Breast Cancer Applications of Optical Imaging Biomarkers measured with Diffuse Optical Spectroscopic Imaging

Albert Cerussi, Wendy Tanamai, David Hsiang, Sophie Chung, Shwayta Kukreti, Rita Mehta, Enrico Gratton, and Bruce Tromberg

AAPM, 20089
Tuesday, July 28
Current Research Team

Laser Medical & Microbeam Program (NIH: P41-RR01192)
Network for Translational Research in Optical Imaging (NIH: U54-CA105480)
Chao Family Comprehensive Cancer Center (NIH: P30-CA62203)
Disclosures

No corporate funding, however ...

Disclose financial interests with:

– Volighten, Inc.

– FirstScan

The nature of this financial interest and the design of the study have been reviewed by the UCI Conflict of Interest Oversight Committee, and this committee has determined that the investigator’s financial interests will not compromise the quality or reliability of the study.
Outline

I. Diffuse Optical Spectroscopic Imaging (DOSI)

II. Optical Imaging Biomarkers

III. Therapeutic Monitoring with DOSI

IV. Newer Optical Imaging Biomarkers
What is DOSI?

• Diffuse

• Optical

• Spectroscopic

• Imaging

NIR Broadband (650-1000 nm) high penetration in tissue
What is DOSI?

- Diffuse
- Optical
- Spectroscopic
- Imaging

\[ \log \left( \frac{I_0}{I} \right) = \varepsilon c L \]

NIR Broadband (650-1000 nm)
high penetration in tissue
What is DOSI?

- Diffuse
- Optical
- Spectroscopic
- Imaging

Quantitative & model-based
What is DOSI?

- Diffuse
- Optical
- Spectroscopic
- Imaging

Photon Density (P1, Inf)

\[
U(r, \omega) = \frac{S(\omega) \exp[-i\phi_0(\omega)]}{4\pi\nu D} \frac{1}{r} \exp[-k(\omega)r]
\]

Wavevector

\[
k^2(\omega) \equiv \frac{\mu_a}{D} \left[ 1 - i \frac{\omega}{\nu\mu_a} (1 + 3\mu_a D) \right]
\]

Diffusion coefficient

\[
\nu D \equiv \frac{\nu}{3(\mu_a + \mu_s')}
\]

Quantitative & model-based
What is DOSI?

• Diffuse
• Optical
• Spectroscopic
• Imaging

endogenous molecular targets (concentration & disposition)
What is DOSI?

- Diffuse
- Optical
- Spectroscopic
- Imaging

non-invasive 2D mapping (no tomography)
What is DOSI?

- Diffuse
- Optical
- Spectroscopic
- Imaging
DOSI Instrumentation

DOSI Instrument

Handheld probe

Integrated:
Frequency-Domain Photon Migration
Steady-state spectroscopy
650-1000nm, 5s/pt

DOSI Instrumentation

DOSI Instrument

DOSI Measurement

DOSI Instrumentation

mDOSI Instrument

DOSI Measurement


Optical Biomarkers

• Biomarker
  – any detectable biological parameter, whether biochemical, genetic, histologic, anatomic, physical, functional, or metabolic.

• Imaging Biomarkers
  – Example: Tumor Volume (T2)
  – NIR sensitivity: hemoglobin, water, lipids
    • Really a “pre-biomarker”

Optical Biomarkers

Genetic Profiles
Protein Expression
Cell Cycle Stages
Lipid Metabolism
Angiogenesis
Proliferation
Apoptosis

? Hemoglobins
Water
Lipids
Amount / Disposition

✓ NIR Absorption Spectra
### Endogenous Biomarkers

<table>
<thead>
<tr>
<th></th>
<th>Spectral Content</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobin</strong></td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td><strong>Water/Lipids</strong></td>
<td>Low, but wider</td>
<td>Medium</td>
</tr>
<tr>
<td><strong>Water Disposition</strong></td>
<td>Higher/denser</td>
<td>Higher</td>
</tr>
<tr>
<td><strong>Malignancy-Specific</strong></td>
<td>Highest, full NIR</td>
<td>Very high</td>
</tr>
</tbody>
</table>

**Tumor**
Therapeutic Monitoring

• Mainly Neoadjuvant Chemotherapy
  – Pre-surgical chemotherapy

• Standard techniques wrt pathology
  – anatomical vs. functional
  – surrogate endpoints

• ACRIN Trial for DOSI (NTROI)
Question #1

What do the NIR absorption spectra of malignant lesions look like?
Tumor Absorption Spectra

N = 58

## Tumor Absorption Spectra

\[ N = 58 \]

<table>
<thead>
<tr>
<th></th>
<th>T max</th>
<th>T base</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ctHHb</td>
<td>9.98±5.02</td>
<td>5.93±2.42</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>ctO(_2)Hb</td>
<td>21.5±11.3</td>
<td>14.6±7.5</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>LIPID</td>
<td>49.7±18.0</td>
<td>63.2±12.3</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>ctH(_2)O</td>
<td>33.8±21.0</td>
<td>20.0±10.5</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>SP</td>
<td>0.830±0.412</td>
<td>0.634±0.278</td>
<td>0.0038*</td>
</tr>
</tbody>
</table>

Tumor Absorption Spectra

Tissue Optical Index (TOI) = \( \frac{ctHHb \times ctH_2O}{Lipid} \)

Question #2

Are NIR optical imaging biomarkers sensitive to therapeutic effects?

Two cases:  
*Photodynamic Therapy (PDT)*  
*Neoadjuvant Chemotherapy (NAC)*
Optical Biomarkers (PDT)

N = 6 (Ovarian Rat Model)

<table>
<thead>
<tr>
<th></th>
<th>Tumor (pre-PDT)</th>
<th>Tumor (during PDT)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ctHHb</td>
<td>22.1±3.2</td>
<td>24.2±2.7</td>
<td>0.013</td>
</tr>
<tr>
<td>ctO₂Hb</td>
<td>34.6±1.5</td>
<td>28.4±2.9</td>
<td>0.0024</td>
</tr>
<tr>
<td>ctTHb</td>
<td>56.7±2.4</td>
<td>52.6±4.0</td>
<td>0.027</td>
</tr>
<tr>
<td>stO₂</td>
<td>61.2±4.3</td>
<td>54.0±3.8</td>
<td>0.0029</td>
</tr>
<tr>
<td>ctH₂O</td>
<td>24.0±1.5</td>
<td>23.4±1.4</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Optical Biomarkers (PDT)

N = 7

• Correlations
  - R=0.817 ($\Delta$ctTHb)
  - R=0.828 (BPD)
  - R=0.953 ($\Delta$stO2)

Optical Biomarker (Chemo)

Optical Biomarker (Chemo)

Part III/IV
Question 2/5

DAYS: -7(20), 7(34), 11(38), 12(39), 14(41)
Optical Biomarker (Chemo)

Question #3

How early do the optical imaging biomarkers change?
Early Biomarker Changes

### Ratio of Tumor @ 1 week to Tumor @ baseline

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>PATH RESPONDER (N=6)</th>
<th>PATH NON-RESPONDER (N=5)</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>ctHHb</td>
<td>0.73±0.17</td>
<td>1.02±0.05</td>
<td>0.008*</td>
</tr>
<tr>
<td>ctO₂Hb</td>
<td>0.67±0.06</td>
<td>0.82±0.10</td>
<td>0.03*</td>
</tr>
<tr>
<td>ctH₂O (relative)</td>
<td>0.80 ±0.08</td>
<td>0.96±0.03</td>
<td>0.008*</td>
</tr>
<tr>
<td>Lipid</td>
<td>1.30±0.30</td>
<td>1.11±0.14</td>
<td>0.41</td>
</tr>
<tr>
<td>SP</td>
<td>0.88±0.20</td>
<td>0.97±0.20</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Question #4

Do NIR optical imaging biomarkers scale with final pathological response?
Biomarker & Path Response

HER2-, ALL TREATMENTS (N=19)

What can be learned from new optical imaging biomarkers (high spectral bandwidth)?
Water Disposition

Water Disposition

Pathological Complete Response

Pathological Partial Response

Part IV/IV
Question 5/5
Malignancy Specific?

Malignancy Specific?

N = 40
Sensitivity = 95%
Specificity = 89%
PPV = 91%
NPV = 94%


Part IV/IV
Question 5/5
Summary

• Optical Imaging Biomarkers
  – Sensitive indicators of breast lesions
  – Change in response to chemotherapy
  – Change early (< 1 week) in response to chemo
  – May track with degree of pathological response
  – New signatures may improve results
Thank You!

Laser Medical & Microbeam Program (NIH: P41-RR01192)
Network for Translational Research in Optical Imaging (NIH: U54-CA105480)
Chao Family Comprehensive Cancer Center (NIH: P30-CA62203)
Therapeutic Monitoring

Pre-Chemo  Post-Chemo  DOSI Spectra  Optical Biomarkers
Optical Biomarker: Total Hb

What does DOSI measure?

- Hemoglobins: HHb, O2Hb, metHb, coHb, THb, sto2
- Water: H2O, Temperature, BWI
- Lipids: Bulk Lipids, STC
- Other: Mb, Cytochromes, melanin