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Monitoring Neoadjuvant Chemotherapy Through Time Domain Diffuse Optical Spectroscopy in Breast Cancer Patients: Preliminary Clinical Results

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ABSTRACT

The purpose of this clinical study is to monitor NeoAdjuvant Chemotherapy through time domain Diffuse Optical Spectroscopy, correlate the optical results with conventional imaging techniques and pathological response and eventually predict the efficacy of NAC in breast cancer patients. Our seven wavelength (635 -1060 nm) optical mammograph is used to perform non-invasive measurements on patients undergoing NAC in this study. The broad spectral range helps us to fully analyze tissue composition, that includes hemoglobin, water lipids and collagen concentration, to track the tumor response during the course of the therapy. In this paper, we present the preliminary results of five patients.

Keywords: Neoadjuvant Chemotherapy; Pathological Response; Diffuse Optical Spectroscopy; Tissue Composition; Collagen.

1. INTRODUCTION

NeoAdjuvant Chemotherapy (NAC) is a pre-surgical therapy administered in order to downsize the tumor. It is widely being accepted these days to treat patients with locally advanced breast cancer as it could allow for breast conserving surgery. The early assessment of the cancer response to this therapy is very essential as it is correlated to patient's survival.

Diffuse optical spectroscopic (DOS) imaging could be a potential technique in this regard. Diffuse Optics studies the propagation of light in highly scattering media, like the breast tissue, which helps to investigate it down to a depth of few centimeters using near-infrared light (650–1000 nm). Hence, it provides an estimation of tissue composition (in terms of lipid, water, blood and collagen concentrations, thanks to absorption properties) and scattering properties, that in the case of breast cancer, can be exploited for risk assessment, lesion nature identification, therapy monitoring and prediction of therapy outcome [1]. The important prospects of this technique are that it is non-invasive, relatively economical and can provide quantitative and operator independent information.

In view of the same an optical mammograph that uses DOS in time domain was developed by our research group at Politecnico di Milano which is now at San Raffaele Hospital, Milan for a clinical study on breast cancer patients. The purpose of this study is to monitor NAC through time domain diffuse optical spectroscopic imaging, correlate the optical results with conventional imaging techniques and pathologic outcome and eventually predict the efficacy of NAC in breast cancer patients to discriminate responding patients from non-responding patients.

2. MATERIALS AND METHODS

2.1 Instrument Set-Up

The optical mammograph includes 7 picosecond lasers that range from 635 to 1060 nm (PDL-828 and LDH-P, PicoQuant, Germany) selected based on characteristic features of the breast chromophores' spectra: oxy and deoxy hemoglobin, water, lipids, and collagen. It operates in time domain and in transmission mode. Light raster scans the mildly compressed breast and then the re-emitted photons are harvested by SiPM-based detectors (S13360-1350PE,

Hamamatsu Photonics, Japan) along the line of sight. A Time-to-Digital Converter (MultiHarp 150 8N, PicoQuant, Germany) implements Time-Correlated Single Photon Counting (TCSPC), that allows to reconstruct the distribution of photons' times of flight inside the tissue [2].

2.2 Clinical Protocol

During the clinical study 6 optical measurements are performed on each subject: a baseline before starting NAC, 2-5 days after starting NAC, 6-8 days later, 2 weeks later, at mid-treatment and one at the end of the treatment. The timeline of the clinical study is represented in Figure 1. In each session, 4 scans are acquired, to probe the combinations of breast (right – R - and left - L) and view (Cranio-Caudal – CC - and Oblique - OB). Thus far, 11 patients were enrolled in this clinical trial with informed consent out of which 5 patients have completed their therapy while it is ongoing with the rest of the 6 patients. Various multidrug, multicycle regimens were used to treat patients.

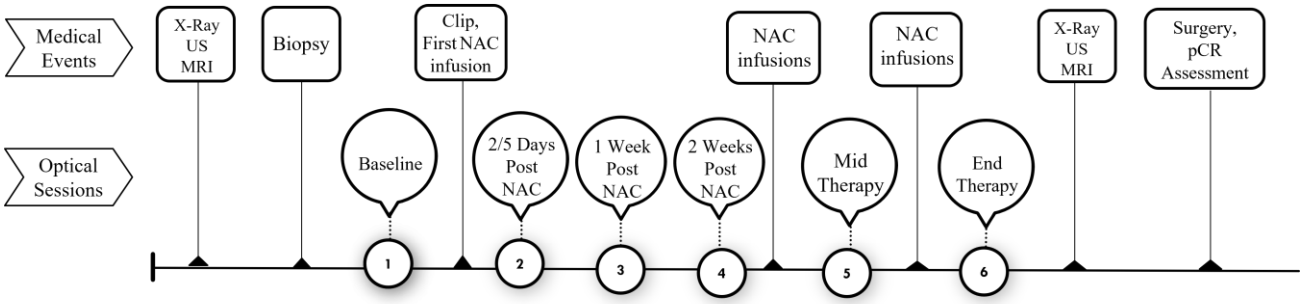

Figure 1 : Timeline of the Clinical Study

2.3 Data Analysis

The data was analyzed applying a spectrally constrained homogeneous model data fit [3] which is based on the Diffusion Approximation of the Radiative Transport Theory and leaves as free parameters lipid, water, collagen oxy- and deoxyhemoglobin concentrations and the scattering amplitude and power. The average concentrations of the breast constituents were retrieved over a rectangular region of interest (approximately about the tumor size) enclosing the tumor.

3. RESULTS

All the 5 subjects who have completed their therapy have at least partially responded to the NAC according to the final surgery information reported by the medical practitioner. The initial tumor size ranges from 28-70 mm while the final tumor size is 0-25 mm. Figure 2 outlines the absolute concentrations of various breast constituents at **baseline and end therapy** sessions averaged over 5 patients on tumor bearing breast and symmetrically on the contralateral healthy breast in both CC and OB views. All parameters have a maximum contrast in the tumor breast with respect to the healthy tissue counterpart at the baseline. The broad spectral range enables collagen assessment, which has never been systematically studied during NAC so far. Preliminary results on five patients' data show that there is significant reduction in the concentrations of total hemoglobin (-33%), water (-25%) and collagen (-60%) and increase in lipids (+20%) by the end of therapy in the tumor bearing breast indicating the response to the therapy. We hypothesize that **collagen** could be a possible biomarker relating to the NAC efficacy, as it shows a maximum reduction in its concentration with (at least partly effective) therapy and it is known to be involved in breast cancer development and progression. Comparing the baseline and end therapy measures, qualitatively the compositional changes occurring during the course of NAC were observed even on the **contralateral healthy breast**. This could be due to the systemic nature of NAC [4], and it is worth noting that these variations are smaller compared to the variations in the tumor bearing breast. The Students' T test on the data showed that at the baseline the tissue composition (for all constituents) seems significantly different in the tumor vs healthy breast, the tumor changes significantly with therapy (baseline vs end therapy) and that leads to no longer significant difference in tissue composition at the end therapy for complete or at least partial responders.

Of the 5 subjects enrolled, 2 patients underwent a **two-regime treatment** with multidrug and multicycle therapy. In one of the patients, marked changes in the constituents' concentrations during the first week of the first regime were observed while in the second regime the trends showed only slight variations. Hence, we suppose that the optical results

may also reveal regimen-dependent changes in breast tumors throughout NAC [5]. In this way, diffuse optical spectroscopic imaging may provide biological insight into the regimen-specific mechanisms of action.

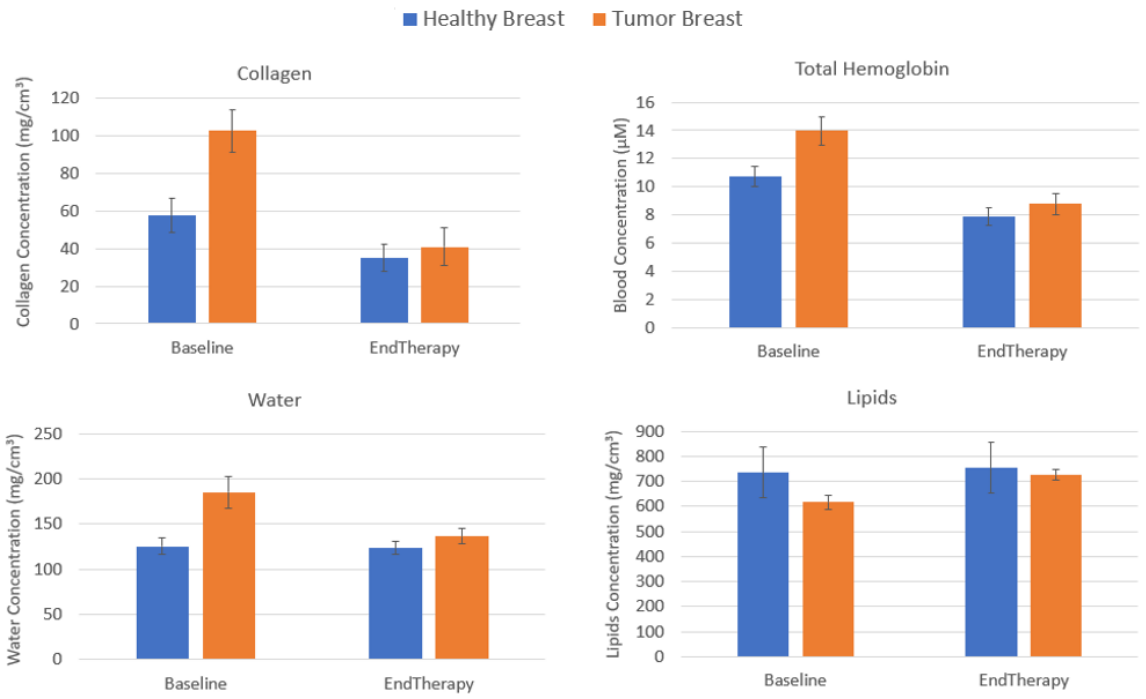

Figure 2 : Collagen, total hemoglobin, water and lipid concentrations at baseline and end therapy sessions averaged over 5 patients both on tumor bearing breast and contralateral healthy breast in both CC and OB views.

4. CONCLUSION AND FUTURE WORK

In summary, optical results with regard to the patients' response to NAC correspond with the standard care imaging techniques and pathologic outcome. Data acquisition from new patients will help us to hopefully strengthen our hypotheses. Future work includes identifying reliable parameters that can help us predict the tumor response for the evaluation of neoadjuvant therapy's effectiveness. We are also exploring a spectral perturbative data analysis model that can help us better quantify the tumor composition by isolating it from healthy background optical properties.

5. ACKNOWLEDGEMENT

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