A Pivotal Study of Opto-Acoustic Imaging to Diagnose Benign and Malignant Breast Masses: A New Evaluation Tool for Radiologists

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Disclosures

- My employer, Northwestern University Feinberg School of Medicine, had a research grant from Seno Medical Instruments, Inc.
- This research study had financial and equipment support from Seno Medical Instruments, Inc.

Imagio™ is an investigational device that embodies the opto-acoustic technology. The information presented in this presentation is preliminary and not based on an FDA-approved device using this opto-acoustic technology.

Images

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- Other images are from the following manuscript which is currently *"In Press"* for *Radiology* and are indicated on the slides as such.

  - Neuschler EI, Butler R, Young CA, Barke LD, Bertrand ML, Böhm-Vélez M, Destounis S, Donlan P, Grobmyer SR, Katzen J, Kist KA, Lavin PT, Makariou E, Parris TM, Schilling K, Tucker FL, Dogan BE. ***A Pivotal Study of Optoacoustic Imaging to Diagnose Benign and Malignant Breast Masses: A New Evaluation Tool for Radiologists***. Radiology. In press.

Introduction

- Strong evidence that early detection of breast cancer from screening mammography saves lives.[1]
- Push back against breast cancer screening by groups that accentuate the harms of mammography versus its benefits.
- Gray-scale ultrasound is the most frequently used diagnostic imaging modality after mammography.[2,3]
- Specificity of diagnostic work-up using conventional mammography and gray scale ultrasound remains limited

Introduction

Breast Cancer Surveillance Consortium Data (BCSC)[4]

- Just under 1.7 million screening mammograms performed between 2007 and 2013 in approximately 790,000 women
- 39 radiologists across 95 facilities in 6 BCSC registries

Positive predictive value (PPV) of screening mammography was moderate to low

- PPV of biopsy recommendations at diagnostic mammography (PPV2) of 25.6%
- PPV of performed biopsies (PPV3) of 28.6%

Diagnostic Breast Imaging

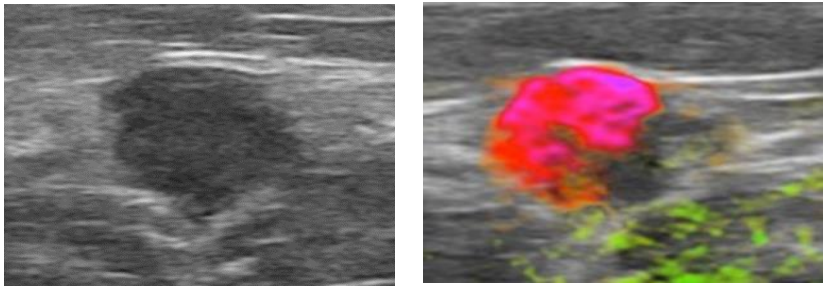
- Gray-scale ultrasound (US) contributes to this low PPV in the diagnostic setting.
- Achieving high sensitivity with gray-scale ultrasound can come at the expense of specificity.
- Overlap in the gray-scale morphology of benign and malignant masses[5]
- Color and power Doppler are of limited value, because there is a significant overlap between vascularization of malignant and benign masses.[6,7]

Functional Imaging

Push to improve specificity has led to increased interest in functional modalities that may reveal non-anatomic characteristics of benign and malignant tumor biology.

What is Opto-Acoustic Imaging?

- Fused anatomic and functional modality
- Gray-scale ultrasound shows morphology
- Opto-acoustic (OA) maps show
  - Amount of hemoglobin (Hgb) in and around breast masses
  - Level of oxygenation (green) vs deoxygenation (red) of Hgb
  - Morphology of tumor vessels



OA/US

Grade III Invasive Ductal Carcinoma

Basis for Opto-Acoustic Imaging

- Malignant tumors produce abnormal neovasculature to support growth once they reach about 2-mm in size[8,9]
- With angiogenesis there is increased blood flow to cancerous tissue
- Cancers are generally more metabolically active and deoxygenate Hgb more than benign entities or normal tissue

Opto-Acoustic Imaging

- According to the photoacoustic effect initially described by Alexander Graham Bell[10] and Wilhelm Roentgen[11], brief illumination of tissues causes slight heating and expansion that generates a sound wave.
- Momentary heating and expansion of Hgb by bursts of low energy laser light create pressure wave with frequency detected as US signal[12-15]
- Received echoes are color coded by wavelength reflecting degree of oxygenation/deoxygenation of Hgb

Investigational Device – OA/US

- Hand-held linear probe which can perform both gray-scale ultrasound as well emits optical pulses via a class 3b laser
- Dual wavelength optical pulses are used to generate the OA images
- Color-coded OA data is temporally interleaved and co-registered with the gray scale ultrasound image in real time

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Class IIIB Laser

- Does not cause damage to the skin but can potentially injure the unprotected eye.
- The laser beam's energy output meets the Laser Institute of America's guidelines for safe use of lasers in health care.
- Subject and all personnel in the experimental area are required to wear protective eyewear.

Opto-Acoustic Imaging

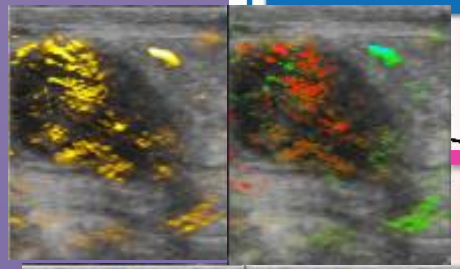
- Pulses of laser light at two wavelengths are applied sequentially to breast tissue
- Near-infrared light (757nm) is absorbed predominantly by deoxygenated Hgb
- Laser light (1064 nm) is absorbed predominantly by oxygenated Hgb

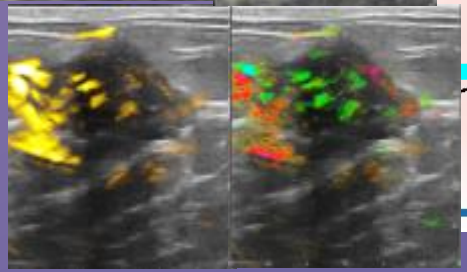
Opto-Acoustic (OA) and Ultrasound Images

Real Time Hemoglobin Map

Malignant more deoxygenated hemoglobin

Benign more oxygenated or absent hemoglobin





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OA/US: Fusion Imaging

Fusion of laser optic imaging and gray-scale imaging in real-time[16-22]

- Optics – high contrast resolution (up to 20/1)
- Ultrasound – high spatial resolution and better penetration than laser alone in diffuse optical tomography

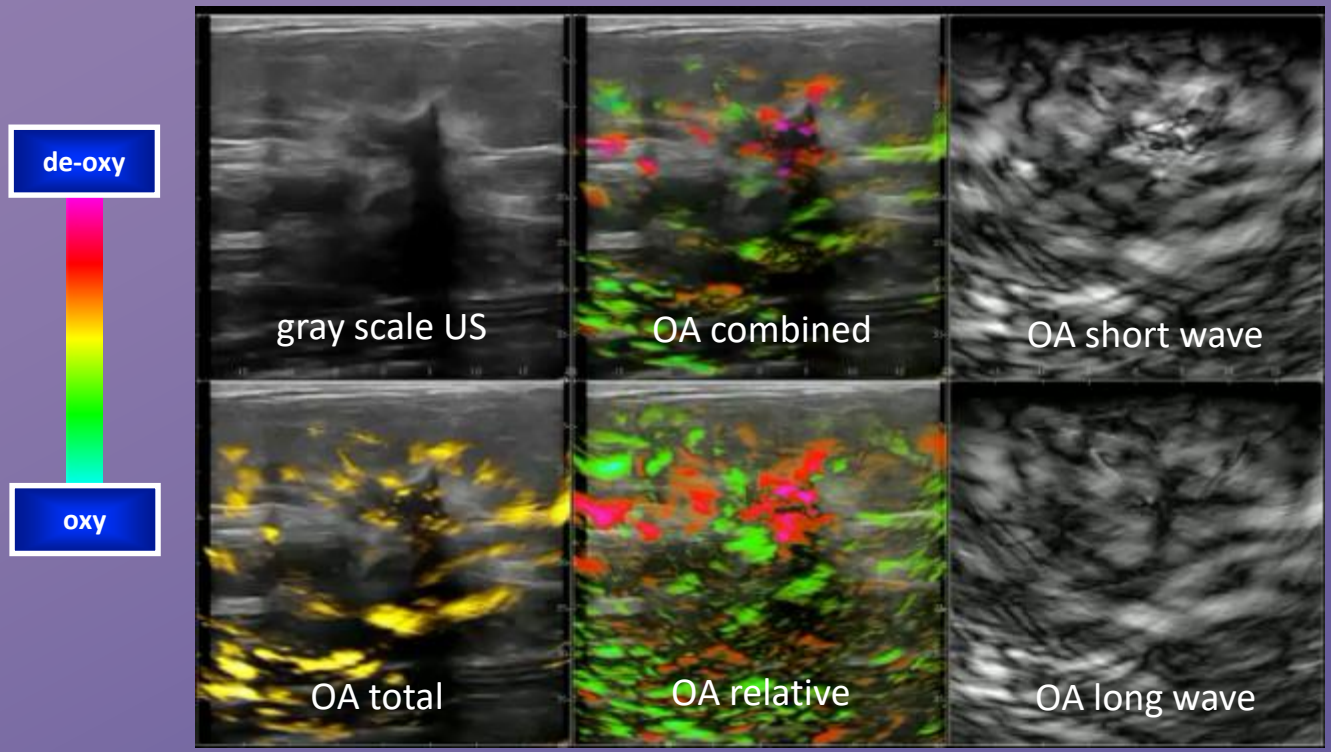
Fusion of anatomy and function

- Anatomy – gray-scale ultrasound anatomy as well as OA demonstration of tumor angiogenesis
- Function – OA demonstration of relative degrees of oxygenation/deoxygenation

OA/US 6-on-1 Real Time Display

1 gray scale map and 5 OA maps are complementary to each other

Invasive ductal carcinoma, grade II



PIONEER-01 Pivotal Study

- A **P**ivotal Study of **I**maging with **O**ptoacoustics to diagnose breast masses detected by mammography and/or clinical findings: A **NE**w Evaluation Tool for **R**adiologists

- HIPPA compliant and IRB-approved prospective, controlled, multicenter observational study.

- Purpose is to compare the diagnostic specificity of OA/US to US alone, utilizing the internal gray-scale US of the OA/US device

- Pivotal study consented 2105 subjects with 2191 masses and 12,283 mass reads was evaluated for the potential ability of OA/US to downgrade BI-RADS (BR) scores in benign masses and upgrade BI-RADS categories of malignant masses.

PIONEER Pivotal Study

2,105 subjects	7 blinded readers	16 sites in the USA

7 academic and 9 private institutions

Subjects and Methods

- Women over 18 years of age referred for diagnostic breast ultrasound
- Indications for ultrasound: palpable mass discovered clinically and/or suspicious imaging findings including mass, architectural distortion, asymmetry, or calcifications, discovered with any screening or diagnostic imaging modality other than ultrasound, within the previous 45 days.
- Subjects with BI-RADS (BR) 3, 4a, 4b, 4c and 5 solid or complex cystic and solid lesions at conventional diagnostic ultrasound were eligible for the study
- December 21, 2012 – September 9, 2015

Inclusion Criteria	Exclusion Criteria
• Female • 18 years of age or older • Suspicious mass(es) diagnosed as BI-RADS 3, 4 or 5 of breast, identified by a health care practitioner within the past 45 days with diagnostic methodology other than conventional ultrasound.	• Presence of a condition or impediment that may interfere with imaging. • Previous biopsy within immediate vicinity of study mass • Current cancer in ipsilateral breast or prior cancer or breast surgery in same quadrant of ipsilateral breast • Greater than 3 suspicious masses • Study mass larger than 4 cm • Pregnant or lactating • Undergoing neoadjuvant therapy • Currently experiencing photosensitivity or photo-toxicity

Subjects and Methods

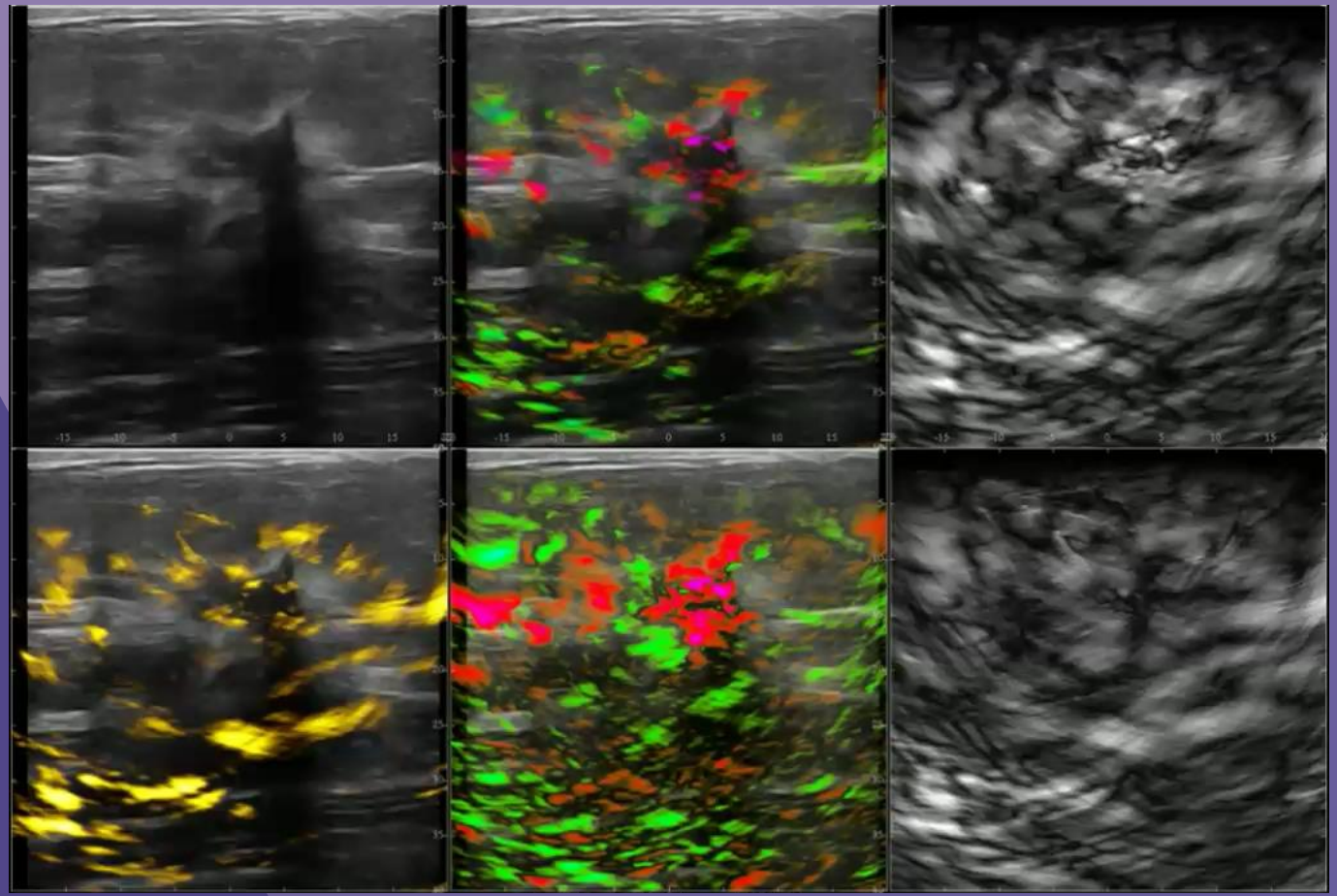
- Intent-to-diagnose (ITD) population defined as those masses exposed to OA/US with interpretable images presented to readers and either underwent biopsy or were determined to be truth panel benign.

- BI-RADS 4 and 5 masses had to undergo biopsy to be included

- BI-RADS 3 masses had to have 12 month follow-up with no upgrade to BI-RADS 4 or 5 and/or diameter change of less than or equal to 20% to be truth panel benign.

Imaging Protocol

- Standardized imaging protocol used at all sites
- Trained site investigator radiologists and sonographers obtained gray-scale images with the OA/US device (internal gray-scale US), immediately before acquiring the OA/US images
- Site investigators did not interpret the internal gray-scale US images or OA/US scans
- Decisions about patient management were based upon standard of care only, i.e. clinical findings, mammography (if performed) and conventional diagnostic US



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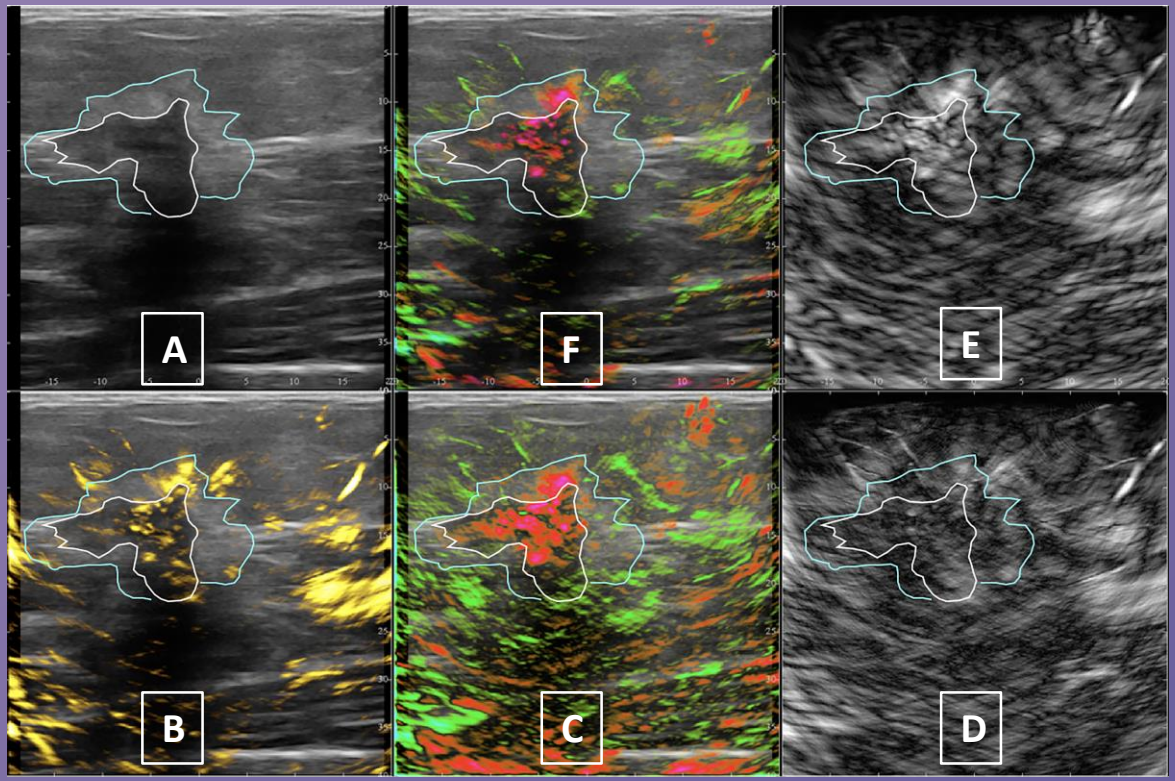
Reader Study

- 7 independent reader radiologists (dedicated breast imagers with over 5 years experience) were trained by an expert reader to identify and score three OA internal features and two OA external features for each mass.
- Independent readers were blinded to clinical data, site imaging and pathology and read all masses from each subject.
- Internal gray-scale US assessment first evaluated with BI-RADS assessment and probability of malignancy assigned and locked prior to reviewing OA/US images.
- OA scores were provided for three internal OA features within the tumor interior and two external OA features

6-on-1 Display



A. Gray scale US

B. Total map – total amount of Hgb

C. Relative map - relative deoxygenation within and surrounding mass

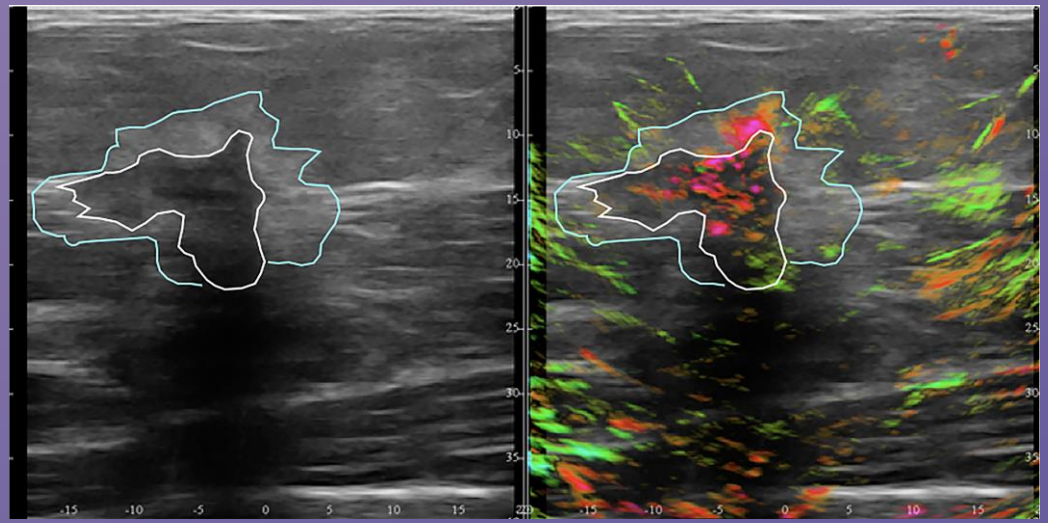
D - E. Long and short wave maps – display anatomical features, i.e. architectural distortion similar to mammography

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



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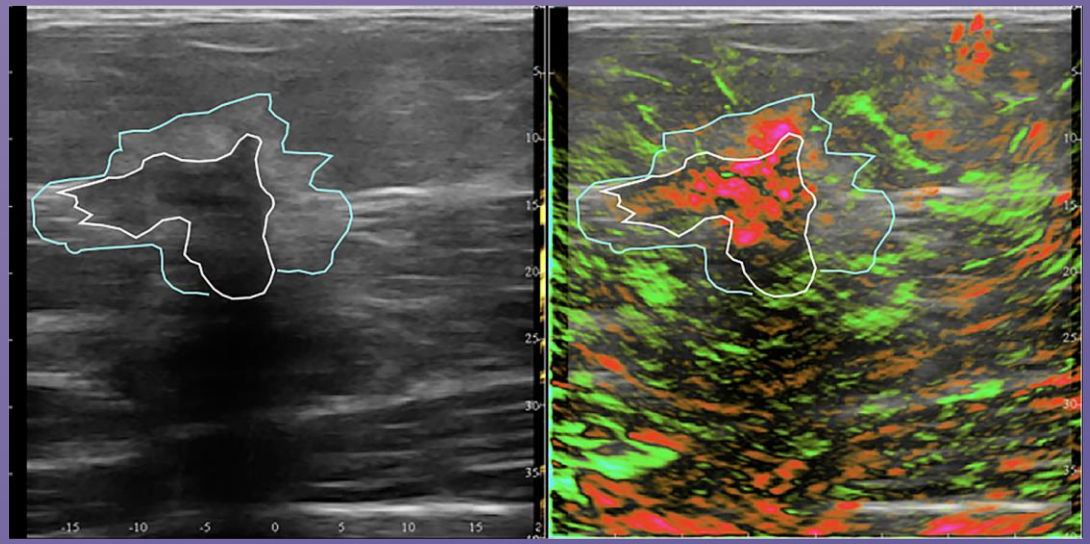

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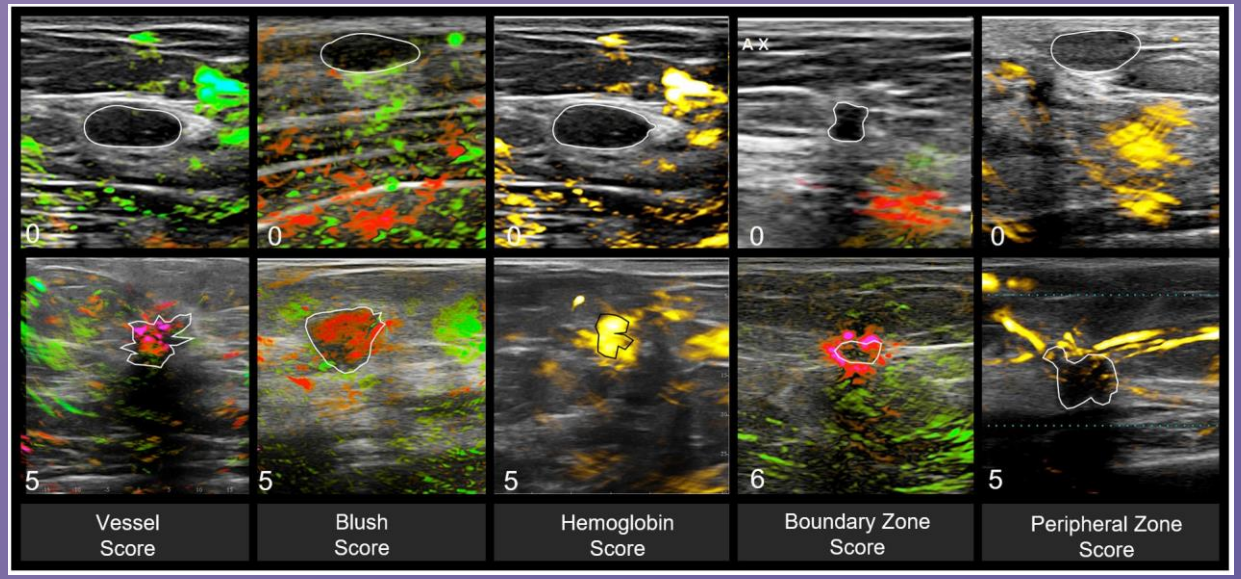
OA Feature Scores and Reference Key

Minimum Feature Score



Maximum Feature Score

Will reference to article in press

OA 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

Subject Populations

- I will have a very similar table to the pivotal paper – however, I do not think I should copy it from article – will construct one that has same data

Table 1

Study Population

Population	No. of Subjects	No. of Masses
Total enrolled	2105 (100%)	2191 (100%)
Subjects excluded from safety population		
OA/US imaging not performed or incomplete*	33 (1.6%)	33 (1.5%)
Pilot study training population	100 (4.8%)	103 (4.7%)
Safety population†	1972 (93.7%)	2055 (93.8%)
Subjects excluded from intent to diagnose population		
Quality/technical failure	169 (8.0%)	177 (8.1%)
BI-RADS 3 mass, no 12-month follow up	38 (1.8%)	38 (1.7%)
BI-RADS 4–5 mass, no biopsy	25 (1.2%)	31 (1.4%)
Consent-related protocol deviation	1	1
Intent-to-diagnose population	1739 (82.6%)	1808 (82.5%)
Subjects excluded from reader study		
High-risk lesion at pathologic evaluation	41 (1.9%)	43 (2.0%)
BIRADS 3 mass, increased size or BI-RADS upgrade at 12-month follow-up but not biopsied	8 (0.4%)	8 (0.4%)
Final reader study population	1690 (80.3%)	1757 (80.2%)

*Technical malfunction or protocol deviation.

†Safety population analyzed for adverse events.

Statistical Analysis

- Multiple reader, multiple case, fixed crossover design in which internal grayscale US assessment locked prior to OA/US evaluation.
- Specificity, sensitivity and BI-RADS score analyses based upon the ITD population, minus BR 3 truth panel change cases, which were not biopsied.
- Effectiveness analyses were performed by using the number of masses, rather than subjects in the ITD population
- Interobserver variability assessed using a weighted Kappa for each reader and summed across readers
- Intraclass coefficients treating the OA feature scale as a continuous variable were also computed to summarize interreader agreement

Results – ITD Subjects and Masses

	Subjects	Masses
Totals	1,739	1,808
Cancer	652 (prevalence = 37.5%)	678 (prevalence = 37.5%)
High Risk	41	43
Benign	848*	889*
Truth Panel Benign (TPB)	190*	190*
Other No Biopsy	8	8
*1,038 benign subjects with 1,079 masses for analysis		

Results – Diagnostic Sensitivity and Specificity

- Independent readers had a mean sensitivity of 98.6% for device US and 96.0% for OA/US.
- Independent readers had a 43.0% specificity with OA/US, which was a 14.9% improvement over internal device US ($p<0.0001$; 99% CI)
- Non-inferiority of OA/US sensitivity relative to IUS is established relative to a 5% non-inferiority margin ($p<0.01$)

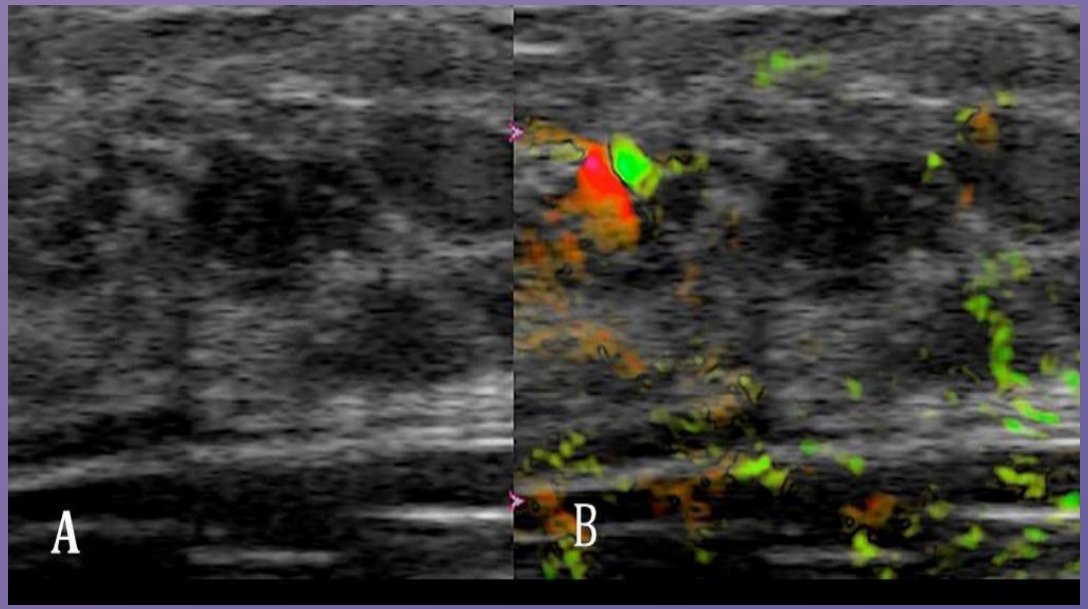
Results – Upgrades and Downgrades

- Using OA/US, 29.1% of benign mass reads classified as BR 4A or higher by internal US were downgraded to BR 3 or 2
- Using OA/US, 48.6% of benign mass reads classified as BR 3 by internal US were downgraded to BR 2
- Using OA/US, 47.0% of malignant mass reads classified as BR 3 by internal US were upgraded to 4A or higher

Results – Upgrades and Downgrades

- 12,283 OA/US reads and 12,289 internal gray-scale US reads compared with diagnostic outcomes of biopsied malignant and biopsied benign plus truth panel benign masses
- Correct downgrades (2,601 reads) was significantly higher than the number of incorrect upgrades (453 reads) with OA/US ($p<0.0001$)
- Correct upgrades (1,453 reads) was significantly higher than number of incorrect downgrades (783 reads) among malignant masses ($p<0.0001$)

Downgrade Case: BI-RADS 4B on Internal US to BI-RADS 3 on OA/US
Biopsy revealed benign fibrocystic changes



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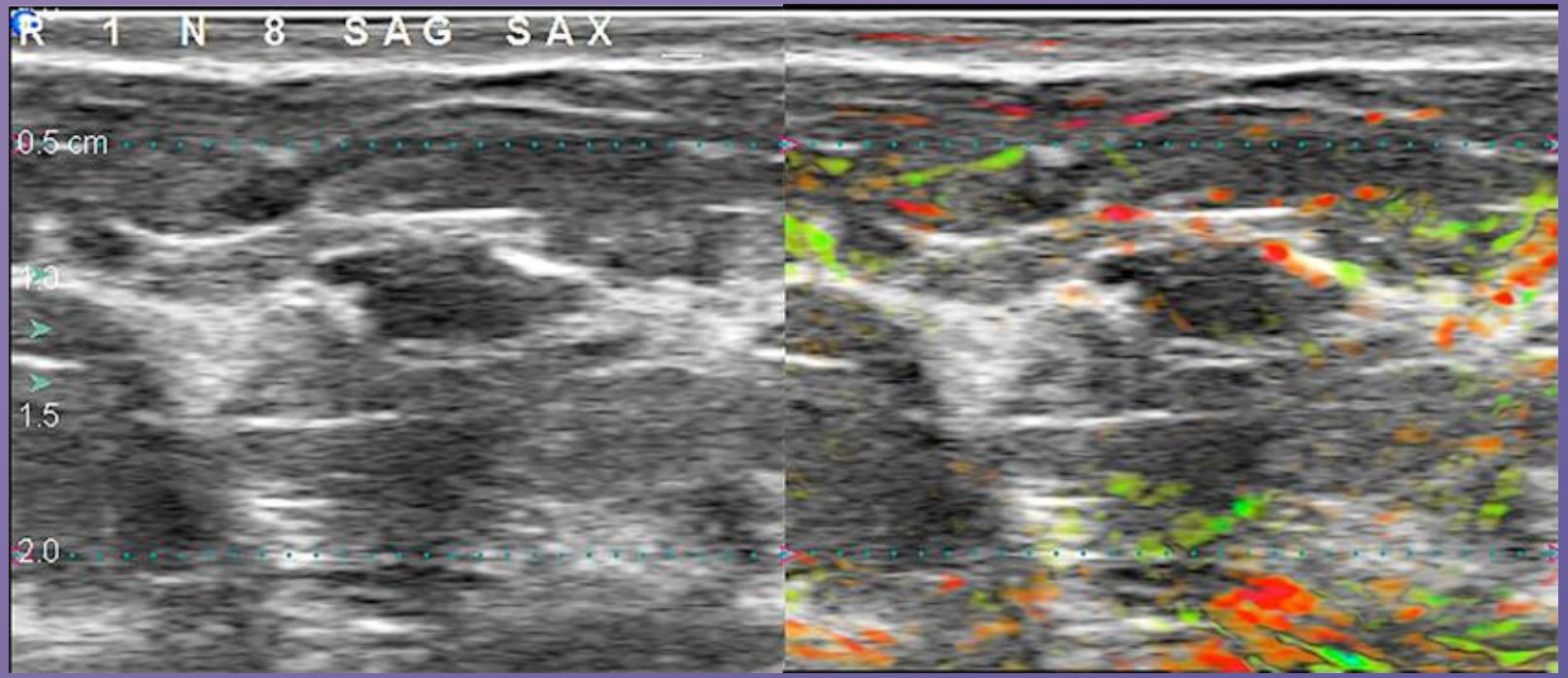
Downgrade Case: BI-RADS 4A on Internal US to BI-RADS 3 on OA/US
Biopsy revealed fibroadenoma



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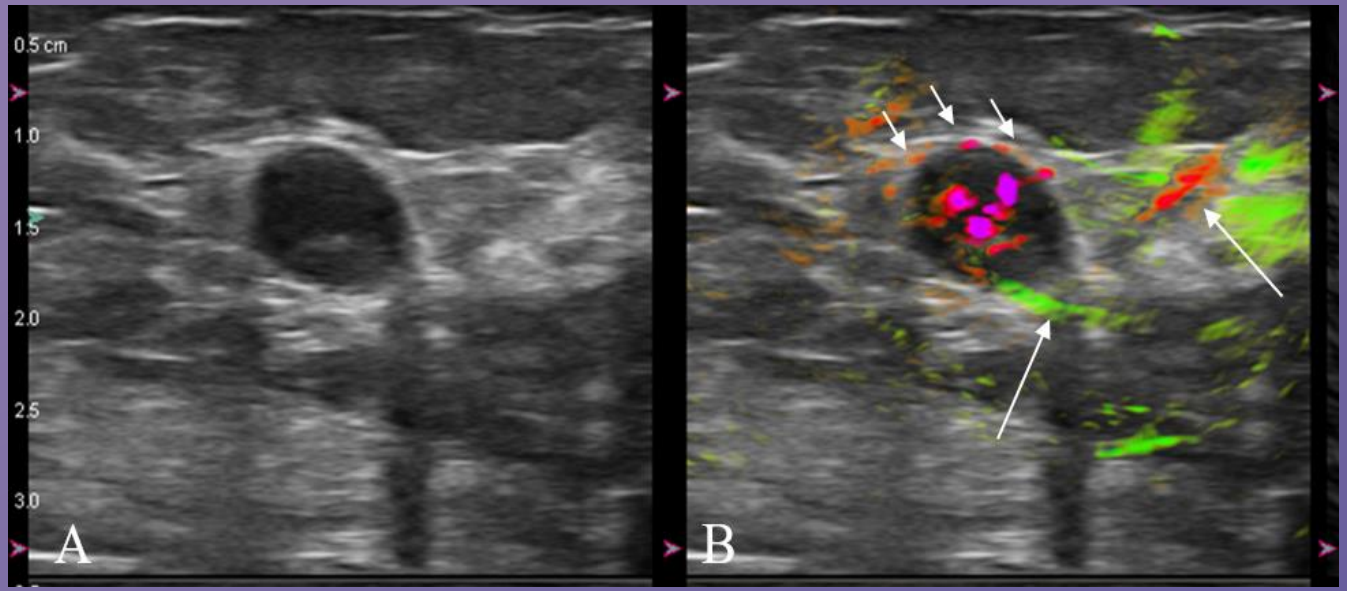
Upgrade Case: BI-RADS 3 on Internal US to BI-RADS 4A on OA/US
Biopsy revealed triple negative invasive ductal carcinoma



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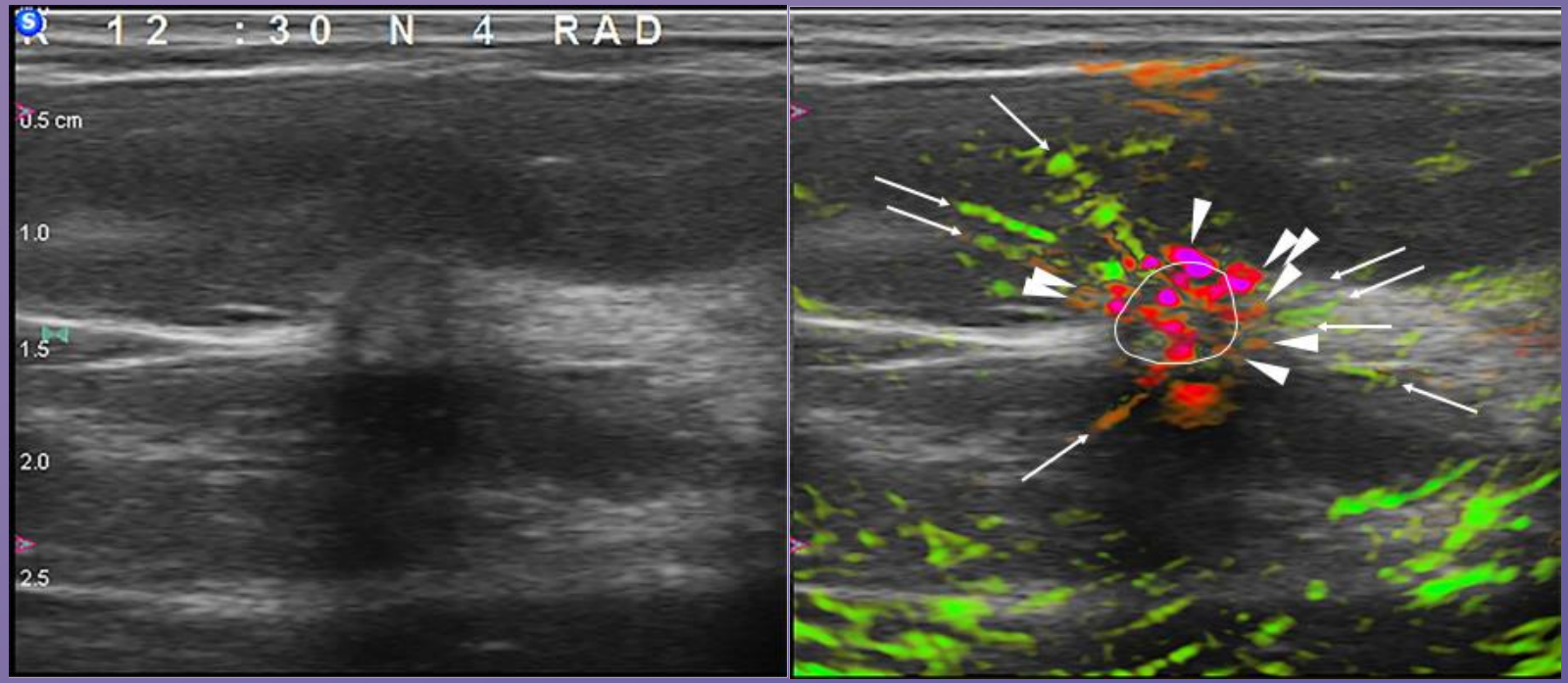
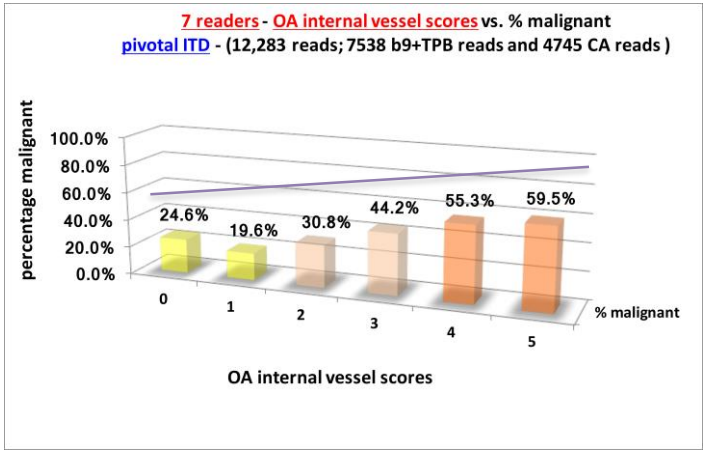
Upgrade case that increased confidence in diagnosis, but did not alter need for biopsy
Biopsy revealed grade 1 invasive ductal carcinoma, with DCIS grade 2

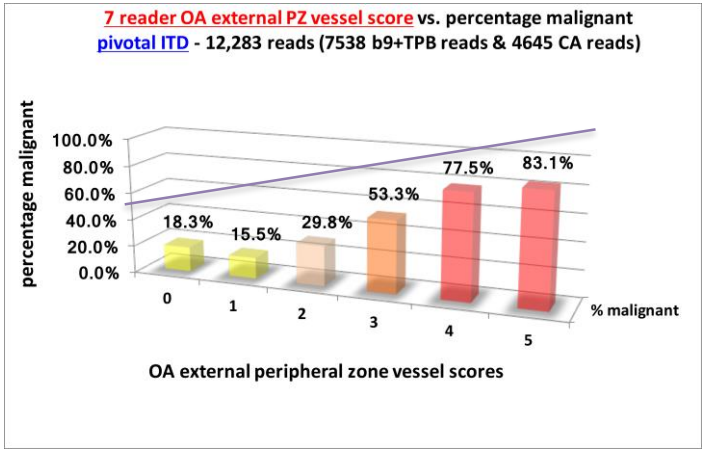


Neuschler EI, Butler R, Young CA, et al. A Pivotal Study of Optoacoustic Imaging to Diagnose Benign and Malignant Breast Masses: A New Evaluation Tool for Radiologists. Radiology. In press.

Results – Feature Analysis

- Mean OA scores for all individual features and summed scores were higher for malignant masses than for benign masses (all $p < 0.0001$).
- Probability of malignancy increases with higher internal, external, and total OA scores





- External features show strongest correlation with malignancy (all $p < 0.0001$)

Results – Subgroup Analyses

- Subgroup analysis by breast density, palpability, and distance from the nipple showed no significant differences in OA/US specificity
- Specificity of OA/US was 8.4% higher in patients <50 years of age than in patients aged 60 to <70 years
- There was no difference in sensitivity by age group.

Adverse Events

- 0.5% (10/1972) of subjects in safety population reported 11 mild procedure-related adverse events
- 10 resolved immediately after completion of procedure
- 1 dermatitis of indeterminate origin and resolved within a few days

Discussion

- Independent readers were able to successfully upgrade or downgrade masses with OA/US relative to internal gray-scale US
- The potential to downgrade benign masses could decrease benign biopsies and reduce follow up examinations
- The potential to upgrade malignant masses could increase diagnostic confidence to recommend biopsy

Limitations

- First generation of study device, image capture and training
- Independent readers were blinded to clinical and imaging information
- OA/US resulted in some false negative reads which requires further evaluation
- 12 month follow-up for BI-RADS 3 satisfied regulatory requirements of the trials but is not considered standard of care

Conclusions

- In this large reader study, 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 $p<0.0001$).
- Diagnostic performance of OA/US compared to the internal gray-scale ultrasound supports its potential for achieving higher specificity in the assessment of benign and malignant masses

Conclusions

- OA/US findings help identify masses that do not require biopsy, and in some cases, even avoid short interval follow-up.

- Conversely, OA/US findings may increase suspicion and add certainty to the need for biopsy of malignant masses

Acknowledgement

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Thank You

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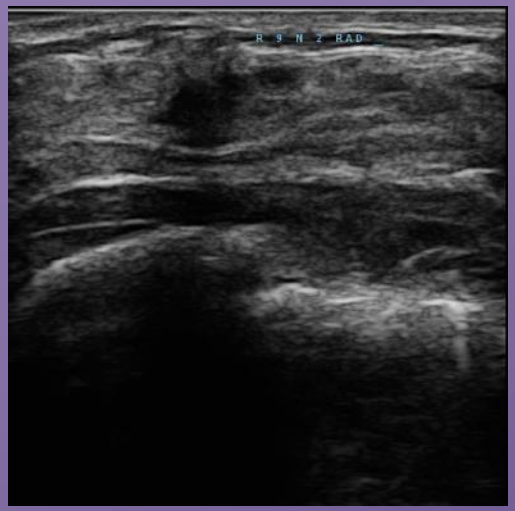
False Negative Interpretation with OA/US

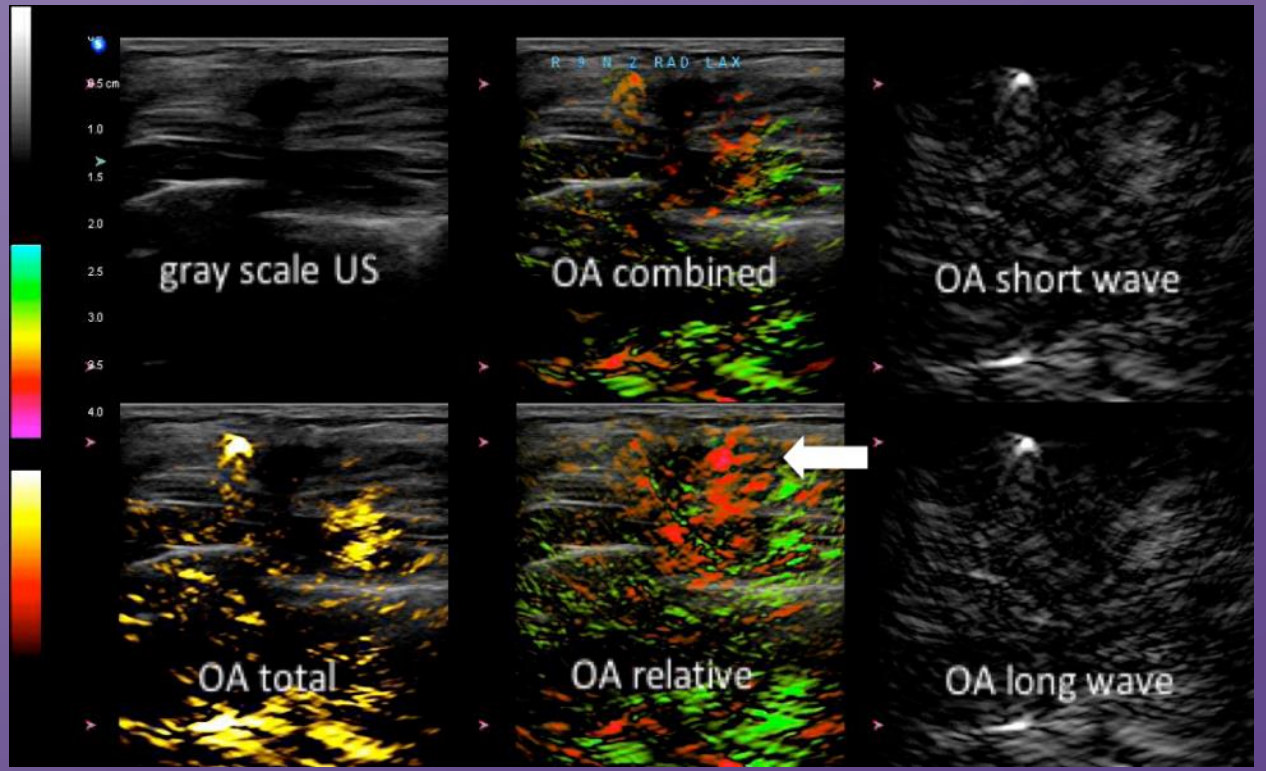
- OA/US resulted in downgrading 27.3% of malignant mass reads classified as BI-RADS 3 with internal grayscale US to BI-RADS 2.
- In total, OA/US resulted in downgrading 16.5% of malignant mass reads, from BI-RADS 4A of higher to a lower BI-RADS category, or from BI-RADS 3 to 2.

False Negative Interpretation with OA/US

- Lack of mammographic correlation
- Underestimation of internal gray-scale US BI-RADS category
- Independent readers were not able to review the examination in real time, as in clinical practice
- Learning curve for site investigators for acquisition of OA/US images
- Technical Issues – OA Colorization is relative
    - Gel standoff
    - Inappropriate depth of field

False Negative Interpretation





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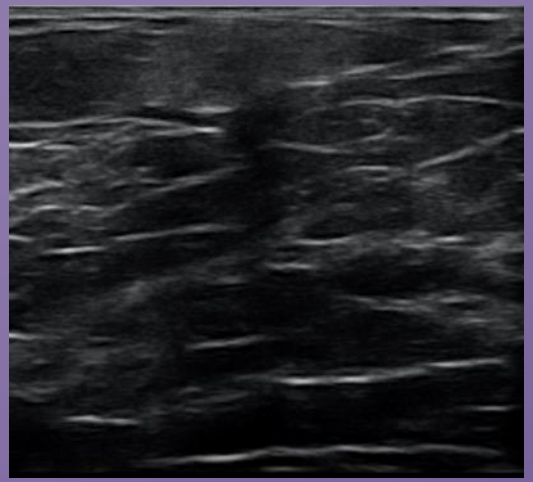
False Positive Interpretation with OA/US

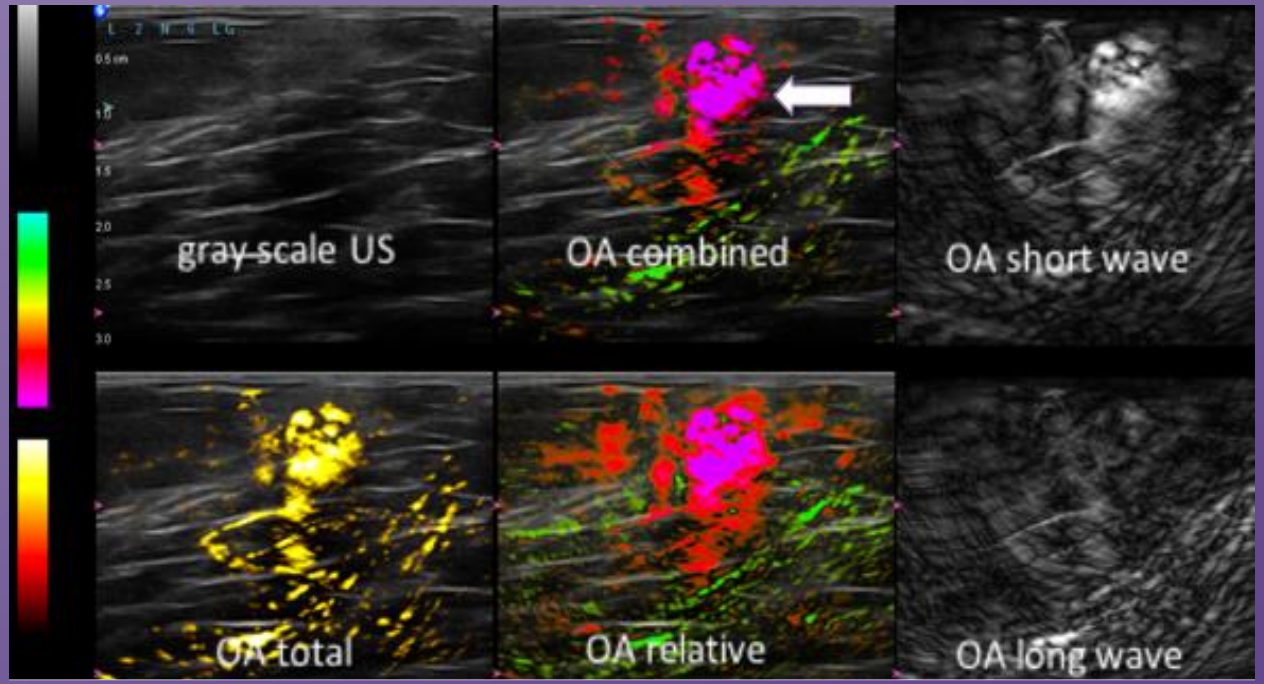
- OA/US results in upgrading 21.3% of benign mass reads classified as BI-RADS 3 with internal grayscale US to BI-RADS 4A or higher
- In total, OA/US resulted in upgrading 6.0% of benign mass reads from BI-RADS 2 to BI-RADS 3 or from BI-RADS 2 or 3 to BI-RADS 4A or higher.

False Positive Interpretation with OA/US

- Angiogenesis is a reactive pathophysiologic process and can be seen with acute inflammation and healing processes, including fat necrosis, as well as malignancy.[11,12]
- Examining the histopathologic basis of these cases suggest the false positive results may be a result of how OA/US reflects inherent tumor biology rather than a limitation of this functional modality.

False Positive Interpretation





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Histopathology

- Independent central pathologist (F.L.T.) with more than 30 years of experience in breast pathology
- Blinded to imaging features reviewed all pathology reports
- Had option to request and review histologic specimen slides to determine the final diagnosis.
- Histologic assessment was based on standard hematoxylin-eosin stains.

Histopathology

- Histologic grading utilized the Nottingham (Scarff-Bloom-Richardson) scheme (SBR).
- Tubule formation (SBR-T), nuclear atypia (SBR-N), mitotic count (SBR-M) and total score (SBR-Total) were recorded.
- Additional lesion attributes measured for each defined tumor zone included tumor cellularity-to-stroma ratio, vessel size, vessel density, and leukocyte density