Flexman¹, Emerson Lim², Hyun Keol Kim³, Mindy Brown⁴, Dawn Hershman⁴, Andreas H. Hielscher¹,3,6

¹Department of Biomedical Engineering, Columbia University, 351 Engineering Terrace, 500 West 120th St., New York, NY 10027
²Department of Internal Medicine, Columbia University, 177 Fort Washington Ave., New York, NY 10032
³Department of Radiology, Columbia University, 630 West 168th St., New York, NY 10032
⁴Herbert Irving Comprehensive Cancer Center, 161 Fort Washington, Avenue, New York, NY 10032
⁵Department of Epidemiology – Mailman School of Public Health, 722 West 168th Street, New York, NY 10032
⁶Department of Electrical Engineering, Columbia University, 1300 S.W. Mudd, 500 West 120th Street, New York, NY 10027

E-mail: jeg2181@columbia.edu, ahh2004@columbia.edu

Abstract: We developed a diffuse optical tomography (DOT) system that can be used to perform longitudinal studies of breast tumors during neoadjuvant chemotherapy. Preliminary results demonstrate that DOT can image early tumor vascular response to treatment.

©2011 Optical Society of America

OCIS codes: (170.3880) Medical and Biological Imaging; (170.6960) Tomography

1. Introduction

Neoadjuvant chemotherapy (NACT) is used to treat women with locally advanced breast cancer. The goal of this therapy is to reduce the tumor size before breast conserving surgery is performed. Furthermore, patients who achieve a pathologic complete response (pCR), have a statistically significant improved overall survival. However, only 13-35% of patients achieve a pCR [1,2], and it is currently not possible to predict who will respond to NACT. If response to treatment can be detected early in the course of NACT, non-responders can potentially be saved months of ineffective and toxic therapies and switched to an alternate treatment [1].

Physical exam, mammogram, ultrasound (US), and magnetic resonance imaging (MRI) have been used to measure tumor size, but are insensitive to the early tumor response of NACT. Furthermore, all of these methods show low correlation to the post-surgery pathological assessment of response. In a study of 41 patients, Schott et al. demonstrated that physical exams, mammograms, US, and MRI had sensitivities of only 50, 50, 25, and 25% when detecting pCR [3].

Diffuse optical tomography (DOT) is a noninvasive, nonionizing, 3D imaging modality that uses the scattering and absorption properties of near-infrared light propagation through tissue to determine the concentrations of oxy-hemoglobin, deoxy-hemoglobin, water, and fat. DOT is sensitive to hemoglobin concentrations and hence it is capable of characterizing changes in vascular structures and blood perfusion in tissue. Since one of the first physiological effects of NACT is a change in vascular structure, we hypothesize that DOT can be used to predict tumor response at early time points [4-8]. To test our hypothesis we have developed a DOT breast imaging system that is capable of acquiring 3D transmission data simultaneously from both breasts and can measure spatially dependent concentrations of oxy- [HbO₂], deoxy- [Hb], and total hemoglobin [HbT]. Here we report on the progression of one breast-cancer patient during the first four weeks of NACT.

2. Methods

2.1 Instrument and Image Reconstruction

For the current study, we further developed and optimized a continuous-wave DOT digital breast imager previously described in ref. [9]. The system uses 64 source fibers and 128 detector fibers to image both breasts simultaneously. The fibers are arranged in four rings per breast that can be adjusted in the coronal plane to compensate for different breast sizes. The largest ring can be removed completely for smaller breast sizes. The source and detector fibers are arranged in an alternating pattern of source-detector-source-detector. Each source is collocated with a detector fiber so that 64 fibers (or 36 fibers if only 3 rings are used) come in direct contact with each breast.

Each source fiber is sequentially illuminated with 765 nm and 827 nm followed by 808 nm and 905 nm, and all detector fibers collect the resulting scattered and transmitted light. The source fiber illumination takes 7 ms to switch between positions, which allows for dynamic imaging with a frame rate of 1.7 Hz. The current system has a large dynamic range (~160 dB) and can obtain sensitive measurements of oxy-hemoglobin and deoxy-hemoglobin concentrations, as well as scattering or water and lipid content.
Approximately 1,000 frames were collected from the patient at each imaging time point. Fifty frames from the patient measurement were selected, and the average and standard deviation for each source-detector measurement was computed. Any source-detector pairs with a signal to noise ratio (SNR) below 15 dB were excluded from the reconstruction to reduce noise artifacts. Three-dimensional reconstructions were obtained using a partial-differential-equation (PDE)-constrained multispectral imaging method, which uses the diffusion approximation as a model for light propagation [9,10]. The code directly reconstructs the chromophore concentrations (in this case [Hb], [HbO₂], and scattering) without first calculating the spatial distribution of the absorption coefficient. In our experience, this direct approach has proven to be more stable and reliable.

The 3D reconstruction was performed on a finite element mesh with ~46,000 voxels, with more, smaller voxels placed near the sources and detectors. A unique mesh was created for each patient using the known geometry of the rings that hold the sources and detectors. Since the rings for the patient interface are adjustable in the coronal direction, the position of the sources and detectors remained fixed in x and y, but varies in the z direction depending on the patient’s breast size. Therefore, a different mesh must be created for each patient according to the coronal translation of the rings. The mesh was extended 2 cm from the largest ring to account for the chest wall. For the case study presented here, 3 rings were used. The mesh shape and reconstruction parameters were kept constant for each time point (Fig. 1).

![Figure 1. The 3D mesh used for breast measurement reconstructions. Three rings were used for the patient, and each ring can be seen in areas of smaller voxel sizes, where the source and detector fibers are located.](BW3A.6.pdf)

2.2 Experimental Protocol
The study was approved by the Columbia University Institutional Review Board and is HIPPA compliant. All subjects gave written consent to participate. The study includes patients over the age of 18 who have been recently diagnosed with stage II to IIC invasive breast cancer and are to undergo NACT involving 12 cycles of weekly paclitaxel followed by 4 cycles of doxorubicin and cyclophosphamide (AC) given every two weeks with growth-factor support. Baseline MRI, mammogram, and DOT imaging were done prior to therapy. For the case study shown here, DOT imaging was performed at baseline (prior to cycle 1 of paclitaxel), week 2 of paclitaxel treatment (prior to cycle 3), and week 4 of paclitaxel treatment (prior to cycle 5). After imaging the patient, a reference measurement was taken immediately afterward with 20% intralipid (Baxter) and 1% India Ink (Higgins) solution diluted and mixed to yield similar optical properties to breast tissue. The pathological response to NACT will not be known until after surgery, but the interim response was assessed with bi-weekly palpation measurements.

3. Results
A 47 year-old premenopausal Caucasian woman underwent NACT for poorly differentiated invasive ductal carcinoma at New York-Presbyterian Hospital. Her baseline BMI was 27.3. She obtained bilateral US and MRI images that confirmed that there was a mass in the right breast with approximate dimensions of 1.4 cm, and 2.3x1.5x2.0 cm determined by each imaging modality, respectively. Preliminary reconstructions show that there is a region of high [HbO₂] and [Hb] compared to the surrounding tissue for baseline images taken before the first cycle of NACT (Fig. 2a). After the first two cycles of paclitaxel (Fig. 2b) were administered the tumor could no longer be visualized. Similarly, the tumor was not apparent before cycle 5 of paclitaxel (Fig. 2c). This correlated with a decrease in tumor size as assessed by palpation measurements at baseline, week2, and week4, which were 3.1x2.8 cm, 2.2x2.0 cm and 2.11x1.8 cm, respectively. The DOT visualization of this patient’s rapid response to treatment agrees with previously published results where the tumor response to NACT can be seen via optical imaging within days of administering the therapy [4-8].
4. Discussion and Conclusion
We have developed instrumentation and methods to image breast cancer patients and create 3D images for a longitudinal study. Our current techniques can extract [HbO2], [Hb] and [HbT] for use in studying the vascularization of advanced breast tumors.

We have observed the early hemoglobin-dependent effects for a single patient throughout the first 4 weeks of NACT. Our preliminary findings show a tumor in the right breast with elevated [HbO2] and [Hb] compared to the surrounding healthy tissue. By week 2 of paclitaxel there is a drop in [HbO2] and [Hb] in both breasts. A decrease in palpation measurements implies that the patient is responding to NACT. Overall, our early results correspond to the weekly physical examinations as well as other reports that have demonstrated early tumor response to NACT. We are continuing to follow this patient throughout the remainder of her NACT and the pathological response to treatment will be determined after surgery. In addition, we currently have 8 patients enrolled in our study and plan to correlate the 3D optical measurements with the pathological response, as well as baseline and pre-surgery MRI images.

This work was supported in part by the Witten Family Fund. Molly Flexman is supported in part by the Natural Sciences and Engineering Research Council of Canada (NSERC).

5. References

![Figure 2](BW3A.6.pdf) Sagittal slices taken through the tumor region of oxy-hemoglobin (top) and deoxy-hemoglobin concentration (bottom) for the right, tumor-bearing, breast at (a) baseline (prior to treatment), (b) week 2 (before cycle 3 of paclitaxel), and (c) week 4 (before cycle 5 of paclitaxel).