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# Diffuse Optical Imaging for Monitoring Treatment Response in Breast Cancer Patients

Omar Falou, *Member, IEEE,* Ali Sadeghi-Naini, *Member, IEEE,* Hany Soliman, Martin J. Yaffe, and Gregory J. Czarnota

*Abstract*—**The necessity for a non-invasive and inexpensive imaging modality to both diagnose and monitor treatment response has lead to renewed interest in the potential of optical imaging. The aim of this study was to investigate the potential of diffuse optical spectroscopy for monitoring of patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy.**

**Fifteen women receiving neoadjuvant treatment for breast cancer had the affected breast scanned 5 times: before, 1 week, 4 weeks, and 8 weeks following initiation of the treatment and prior to surgery. Data was collected using a commercial optical system at four different wavelengths (690 nm, 730 nm, 780 nm, and 830 nm) and used to create three dimensional tomographic images. Mean measured values of deoxyhemoglobin (Hb), oxyhemoglobin (HbO2), and water in the entire breast were obtained and integrated over the entire breast volume to calculate the integrated optical index for each parameter. Volume-of-interest weighted tissue Hb, HbO2, and water corresponding to the tumor were also calculated. Patient response to the treatment was evaluated from clinical and pathological response using whole-mount pathology after mastectomy.**

**For the volume-weighted method, optical parameters averaged for responders and non-responders were significantly different at 4 weeks for both Hb and water ($p<0.05$), but not for HbO2 ($p>0.05$). None of these parameters were significantly different at week 1 ($p>0.05$). For the whole-breast method, responders and non-responders were significantly different for Hb , HbO2, and water ($p<0.05$) 1 week after treatment initiation.**

**These findings suggest that diffuse optical spectroscopy can be potentially used to predict and monitor tumor responses to neoadjuvant chemotherapy in breast cancer patients. This could potentially form a basis for the customization of chemotherapy regimens in which inefficacious treatments can be changed to more efficacious therapies.**

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Omar Falou is with the Departments of Medical Biophysics and Radiation Oncology, University of Toronto, Toronto, ON, Canada | also with the Department of Radiation Oncology and Imaging Research, Sunnybrook Health Sciences Centre, Toronto, ON M4N 3M5 Canada (phone: 416-480-6100 x83719; fax: 416-480-6002; e-mail: Omar.Falou@sunnybrook.ca).

A. Sadeghi-Naini is with the Departments of Medical Biophysics and Radiation Oncology, University of Toronto, Toronto, ON, Canada | also with the Department of Radiation Oncology and Imaging Research, Sunnybrook Health Sciences Centre, Toronto, ON M4N 3M5 Canada (e-mail: Ali.Sadeghi-Naini@sunnybrook.ca).

H. Soliman was with the Department of Radiation Oncology, University of Toronto, and Sunnybrook Health Sciences Centre, Toronto, ON M4N 3M5 Canada. He is now with the Carlo Fidani Cancer Centre, Credit Valley Hospital, Mississauga, ON L5M 2N1 Canada (e-mail: Hany.Soliman@rogers.com).

M. J. Yaffe is with the Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada | also with Imaging Research, Sunnybrook Health Sciences Centre, Toronto, ON M4N 3M5 Canada (e-mail: Martin.Yaffe@sunnybrook.ca).

G. J. Czarnota is with the Departments of Medical Biophysics and Radiation Oncology, University of Toronto, Toronto, ON, Canada | also with the Department of Radiation Oncology and Imaging Research, Sunnybrook Health Sciences Centre, Toronto, ON M4N 3M5 Canada (e-mail: Gregory.Czarnota@sunnybrook.ca).

## I. Introduction

Breast Cancer is the most common malignancy for women in North America. Approximately 5-15% of new cases diagnosed each year will present with locally advanced breast cancer (LABC) [1, 2]. This diagnosis includes tumors larger than 5 centimeters or tumors which have spread to the skin or the chest wall. Women with LABC have a very poor outcome in terms of both local and systemic recurrence (5-year survival rate of ~50%) [3]. Standard treatment for these patients is now usually neoadjuvant systemic treatment (chemotherapy or less frequently endocrine therapy) followed by surgery and radiotherapy [4]. Conventional clinical surrogates based on anatomical information such as physical assessment, X-ray mammography, and standard clinical imaging such as ultrasound suffer from an inability to objectively assess treatment response early during the course of treatment [5].

The need for a non-invasive and inexpensive imaging modality to monitor treatment response has lead to renewed interest in the potential of optical imaging [6-8]. Diffuse optical spectroscopy (DOS) is a non-invasive, non-ionizing techniques that employ near-infrared (NIR) light to rapidly provide quantitative spectral information (in tens of seconds) regarding the absorption and scattering properties of tissue [9, 10]. Measured optical properties can be converted to parameters related to tissue microstructure and biochemical composition such as deoxygenated hemoglobin (Hb), oxygenated hemoglobin (HbO2) concentrations, and water percentage. This functional information is not readily available through conventional structural imaging techniques. Since optical contrast comes from intrinsic tissue components, the technique does not require exogenous contrast agents making it ideal for frequent, repeat monitoring.

TABLE I. PATIENT CHARACTERTISTICS

| Characteristic | | Value |
|---|---|---|
| Mean Age | | 49 years (range 36 – 64) |
| Mean Maximum Tumor Size | | 7.9+/- 2.6 cm (range 3.2 – 12) |
| Menstrual Status Prior to Treatment | | |
| | Pre-menopausal | 9 patients |
| | Post-menopausal | 6 patients |
| Neoadjuvant Treatment | | |
| | AC + paclitaxel,trastuzumab | 4 patients |
| | Chemoradiotherapy | 3 patients |
| | AC + paclitaxel | 2 patients |
| | FEC + docetaxel | 2 patients |
| | Epirubicin,docetaxel | 2 patients |
| | Sunitinib,trastuzumab → docetaxel,trastuzumab,pamidronate | 1 patient |
| | Docetaxel,carboplatinum,trastuzumab | 1 patient |
| Tumor Histology | | |
| | Lobular Carcinoma | 2 patients |
| | Ductal Carcinoma | 13 patients |
| Hormone receptor (estrogen or progesterone receptor) | | |
| | Positive | 10 patients |
| | Negative | 5 patients |
| Her-2-neu | | |
| | Positive | 7 patients |
| | Negative | 8 patients |
| Grade | | |
| | 1 | 2 patients |
| | 2 | 12 patients |
| | 3 | 1 patient |

AC: Adriamycin and Cytoxan
FEC: Fluorouracil (5FU), epirubicin and cyclophosphamide

In this work, we investigate the potential of diffuse optical spectroscopy (DOS) for monitoring of patients with locally advanced breast cancer (LABC) undergoing neoadjuvant chemotherapy. First, we use a whole-breast approach to predict the treatment response by monitoring changes in optical parameters and relating them to clinical and postsurgical pathologic outcome. We report the results of multi-time study on 15 patients who received a variety of neoadjuvant treatment regimens. We also compare results to a volume-weighted method indicating the whole-breast method can potentially detect changes earlier.

## II. METHODS

The study included 15 LABC patients treated at the Odette Cancer Centre of the Sunnybrook Health Sciences Centre. These included ten patients from the previous study using the volume-weighted method [11] in addition to five new patients. The affected breasts were scanned at five times: before treatment, and 1 week, 4 weeks, and 8 weeks following initiation of treatment, and prior to surgery.

Diffuse optical spectroscopy images were collected using a commercial optical system (SoftScan®, ART, Inc., Montreal, QC, Canada) composed of four individual pulsed semiconductor diode lasers (LDH-P, PicoQuant, Berlin, Germany) operating at 690 nm, 730 nm, 780 nm and 830 nm, with a pulse duration FWHM <150ps, an average output of 0.5 mW when driven at 20 MHz (PDL 808, PicoQuant, Berlin, Germany), with an oscillator module to synchronize drivers. Photons were collected by a mobile detector in a 1 cm-X constellation comprised of five optical fibres and detected by a photomultiplier (H7422P-50, Hamamatsu, Bridgewater, NJ, USA). A router processed the electrical pulse from the photomultiplier before sending it to a time correlated single photon counting board (TCSPC, SPC-130, Becker & Hickl, Berlin, Germany). The count was time correlated with the synchronization signal provided by the laser system driver. Patients were scanned in a prone position and positioned into the breast aquarium under the guidance of a clinical research nurse. The aquarium was filled with a liquid optical compensation medium (an oil-in-water emulsion that mimics average optical properties of the human breast, with an average absorption coefficient of 0.04 $cm^{-1}$ and an average effective scattering coefficient=10 $cm^{-1}$) to minimize light reflections at the breast interface that can degrade image quality. The scanning area encompassed the whole breast. Stabilizing plates were used to secure the breast in place and all imaging parameters (i.e. angle, height, distance, etc.) at baseline were recorded and employed for all subsequent scans. The acquired data was reconstructed using commercially available software associated with the SoftScan® device and three dimensional tomographic images were created from the optical parameters [12].

Clinical examinations were also carried out prior to each imaging session in addition to regular patient visits. A 1.0 Tesla MRI study (GE Healthcare, Waukesha, WI) using a dedicated radiofrequency coil was performed only at baseline and immediately prior to surgery as measure of tumor size. Pathology was examined after mastectomy on full mount [13] 5"x7" pathology slides digitized using a confocal scanner (TISSUEscope™, Huron Technologies, Waterloo, ON) at 2 micron resolution. Data on grade, histologic subtype, size, and tumor response were recorded. Patients were categorized as responders or non-responders. Mean measured values of Hb, HbO2, and water in the entire breast were obtained and integrated over the entire breast volume to calculate the integrated optical index for each parameter. Volume-weighted parameters were also calculated as before [11]. Percentage change in the values from baseline between responders and non-responders at each time for each of the optical parameters were compared independently. Statistical analysis using a *t* test (two-sided, 95% confidence) was carried out to assess if patients showing statistically significant changes in optical parameters at weeks 1 and 4 correlated to patient population demonstrating treatment response as defined by clinical criteria.

## III. RESULTS

All patient characteristics are given in TABLE 1. Eight patients had a good clinical and pathological response. Six patients were found to be non-responders. One patient initially had a poor response but after a change in chemotherapy had a good clinical response.

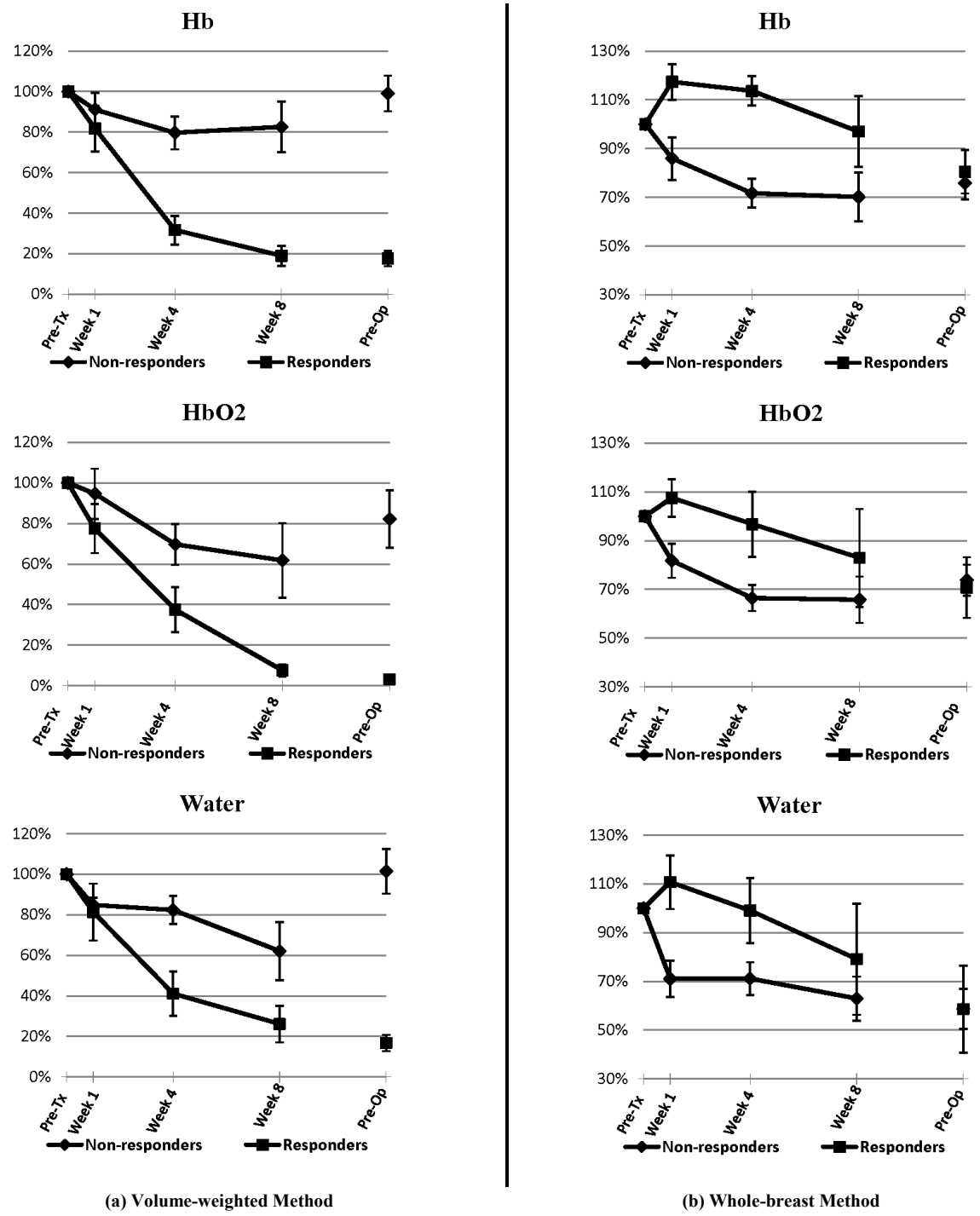


Figure 1. Changes in DOS parameters measured in responders and non-responders using (a) volume-weighted method and (b) whole-breast method.

For the volume-weighted method, optical parameters averaged for responders and non-responders were significantly different at 4 weeks for both Hb ($p=0.005$) and water ($p=0.04$), but not for HbO2 ($p>0.05$). As shown in Fig. 1(a), responding patients demonstrated a decrease of 68±7% SE, 63±11%, and 59±11% in Hb, HbO2 concentrations, and water percentage, from baseline 4 weeks after treatment initiation, respectively. In contrast, non-responding patients demonstrated a decrease of 20±8% SE, 30±10%, and 18±7% in Hb, HbO2 concentrations, and water percentage, respectively. None of these parameters were significantly different at week 1 ($p>0.05$).

For the whole-breast method, responders and non-responders were significantly different for Hb ($p=0.04$), HbO2 ($p=0.04$), and water ($p=0.01$) at week 1. Responding patients demonstrated an increase of 17±7% SE, 8±8%, and 11±11% in Hb, HbO2 concentrations, and water percentage, from baseline 1 week after treatment initiation, respectively as shown in Fig. 1(b). In contrast, non-responding patients

demonstrated a decrease of 14±9% SE, 18±7%, and 29±7% in Hb, HbO2 concentrations, and water percentage, respectively.

## IV. Discussion and Conclusions

The results reported in this study are encouraging and provide further support the potential of using diffuse optical spectroscopy to monitor treatment response in locally advanced breast cancer patients. The whole-breast method was found to be superior to the volume-weighted method since it permitted the separation between responders and non-responders as early as 1 week after treatment initiation when using any of the parameters as a predictor of treatment response. We hypothesize that this is likely due to concurrent changes in these parameters within the tumor as well as its surrounding normal tissue over the treatment course as reported by previous investigators [7]. The whole- breast method introduced in this work also offers a potential major advantage over volume-weighted method since it does not require any knowledge of the tumor size and location, which makes it simple and ideal for clinical settings.

In conclusion, results of this study indicate that diffuse optical spectroscopy has the potential to quantify changes in tumors during treatment and hence may provide non-invasive method to monitor treatment response in breast cancer patients receiving neoadjuvant chemotherapy.

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