Opto-Acoustic Nomograms for Improving Breast Cancer Diagnosis

San Antonio Breast Cancer Symposium, San Antonio, Texas, December 9 – 13, 2014

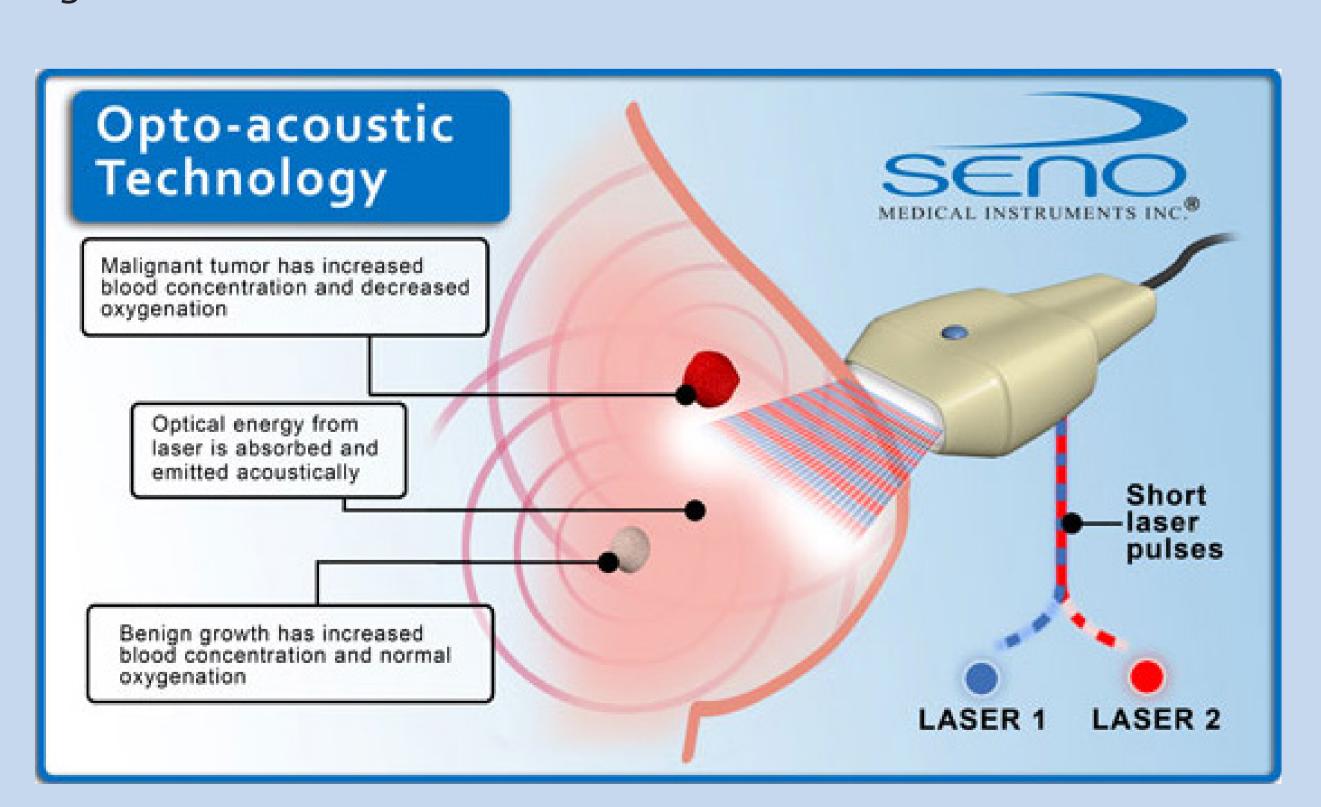### Philip Lavin PhD[1] and A. Thomas Stavros MD[2]

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BACKGROUND

Imagio® (Seno Medical Instruments, Inc.) is currently an investigational medical device being tested in a Pivotal Study for FDA approval. Imagio is a fusion of dual wavelength laser opto-acoustics co-registered with B-mode gray scale ultrasound and shows both structural and functional imaging information about potentially suspicious breast masses without the need for administering contrast agents, radionuclides, or exposing patients to x-irradiation. This hybrid imaging technology has been previously introduced in presentations at medical conferences (1, 2, 3). It may have the ability to increase both sensitivity and specificity of sonographically evident breast masses (1, 2, 3).
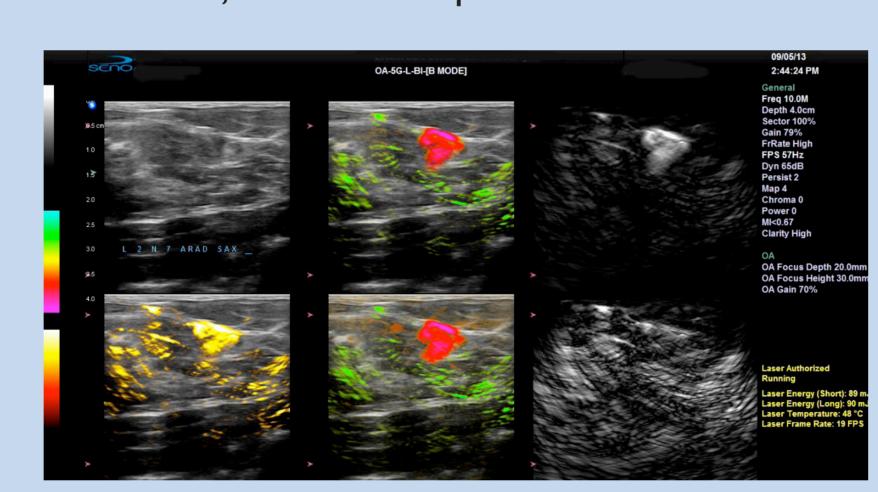
OBJECTIVES

Diagnostic specificity remains disappointingly low for breast imaging modalities that are optimized to achieve near 100% sensitivity. Opto-acoustic (OA) imaging is a fusion of real time co-registered, interleaved OA and gray scale information that shows both functional findings (relative de-oxygenation of hemoglobin) and morphologic data (tumor angiogenesis) within and around breast masses using a hand-held duplex OA probe. We assess the improvement in sensitivities and specificities achieved with nomograms (N) based upon regression models that simultaneously classify (CL) benign (B) vs. malignant (M) and also project probability of malignancy (POM) based on five semi-quantitative OA features that were scored by 23 independent readers (IRs) and an expert reader (ER). We examined both OA individual feature scoring alone and OA feature scoring aided by nomograms for their performances in distinguishing between benign and malignant breast masses.

Opto-acoustic Technology

Malignant tumor has increased blood concentration and decreased oxygenation

Optical energy from laser is absorbed and emitted acoustically

Benign growth has increased blood concentration and normal oxygenation
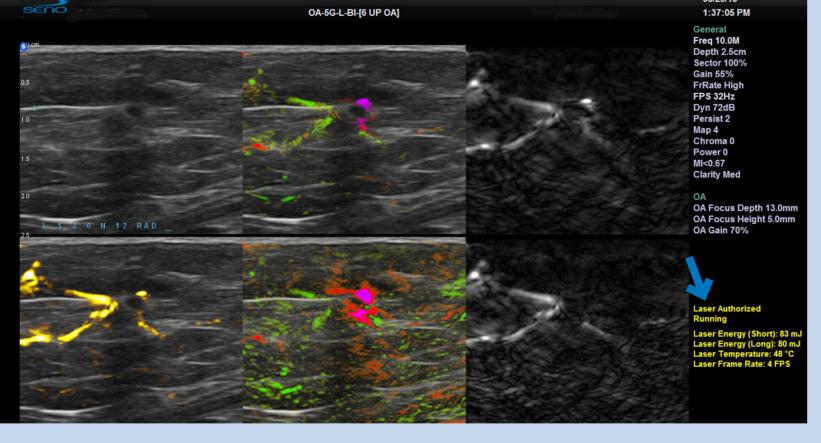
Short laser pulses

LASER 1   LASER 2

METHODS

102 masses from a series of 100 subjects with 80 biopsies (42 B, 38 M) were blindly evaluated and their features scored by 23 independent readers and one expert reader prior to core biopsy in 80 subjects, (22 masses considered BI-RADS 3 were not biopsied.) Three internal OA findings (density of vascularity [V], relative blood oxygen saturation [O], and hemoglobin [H]) and two external OA findings (boundary zone [Z] and peri-tumoral radiating vessels [R]) were assigned 0-5/6 ordinal scores. Feature distributions were compared using a two-sided, Kruskal-Wallis test for benign vs. malignant masses and for benign vs. not biopsied masses.
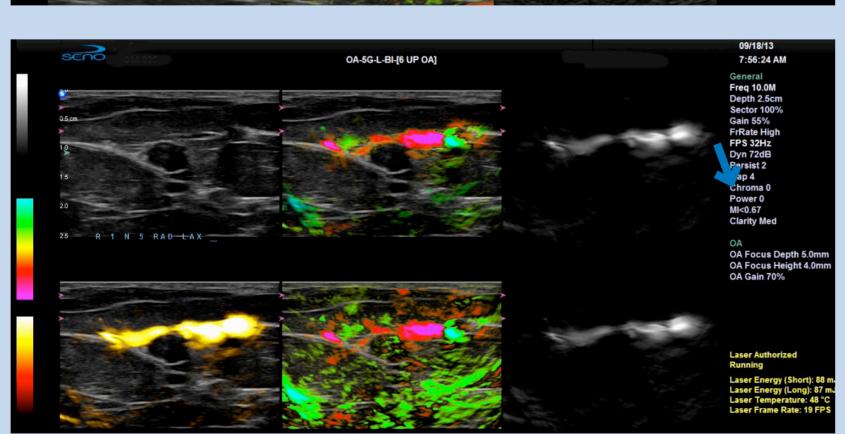
Separate nomograms were constructed using a logistic regression model for the probability of malignancy (CL) and using a linear regression model with an arc sine transformation (POM); both models only used the ordinal feature scores. The coefficients for each model were based on the outcomes of the expert reader (ER). For each mass read, the predicted outcomes were generated. The predicted outcomes were evaluated using an averaged 10% threshold, which was pre-defined.

Figure 1

This 1.1 cm grade 3 invasive duct carcinoma shows an intense red (de-oxygenated) blush that fills the entire lesion. Histopathologic correlations show that diffuse blushes such as this to correspond to innumerable tightly clustered small tumor vessels that are too small to resolve individually.

Figure 2

This tiny (maximum diameter = 3.4 mm) grade 1 invasive duct carcinoma has red (de-oxygenated) tumor vessels on its surface and extending into the surrounding tissues, but relatively little demonstrable tumor vascularity in its central nidus.

Figure 3

This 0.9 cm fibroadenoma is devoid of internal tumor vascularity and internal de-oxygenation. It only slightly indents a prominent, but normal, breast vein that passes directly anterior to the fibroadenoama.

RESULTS

There were consistent significant differences between the feature distributions for benign vs. malignant: density of vascularity (17/23 IRs), relative blood oxygen saturation (11/23 IRs), hemoglobin (17/23 IRs), capsular boundary zone (all IRs), and peri-tumoral radiating vessels (all IRs) always with lower scores for benign vs. malignant.

Differences were minimal for benign vs. not biopsied: density of vascularity (17/23 IRs), relative blood oxygen saturation (11/23 IRs), hemoglobin (17/23 IRs), capsular boundary zone (all IRs), and peri-tumoral radiating vessels (all IRs) always with lower scores for benign vs. malignant.

FEATURE COMPARISONS (23 READERS)

		Vessels	Blush	Hemoglobin	Capsular BZ	Ext PRV
Benign vs. Malignant	% p<0.05	17/23	11/23	17/23	23/23	23/23
	KW P- value	All highly significant: p<0.0000001				
Benign vs. Not Biopsied	% p<0.05	0/23	0/23	1/23	0/23	2/23
	KW P- value	P=0.13	P=0.29	P=0.028	P=0.007	P=0.0014
		Masses not biopsied being re-evaluated after 12 months				

The mean IR sensitivity across all 23 readers was 97.6% and was 97.2% for the expert reader.

The mean IR specificity across all 23 readers was 38.2% and was 71.8% for the expert reader.

The mean specificities from the nomograms were 49% (POM), 43% (CL), and 47.2% (averaged) across all 23 readers.

This represents a 9% absolute increase in the specificity across all 23 readers.

Seno PIONEER Pilot OA Specificity Enhancement Using Averaged Prediction Models

	Observed		10% Threshold	
Reader	Sensitivity	Specificity	Sensitivity	Specificity
All 23	97.6%	38.2%	91.1%	47.2%
Expert	97.2%	71.8%	94.4%	66.7%
Pooled	97.6%	39.6%	93.3%	48.1%
9.2% Absolute Gain in Specificity for Pre-defined Averaged 10% Prediction Threshold				

CONCLUSION

The study results indicate that:

- OA findings to differentiate between benign and malignant masses can be independently and quickly mastered by practicing IRs to consistently differentiate between benign and malignant breast masses.

- Nomograms may offer further confidence to enhance decision making to improve specificity by helping readers use the individual features scores together more effectively.

If confirmed in the Pivotal Study, OA findings may be useful in differentiation and thus sparing biopsies in addition to performing more customized surgeries.

REFERENCES

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IMAGIO SYSTEM

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