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Evaluation of NeoAdjuvant Chemotherapy-Induced Changes in Contralateral Healthy Breast Tissue Through Diffuse Optical Spectroscopy

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ABSTRACT

This study aims at evaluating the effect of NeoAdjuvant Chemotherapy (NAC) on the contralateral tumor-free breast tissue through time domain diffuse optical spectroscopy. The breast tissue composition consisting of hemoglobin, water, lipid, and collagen concentrations is quantitatively derived using our seven-wavelength (635-1060 nm) optical mammograph. Preliminary analysis of ten patients' data shows compositional changes occurring in the non-tumor breast in addition to the tumor breast. This includes reduction in breast density and components' concentrations through the course of the therapy. The final goal is to eventually identify if there is a correlation of these effects with pathological complete response.

Keywords: Neoadjuvant Chemotherapy; Pathological Response; Diffuse Optical Spectroscopy; Tissue Composition; Collagen; Breast Density; Tumor-Free Breast

1. INTRODUCTION

NeoAdjuvant Chemotherapy (NAC) is a pre-surgical therapy administered in order to downsize the tumor. It is important to assess the efficacy of NAC as early as possible because the response to the treatment can be a strong predictor of the patient's overall prognosis and survival. If the NAC is not effective at reducing the size of the tumor, alternative treatment options may be considered. On the other hand, if the NAC is effective, it can potentially allow for breast-conserving surgery to be performed, which may improve the patient's quality of life and long-term outlook.

Diffuse Optical Spectroscopy (DOS) is a technique that uses near-infrared light to study the absorption, scattering, and fluorescence properties of tissues. It is commonly used in biophotonics research to study various biological phenomena, including the blood flow in tissues, oxygenation of tissues, and the metabolic state of tissues. Hence, DOS could be used to monitor the changes in the biological properties of the breast tissue during the NAC treatment and can help to assess the response to chemotherapy and guide treatment decisions. The key benefits of DOS is that it is a non-invasive technique that can provide operator-independent, quantitative information about tissue composition at a relatively low cost.

This study involves bilateral optical measurements on breast cancer patients, with both affected and healthy breast being scanned using Time-Domain Diffuse Optical Spectroscopy (TD-DOS). The preliminary analysis on these patients shows compositional changes occurring in the non-tumor breast in addition to the tumor breast. This includes reduction in breast density and components' concentrations through the course of the therapy. This paper aims to quantify these changes and eventually identify if there is a correlation of these effects with pathological complete response (pCR).

2. MATERIALS AND METHODS

2.1 Instrument Set-Up

The measurements were performed using a seven-wavelength (635-1060 nm) optical mammograph that is designed to collect projection images of the compressed breast, i.e., in the same geometry as used for conventional x-ray mammography, but with soft compression of the breast. The breast is raster-scanned by the light transmitted through an injection fibre, which is axially aligned with a detection probe composed of SiPMs (Silicon PhotoMultipliers). The output signals are then amplified and directed to the Time-To-Digital Converter, that constructs the time-dependent photon

distribution of the re-emitted photons, i.e. the transmittance curves, from where the optical properties of the tissues are derived [1].

2.2 Clinical Protocol

A study on the optical monitoring of NAC in patients with breast cancer is ongoing at San Raffaele Hospital, Milan, Italy. Up to now, 10 enrolled patients have completed their participation in the study. Each patient received multicycle and multi-regime NAC treatment. Before the start of the study, a signed informed consent was obtained from these patients. Each subject undergoes six optical sessions with the optical mammograph: 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. In each session, 4 scans are acquired, to probe the combinations of both breasts (right – R - and left - L) and views (Cranio-Caudal – CC - and Oblique - OB).

2.3 Data Analysis

The data is processed using a spectrally constrained homogeneous model data fit, which is based on the Diffusion Approximation of the Radiative Transport Theory, that returns lipid, water, collagen oxy- and deoxyhemoglobin concentrations, scattering amplitude and power as the final output [2]. This output is visualized in the form of bi-dimensional images of each constituents' concentration using a customized MATLAB script. The average concentrations of the breast constituents were retrieved over a rectangular region of interest (approximately about the tumor size) enclosing the tumor or a mirror site on the contralateral breast on these images.

3. RESULTS

It was observed that the breast density (estimated as [collagen]*[water]/[lipids]) of the tumor-free breast decreases by 33% ($p = 0.05$) from the baseline (before NAC) to end therapy, while in the tumor region the decrease is much stronger (about 55%, $p = 0.024$). Several other studies have reported a consistent reduction of breast density after breast cancer treatment [3]–[5]. This could be due to the rapid changes in estrogen and progesterone levels through suppression in ovarian function induced by chemotherapeutic agents contributing to secondary change in breast tissue composition, and consequently, an impact in mammographic breast density [6]. Breast density has been proved to be strong independent risk factor for breast cancer [7]. It may be possible to use the reduction of density as a biomarker to predict NAC efficacy and also in reducing contralateral cancer risk. There was also reduction in the concentrations of total hemoglobin that includes oxy and de-oxy hemoglobin (-29%), water (-19%), collagen (-8%) and increase in lipids (+8%) by the end of therapy as summarized in Table 1. These changes are milder when compared to those observed in the tumor region.

Our results also showed that there was a significant reduction in the oxy-hemoglobin concentration in the healthy breast by about 39% ($p = 0.002$) from baseline to end therapy when averaged over all patients. Out of all patients, the patients who achieved pCR to NAC saw a statistically significant mean decrease in oxyhemoglobin in healthy breast by 3.1 µM already by the end of 2-3 weeks compared to baseline ($p = 0.04$) while the partial responders showed a mean decrease by 1.86 µM, and it did not reach the statistical significance ($p = 0.1$). This could be due to the drugs used as part of the NAC regime that can damage the lining of the blood vessels, which can lead to inflammation and decreased oxygen delivery to the tissues. These can affect also the production of red blood cells, which can lead to anemia and decreased oxygen delivery to the tissues [8]. Figure 1 represents the change in the concentration of oxy-hemoglobin concentration in the contralateral tumor-free breast during the course of NAC.

Table 1 : Changes in collagen, de-oxy, oxy and total hemoglobin, lipid and water concentrations in tumor-free breast.

	Mean_Baseline	Mean_EndTherapy	Overall Change(%)	p value
Collagen *(mg/cm^3)*	56.85	52.43	-8%	0.314
Hb *(µM)*	2.51	2.59	3%	0.406
HbO2 *(µM)*	8.29	5.09	-39%	0.002
HbTot *(µM)*	10.80	7.69	-29%	0.004
Lipid *(mg/cm^3)*	640.25	689.21	8%	0.057
Water *(mg/cm^3)*	201.46	163.17	-19%	0.057

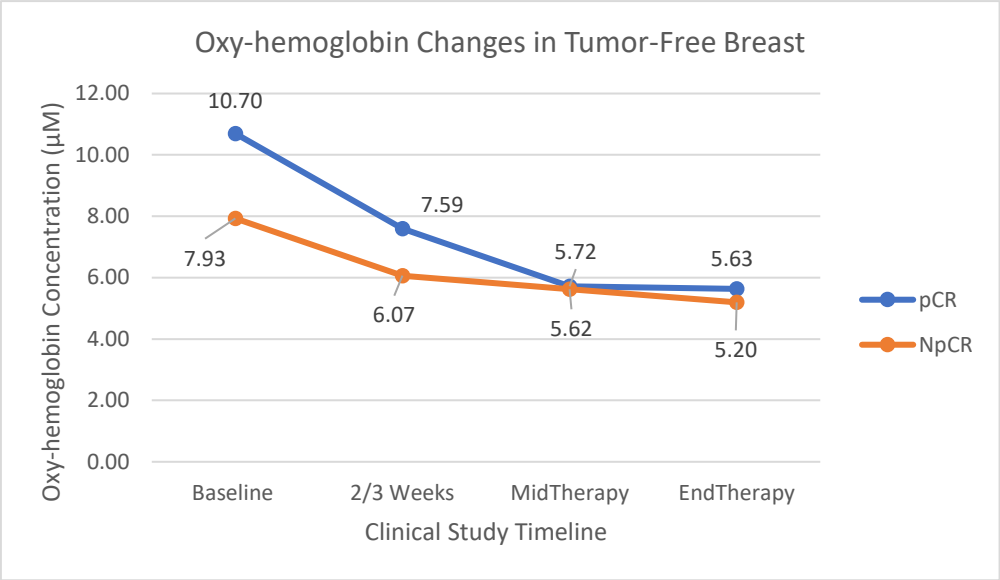

Figure 1 : Changes in the oxy-hemoglobin concentration in the contralateral tumor-free breast during the course of NAC. pCR refers to pathological complete response while NpCR refers to no pathological complete response.

4. CONCLUSION

Although from a limited dataset, these initial results obtained using DOS show that NAC may have systemic effects on the contralateral healthy breast tissue in addition to that of the tumor breast. The study is ongoing to collect more data and further research is needed to strengthen the hypothesis and provide more insight into these effects on pCR. More quantitative data analysis is also under evaluation. If validated, DOS could be a promising technique to monitor NAC and help in personalized cancer care treatment based on the patient's response.

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6. REFERENCES

[1] G. Maffeis, E. Ferocino, A. D. Mora, A. Pifferi, R. Cubeddu, and P. Taroni, "In vivo test-driven upgrade of a time domain multi-wavelength optical mammograph," *Biomed. Opt. Express*, vol. 12, no. 2, p. 1105, Feb. 2021, doi: 10.1364/BOE.412210.

[2] C. D'Andrea *et al.*, "Time-resolved spectrally constrained method for the quantification of chromophore concentrations and scattering parameters in diffusing media," *Opt. Express*, vol. 14, no. 5, p. 1888, 2006, doi: 10.1364/oe.14.001888.

[3] T. D. O'Sullivan *et al.*, "Optical imaging correlates with magnetic resonance imaging breast density and reveals composition changes during neoadjuvant chemotherapy," *Breast Cancer Res.*, vol. 15, no. 1, p. R14, 2013, doi: 10.1186/bcr3389.

[4] J. A. Knight *et al.*, "The association of mammographic density with risk of contralateral breast cancer and change in density with treatment in the WECARE study," *Breast Cancer Res.*, vol. 20, no. 1, pp. 1–10, 2018, doi: 10.1186/s13058-018-0948-4.

[5] K. A. Bertrand, A. H. Eliassen, S. E. Hankinson, B. A. Rosner, and R. M. Tamimi, "Circulating Hormones and Mammographic Density in Premenopausal Women," *Horm. Cancer*, vol. 9, no. 2, pp. 117–127, 2018, doi: 10.1007/s12672-017-0321-6.

[6] J. H. Chen *et al.*, "Decrease in breast density in the contralateral normal breast of patients receiving neoadjuvant chemotherapy: MR imaging evaluation," *Radiology*, vol. 255, no. 1, pp. 44–52, 2010, doi: 10.1148/radiol.09091090.

[7] P. Taroni *et al.*, “Breast Tissue Composition and Its Dependence on Demographic Risk Factors for Breast Cancer: Non-Invasive Assessment by Time Domain Diffuse Optical Spectroscopy,” *PLoS One*, vol. 10, no. 6, p. e0128941, Jun. 2015, doi: 10.1371/journal.pone.0128941.
[8] M. L. Altoe *et al.*, “Effects of neoadjuvant chemotherapy on the contralateral non-tumor-bearing breast assessed by diffuse optical tomography,” *Breast Cancer Res.*, vol. 23, no. 1, pp. 1–9, 2021, doi: 10.1186/s13058-021-01396-w.