Near-infrared scattering spectrum differences between benign and malignant breast tumors measured in vivo with diffuse tomography

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Astract: Near-infrared spectral tomographic imaging was used to show that a statistically significant difference exists in the spectral scattering power and amplitude between a group of benign (n=7) and malignant (n=6) tumor tissues imaged in vivo.

OCIS codes: (170.3830) Mammography; (170.6960) Tomography

1. Introduction

Near-infrared multi-spectral imaging is now being evaluated for breast tumor characterization in a number of centers [1-5], and some striking evidence has been presented that near-infrared images can provide functional information about tumor tissue that is specific to the disease type and stage. A considerable focus has been placed upon hemoglobin concentration and oxygen saturation, as these are the strongest absorbing features that can be measured in tissue with diffuse NIR light. However, in addition to these absorption features, there are also scattering features that can be reconstructed which may provide functional information on the cellular and extra-cellular microscopic structure of tissue.

An important feature of NIR measurements is that the underlying signal changes are sensitive to microscopic changes in absorbers and scatterers because the signal measures multiple scattering paths. Thus, small microscopic changes over broad tissue regions contribute to large signal changes because the pathlength of the light transport in tissue is increased 4-6 times from multiple scattering. Increased pathlength results in an increased change in the signal due to local heterogeneities in the tissue.

It is generally thought that bulk scattering coefficient changes result from alterations in the particle size and number density of all of the microscopic elemental changes in refractive index, which contribute to optical scattering. With our current NIR tomography system, we analyze the changes in scattering by fitting the scattering spectrum to an empirical equation which approximates the scattering spectrum of Mie-type scatterers (i.e. Mie scattering occurs when the mean particle size is the same order of magnitude in dimension as the wavelength of light). We have examined both normal and diseased tissues for changes in their scattering spectrum and have found that significant differences exist in the recovered spectral parameters. In this paper, the results of these patient studies are presented.

2. Methods

2.1 NIR Tomography System

The hardware and software associated with the instrumentation sub-systems have been described in detail in previous papers [6, 7], but basically exploits frequency-domain signals to measure the optical transmission through breast tissue. Three planes of 16 fibers each are used to contact the breast and two online monitors are used to adjust the contact pressure of the array on the breast. Each of the 48 fibers can be used as either a source or a detector, providing 3 planes of 240 measurements around the periphery of the breast. The images are reconstructed using a diffusion theory finite element simulation of the light propagation, and a non-linear iterative Newton-style reconstruction algorithm. Images are acquired at 6 wavelengths and the data is fit on a pixel by pixel basis to estimate the absorber and scatterer images.

2.2 Human Subject Studies

Women have been recruited through the Breast Imaging Center at the Dartmouth-Hitchcock Medical Center to participate through informed consent in this institutionally approved clinical protocol. The study design included

imaging of both breasts in multiple planes and the reconstruction of images of hemoglobin concentration, oxygen saturation, water content and scattering spectra analysis. The patient is positioned prone during the exam with one breast pendent through a hole in the imaging system table that allows direct tissue contact with the circular ring of optical fibers.

2.3 Spectral Analysis

When the absorption and scattering coefficient images are retrieved at all six wavelengths, theses images are processed through spectral fitting on a pixel by pixel basis to create images of absorber concentration and scatterer parameters. Each of these two fitting procedures are briefly described here.

From the absorption coefficient images the chromophores are assumed to be entirely composed of water, hemoglobin and oxyhemoglobin, and a three parameter fit is performed to optimally estimate the measured spectrum at each pixel in the image. This is achieved by a constrained least-squares algorithm using the linear model:

$$\mu_a(\lambda) = \varepsilon(i, \lambda)\, C(i)$$

where ε is the molar absorption coefficient of each species, i, at wavelength λ, and with a concentration C. This 3x3 matrix equation is solved numerically with the constraints that the concentrations must be positive and that the fraction of water cannot be greater than 100%.

For the scattering spectrum analysis, the model equation has the form:

$$\mu_s'(\lambda) = A\, \lambda^{-SP}$$

where μ_x' is the reduced scattering coefficient, for wavelength λ, and where A and SP are the fitting parameters referred to as the scattering amplitude and scattering power, respectively. For each measurement on a subject, we fit the measured spectrum of $\mu_x'(\lambda)$ the logarithm of this equation and estimate values of log(A) and SP which best fit the data in order to classify the tissue spectrum.

Cancer tumors	**Hb_T (uM)**	**StO_2 (%)**	**Water (%)**	**SP**	**Log(A)**
i) Mean abnormal ROI	49.7	64.8	50.8	11.4	1.7
p-value (t-test)	**0.005**	**<.001**	**0.047**	**<.001**	**<.001**
ii) Mean ROI/contraROI (%)	266%	88%	76%	261%	257%
p-value (paired t-test)	0.11	0.11	0.83	**0.004**	**0.003**
iii) Mean ROI/outsideROI (%)	254%	98%	73%	210%	209%
p-value (paired t-test)	**0.052**	0.34	0.72	0.057	0.059
Benign tumors	**Hb_T (uM)**	**StO_2 (%)**	**Water (%)**	**SP**	**Log(A)**
i) Mean abnormal ROI	32.6	62.6	28.4	8.3	1.2
p-value (t-test)	**<.001**	**<.001**	**0.026**	**<.001**	**<.001**
ii) Mean ROI/contraROI (%)	148%	89%	49%	77%	76%
p-value (paired t-test)	0.063	0.27	**0.044**	0.16	0.16
iii) Mean ROI/outsideROI (%)	130%	95%	59%	108%	94%
p-value (paired t-test)	0.083	0.73	0.076	0.92	0.84
Cancer-Benign difference	**Hb_T (uM)**	**StO_2 (%)**	**Water (%)**	**SP**	**Log(A)**
i) Mean abnormal ROI	17.0	2.2	22.5	3.1	0.4
p-value (t-test)	0.17	0.79	0.32	0.18	0.21
ii) Mean ROI/contraROI (%)	120%	0%	30%	180%	180%
p-value (t-test)	0.11	0.95	0.50	**0.033**	**0.023**
iii) Mean ROI/outsideROI (%)	124%	3.3%	14%	102%	115.0%
p-value (t-test)	0.10	0.74	0.72	**0.009**	**0.004**

Table 1. Mean values of the region of interest (ROI) and t-test analysis for cancers, benign lesions and their differences. In each of the three sections, the first test (i) is the difference between the ROI and the background in that breast, the second test (ii) is the difference in the ratio of the abnormal ROI to the ROI in a paired location in the controlateral breast (contraROI) relative to a ratio of 1.0. The third test (iii) is the difference in the ratio of the ROI to the background value in the same breast relative to a ratio of 1.0. The significant differences (p-value ≤ 0.05) are in bold font.

2.4 Image Analysis

In each image from a symptomatic subject, the location of the abnormality was defined by the radiologist (SPP) using the mammographic views. Then, based upon the location and the size of the abnormality specified, the region of interest (ROI) was analyzed from the NIR breast images, taking care to ensure that the heterogeneities sampled

were within the same quadrant as the ROI specified by the mammogram interpretation. The values of hemoglobin, oxygen saturation, water and scattering power and amplitude were assessed in and outside the ROI, as well as in a mirror view in the contralateral breast as an additional control measurement.

Statistical analysis of the differences in ROI values was completed using paired t-tests for analysis of differences within and outside the ROIs, and using an unpaired t-test to examine differences between the benign and malignant cases.

3. Results

The resulting values are shown on average in Table 1, where statistically significant differences are highlighted with p-values in bold font. The chart is grouped into three sections with cancer tumors (n=6) at the top, benign tumors (n=7) in the middle, and the differences between the two groups in the bottom section of the table. The first metric reported (i) is the mean value in the abnormal ROI. Measures (ii) and (iii) in each section show the ratio of the mean ROI value to the control ROI value taken from the contralateral breast area. These results show that there are significant differences between the ROI and the background for some of the five properties investigated here in cancer tumors but not benign processes. Interestingly, when examining the differences between the benign and the malignant tumor cases only the relative scattering power and amplitude changes show a significant difference based upon the t-tests in this patient group. In the cancer subjects the scattering power and amplitude show significant differences in relative ROI values as a ratio to the contralateral ROI, and the hemoglobin ratio of ROI value relative to the background is significantly different from a ratio of 1.0. In the benign tumors, only the water concentration indicates a significant difference from a ratio of 1.0.

4. Discussion

The results shown here indicate that there are significant changes which occur in the breast in areas identified, which can be measured with NIR spectral tomography. Specific features are signfiicatly different in the region of interest relative to the background in each breast, such as the scattering parameters for cancer tumors, and the water fraction for benign tumors. However, when comparing tumors that are benign to tumors that are malignant, the last section of Table 1 illustrates that the only significant differences detected were in the scattering spectrum parameters, at least within this patient group. While this is a limited sample (n=6 for cancer and n=7 for benign) we can conclude that the evidence suggests that there may be scattering changes which occur in the breast generating these signatures. Interestingly, the differences are only significant when the ratio of ROI to background or ROI to contralateral control-ROI are examined. This would indicate that the inter-subject variation is likely high, and hence it will be likely easier to track contrast changes rather than absolute changes between subjects.

5. Acknowledgements

This work has been sponsored by the National Cancer Institute through grants RO1CA78734 and PO1CA80139.

6. References

1. A. Li, E.L. Miller, M.E. Kilmer, T.J. Brukilacchio, T. Chaves, J. Stott, Q. Zhang, T. Wu, M. Chorlton, R.H. Moore, D.B. Kopans, and D.A. Boas, "Tomographic optical breast imaging guided by three-dimensional mammography." Applied Optics., vol. 42(25) pp. 5181-90.2003.
2. Q. Zhu, N. Chen, and S.H. Kurtzman, "Imaging tumor angiogenesis by use of combined near-infrared diffusive light and ultrasound." Optics Letters., vol. 28(5) pp. 337-9.2003.
3. S. Srinivasan, Pogue, B. W., Jiang, S., Dehghani, H., Kogel, C., Soho, S., Chambers, J. G., Tosteson, T. D., Poplack, S. P., Paulsen, K. D., "Interpreting hemoglobin and water concentration, oxygen saturation, and scattering measured by near-infrared tomography of normal breast in vivo." Proceedings of the National Academy of Sciences of the United States of America, vol. 100(21) pp. 12349-12354.2003.
4. V. Ntziachristos, A.G. Yodh, M.D. Schnall, and B. Chance, "MRI-guided diffuse optical spectroscopy of malignant and benign breast lesions." Neoplasia (New York). vol. 4(4) pp. 347-54.2002.
5. A.E. Cerussi, D. Jakubowski, N. Shah, F. Bevilacqua, R. Lanning, A.J. Berger, D. Hsiang, J. Butler, R.F. Holcombe, and B.J. Tromberg, "Spectroscopy enhances the information content of optical mammography." Journal of Biomedical Optics., vol. 7(1) pp. 60-71.2002.
6. T.O. McBride, B.W. Pogue, S. Jiang, U.L. Osterberg, and K.D. Paulsen, "Development and Calibration of a Parallel Modulated Near-Infrared Tomography System for Hemoglobin Imaging In Vivo." Rev. Sci. Instr., vol. 72(3) pp. 1817-1824.2001.
7. H. Dehghani, B.W. Pogue, S.P. Poplack, and K.D. Paulsen, "Multiwavelength three-dimensional near-infrared tomography of the breast: initial simulation, phantom, and clinical results." Appl. Opt., vol. 42(1) pp. 135-145.2003.