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

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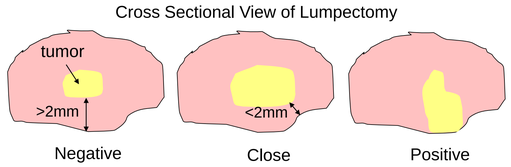
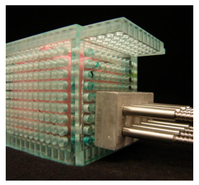
Introduction

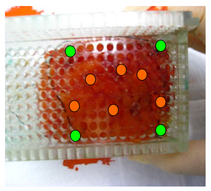
Breast cancer is one of the most prevalent cancers among American women; 1 in 8 women will develop invasive breast cancer at some point in their life. The American Cancer Society estimates that in 2009, 192,370 women in the United States will be diagnosed with invasive breast cancer and another 62,280 will be diagnosed with carcinoma in situ (CIS). 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.



Breast Conserving Surgery (also known as a lumpectomy or partial mastectomy) In BCS, the surgeon attempts to excise the tumor along with a 2mm margin (or rim) of normal tissue as shown in the cartoon.

Methods





Instrumentation & System Characterization

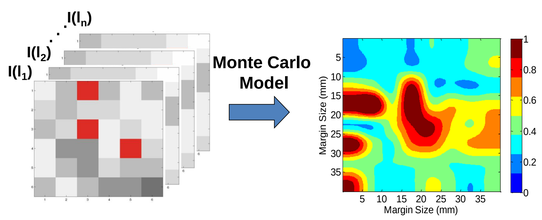
- Device consists of a broadband illumination source, imaging spectrograph, 1024x256 CCD, and 8-channel fiber-optic imaging probe
- The system was characterized retrospectively. The optical properties of all the extracted data were used in Monte Carlo simulations to determine sensing depth and crosstalk. Reproducibility was calculated by taking 10 sequential measurements on 4 specimens and calculating the coefficient of variation for each extracted parameters. 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 (<μ_s'>) 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.



	Total
# of Imaged Patients	48
# of Imaged Margins	55
# of Positive/Close Margins	34
# of Negative Margins	21

Results

System Characterization

	Values
Sensing Depth, by tissue type	Positive: 0.90 ± 0.43 mm Adipose: 1.33 ± 0.63 mm Fibro-glandular: 1.00 ± 0.37 mm
Accuracy - % error of Monte Carlo model	<μ_a>: 6.29% <μ_s'>: 9.81%
Crosstalk from adjacent fibers	< 1%
Reproducibility of measurements	Coefficient of variation < 0.1 for all extracted parameters

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

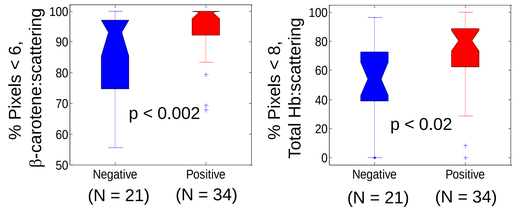


Figure 2. Boxplots of the two descriptive variables that were used to create a predictive model for differentiating positive and negative margins. P-values were calculated using a Wilcoxon rank-sum test.

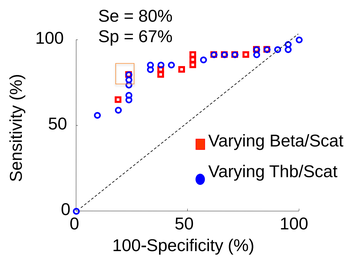


Figure 3. An ROC curve of the predictive model based on the descriptive variables shown in the boxplots. The best sensitivity and specificity achieved with this analysis were 80% and 67% respectively.

Example Data

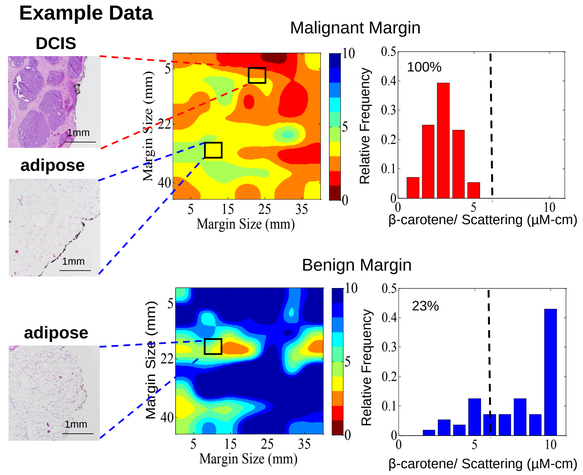


Figure 1. Optical images and histograms that show the ratio of β-carotene concentration to <μ_s'> of a malignant and benign margin. Two sites are shown on the malignant margin: one that contained ductal carcinoma in situ (DCIS) and another that consisted entirely of adipose cells.

Clinical Impact

	All Margins		Positive Margins, by Distance of Disease from Surface			
	Path- Positive	Path- Negative	At Surface	Close, < 1mm	Close, 1-2mm	Unknown
Probe-Positive	27	7	14	5	5	3
Probe-Negative	7	14	3	2	1	1
Sensitivity	79.4%		82.4%	71.4%	83.3%	75.0%
Specificity	66.7%					

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 the margin surface. "Unknown" refers to a close site where disease depth was not stated in the surgical pathology report.

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 μ_a and μ_s' 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.

DUKE BME

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