Predicting Tumor Response in Breast Cancer Patients Using Diffuse Optical Tomography

Jacqueline E. Gunther1, Emerson Lim2, Hyun Keol Kim1,3, Molly Flexman1, Susan Refice4, Mindy Brown4, Kevin Kalinsky2,4, Dawn Hershman2,4,5, 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 have developed a diffuse optical tomography imaging system to track breast tumor progression in patients undergoing neoadjuvant chemotherapy. Preliminary results have shown that tumor response can be predicted by the second week of treatment.

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

1. Introduction

Neoadjuvant chemotherapy (NACT) is a treatment given to patients with locally advance breast cancer. The goal of the treatment is to decrease size of the tumor before surgery in order to preserve breast tissue. Tumors which demonstrate a pathologic complete response (pCR) associate with improved disease-free survival. However, pCR is achieve in as low as 10% of patients.1-3 Furthermore, NACT is and expensive and toxic treatment that takes a few months to completely administer. If the tumor response could be predicted beforehand, the patient would be relieved of any unnecessary discomfort due to treatment and their outcome could be improved.1,2 Current imaging modalities cannot predict which patients will have a pCR to treatment. Physical exam, mammogram, ultrasound (US), and magnetic resonance imaging (MRI) are insensitive to tumor response, and are mostly used to measure tumor size, which may not correlate with pCR.3 Previous studies using diffuse optical imaging have shown that tumor response can be predicted within a few weeks or days of treatment initiation.4-7

Diffuse optical tomography (DOT) is a non-invasive imaging technology that can be used to determine concentrations of oxy-hemoglobin, deoxy-hemoglobin, and water percentage in tissue. We found in earlier studies and in our preliminary results that these parameters can be used to detect breast tumors.8-10 Here, we have developed a DOT imaging system for monitoring the response of breast cancer patients to NACT. The goal was to predict response to anti-cancer therapy early, so as to develop personalized treatments and optimize the patient’s results.

2. Methods

2.1 Instrumentation and Image Reconstruction

Our current DOT system is a continuous wave dynamic imaging system that emits four wavelengths (Fig. 1). Two of wavelengths (765 and 808 nm) are modulated at 5 kHz, and the other wavelengths (827 and 905 nm) are modulated at 7 kHz. Modulated light sources were used to implement a lock-in detection system to reduce noise. There are a total of 64 sources and 128 detectors (32 sources and 64 detectors per breast).8,9 The frame rate for imaging is about 1.7 Hz when all sources and detectors are used. The fast frame rate allows for the observation of hemodynamic changes inside the breast. The patient interface is comprised of two sets of four concentric rings that hold the source and detector fibers in place, and can be adjusted to accommodate different breast sizes. Each set of the rings holds a total of 64 fibers in which all fibers are detectors, but half are collocated sources. Fibers are placed in a source-detector-source-detector pattern around each ring.9

Meshes for image reconstructions were created using the geometry of the rings and known locations of each source and detector. Therefore, each subject has their own individualized mesh for accurate image reconstructions. Images were created using a PDE-constrained multispectral imaging method that uses the diffusion approximation as a model for light propagation.11 Quantification of images was accomplished by looking at a region of interest and averaging the DOT parameters over a 1 cm sphere.
2.2 Patient Imaging
Women over the age of 18 who were diagnosed with stage II or stage III breast cancer and were to undergo NACT were eligible for the study. Each patient receives twelve weekly treatments of Taxane followed by four cycles of Doxorubicin and Cyclophosphamide (AC) given every other week. There are six DOT imaging time points: baseline, cycle 3 and 5 of Taxane, before cycle 1 and 2 of AC, and before surgery (Fig 1). Imaging time points were selected early on for each treatment to analyze early effects.

![Figure 1. Diffuse optical tomography breast imaging system.]

Figure 2. Timeline for subject treatment and DOT imaging.

Once the subject imaging was complete a reference solution was also imaged. The reference solution was composed of 20% Intralipid and 1% India Ink, which was diluted to have similar optical properties as breast tissue. By using a reference solution of known optical properties, static 3D images of oxy-hemoglobin concentration ([HbO₂]), deoxy-hemoglobin concentration ([Hb]), and water percentage can be made. Total hemoglobin ([HbT]) was calculated using the summation of [HbO₂] and [Hb]. Response to treatment was based on histology performed after surgery. The study was approved by the Columbia University IRB and is HIPPA compliant.

3. Results
In figure 2 we show the sagittal slices of 3D images that were taken for one subject that had a pCR and another that had a partial response (PR) to treatment. The patient that had a pCR was a 47 year old pre-menopausal woman who was diagnosed with poorly differentiated ductal carcinoma. The initial size of the tumor base on MRI imaging was 2.3 x 1.5 x 2 cm. This subject shows an immediate drop by week two for [HbO₂], [Hb], [HbT], and percent water. Each parameter continued to drop until the tumor was undetectable in the optical images.
As for the subject with the PR, she was a 46 year old post-menopausal woman with poorly differentiated ductal carcinoma. The initial size of the tumor was 2.2 x 2.0 x 1.5 cm based on MRI imaging. DOT imaging shows that there is a gradual decrease over time. Post-surgical histology indicated that she still had a 1.4 cm mass.

Figure 3. Sagittal slices of 3D DOT images for tumor bearing breast for subject with a pathological complete response (left) and a partial response (right).

To date we have completed studies with 10 subjects. Two subjects had a pCR (n=2), while 6 subjects did not have a pathological complete response (non-pCR). Two subjects were excluded from the study due to insufficient data and too much movement during imaging. The average age of all subjects was 45 with an average BMI of 31.3. Two of the subjects were post-menopausal. As shown in figure 3, subjects with a pCR show a decrease at week 2 of 31.9% ± 0.51% and 23.8%±4.56% for [HbO2] and [Hb], respectively. At week 2, subjects with a non-pCR demonstrate a less drastic change to treatment showing a percent change of -1.70% ± 10.2% for [HbO2] and 0.34% ± 9.4% for [Hb]. The percent change for [HbT] for pCR subjects and non-pCR subjects correspondingly was -29.9%± 0.55% and -1.34 % ± 12.1%. As for water the percent change for pCP patients was -6.87% ± 2.45% and for non-pCR subjects was -0.19 % ± 1.84%. All four parameters show statistical significance with [HbO2] and percent water showing the greatest significance (p<0.01).
4. Discussion and Conclusion

Currently, 24 subjects have been recruited into the study with 10 subjects that have finished their treatment and have received surgery. One of the limitations of the current analysis has been the low number of subjects that have finished treatment and had a pCR. However, the number of patients in our study that have a pCR was about 25%, which corresponds to similar numbers in the literature. Yet, our preliminary analysis has shown promising results, with significant difference in percent change of [HbO2], [Hb], [HbT], and water percentage at the week 2 time point.

Our results correspond with previous studies where pCR patients show a drop in [HbT] after the first few weeks of treatment. However, in other studies, subjects received different chemotherapy regimens or have taken additional medication. In the current study we look at subjects that have all undergone the same treatment, throughout the length of their therapy.

Currently patients that have had non-pCR have been placed into one category. However, the degree to which the tumor responded can be categorized pathologically. The non-pCR patients show a great variability between the degrees of response, which most likely corresponds to the higher variability we have seen for this group. Yet, correlating the tumor grade with the parameters that we have recently study could lead to more significant findings.

In addition to the current parameters being examined, our system is capable of looking at other markers that might be useful when determining tumor response, such as oxygen saturation or scattering. Furthermore, since our imaging system is capable of capturing dynamic information, it is possible to analyze the dynamic effects of tumors throughout treatment, such as hemodynamic changes that occur when a subject holds her breath.

DOT is a non-invasive, non-ionizing imaging technique that is capable of tumor monitoring in breast cancer patients. Preliminary results show that [HbO2], [Hb], [HbT], and percent water can be promising biomarkers for determining tumor response to NACT. This information is directly linked to tissue vascularity, and hence DOT appears well suited to monitor the response to anti-angiogenic therapy. Initial results are promising and if further confirmed DOT could become a valuable imaging modality for monitoring treatment response in neoadjuvant therapy and other diseases.

5. References


