Optical imaging of breast tumor margins: influence of clinical factors on measured data

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BACKGROUND

Optical spectroscopy can quantify the tissue composition of normal and malignant breast tissues. Our multi-disciplinary group is seeking to utilize optical technology for the intra-operative assessment of tumor margins during breast-conserving surgery (BCS) due to the high re-excision rate in this patient population (20-70%)[1]. A multivariate model to differentiate positive/close margins from negative margins was developed on data from 48 patients and had a sensitivity of 79.4% and a specificity of 66.7%[2].

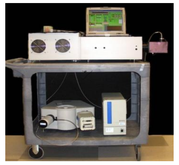
OBJECTIVES

✓ Demonstrate the feasibility of a handheld optical spectral imaging probe for intra-operative assessment of breast tumor margins

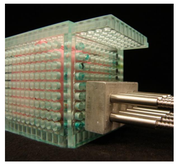
✓ Determine the effect of menopausal status and breast density on the accuracy of the margin prediction model

✓ Determine the effect of menopausal status and breast density on the underlying sources of optical contrast used in the margin prediction model

INSTRUMENTATION



Portable spectrometer and computer interface



Adjustable plexi-glass box and 8-channel fiber optic imaging probe

Sensing Depth of Probe	
Malignant	0.50-1.50 mm
Adipose	0.70-2.20 mm
Fibro-glandular	0.60-1.50 mm

Table 1. Sensing depth was determined with Monte Carlo simulations based on the optical properties of sites with pathological confirmation.

The fiber optic probe covers an area of ~1cmx3cm and takes ~25 seconds for data acquisition and processing. The sensing depth for clear margins at Duke University Medical Center is 2mm; the probe design was optimized to sense close and positive margins.

References:

1Jacobs, L., *Positive margins: the challenge continues for breast surgeons.* Ann Surgical Oncology, 2008. 15(5): p. 1271-2.

2 Wilke, L.G., et al., *Rapid noninvasive optical imaging of tissue composition in breast tumor margins.* Am J Surg, 2009. 198(4): p. 566-74.

3 Palmer, G.M. and N. Ramanujam, *Monte Carlo-based inverse model for calculating tissue optical properties. Part I: Theory and validation on synthetic phantoms.* Applied Optics, 2006. 45(5): p.1062-1071.

4 Palmer, G.M., et al., *Monte Carlo-based inverse model for calculating tissue optical properties. Part II: Application to breast cancer diagnosis.* Applied Optics, 2006. 45(5): p. 1072-1078.

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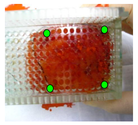
METHODS

Clinical Study: Patients undergoing BCS were consented under an IRB approved protocol. 10-15 minutes after excision, the lumpectomy specimen was oriented in a plexi-glass box for optical imaging. The fiber optic probe was interfaced with the margin surface via the holes of the plexi-glass box.

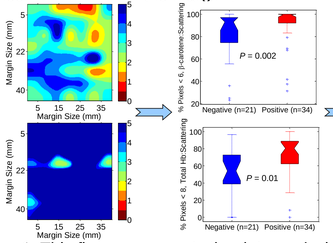
	Set #1	Set #2
# of Imaged Patients	48	92
# of Imaged Margins	55	118
# of Positive/Close Margins	34	63
# of Negative Margins	21	55

Table 2. Breakdown of the number of imaged margins. A close margin is defined as disease < 2mm from the margin. A predictive model based on the data from Set #1 has been published[2]. Set #2 includes the margins from Set#1 plus the remaining imaged margins as of June 2009.

Comparison to pathology: The area imaged by the probe was delineated with green ink for pathologic correlation of margin surfaces. Pathologic margin status of the inked areas was collected from standard surgical pathology reports.



Data Analysis: Total hemoglobin (THb) and β-carotene (which is related to adipose tissue) concentrations, along with the wavelength averaged reduced light scattering coefficient (<μ_s'>) which reflects cell density and collagen density were extracted from each site using an inverse Monte Carlo model[3,4]. 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 predictors. A multivariate model based on the descriptive variables of %pixels less than 6μM-cm for β-carotene:<μ_s'> and %pixels less than 8μM-cm for THb:<μ_s'> was developed and resulted in a sensitivity of 79.4% and a specificity of 66.7% for detecting cancer within 2mm of the margin[2].



	Path +	Path -
Probe +	27	7
Probe -	7	14
Sensitivity	79.4%	
Specificity		66.7%

Figure 1. This figure represents the data analysis steps. Images are of β-carotene:<μ_s'> (one of the two descriptive parameters). The top image is from a margin with DCIS while the bottom image is from a negative margin. The box and whisker plots are for the two descriptive variables in the multivariate model and the table shows the classification results from the model.

RESULTS

How well does a predictive model perform for different patient characteristics?

A)

	Pre-Menopause		Post-Menopause	
	Path +	Path -	Path +	Path -
Probe +	9	2	18	5
Probe -	0	6	7	8
Total	9	8	25	13
Sensitivity	100.0%		72.0%	
Specificity		75.0%		61.5%

B)

	Low Density		High Density	
	Path +	Path -	Path +	Path -
Probe +	10	5	17	2
Probe -	5	6	2	8
Total	15	11	19	10
Sensitivity	66.7%		89.5%	
Specificity		54.5%		80.0%

Table 3. Predictive results from the 48-patient (Set #1) multivariate model. Path + margins contain both positive and close (<2mm) margins. The majority of patients were chemo-naive. A) Breakdown by menopausal status. Path-positive margins in pre-menopausal women contained 5 IDC margins, 2 DCIS, and 2 other types of cancer. Post-menopausal contained 9 IDC, 7 DCIS, and 9 other. B) Breakdown of low and high density breast tissue. Density was calculated from a 4-point mammographic density scale, where low density refers to a 1 or 2 and high density is 3 or 4. Path-positive margins in low density women contained 7 IDC, 5 DCIS, and 3 other. High density women contained 7 IDC, 4 DCIS, and 8 other.

How does breast density affect the underlying contrast between negative and positive margins?

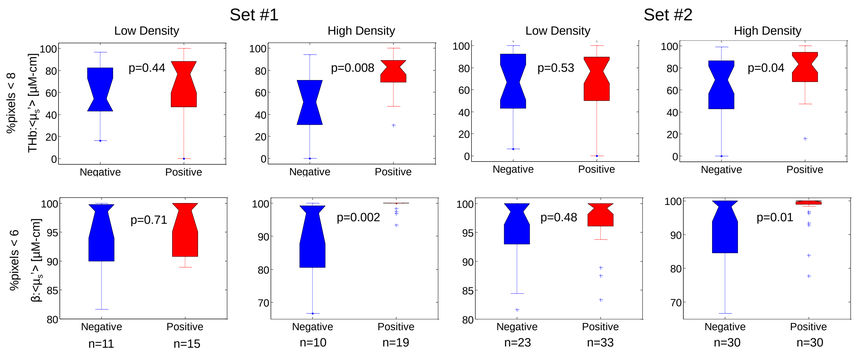


Figure 2. Box and whisker plots of negative and positive/close margins from Set #1 and Set #2 for the descriptive variables used in the predictive model. Plots are separated by low (1-2) and high (3-4) density breast tissue.

What descriptive variables provide the best contrast between negative and positive margins?

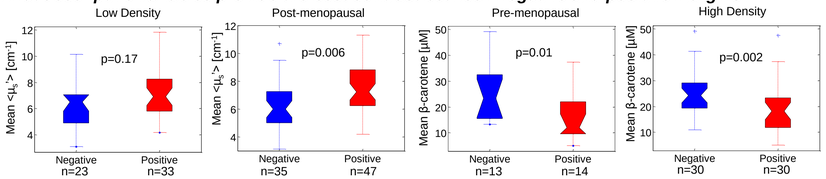


Figure 3. Box and whisker plots of negative and positive/close margins from Set #2. These variables provide the best contrast between negative and positive/close margins. There are additional descriptive variables which also show good contrast for the specific patient characteristics shown here.

DISCUSSION

✓ This preliminary predictive model is best at distinguishing negative from positive margins in patients with high density breast tissue and/or in women who are pre-menopausal.

✓ These results show that breast density and menopausal status will be important parameters in building future predictive models. Patient characteristics clearly have an impact on the optical properties of tissue. Therefore, separating margins by patient characteristics or including patient characteristics as predictors in a model may yield better results.

✓ In post-menopausal women or women with low breast density, contrast in β-carotene is diminished due to more adipose tissue in the margin. The median value of β-carotene (post-menopausal) in negative margins is 21.4μM and in positive margins is 20.0μM. In pre-menopausal women or women with high breast density, this contrast is not confounded by the adipose tissue. The median value of β-carotene (pre-menopausal) in negative margins is 23.3μM and in positive margins is 11.97μM. Median values show much greater contrast in pre-menopausal breast.

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