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Citation Format:

P. Taroni, R. Cubeddu, A. Dalla Mora, L. Di Sieno, G. Maffeis, N. Mule, and A. Pifferi, "Time Domain Multi-Wavelength Diffuse Optics for Breast Cancer Management," in *Optica Biophotonics Congress: Biomedical Optics 2024 (Translational, Microscopy, OCT, OTS, BRAIN)*, Technical Digest Series (Optica Publishing Group, 2024), paper TS1B.1.

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DOI abstract link:

https://doi.org/10.1364/TRANSLATIONAL.2024.TS1B.1

Time Domain Multi-Wavelength Diffuse Optics for Breast Cancer Management

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Abstract: Time-domain multi-wavelength diffuse optics (635-1060 nm) can be applied for the estimate of tissue composition, and effectively contribute to different stages of breast cancer management, including diagnosis, monitoring of therapy, and risk assessment.

1. Introduction

One in eight women will develop breast cancer in their lifetime. Screening mammography is key to reduce mortality for breast cancer but has limitations. A major one is the high false positive rate, leading to a huge number of further needless examinations, including biopsies, that are presently being performed after a false positive mammogram. A more specific non-invasive diagnosis is certainly a medical need.

NeoAdjuvant Chemotherapy (NAC) is more and more administered as a presurgical treatment to reduce the tumor volume and improve the surgical outcomes. Furthermore, the response to the treatment can be a strong predictor of the patient's overall prognosis and survival. However, only approximately 30% of patients respond completely, and no effective non-invasive way is available to monitor patient's response during the treatment course.

Breast density is the strongest independent risk factor for developing breast cancer (apart from gender and age). It would be useful to know breast density early in lifetime to design personalized monitoring and even preventive treatments for women at high risk. However, nowadays, breast density is assessed from x-ray mammograms and then only becomes known after the first screening mammogram (typically at age 50).

Time domain diffuse optical measurements performed at several wavelengths (7-8) over a broad spectral range (635-1060 nm) allow the non-invasive assessment of breast tissue composition and provide information of its microscopic structure, derived from the absorption and reduced scattering properties, respectively. Thus, they can provide valuable information and help improve discrimination between malignant and benign lesions, monitor NAC effects, and identify women at high risk due to their high breast density.

2. Instrumental set-ups, data acquisition and analysis

2.1. Multimodal imaging (the SOLUS system)

The SOLUS multimodal probe operates in reflectance geometry (the same as clinical ultrasound) and allows simultaneous B-mode ultrasound (for morphologic information), shear-wave elastography (for stiffness), Color Doppler (for vascularization), and multi-wavelength time domain diffuse optical tomography (DOT, for tissue composition – water, lipids, and collagen content – as well as blood parameters – total hemoglobin content and oxygen saturation) [1].

To perform ultrasound imaging techniques the SOLUS system relies on a high-end commercial instrument (Aixplorer Mach30, SuperSonic Imagine S.A.), while the multimodal probe was designed and realized as part of the EU project SOLUS (*Smart optical and ultrasound diagnostics of breast cancer*).

Eight optodes are arranged around the US transducer, 4 on each long side. Each optode is a stand-alone device for time domain multiwavelength diffuse optics and contains 8 picosecond pulsed diode lasers (emitting at wavelengths between 635 and 1060 nm), a wide-area time-gated SiPM detector, and an integrated Time-to-Digital Converter for data processing, all developed specifically for the SOLUS probe [2].

Water cooling guarantees optimal operation temperature on the probe front end (in contact with the patient's skin) and internally, for reliable operation of the electronics. The probe is also equipped with a position sensor and a contact sensor. A second screen and a dedicated PC complete the part of the multimodal system dedicated to DOT.

Multimodal data are collected with the probe: i) aligned along the major lesion diameter, ii) on the lesion, orthogonal to the previous position, iii) far from the lesion in the same breast, iv) in a mirror position in the contralateral breast. The measurement is repeated by 3 radiologists to test the independence of the results from the operator.

DOT reconstructions are obtained with the Born approximation of the diffusion equation in heterogeneous settings. Average values for the absorption and composition parameters of the lesions are computed based on the 3D extrapolation from segmentation implemented on the B-mode image. Tissue composition is derived in terms of water, lipids, collagen, oxy- and deoxyhemoglobin. A KNN supervised machine learning algorithm (K-nearest neighbors, K=1) was tested to classify benign and malignant lesions either exploiting only 13 optically derived predictors (absorption coefficients at the 8 wavelengths and 5 tissue constituents) or including also information form ultrasound imaging.

2.2. Time domain multiwavelength optical mammograph

The optical mammograph includes 7 picosecond pulsed diode lasers, emitting in the range of 635 to 1060 nm [3]. It operates in time domain and in transmission mode with the breast mildly compressed between parallel plates. Light pulses raster scans the breast and transmitted light is collected along the line of sight by a SiPM-based detection probe (made of 8 SiPMs, S13360-1350PE, Hamamatsu Photonics, Japan). A high throughput Time-to-Digital Converter (MultiHarp 150 8N, PicoQuant, Germany) takes care of data processing for time-correlated single photon counting.

Four images are routinely acquired from each subject (cranio-caudal and oblique views of both breasts). The measure is run by dedicated software. Data are analyzed with a homogeneous model based on the diffusion equation. Tissue composition is estimated with a spectrally constrained procedure applied directly to the time-of-flight distributions collected at the different wavelengths.

3. Results and Discussion

3.1. Lesion discrimination with the multimodal SOLUS system

Up to now data has been collected from patients with 21 benign and 12 malignant lesions.

Looking at the tissue composition (estimated with the Born approximation), there seems not to be a strong statistically significant difference between malignant and benign lesions.

Lesion discrimination based on the KNN approach applied to optical data (absorption and composition) led to sensitivity of 97% and specificity of 57%. Including ultrasound predictors, the results improved to 100% and 77%. The clinical validation of the SOLUS system is on-going, and the new aspects of data analysis are under evaluation. Limits of the present analysis and perspectives will be discussed.

3.2. Therapy monitoring with the time domain multiwavelength optical mammograph

Up to now 10 patients have completed the study, with a protocol including acquisitions at baseline, 2-5 days after starting therapy, 6-8 days later, 2 weeks later, at mid-therapy and at the end of therapy.

In general, an effective therapy (complete or at least partial pathologic response) leads to a progressive reduction in collagen, total hemoglobin content, blood oxygenation, and (less clear) water, while lipids increase. We are working to identify specific correlations, but the limited number of subjects and the fact that they underwent different therapy regimens and protocols makes it difficult for now to draw clear-cut conclusions.

Work is ongoing to collect more patient data and extend the analysis to a more accurate model, accounting for the presence of an inhomogeneity (lesion).

3.3. Risk prediction with the time domain multiwavelength optical mammograph

Based on data collected from 218 subjects, optically derived tissue composition correlates with breast density, with high collagen and water and low lipid content corresponding with high breast density.

Analysis of collagen content in healthy women compared with tumor-bearing women suggests that high collagen content might also represent a risk factor independent of mammographic breast density.

4. Acknowledgements

Partial financial support from the EU Horizon 2020 Research and Innovation Programme under grant n° 731877.

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