OPTO-ACOUSTIC BREAST IMAGING

Imaging-Pathology Correlation of Opto-Acoustic Features in Benign and Malignant Breast Masses

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FINANCIAL DISCLOSURES

- Dr. Butler's employer, Yale University School of Medicine, had a research grant from Seno Medical Instruments, Inc.
- Dr. Tucker has a research contract with Seno Medical Instruments, Inc. to provide central pathology review and histopathology analysis services.
- Dr. Lavin's employer, Boston Biostatistics Research Foundation, has a research contract with Seno Medical Instruments, Inc. to provide study design and analysis services.
- Dr. Neuschler's employer, Northwestern University Feinberg School of Medicine, had a research grant from Seno Medical Instruments, Inc.

INTRODUCTION

- Continued advances in technology and adoption of supplemental screening modalities, such as whole-breast US in women with dense breasts, increase sensitivity of screening
- Specificity of diagnostic work-up using conventional mammography and gray-scale ultrasound remains limited
- Recent national benchmark study[1] reports PPV of biopsy recommendations at diagnostic mammography (PPV2) of 25.6%, and PPV of performed biopsies (PPV3) of 28.6%
- PPVs are within recommended range of mammography performance standards
- BI-RADS 4 category includes broad spectrum of levels of suspicion from as low as >2% for BI-RADS 4A to as high as <95% for BI-RADS 4C

[1]Lehman CD, Arao RF, Sprague BL, et al. National Performance Benchmarks for Modern Screening Digital Mammography: Update from the Breast Cancer Surveillance Consortium. Radiology 2016:161174

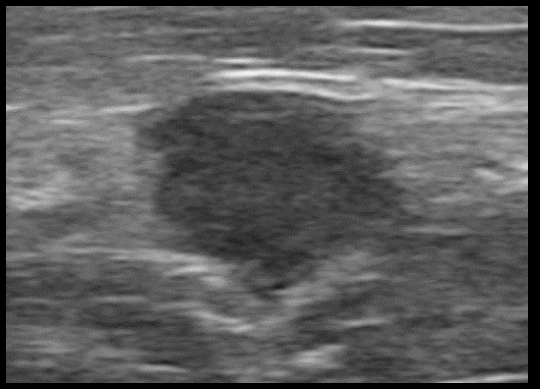
INTRODUCTION

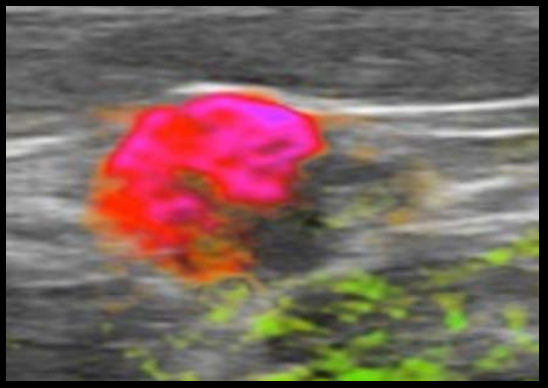
- Harms of false positive imaging have been a topic of considerable discussion
- While the risk/benefit ratio may be debated, it is generally acknowledged that false positive studies are not inconsequential [1-4]
  - Anxiety
  - Discomfort and discouragement from further screening
  - Health care cost
  - Radiation risk
- OA/US may improve specificity through added functional data

[1]Maturitas 2016;92:150-153.
[2]Ann Intern Med 2016;164(4):226-235.
[3]Acta Radiol 2014;55(10):1174-1179.
[4]Breast 2013;22(4):389-394.

WHAT IS OPTO-ACOUSTIC IMAGING?

- Fused anatomic and functional modality – OA/US
- Gray-scale US shows morphology
- OA maps show
  1. Amount of Hgb in and around breast masses
  2. Level of oxygenation (green) vs. deoxygenation (red) of Hgb
  3. Morphology of tumor vessels
- Based on tumor pathophysiology
  - Malignant tumors trigger neoangiogenesis once they reach a size of about 2 mm
  - Malignant tumors are abnormally metabolically active, extracting oxygen from Hgb to a greater degree than most benign masses or normal tissue





Grade III Invasive Ductal Carcinoma

BACKGROUND

Photoacoustic Imaging

- Photoacoustic effect described by Bell[1] and Roentgen[2]
- Brief illumination of tissues causes slight heating and expansion that generates a sound wave

OA/US

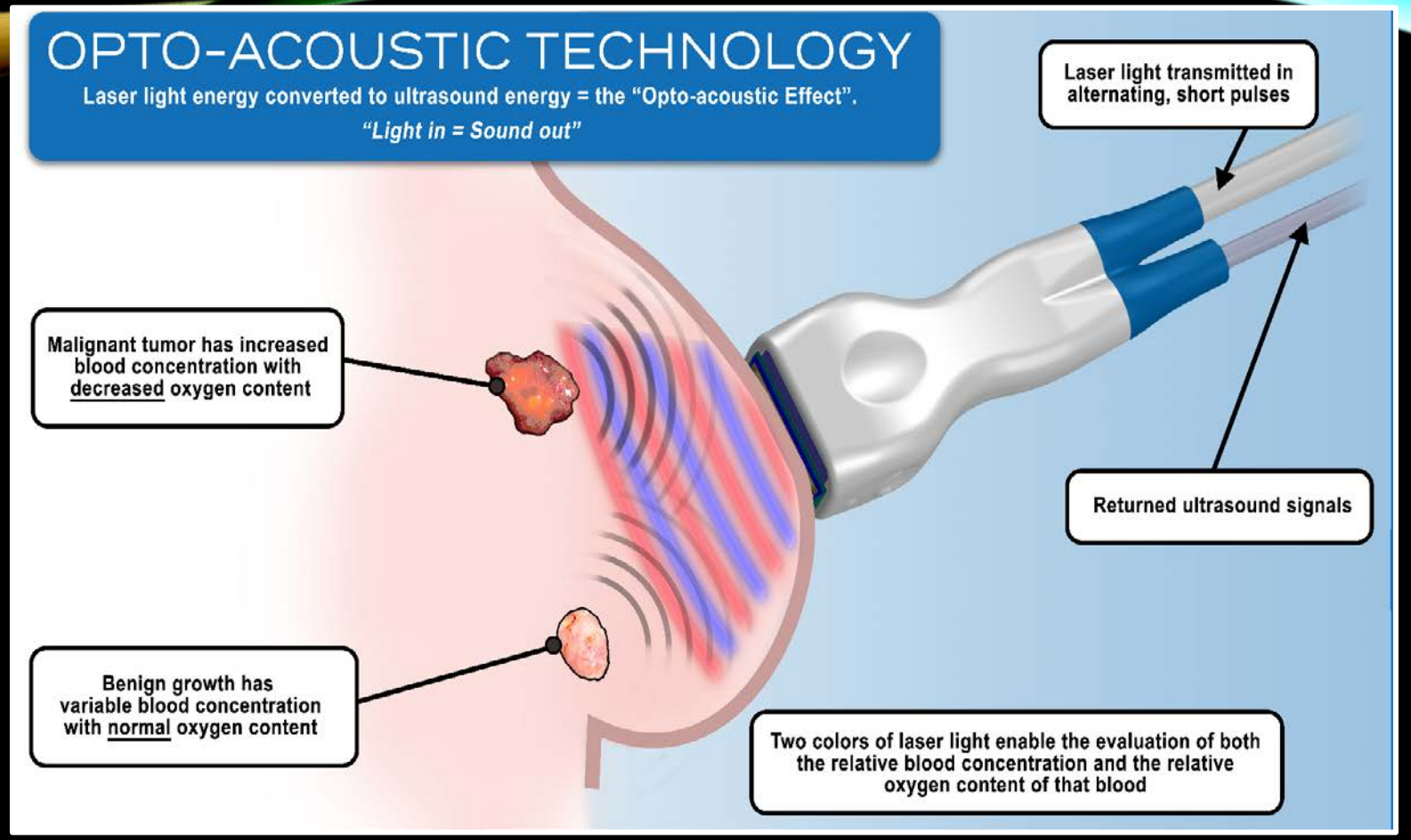
- Duplex transducer emits short pulses of laser light at two wavelengths
  - 757 nm absorbed primarily by deoxygenated Hgb
  - 1064 nm absorbed primarily by oxygenated Hgb
- Momentary heating and expansion of Hgb by bursts of low energy laser light create pressure wave with frequency detected as US signal
- Received echoes are color coded, reflecting degree of oxygenation/deoxygenation of Hgb
- Color-coded data is temporally interleaved and co-registered with the gray-scale ultrasound image in real time
- First ever in a clinical device
- Currently, the subject of a United States PMA filing with the FDA

[1]Am J Sci 1880;(118):305-324
[2]Philos Mag 1881;68(5):308-311

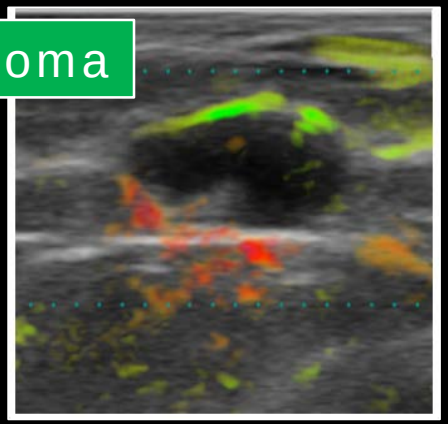
OPTO-ACOUSTIC TECHNOLOGY

Laser light energy converted to ultrasound energy = the "Opto-acoustic Effect".

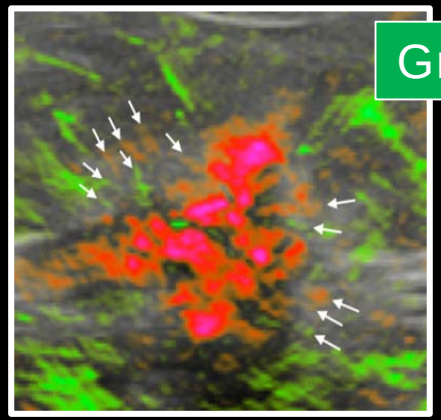
"Light in = Sound out"



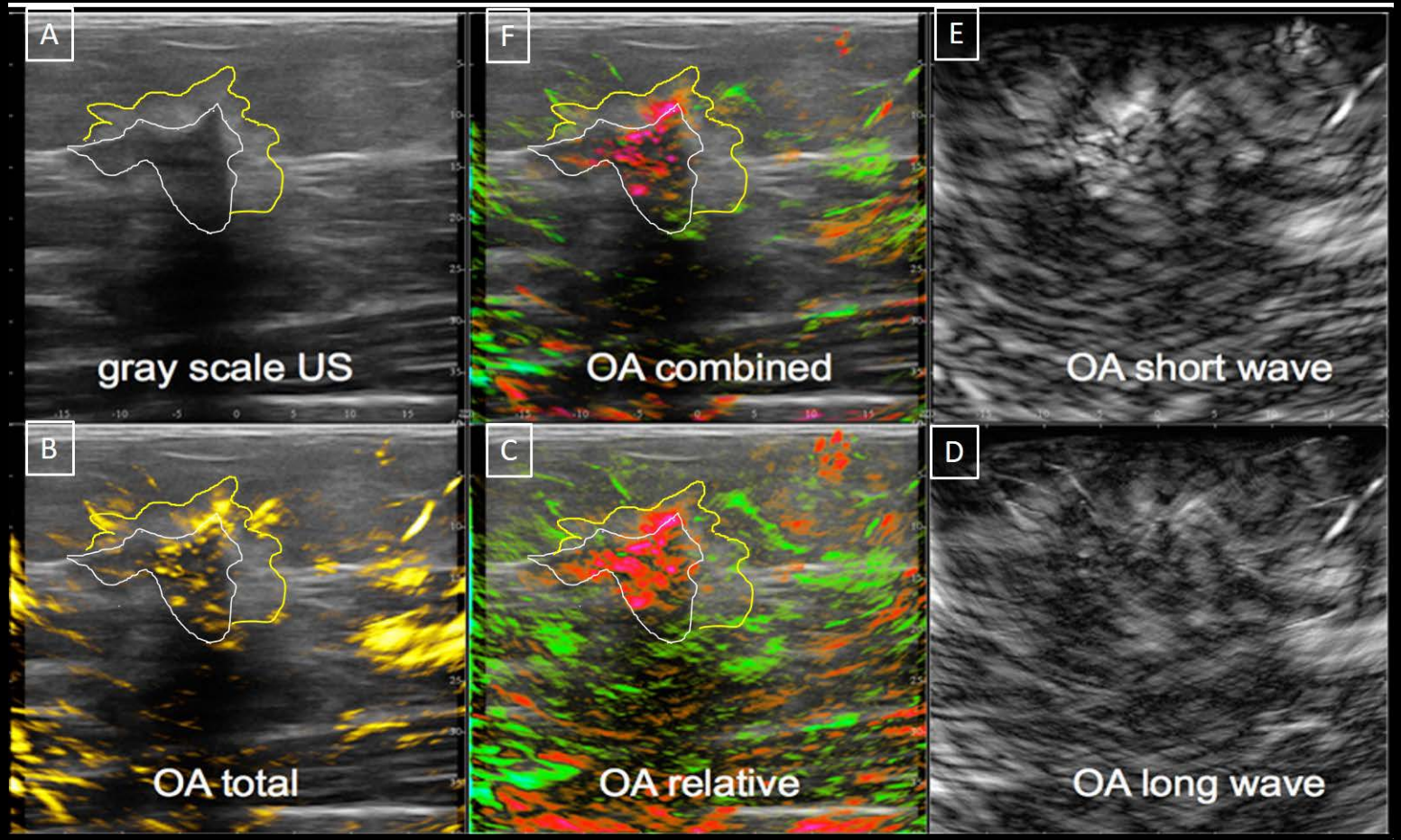
Fibroadenoma



Grade II IDC



6-on-1 DISPLAY



A. Gray-scale US

B. Total map – total amount of Hgb

C. Relative map - relative deoxygenation within and surrounding mass

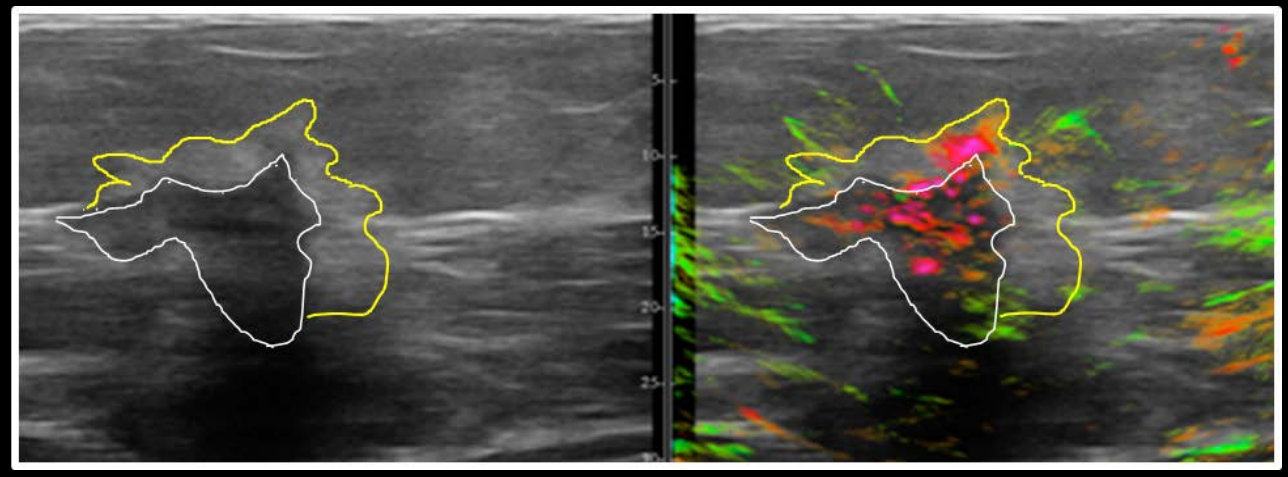
D - E. Long and short wave maps – display anatomical features, i.e. architectural distortion similar to mammography

F. Combined map - degree of deoxygenation within regions containing the most Hgb

TUMOR ZONES

Pathophysiology of benign and malignant tumors defined by 3 zones

- Tumor interior – hypoechoic nidus on gray-scale US
- Boundary zone – hyperechoic “halo” on gray-scale US
- Peripheral zone – tissue surrounding tumor boundary zone



OA/US FEATURE SCORES

Internal Features (3)

- Vessel Score – number and level of deoxygenation of internal vessels
- Blush Score – extent and level of deoxygenation of internal vessels too small to resolve
- Hemoglobin Score – amount of internal Hgb relative to background

External Features (2)

- Boundary Zone Score – number and level of deoxygenation, as well as morphology and orientation of BZ vessels
- Peripheral Zone Score – number and orientation of radiating PZ vessels

OA/US FEATURE SCORES

Internal Features

OA Internal Vascularity and De-oxygenation (Vessel Score)	
0	No internal vessels
1	Normal internal vessels without branches, red or green
2	Normal internal vessels with branches, mostly green
3	Internal signal; green = red in amount and less red than background
4	Internal signal; red > green and red > background
5	Multiple internal red vessels

OA Internal Tumor Blush and De-oxygenation (Blush Score)	
0	No internal vessels
1	Minimal internal signal, all green
2	Mild internal signal; red=green and red + green < background
3	Mild internal signal; red > green and both < background
4	Moderate internal signal; red > green and red also > background
5	Red blush almost fills lesion

OA Relative Internal Hemoglobin (Hemoglobin Score)	
0	No internal hemoglobin (Hgb)
1	Minimal internal Hgb, less Hgb than background
2	Minimal internal Hgb in discrete vessels, Hgb = background
3	Moderate internal Hgb in discrete vessels, Hgb = background
4	Many large internal vessels containing Hgb amount > background
5	Many large Hgb filled vessels almost fill central nidus of mass

External Features

OA External Boundary Zone (BZ) Vascularity and De-oxygenation (BZ Score)	
0	No capsular/BZ vessels
1	Normal capsular/ BZ vessel(s) without branches (long, curved, parallel to capsule, not perpendicular to capsule)
2	Normal capsular/ BZ vessel(s) with normal tapering acutely angled branches, mostly green
3	Capsular/ BZ signal; green = red; red < background red
4	Capsular/ BZ signal; red > green; red > background red
5	>= 3 capsular/ BZ red vessels, some perpendicular
6	Boundary zone de-oxygenated blush

OA Peripheral Zone Radiating Vessels Score (Peripheral Zone Score)	
0	No peripheral zone peri-tumoral vessels
1	1 or 2 peripheral zone feeding or draining vessels, at least one green, not in a radiating pattern
2	> 2 peripheral zone vessels, but random orientation, not radiating perpendicular to the surface of the mass
3	1 or 2 peripheral zone radiating vessels
4	> 2 peripheral zone radiating vessels on one side of the mass
5	> 2 peripheral zone radiating vessels on more than one side of the mass

Note: Higher numbered scores are more suspicious.

PURPOSE

To investigate potential of OA/US to enhance distinction between benign and malignant masses by analyzing the strength of its imaging-pathology correlation.

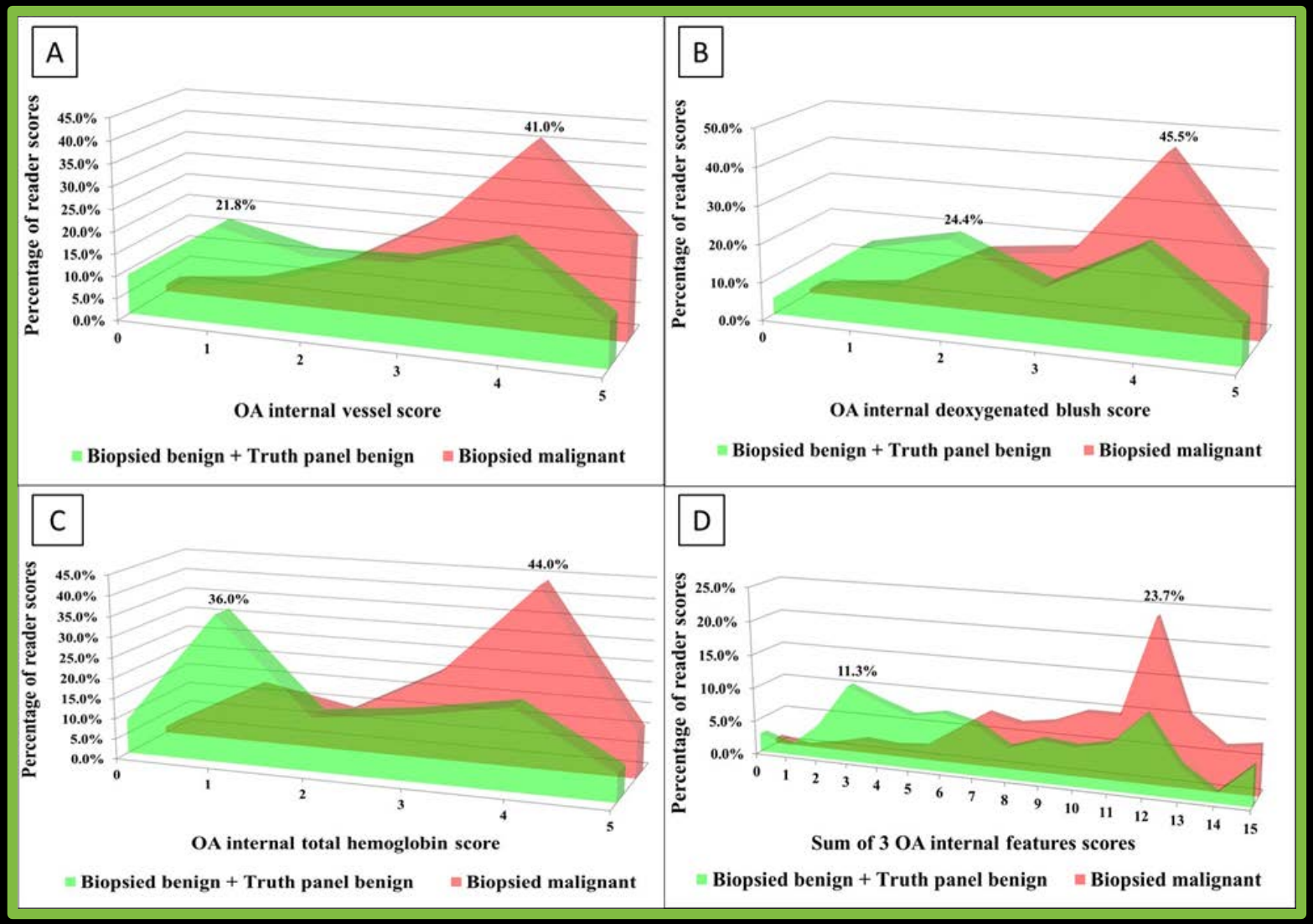
SUBJECTS AND METHODS

- HIPAA-compliant, IRB-approved multi-site study
- Pilot study for larger clinical trial of >2,000 subjects at 16 U.S. sites
- 94 masses in 92 subjects assessed as BI-RADS 3, 4, or 5 on conventional work-up with mammography and gray-scale US were subsequently imaged with OA/US
- Each mass was scored by blinded independent readers on 3 internal and 2 external OA features
- Mean OA/US scores were correlated with histology for biopsied benign and malignant masses and for non-biopsied BI-RADS 3 masses considered benign if stable at 12 month follow-up
- Statistical significance was analyzed using a two-sided Wilcoxon Rank Sum test using a 0.05 significance level

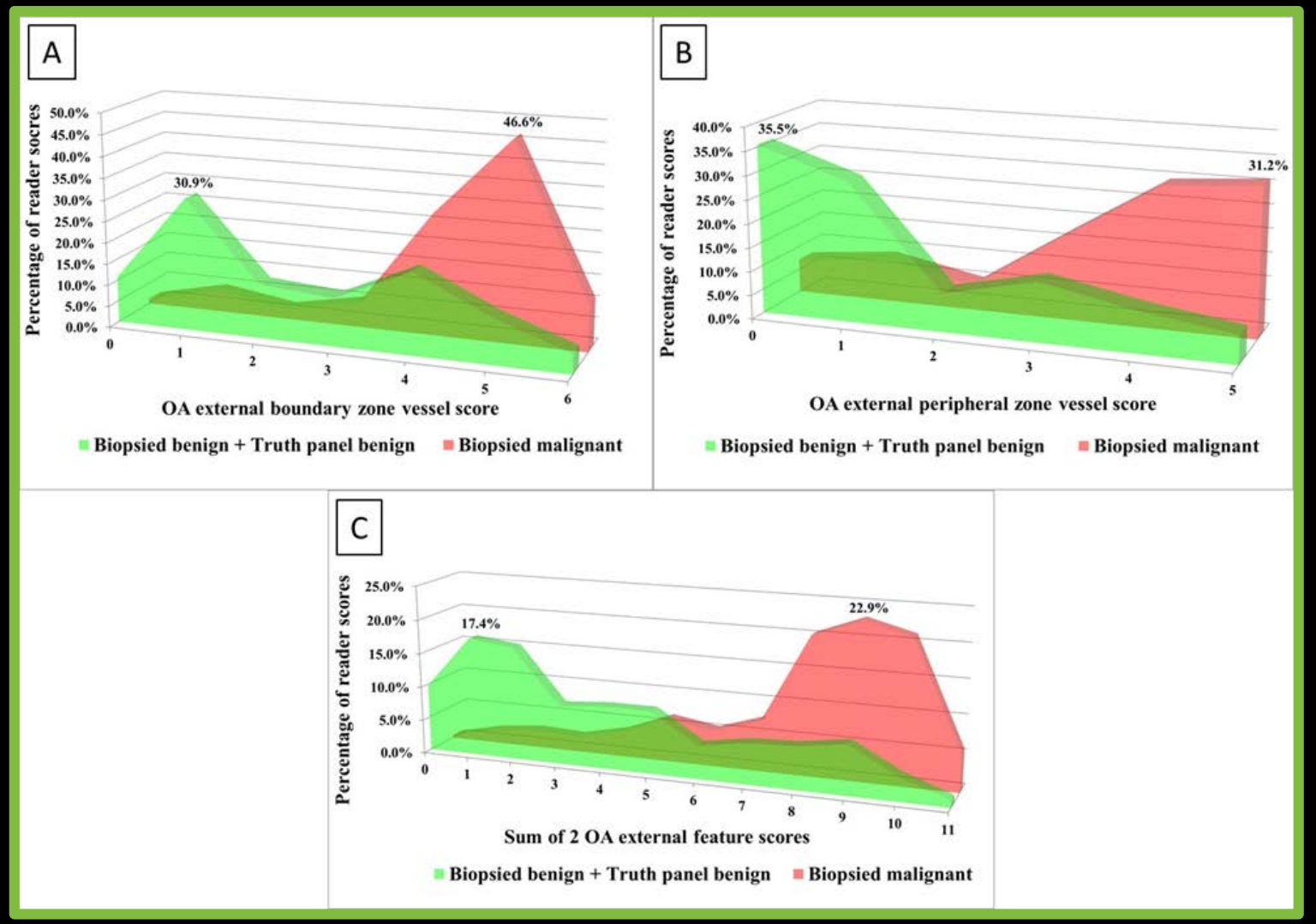
RESULTS

1. Mean OA/US scores for all individual features, as well as summed scores, were higher for malignant masses than for benign masses ($p < 0.0001$).

CORRELATION OF *INTERNAL* OA SCORES WITH BENIGN AND MALIGNANT HISTOLOGY



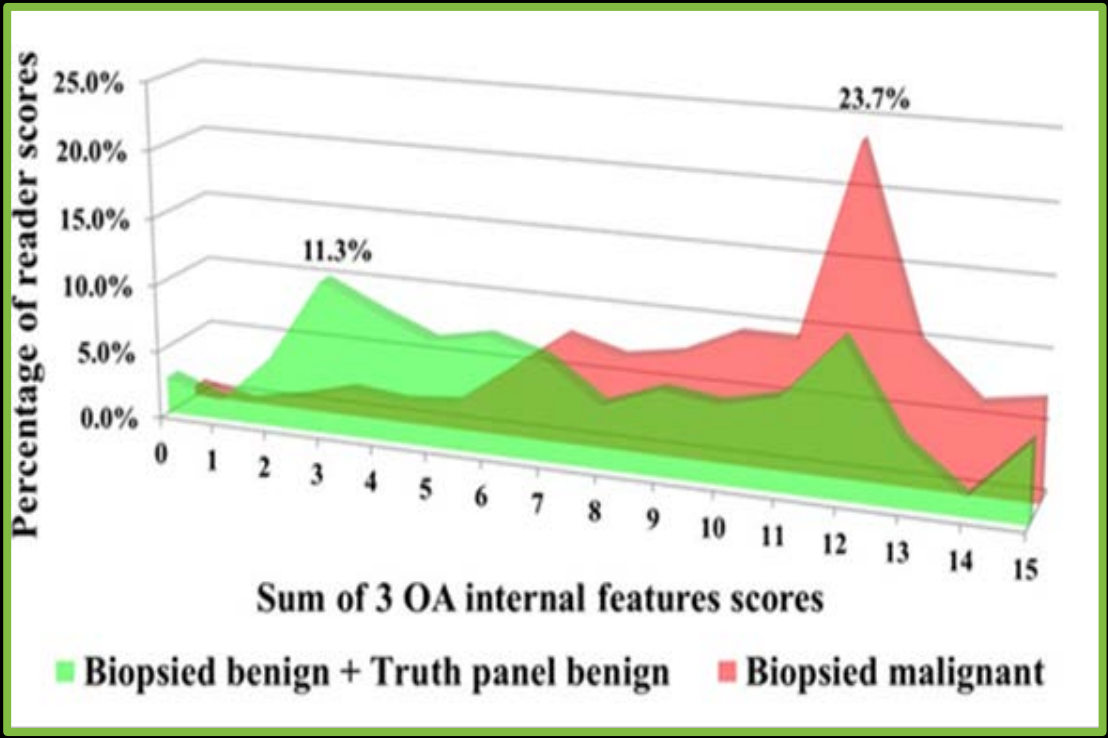
CORRELATION OF *EXTERNAL* OA SCORES WITH BENIGN AND MALIGNANT HISTOLOGY

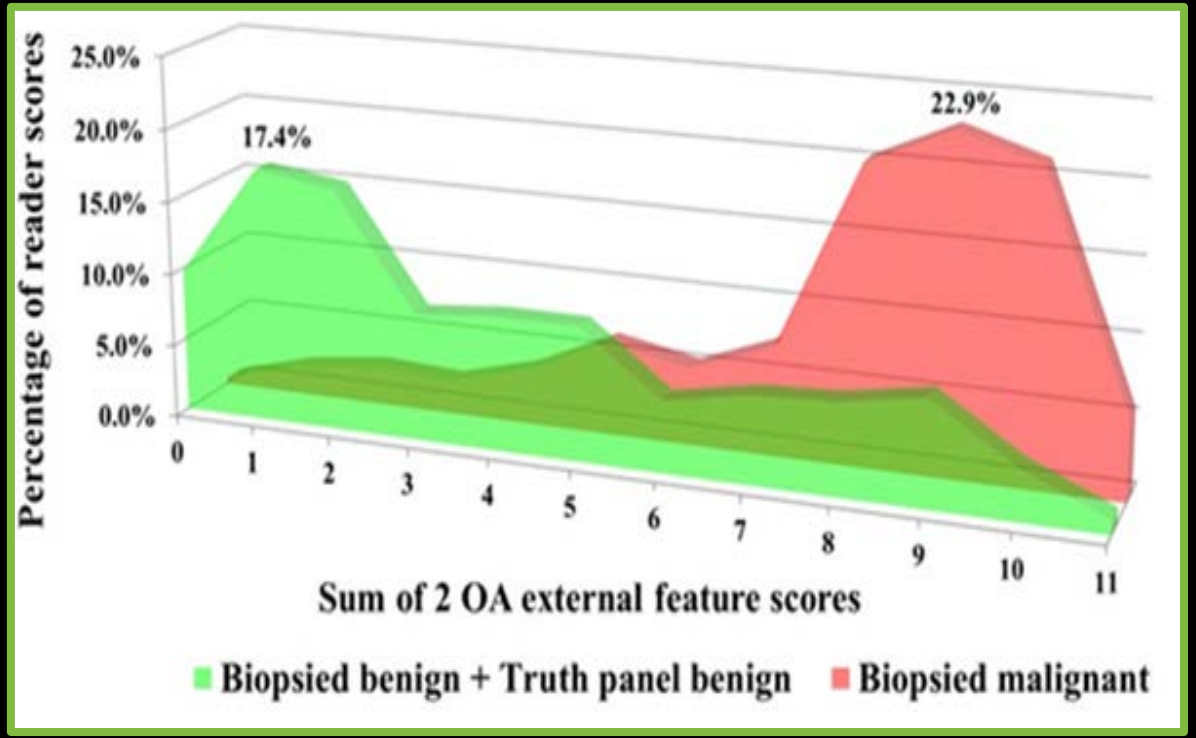


RESULTS

2. Less overlap between benign and malignant masses was observed for external OA features than for internal OA features, suggesting that features in the mass boundary zone and periphery may be more consistent in differentiating between benign and malignant masses than those in the tumor interior.

DISTRIBUTION OF INTERNAL AND EXTERNAL SCORES IN BENIGN AND MALIGNANT MASSES

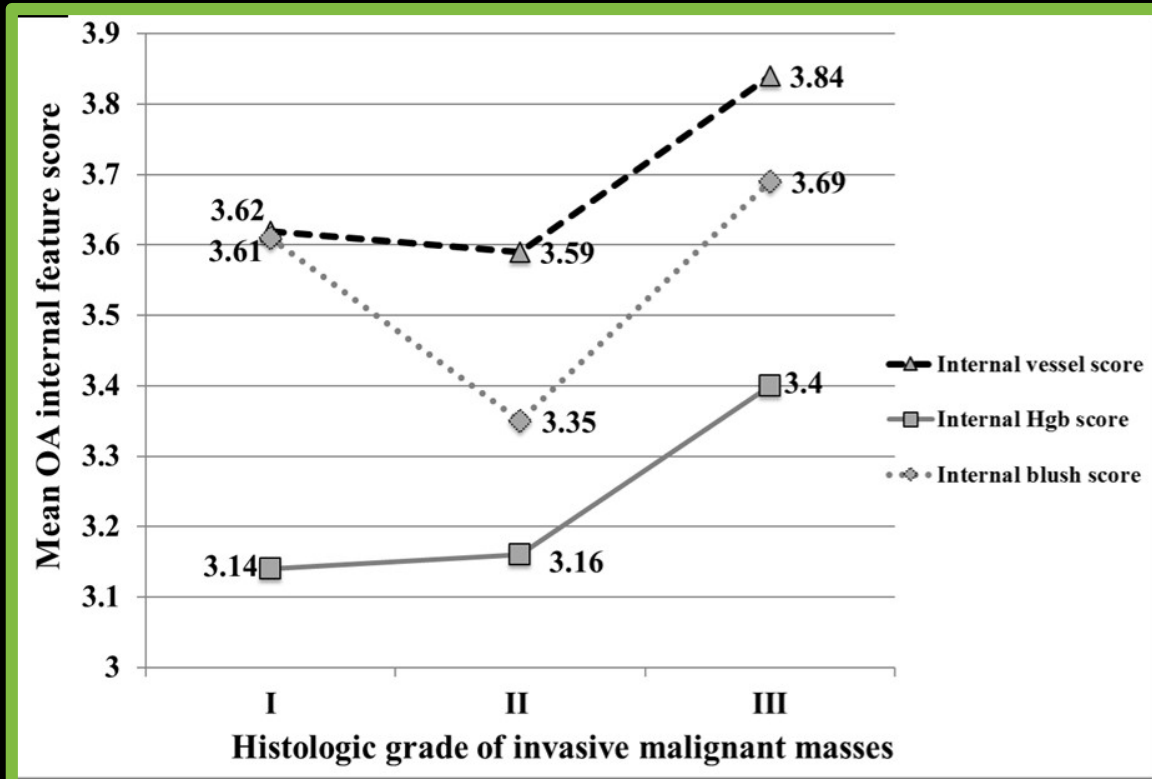


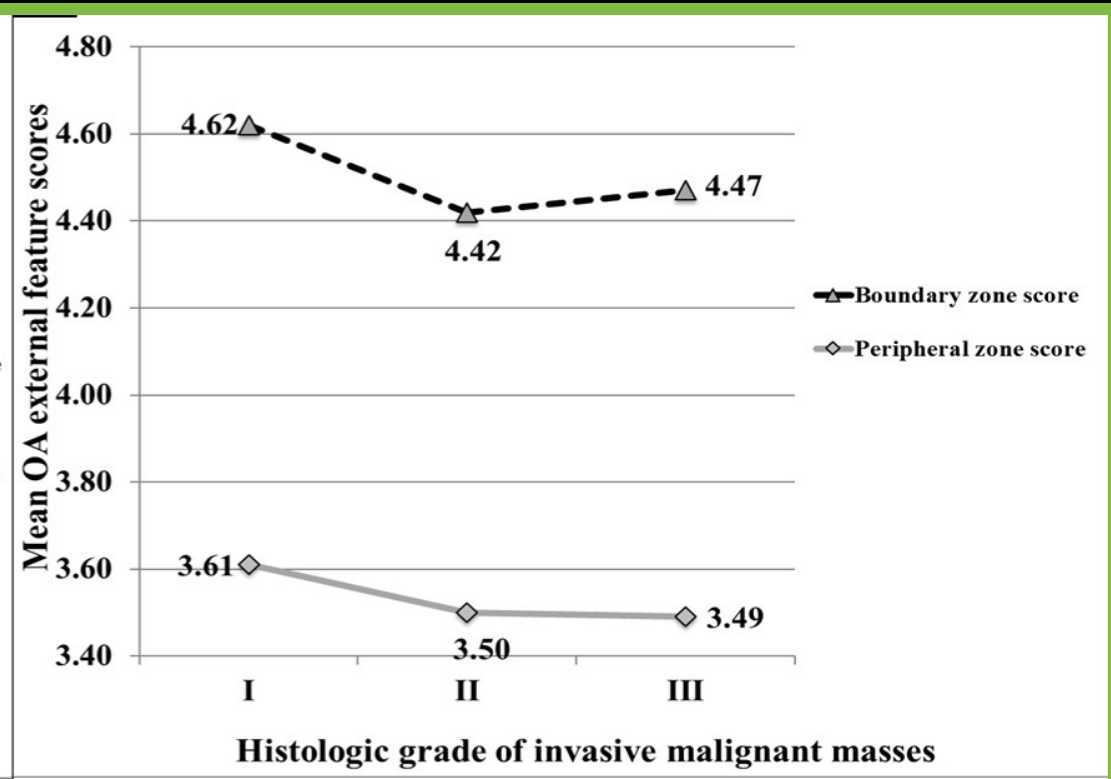


RESULTS

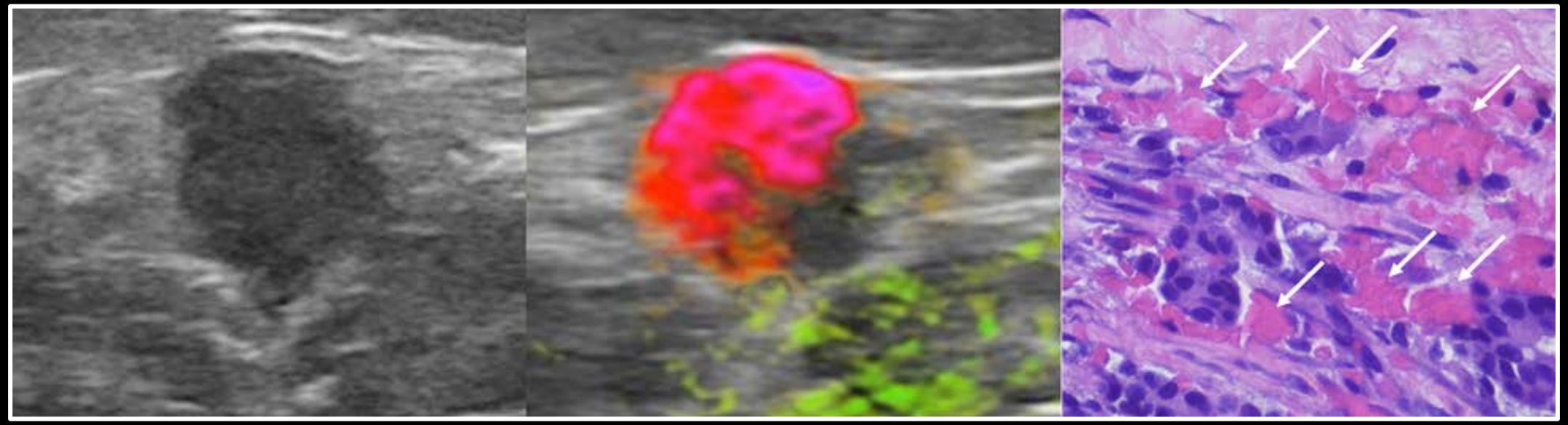
3. Among malignant masses, a trend was observed in the distribution of OA/US features within the 3 tumor zones, with grade I carcinomas yielding low internal and high external scores, while grade III carcinomas produced high internal and low external scores.

MEAN INTERNAL AND EXTERNAL OA SCORES BY HISTOLOGIC GRADE OF INVASIVE MALIGNANCIES

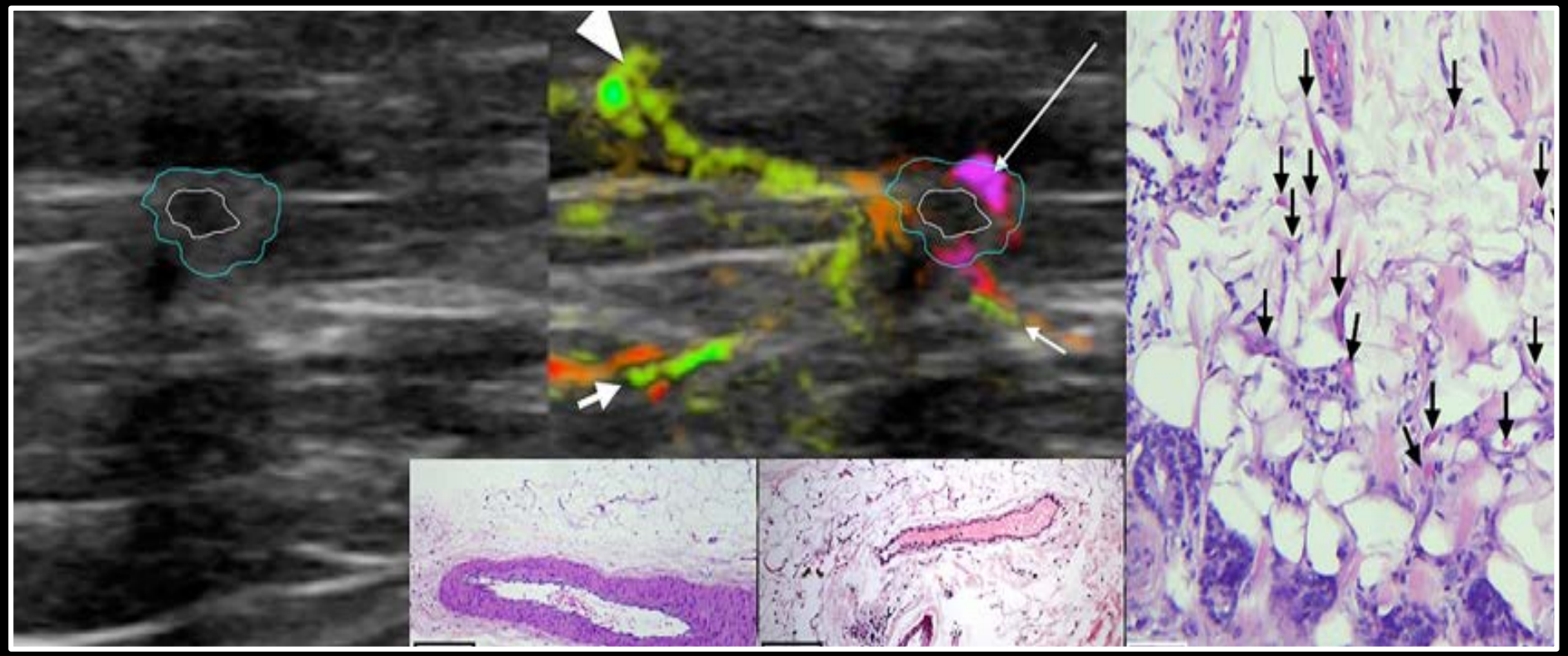




HIGH GRADE (GRADE III)
INVASIVE DUCTAL CARCINOMA WITH PAPILLARY FEATURES



LOW GRADE (GRADE I)
INVASIVE DUCTAL CARCINOMA



CONCLUSIONS

- OA/US provides anatomic and functional data without the need for contrast injection or ionizing radiation.
- In this relatively small population, highly significant differences were observed between benign and malignant masses for all individual internal and external OA scores, summed internal OA scores, summed external OA scores, and total OA scores (all $p<0.0001$).
- Non-significant trends were observed in the OA/US features of low versus high-grade invasive carcinomas.
- Further data based on large, clinical multi-site trial of >2,000 subjects is forthcoming.

Thank you!