Quantitative Physiology of the Breast: Impacting Patient Care on Multiple Levels

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Current Strategies in the Breast Clinic

Screening

www.madisonradiologists.com

www.britannica.com

www.cooperhealth.org

http://images.google.com/
Tissue Absorbers, Scatterers and Fluorophores

Absorption (O.D.)

Soret

α β

Absorption (O.D.)

Fluorescence

Wavelength (nm)

Scatterers
- Cells
- Nuclei
- Chromatin / DNA
- Mitochondria / organelles
- Melanin granules
Quantitative Optical Physiology “Toolbox”

**Optical spectrometer**

- Xenon Arc Lamp + Monochromator
- Illumination Fibers
- Collection Fibers
- Imaging Spectrograph
- Cooled CCD

**Inverse Monte Carlo Models**

\[ F(\lambda) \quad R(\lambda) \]

\[ \rightarrow \text{Tissue composition} \]

**Fiber-optic probes**

**Real-time Control / Analysis Software**

- In vivo Breast Tissue Illumination
- Imaging Spectrograph
- Cooled CCD
Inverse MC: An Enabling Technology for Quantitative Physiology

\[ R(\lambda) \rightarrow \text{Monte Carlo Reflectance Model}^1 \]

\[ \text{Optical Properties} (\lambda_x, \lambda_m) \rightarrow \text{Monte Carlo Fluorescence Model}^2 \]

\[ F(\lambda_x, \lambda_m) \rightarrow \text{Intrinsic Fluorescence Properties} \]

\(^1\text{Palmer, GM et al., Appl. Opt. 2006}\)

\(^2\text{Palmer, GM et al., JBO, 2008}\)
Clinical Studies – 1) *In vivo* Optical Biopsy (40 Patients)

Fiber probe inserted into normal and diseased tissues under ultrasound guidance

Diffuse reflectance and Fluorescence EEM’s in UV-Visible

Robust tool for use at time of biopsy
- diagnostics
- prognostics / prescription
- therapeutics
Hypoxia = Aggressive tumors

- Under hypoxic conditions, HIF-1 is upregulated
- HIF-1 upregulates >100 genes that promote angiogenesis, anaerobic metabolism, therapy resistance, metastasis

Applications
- Drug discovery (pre-clinical)
- Prognosis
- Therapy planning
- Therapy monitoring

Dewhirst, Radiother and Oncol 2007
Quantitation of Tumor Oxygenation

*Hemoglobin saturation converted to pO₂ using a model of hemoglobin dissociation. Assumptions: T = 37°C, pH = 7.4, pCO₂ = 40 mmHg, (P₅₀ = 26.6 mmHg)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Malignant</th>
<th>Non-malignant</th>
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<tr>
<td><strong>Badib et al. 1969</strong></td>
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<td>pO₂</td>
<td>21</td>
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<td><strong>Brown et al. 2008</strong></td>
<td>20</td>
<td>59</td>
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<tr>
<td>pO₂</td>
<td>24</td>
<td>39</td>
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Hemoglobin Saturation Histography

Why is there such a diverse range in tumor oxygenation?
A tumor’s oxygenation state at the time of diagnostic biopsy can have important prognostic and therapeutic implications!
Clinical Studies – 2) Breast tumor margin assessment ex vivo (80 Patients)

- Women with stage 0, I, II undergo breast conservation surgery
- The pathologic margin status is an important predictor of local recurrence after BCS.
- 20-70% of women undergo re-excision surgery because of positive tumor margins*

The Clinical Device (alpha version)

Computer + software

Xenon lamp + monochromator

Probe interfaced with tissue

Tissue interface

Spectrograph

CCD
Informative Parameter Maps From Diffuse Reflectance
Margin image analysis

**QuantiPhysiology Toolbox**

**In Vivo Optical Biopsy**

**Ex Vivo Margin Assessment**

### Margin Size (mm)

#### Positive

- Posterior Margin: Positive
- Superior Margin: Negative
- Lateral Margin: Negative

#### Negative

- Posterior Margin: Positive
- Superior Margin: Negative
- Lateral Margin: Negative

### Frequency (samples in bin/total samples)

#### BC/µs'

- Superior Margin: Negative
- Posterior Margin: Positive
- Lateral Margin: Negative

#### THb/µs'

- Superior Margin: Negative
- Posterior Margin: Positive
- Lateral Margin: Negative
The parameter ratios shown above indicate there are significant differences between normal and cancerous margins.
What is the Potential Clinical Impact?

Without probe: 29% re-excision rate, 65% unnecessary tissue removal rate

- Surgeon incompletely removes cancer (FN) 29% 29
- Surgeon completely removes cancer (TN) 71% 71
- Probe correctly classifies cancer (TP) 68% 20 (Probe saves from re-excision)
- Probe incorrectly classifies cancer (FN) 32% 9 (goes back into OR)
- Probe misclassifies negative (FP) 26% 18 (unnecessary re-shaving)
- Probe correctly classifies negative (TN) 74% 53 (Probe confirms tumor-free margins)

With probe: 9% re-excision rate, 18% unnecessary tissue removal rate
Summary and Future Directions

• Quantitative optical spectroscopy of the breast may be a useful tool for clinical breast cancer management
  – Results from over 150 patients in 2 parallel clinical studies are promising
  – Applications: Diagnostic biopsy, prognosis and prediction, therapeutic monitoring, surgical margin assessment

• Future directions:
  – *Optical biopsy*: Investigate optical biomarkers which predict response, or are modulated by response to neo-adjuvant chemotherapy (pilot study underway)
  – *Margin assessment*: Complete 150-patient clinical study; Complete development of faster beta device
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