Using Diffuse Optical Tomography to Monitor Tumor Response to Neoadjuvant Chemotherapy in Breast Cancer Patients
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ABSTRACT

Breast cancer patients often undergo neoadjuvant chemotherapy to reduce the size of the tumor before surgery. Tumors which demonstrate a pathologic complete response associate with improved disease-free survival; however, as low as 10% of patients may achieve this status. The goal is to predict response to anti-cancer therapy early, so as to develop personalized treatments and optimize the patient’s results. Previous studies have shown that tumor response can be predicted within a few days of treatment initiation. We have developed a diffuse optical tomography (DOT) imaging system for monitoring the response of breast cancer patients to neoadjuvant chemotherapy.

Our breast imaging system is a continuous wave system that uses four wavelengths in the near-infrared spectrum (765 nm, 808 nm, 827 nm, and 905 nm). Both breasts are imaged simultaneously with a total of 64 sources and 128 detectors. Three dimensional reconstructions for oxy-hemoglobin concentration ([HbO2]), deoxy-hemoglobin ([Hb]) concentrations, and water are performed using a PDE-constrained multispectral imaging method that uses the diffusion approximation as a model for light propagation.

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, week 3 and 5 of Paclitaxel, before cycle 1 and 2 of AC, and before surgery. Preliminary results show that there is statistical significance for the percent change of [HbO2], [Hb], [HbT], and percent water at week 2 from the baseline between patients with a pathologic response to chemotherapy.

Keywords: Diffuse Optical Tomography, Breast Imaging, Neoadjuvant Chemotherapy

1. INTRODUCTION

Breast cancer causes about 40,000 deaths a year, with one in eight women being diagnosed with the disease in their lifetime. However, from 1975 to 2000 the mortality rate of breast cancer in America was reduced by 24% due to screening and adjuvant chemotherapies [1, 2]. One treatment option has been neoadjuvant chemotherapy (NACT), which is administered before the patient undergoes surgery to reduce the size of the tumor and conserve breast tissue. Yet only about 10-30% of patients achieve a pathological complete response (pCR) to treatment [3-5]. With an increasingly wide range of chemotherapy agents available, the timing and selection of certain agents can be better optimized based on patient response. If tumor response can be predicted at the beginning of NACT then treatment could be changed for patients that are not showing a response and improve their outcome [3-4]. Studies have shown that tumor response can be predicted within a few days of initial treatment using diffuse optical imaging techniques [6-10].
Most current imaging modalities are not capable of predicting pCR in patients with breast cancer. Physical exam and imaging modalities such as ultrasound, magnetic resonance imaging are mostly used to determine tumor size, which may not correlate to pCR. Schott et. al demonstrated in a study using post-treatment measurements or images for 41 patients physical exams mammograms, US, and MRI had low sensitivities when determining pCR. Dynamic contrast enhancement MRI (DCE-MRI) has been able to predict tumor response as show by Johansen et. al. However, DCE-MRI involves injecting patients with contrast agents and MRI examinations are costly, ranging in the thousands of dollars per examination [3, 11]

Diffuse optical tomography (DOT) is a non-invasive, non-ionizing imaging technique that offers the ability for longitudinal imaging of tumor progression. DOT works by illuminating the breast with near-infrared light at multiple positions on a tissue surface and measuring the transmitted and reflected light intensities. Three-dimensional maps of oxy-hemoglobin and deoxy- hemoglobin concentrations, water, and lipid can be created using iterative reconstructive methods [12-13]. These parameters have been shown to be highly sensitive to tumor response to treatment [13].

We have developed a diffuse optical tomography (DOT) imaging system for monitoring the response of breast cancer patients to neoadjuvant chemotherapy. 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

The current system is a dynamic continuous wave DOT imaging system that can image both breasts simultaneously and uses four near-infrared wavelengths (Figure 1A). Two of the wavelengths are modulated at 5 kHz (765 nm and 808 nm) and the other two wavelengths (827 nm and 905 nm) are modulated at 7 kHz for the lock-in detection, which essentially reduces the noise of the acquired signal. The system uses 32 sources and 64 detectors for each breast (64 sources and 128 detectors total). Depending on the number of sources and detectors used, the frame rate of the system is between 1.7 Hz – 111 Hz. Since the detected signals vary due to the large geometry of the breast, the system has a large dynamic range of about 120 dB [12].
2.2 Patient Interface
The patient interface is made up of two sets of four concentric rings. From the smallest to largest ring there are 8, 12, 16, and 28 fibers (Figure 1B). The fibers are placed in a detector-source-detector-source pattern in which each source is also a detector. The height of each ring can be changed to accommodate different breast sizes and the largest ring can even be removed for smaller breasts.

2.3 Patient Treatment and Imaging
The height of the translating ring was adjusted for each individual patient before imaging to assure maximum coverage of the fibers. Then the patient was placed in the probe and imaged for approximately two minutes. After each imaging session, a reference solution was imaged. The reference solution was comprised of 20% Intralipid and 1% India Ink mixed with water to mimic the optical properties of breast tissue. By using a reference solution with known optical properties, absolute concentrations of oxy-hemoglobin ([HbO2]) and deoxy-hemoglobin ([Hb]), as well as, water percentage (%water) could be calculated. Total hemoglobin ([HbT]) was calculated using the summation of [HbO2] and [Hb].

2.4 Image Reconstruction and Image Analysis
Meshes containing 60,000 to 70,000 elements were created using the known geometry and height of the translating rings. Therefore, each subject had a different mesh corresponding to the individual’s ring settings. The mesh was extended past the largest ring by 2 cm to account for the effects of the chest wall.

Fifty frames from the patient and reference solution measurement were averaged to be used for reconstruction. Source detector pairs that had an SNR less than 10 dB were removed from prior to reconstruction. Images were reconstructed using a PDE-constrained multispectral imaging method that uses the diffusion approximation as a light propagation model [14].

A region of interest was selected according to the known tumor location. Reconstructed DOT values were averaged over a 1 cm sphere and computed for each time point. Average percent change from baseline imaging of [HbO2], [Hb], and %water for patients that had a pathological complete response (pCR) and did not have a pathological complete response (non-pCR). Statistical significance was found using a student t-test between pCR and non-pCR groups.

2.5 Clinical Study
The study was approved by the Columbia University Institutional Review Board and is HIPPA compliant. All subjects gave written consent to participate. Subjects over the age of 18 and were diagnosed with either stage II or IIC invasive breast cancer were recruited for the study. Each subject received the same NACT treatment involving 12 cycles of taxane administered weekly and 4 cycles of doxorubicin and cyclophosphamide (AC) administered biweekly. Baseline imaging was acquired the day before the first taxane treatment and then before the third and fifth cycle of taxane (Figure 2). Also, imaging occurred before the first and second cycles of AC and once before surgery. Time points were concentrated near the beginning of treatment to assess early response. Pathological response is based on biopsy results after each subject had surgery. Currently 10 patients have completed the study with two having a pCR and nine that had a non-pCR.

Two subjects were excluded from the study due to too much movement during imaging and insufficient data.

![Figure 2. Timeline for patient treatment and DOT imaging.](http://proceedings.spiedigitallibrary.org/ on 07/23/2013 Terms of Use: http://spiedl.org/terms)
3. RESULTS

3.1 Case Study 1: Pathological Complete Response

In Figure 3 we show the sagittal slices of 3D images were taken for a subject that had a pCR. The subject was a 47 year old pre-menopausal woman who was diagnosed with poorly differentiated ductal carcinoma (Fig 3). The initial size of the tumor base on MRI imaging was 2.3 x 1.5 x 2 cm (not shown). This subject showed an immediate drop by week two for [HbO2], [Hb], [HbT], and %water. However, % water shows the least amount of change by the pre-surgical time point, but each parameter continues to drop until the tumor is undetectable on optical imaging.

![Figure 3 Mammogram image before receiving treatment in the axial plane (A). PET-CT image of subject with mass in the right breast (B). Percent change from the baseline image of the absolute concentrations in the affected breast in the region of interest over the course of treatment (C). Static optical images of sagittal slices of the tumor-bearing breast of one subject that had a pathological complete response (D).](image)

3.2 Case Study 2: Partial Response

Another subject was a 46 year old post-menopausal woman with poorly differentiated ductal carcinoma who had a partial response (PR) to treatment. 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 (Fig 4). Post-surgical histology revealed that she still had a 1.4 cm tumor. Therefore, even though this subject did not experience a pCR, the tumor did shrink over the course of treatment. DOT imaging shows that at the week two time point that there was very little change from the baseline imaging. There was however, a slow decrease for all the parameters over time. The water percentage showed the least amount of change over time. The subject did exhibit a clinical response where the mass was not palpable by the first cycle of AC treatment.
Figure 4 Mammogram image before receiving treatment in the sagittal plane (A). PET-CT image of subject with mass in the left breast (B). Percent change from the baseline image of the absolute concentrations in the affected breast in the region of interest over the course of treatment (C). Static optical images of sagittal slices of the tumor-bearing breast of one subject that had a partial response (D).

4. DISCUSSION

DOT offers an efficient means of tumor monitoring that other imaging modalities do not offer. Unlike X-ray mammography, DOT uses non-ionizing radiation which allows for multiple imaging sessions to be scheduled within a short amount of time. Also, NACT monitoring using DOT would be an affordable option compared to MRI which would be relatively expensive [3]. In addition, there is no need for painful compression or injection of contrast agents, in which concentrations could vary from time point to time point.

Currently 20 subjects have been recruited into the study with 10 subjects that have finished their treatment and have received surgery. A limitation of our study has been the low number of subjects that have received a pCR. In the small group of subjects that have currently completed the study only two of them received a pCR or 20%, which is similar to what is found in the literature [3-5].

Image reconstructions are greatly affected by consistent movement during imaging. One possible cause is due to improper contact with fibers that may occur if a subject moves during imaging, which causes large artifacts to form in the DOT images.
5. CONCLUSION

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 % water can be promising biomarkers for determining tumor response to NACT. However, more subjects are necessary to understand how these parameters change in pCR subjects.

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