Preliminary Clinical Results Using an Optical Imaging Device for Breast Tumor Margin Assessment

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Introduction

Breast cancer is one of the most prevalent cancers among American women; 1 in 8 women will develop invasive breast cancer at some point in their life. The American Cancer Society estimates that in 2009, 192,370 women in the United States will be diagnosed with invasive breast cancer and another 62,280 will be diagnosed with carcinoma in situ (DCIS). Reports indicate that 20-50% of patients undergoing breast conserving therapy must undergo multiple surgeries for complete resection of a breast cancer. Currently, surgeons do not have adequate intraoperative assessment tools to ensure that the cancer has been completely removed at the time of first surgery. To address this unmet clinical need, our group has developed a multi-channel optical device that can image breast tumor margins intraoperatively. This device uses diffuse reflectance spectral imaging to sense biochemical and morphological changes associated with cancer. The goal of this study was to determine the potential use for an optical device to reduce surgical re-excision rates.

Methods

Instrumentation & System Characterization
- Device consists of a broadband illumination source, imaging spectrograph, 1024x256 CCD, and 8-channel fiber-optic imaging probe
- The system was characterized retrospectively. The optical properties of all the extracted data were used in Monte Carlo simulations to determine sensing depth and crosstalk. Reproducibility was calculated by taking 10 sequential measurements on 2 specimens and calculating the coefficient of variation for each extracted parameter. Accuracy of the Monte Carlo model was determined from a tissue mimicking phantom study covering the range of optical properties seen in the ex vivo breast tissue.

Clinical Study
- Patients undergoing BCS are consented under an IRB approved protocol.
- 10-15 minutes after the lumpectomy specimen has been removed it is oriented in a plexi-glass box for optical assessment.
- The fiber optic probe images an area of ~1cm x 3cm.
- Diffuse reflectance measurements are made for every hole in the plexi-glass box; the entire specimen is measured with multiple placements.
- 6-10 holes (sites) are inked and correlated with specific pathological diagnosis
- A margin level diagnosis is also obtained from surgical pathology reports

Data Analysis
- Total hemoglobin and β-carotene concentrations along with the wavelength averaged reduced scattering coefficient (<μs>) were extracted from each diffuse reflectance spectral measurement using an inverse Monte Carlo model.
- These parameters were used to create images of the entire measured tumor margin.
- Image descriptive variables were obtained for each parameter map using simple statistics to identify discriminating parameters. ROC analysis was used to build a multivariate model.

Results

System Characterization

<table>
<thead>
<tr>
<th>Values</th>
<th>Sensing Depth, by tissue type</th>
<th>Sensing Carotene, by tissue type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensing Depth, by tissue type</td>
<td>Positive: 0.90 ± 0.43 mm</td>
<td>Positive: 0.90 ± 0.33 mm</td>
</tr>
<tr>
<td></td>
<td>Fibro-glandular: 1.00 ± 0.37 mm</td>
<td>Fibro-glandular: 1.00 ± 0.35 mm</td>
</tr>
<tr>
<td>Accuracy - % error of Monte Carlo model</td>
<td>&lt;2%</td>
<td>β-carotene: &lt;1%</td>
</tr>
<tr>
<td>Reproducibility of measurements</td>
<td>Coefficient of variation &lt; 0.1</td>
<td>Coefficient of variation &lt; 0.1</td>
</tr>
</tbody>
</table>

Table 1. A retrospective evaluation of the characteristics of the system. Sensing depth and crosstalk where determined with Monte Carlo simulations based on the optical properties of all sites with pathological confirmation. Accuracy is based on a tissue mimicking phantom study that covered the range of optical properties seen in ex vivo breast tissue. Reproducibility was tested on 8 sites on 4 different lumpectomy specimens.

Preliminary Results

Table 2. Cross-validated performance of a predictive model on all margins, as well as on positive or close margins only, stratified by depth of disease from margin surface. “Unknown” refers to a close site where disease depth was not stated in the surgical pathology report.

Clinical Impact

Conclusions

The retrospective characterization of the system showed that the device is capable of probing tissue approximately 1mm from the margin and can do so in a reproducible manner with <1% crosstalk between adjacent channels. The phantom study showed that μs and β-carotene can be extracted with <10% error. Simple statistics and a multivariate model were developed and cross-validated, resulting in a sensitivity of 79.4% and a specificity of 66.7%. These preliminary results show that we can optically differentiate negative and positive margins and can have a potential impact on margin assessment. In the future, we will investigate building similar multivariate models with a larger dataset and will also investigate a pixel-level approach where a model can be developed from pathologically confirmed sites/pixels.

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