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Functional Imaging of Neoadjuvant Chemotherapy Response in Women with Locally Advanced Breast Cancer using Diffuse Optical Spectroscopy

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Abstract— **Functional imaging with tomographic near infrared diffuse optical spectroscopy (DOS) can quantitatively measure tissue parameters such as the concentration of deoxy-hemoglobin (Hb), oxy-hemoglobin (HbO2), percent water (%water), and scattering power (SP). The purpose of this study was to evaluate the correlation between DOS functional parameters with pathologic outcomes.**

Patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy or chemoradiotherapy were recruited to this study (n=10). Five scans were conducted per patient: a baseline scan was taken up to 3 days prior to treatment and at 1 week, 4 weeks, 8 weeks, and after neoadjuvant treatment prior to surgery. At each scan the patient lay prone with the breast suspended between immobilization plates in optical coupling medium. Pulsed near-infrared laser light was used to scan the breast at four different wavelengths and data was used for tomographic reconstruction. Volume-of-interest (VOI) weighted tissue Hb, HbO2, %water, and SP corresponding to the tumour was calculated and compared to clinical and pathological response as determined from full mount mastectomy pathology.

For all 10 patients the tumour-based VOI was significantly different than background tissue for all functional parameters ($p<0.001$). Five patients had a good clinical and pathologic response. Four patients were considered non-responders. One patient initially had a poor clinical response to chemotherapy but after a change in chemotherapy had a good clinical and radiographic response. Responders and non-responders were significantly different for all of the functional parameters ($p<0.05$) at the 4-week scan. In the 5 patients with a good response the mean drop in Hb, HbO2, %water, and SP from baseline to the 4-week scan was 70.4% (SD=18.6), 66.5% (SD=24.5), 59.6% (SD=30.9), and 60.7% (SD=29.2), respectively. In contrast, the 4 non-responders had a mean drop of 17.7% (SD=9.8), 18.0% (SD=20.8), 15.4% (SD=11.7), and 12.6% (SD=10.2), for Hb, HbO2, %water and SP, respectively.

Functional imaging using tomographic diffuse optical spectroscopy parameters of Hb, HbO2, %water and SP could be used as an early detector of final clinical and pathologic tumour response. This could be evaluated in the future to assess response and potentially adjust chemotherapy regimens.

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I. Introduction

BREAST cancer is the second leading cause of cancer-related mortality in women in North America. Locally advanced breast cancer (LABC) represents 5% to 20% of all newly diagnosed breast cancers in the United States. This diagnosis includes tumours greater than 5 cm or involving the skin or chest wall, or inflammatory breast cancer. It also includes patients with supraclavicular, infraclavicular, internal mammary or fixed or matted axillary lymph nodes. All stage III and a subset of stage IIB (T3N0) tumours are usually considered locally advanced. Women with LABC typically have poor outcomes in terms of local and systemic control. The emerging standard treatment for LABC involves multimodality treatment with neoadjuvant chemotherapy.

Traditional methods of monitoring tumour response including clinical palpation, X-ray mammography, ultrasonography and magnetic resonance imaging (MRI) have been typically used as an anatomical marker of disease. However, response seen through anatomical imaging is often delayed and does not correlate well with final pathologic outcome. The need for a non-invasive and inexpensive imaging modality to both diagnose disease and monitor treatment response early in treatment has given new enthusiasm to optical imaging. Functional imaging with tomographic near infrared diffuse optical spectroscopy (DOS) can quantitatively measure tissue parameters such as the concentration of deoxy-hemoglobin (Hb), oxy-hemoglobin (HbO2), percent water (%water), and scattering power (SP). Although, functional imaging with DOS in comparison to conventional imaging modalities provides less spatial resolution, it provides valuable functional information potentially shortly after initiation of cancer treatment.

II. Methods

Ten patients with locally advanced breast cancer were recruited to take part in this study. Five scans were conducted for each patient: a scan was taken up to three days prior to treatment and at one week, four weeks, eight weeks, and then after neoadjuvant treatment prior to surgery. DOS images were obtained with the patient wearing protective

eyewear lying prone with the pendant breast suspended and stabilized between polymethyl methacrylate plates in an aquarium. Optical compensation medium with optical properties similar to breast tissue was added to the aquarium. DOS images were acquired with the Softscan platform

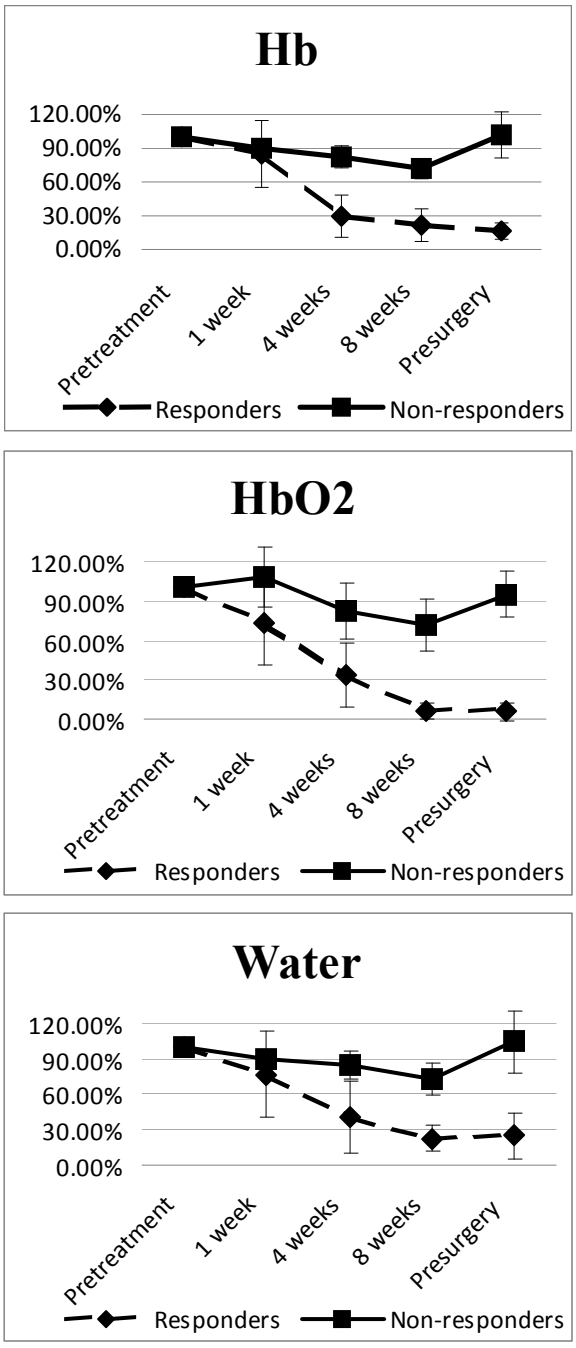

Fig. 1. Representative Diffuse Optical Spectroscopy Data. The graphs illustrate the functional Hb, HbO2 and water parameter plotted as a % change from pretreatment of responders versus non-responders at different times. At 4 weeks HbO2, Hb, %water and SP were all lower for responders as compared to non-pathologic responders.

(Advanced Research Technologies, Montreal, Quebec, Canada) under the supervision of the clinical research nurse.

The acquisition platform used in the study, was a time-resolved, optical imaging device used to measure photon migration through the breast in the near infrared range. The laser emission assembly was composed of four individual pulsed semiconductor diode lasers (LDH-P, PicoQuant, Berlin Germany) operating at 690nm, 730nm, 780nm and 830nm with a pulse duration (FWHM) <150ps average output of 0.5 mW when driven at 20 Mhz (PDL 808, PicoQuant, Berlin, Germany) and an oscillator module to synchronize the drivers. The pulses are time-multiplexed (12.5ns) through a single fiber on the emission side of the breast. Photons were collected through 5 optical fibers positioned on a mobile detector head in an "M" configuration on the collection side of the breast and detected by a photomultiplier (H7422P-50, Hamamatsu, Bridgewater, NJ, USA). Patients were positioned prone on a tabletop with a pendant breast scanned in an aquarium in a raster pattern. The optical compensation medium was an oil-in-water emulsion that mimicked average optical properties of the human breast (coefficient of absorption = 0.04cm-1 and coefficient of scatter = 10cm-1).

The acquired data was reconstructed and tomographic functional images created from the optical parameters. The tumour was identified in the pretreatment DOS images for each of the functional parameters and verified using information from each patient's clinical exam, mammogram,

TABLE I
PATIENT CHARACTERISTICS

Characteristic	Value
Mean Age	50 yrs (38 – 64)
Menstrual status prior to treatment	
Pre-menopausal	6 patients
Post-menopausal	4 patients
Neoadjuvant Treatment	
Chemoradiotherapy	4 patients
Epirubicin and docetaxel	2 patients
AC + T	2 patients
FEC + D	1 patient
Sunitinib/Trastuzumab → Docetaxel	1 patient
Trastuzumab Pamidronate	
Docetaxel/Carboplatinum/Trastuzumab	1 patient
Mean Maximum Tumour Size	7.7 +/- 2.4 cm
Tumour Histology	
Lobular Carcinoma	2 patients
Ductal Carcinoma	8 patients
Hormone receptor (estrogen or progesterone receptor)	
Positive	7 patients
Negative	3 patients
Mean BMI	25.2 +/- 7.0
Her-2-neu	
Positive	4 patients
Negative	6 patients
Triple Negative (estrogen, progesterone and Her-2-neu)	2 patients
Grade	
1	0 patients
2	10 patients
3	0 patients

ultrasound and MRI, tumour size and location were obtained. A volume of interest (VOI) for each of HbO2, Hb, %water, and SP on all of the DOS scans was created by obtaining a threshold value that was a fraction of the maximum measured value. This threshold value was adjusted such that the VOI corresponded in size and location as close as possible to the actual tumour as known through other imaging and clinical exam. Mean measured values in the VOI of each of the functional parameters were obtained.

I. Results

All the patient characteristics are detailed in table 1. For all patients the tumour-based VOI was significantly different than background tissue for all functional parameters ($p<0.001$). Five patients had a good clinical, radiographic and pathologic response. Four patients were considered non-responders clinically. One patient initially had a poor clinical response to chemotherapy but after a change in chemotherapy had a good clinical and radiographic response. Responders and non-responders were significantly different for all of the functional parameters ($p<0.05$) at the four week scan, except %water which approached significance ($p=0.06$), see figure 1. In the five patients with a good response the mean drop in Hb, HbO2, %water, and SP from baseline to the four week scan was 70.4% (SD=18.6), 66.5% (SD=24.5), 59.6% (SD=30.9), and 60.7% (SD=29.2), respectively. In contrast, the four non-responders had a mean drop of 17.7% (SD=9.8), 18.0% (SD=20.8), 15.4% (SD=11.7), and 12.6% (SD=10.2), for Hb, HbO2, %water and SP, respectively.

II. Conclusion

Functional imaging using tomographic diffuse optical spectroscopy parameters of Hb, HbO2, %water and SP could be used as an early detector of final clinical and pathologic tumour response. Responders and non-responders appear to separate at approximately four weeks post initiation of neoadjuvant treatment. This could be potentially used in the future to assess response and adjust chemotherapy regimens.

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