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Optical Characterization of Benign and Malignant Breast Lesions by Perturbative Model

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Abstract: The characterization of benign and malignant breast lesions was performed by the use of a perturbative model. Concentrations of blood, lipid, water and collagen were obtained. Differences between lesions and healthy tissue were observed.

OCIS codes: (170.5280) Photon migration; (170.6510) Spectroscopy, tissue diagnostics; (170.3830) Mammography; (170.6920) Time-resolved imaging.

1. Introduction

Breast cancer is one of the most common tumours and one of the leading causes of death in women [1]. Early diagnosis and consequent therapy significantly reduce mortality [2]. Optical mammography is an interesting emerging diagnostic tool which can operate at multiple wavelengths so as to combine imaging and spectroscopic information for lesion detection and characterization at the same time. Breast lesion characterization by non-invasive optical means is important since the evaluation of lesion composition could lead to reduce the biopsy examination, which at present is the only one able to establish the histological nature of the lesions, but it is invasive. Breast cancers are usually identified through the detection of neovascularized areas. Thus they appear as strongly absorbing areas at red wavelengths, where blood absorption is dominant. Collagen is also involved in the onset and progression of the breast cancer, and the evaluation of this chromophore could be of great importance in the detection and characterization of breast lesions.

A perturbation model, based on the calculation at high order of the pathlength of photons inside the defect, has been applied to enhance the accuracy in predicting the optical properties and the constituent concentration of a small inhomogeneity embedded in a homogeneous medium. In this work for the first time benign and malignant lesions were characterized in terms of the main constituents of the breast tissue such as blood, lipid, water and collagen.

2. Materials and methods

Instrument set-up

The instrument is designed to collect projection images in compressed breast geometry. Time-resolved transmittance measurements are performed at seven wavelengths (635, 685, 785, 905, 930, 975, 1060 nm) using picosecond pulsed diode lasers and two PC boards for time-correlated single photon counting. The compressed breast is raster-scanned continuously, recording data every millimeter. A detailed description of the set-up is reported in [3].

Patient study

The Institutional Review Board at the European Institute of Oncology approved the clinical study. Written informed consent is obtained from all the participants. The study has twofold aim: the non-invasive assessment of breast density by optical means, and the optical characterization of malignant and benign lesions.

Up to now 212 subjects enrolled (mean age 51 years, age range 19-79 years). For this work, data were analyzed for 33 patients with a malignant lesion and 29 with a benign lesion. Different types of lesions were included in each group.

Data analysis for homogenous medium [3]

Absorption and reduced scattering coefficients at each wavelength are estimated by fitting the experimental data to an analytical solution of the diffusion approximation (with the extrapolated boundary condition) for an infinite homogeneous slab.

The Beer law is used to relate the absorption properties to the concentrations of the main tissue constituents. The scattering properties are modeled through the simple approximation to Mie theory. A spectrally constrained global fitting procedure is applied, where free parameters are the concentrations of oxy- and deoxy-hemoglobin, water, lipids, and collagen, together with the scattering amplitude a and power b.

Perturbative model for lesion characterization

For this work a novel perturbative approach was defined in which the perturbation, due to an absorbing inclusion inside a diffusive medium, is represented by using the internal pathlength moments of the Generalized Temporal Point-Spread Function (GTPSF). This method, proposed by Sassaroli et al. [4], for studying the effect of absorbing defects, is able to

give a rather rigorous analytical expression for the mean pathlength l spent by photons inside the volume occupied by the defect, derived under the Diffusion Approximation to the Radiative Transfer Equation for an 8th order perturbative series term. The absorption variation $\Delta\mu_a$ between lesion and healthy tissue can be simply estimated as:

$$\Delta\mu_a = -\frac{1}{l}\ln\left(\frac{T_{pert}}{T_0}\right) \qquad (1)$$

where T_{pert} and T_0 are the perturbed and the background reference transmittance curves, respectively. The absorption variation can be obtained knowing the pathlength, which can be evaluated by exploiting the temporal information of the time-resolved approach, that is the mean time spent by photons inside the inclusion, which can be calculated starting from the modified Lambert-Beer law, using the differential definition [4].

The background unperturbed curves are taken from a reference area that excludes boundaries and marked inhomogeneities, but still includes most of the breast. To select that area, the mean time-of-flight (*i.e.* the first moment of the time-resolved transmittance curve) is calculated for each image pixel, and only pixels with mean time-of-flight greater than or equal to the median of the distribution are included in the reference area.

The experimental perturbed curves are obtained from an area extrapolated from the corresponding inhomogeneity (*i.e.* the lesion) position. The area size strictly depends on the lesion size. For data reported in this paper, for lesion diameters >15 mm, an area of 9x9 mm^2 is selected, otherwise 5x5 mm^2. The perturbation method adopted relies on an *a priori* knowledge of the volume and location of the inhomogeneity. We always assumed a spherical inhomogeneity located at halfway between source and detector. For the size, we considered an equivalent sphere based only on the maximum diameter of the lesion obtained by histopathology, when available, or by RX or US for the other cases. For small lesion volumes the perturbative model greatly amplifies the optical changes. Thus, we imposed a regularization factor to the volume to yield always physically consistent results with non negative concentrations of tissue constituents.

To calculate the absorption variation at each wavelength, a fraction gate approach was used. Data were analyzed dividing the transmittance curves in 10 equal-counts windows. The 8th gate was considered for the analysis to provide information on the absorption of the investigated medium, since it is related to late photons. Moreover, to take into account the real instrument response function (IRF) of our optical mammograph, which can not be assumed as ideal, its convolution with the time resolved transmittance curves was performed.

Starting from $\Delta\mu_a$ and knowing the extinction coefficient of the main constituents of the breast, by the Beer law, the variation of the concentrations ΔC_i between lesion and background tissue (in terms of blood, water, lipid and collagen) were achieved. Once ΔC_i is known, the constituent concentrations of the lesion were then obtained summing the ΔC_i and the $C_{i,bkg}$ which is the i-concentration related to the background area.

3. Results and discussion

The characterization of lesions leads to collect mammograms on patients with different type of lesions, benign and malignant, at least 1 cm in diameter. After the analysis, 3 malignant cases and 3 benign ones were excluded due to fitting problems caused probably by the weak signal. In some cases, the lesion was analysed in both views (cranio-caudal and oblique). As first step of our analysis we perform the correlation between lesions and background area, both in terms of absorption coefficient at the 7 wavelengths and of constituent concentrations, to understand the capability of the method to distinguish between tumor and healthy tissue. A graph reporting the constituent concentrations for malignant vs healthy tissue is shown in Figure 1.

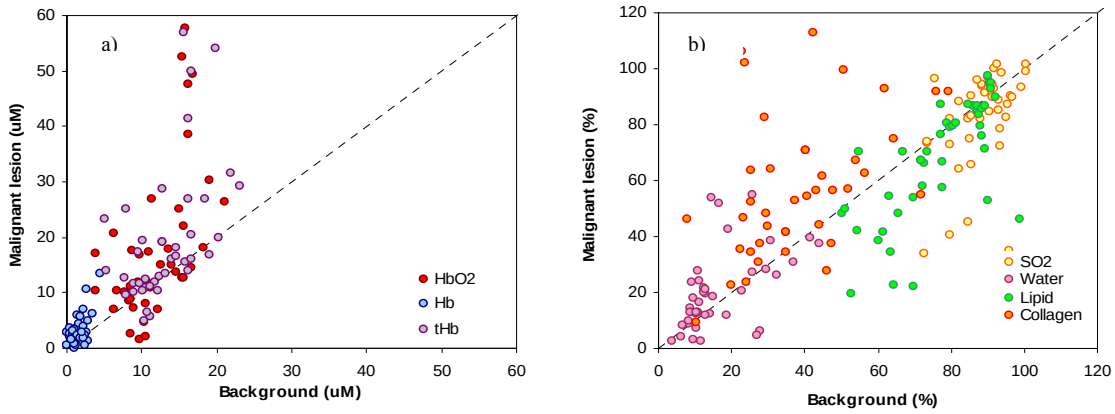

Fig. 1. Background vs malignant lesions constituents concentrations. a) Oxy-hemoglobin (HbO_2), deoxy-hemoglobin (Hb) and total hemoglobin (tHb); b) oxy-saturation (SO_2), water, lipid and collagen concentration.

Figure 1 shows a higher blood content in malignant lesions with respect to the background. This result agrees with the fact that the tumor is a highly vascularized area. Moreover, a marked increase in collagen can be observed in the tumor area with respect to the healthy tissue. This is an interesting result, since up to now the quantification of collagen has never been carried out, neglecting the importance of this constituent which is involved in the onset and progression of breast cancer. Opposite behaviour can be observed in the lipid content, which is higher in the healthy tissue. For benign lesions also an increase of blood and collagen content was observed with respect to the healthy tissue, even if a smaller one.

Significant *p*-values were obtained (from the paired *t*-test) for both malignant and benign lesions with respect to the relative background for most of the main constituents, as reported in table 1.

Table 1. *p*-value obtained by paired *t*-test for benign and malignant lesions with respect to the background for all the constituents concentrations

Lesion type	Hb	HbO_2	tHb	SO_2	Lipid	Water	Collagen
Malignant	0.0001	0.002	0.0001	0.009	0.0001	0.045	0.0001
Benign	0.003	0.3	0.03	0.04	0.02	0.2	0.001

The correlation between malignant and benign lesions was also performed. Significant differences (*p*-values <0.05) were obtained for the absorption coefficients at all wavelengths. For what concerns the analysis of constituent concentrations between malignant and benign lesions, a comparison of the results is reported in Figure 2.

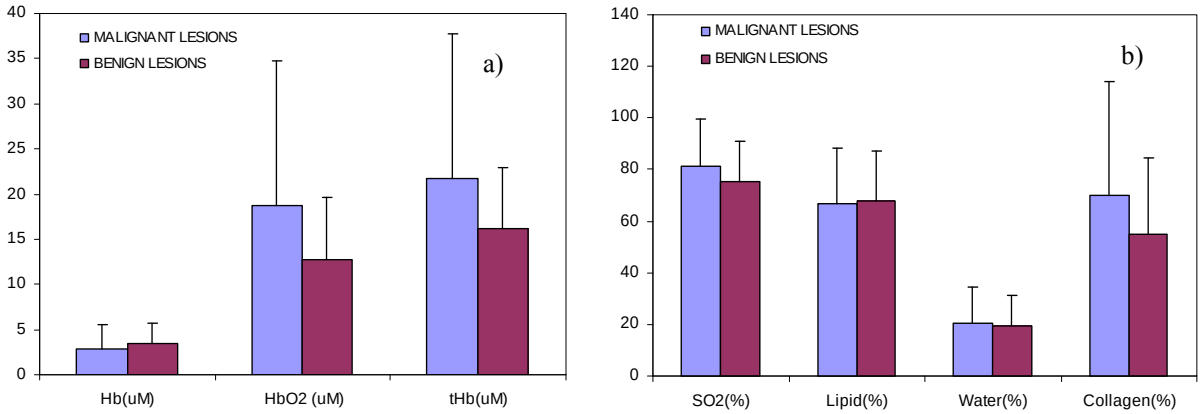

Fig. 2. Comparison of the main constituent concentrations obtained by the perturbative model for malignant and benign lesions. a) Oxy-hemoglobin (HbO_2), deoxy-hemoglobin (Hb) and total hemoglobin (tHb); b) oxy-saturation (SO_2), water, lipid and collagen concentration.

A higher hemoglobin and collagen content in malignant with respect to the benign lesions can be observed in Figure 2. The correlation performed by the unpaired *t*-test led to a significant *p*-value only for the HbO_2 and tHb content.

4. Conclusions

The characterization of benign and malignant breast lesions was performed using a perturbative model. For the first time all the main constituents of the breast tissue such as blood, lipid, water and collagen were obtained. A good discrimination was obtained between lesions (both malignant and benign) and healthy tissue. In particular an increase of blood and collagen was observed in lesions with respect to the background tissue. As a first analysis, a discrimination between malignant and benign lesions seems possible based on the total blood content. More accurate analysis has to be performed in order to better understand the capability of the perturbation method in discriminating different nature of lesions.

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