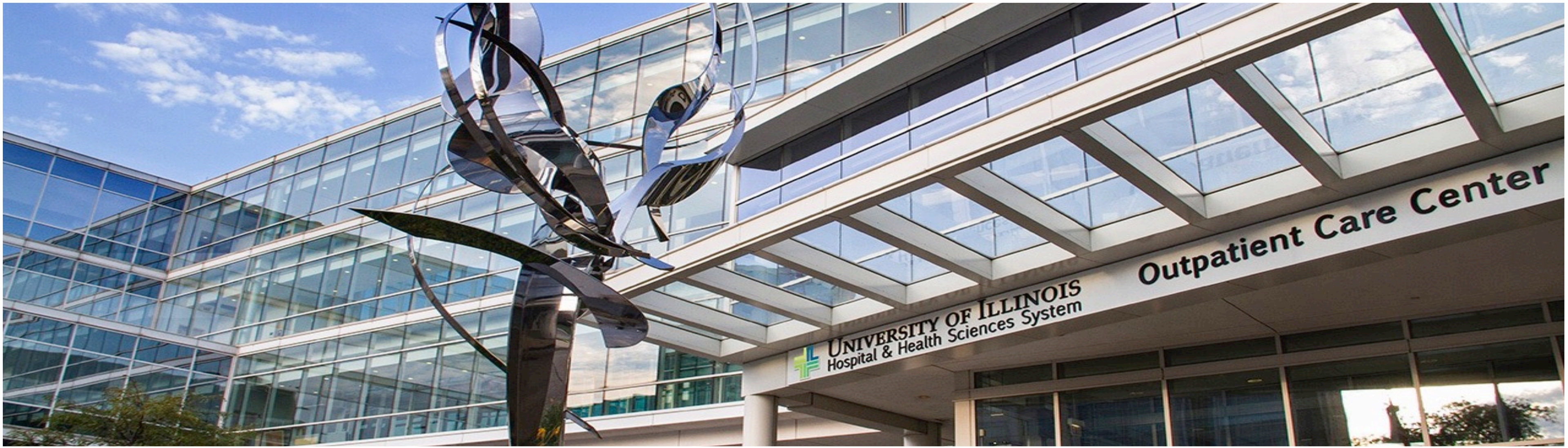

Future Strategies for Reducing False Positives: Optoacoustics and Contrast

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DISCLOSURES

Imagio® Breast Imaging System 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.

Some images in this talk are taken with the Seno Imagio^{TM} system and are not to be reproduced. These images are indicated on slides to be images proprietary to Seno Medical Instruments, Inc.

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]

1. Tabár L, Vitak B, Chen TH, et al. Swedish Two-County Trial: impact of mammographic screening on breast cancer mortality during 3 decades. Radiology 2011; 260:658-663.
2. Mendelson EB, Böhm-Vélez M, Berg WA, et al. ACR BI-RADS® Ultrasound. In: ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013.
3. American College of Radiology. ACR Practice Guideline for the Performance of a Breast Ultrasound Examination. Available at: http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/US_Breast.pdf. Accessed July 5, 2016.

INTRODUCTION

- Breast Cancer Surveillance Consortium Data (BCSC)[1]
  - 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
  - PPV of biopsy recommendations at diagnostic mammography (PPV2) of 27.5%
  - PPV of performed biopsies (PPV3) of 30.4%

Sprague BL, Arao RF, Miglioretti DL et al. National Performance Benchmarks for Modern Diagnostic Digital Mammography: Update from the Breast Cancer Surveillance Consortium. Radiology 2017; 283(1) 59-69.

DIAGNOSTIC BREAST IMAGING

- Gray-scale ultrasound 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[1]
- Color and power Doppler are of limited value, because there is a significant overlap between vascularization of malignant and benign masses.[6,7]

1. Skaane P, Engedal K. Analysis of sonographic features in the differentiation of fibroadenoma and invasive ductal carcinoma. AJR 1998; 170:109-114.
2. Svensson WE, Pandian AJ, Hashimoto H. The use of breast ultrasound color Doppler vascular pattern morphology improves diagnostic sensitivity with minimal change in specificity. Ultraschall Med 2010; 31: 466-474.
3. Tozaki M, Fukuma E. Does power Doppler ultrasonography improve the BI-RADS category assessment and diagnostic accuracy of solid breast lesions? Acta Radiol 2011; 52: 706-710.

FUNCTIONAL MODALITIES

- Imaging modalities which can demonstrate non-anatomic features of breast lesions

- Opportunity to increase specificity

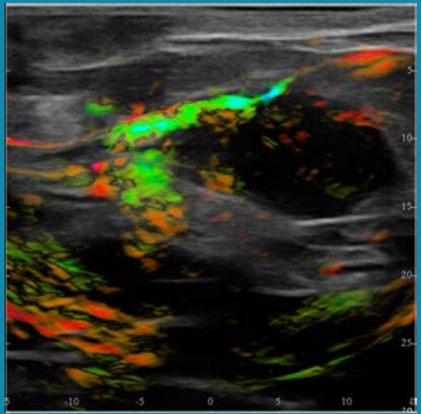
- Opto-Acoustic Imaging (OA/US)

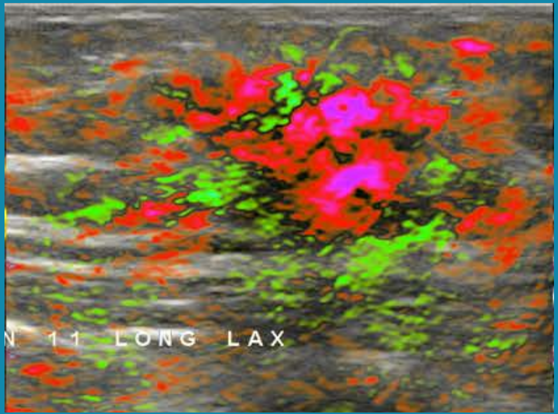
- Contrast-Enhanced Ultrasound (CEUS)

OPTO-ACOUSTIC IMAGING

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





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OA/US: FUSION IMAGING

- Fusion of laser optic imaging and gray-scale imaging in real-time
  - 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

BASIS FOR OPTO-ACOUSTIC IMAGING

- Malignant tumors produce abnormal neovasculature to support growth once they reach about 2-mm in size[1,2]
- 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-acoustics demonstrates the relatively greater de-oxygenation that occurs in and near malignant lesions

1. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971; 285:1182-1186
2. Folkman, J. Clinical applications of research on angiogenesis. N Engl J Med 1995; 333:1757-1763.

OPTO-ACOUSTIC IMAGING

- Brief illumination of tissues causes slight heating and expansion that generates a sound wave, also known as the photoacoustic effect[1,2]
- Momentary heating and expansion of Hgb by bursts of low energy laser light create pressure waves with frequency detected as US signal[3-6]
- Received echoes are color coded by wavelength reflecting degree of oxygenation/deoxygenation of Hgb

1. Bell A. On the production and reproduction of sound by light. Am J Sci 1880(118):305-324.
2. Roentgen W. On tones produced by the intermittent irradiation of a gas. Philos Mag 1881;68(5):308-311.
3. Oraevsky A, Jacques S, Esenaliev T: Laser Optoacoustic Imaging System for Medical Diagnostics, USPTO Serial #05,840,023 (priority date 31 Jan 1996).
4. Oraevsky AA, Karabutov AA: "Optoacoustic Tomography", in Biomedical Photonics Handbook, ed. By T. Vo-Dink, CRC Press, Boca Raton, Florida, Vol. PM125, Chapter 34, pp. 34/1-34/34.
5. Oraevsky AA: Optoacoustic tomography of the breast, Chapter 33 in "Photoacoustic imaging and spectroscopy", ed. By L. Wang, Taylor and Francis Group, New York, 2009.
6. Ermilov SA, Fronheiser, MP, Nadvoretsky V, Brecht HP, Su R, Conjusteau A, and Oraevsky AA: Real-time optoacoustic imaging of breast cancer using an interleaved two-laser imaging system coregistered with ultrasound, in "Photons Plus Ultrasound: Imaging and Sensing", San Jose, CA, January 24, 2010 *Proc. SPIE* vol. 7564: 75641W, pp. 1-7.

INVESTIGATIONAL DEVICE – OA/US

- Hand-held linear probe which can perform gray-scale ultrasound and emit 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

Images proprietary to Seno Medical Instruments, Inc.

OPTO-ACOUSTIC IMAGING

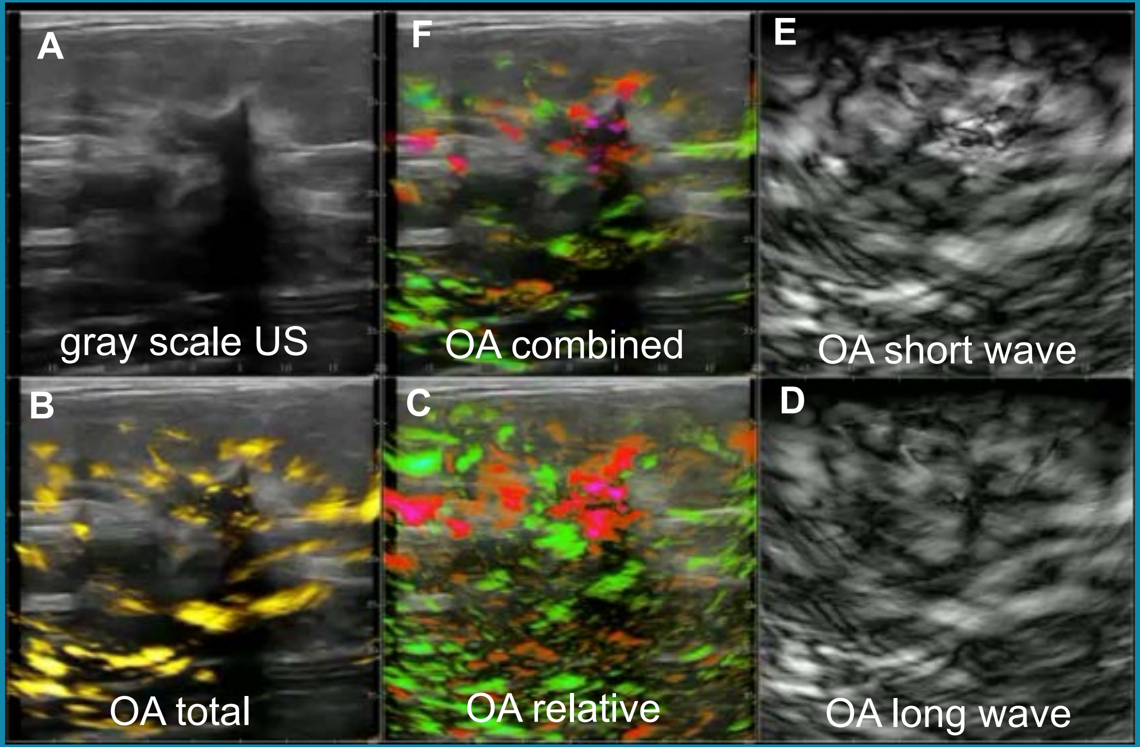
- Pulses of laser light at two wavelengths are applied sequentially to breast tissue
- Near-infrared light (757nm) is absorbed predominantly by deoxygenated Hgb
- Laser light (1064 nm) is absorbed predominantly by oxygenated Hgb

CLASS IIIB LASER

- Has not been shown to 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.
- For research studies performed, subjects and all personnel in the experimental area were required to wear protective eyewear.

OA/US 6-on-1 Real Time Display

Invasive ductal carcinoma, grade II



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A. Gray scale US

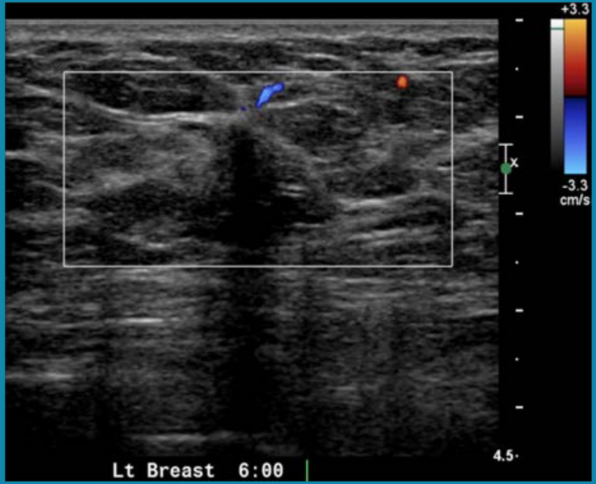
B. Total map – total amount of Hgb

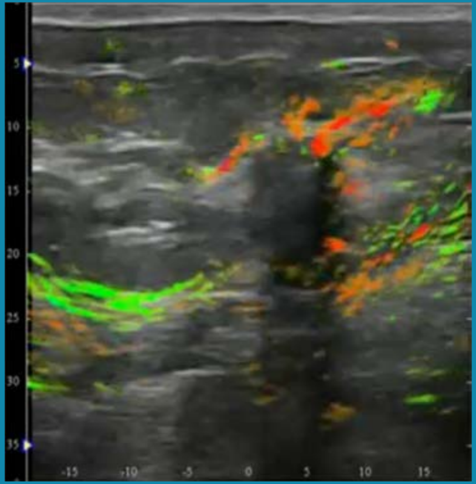
C. Relative map - relative deoxygenation within and surrounding mass

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

OA/US VERSUS COLOR DOPPLER



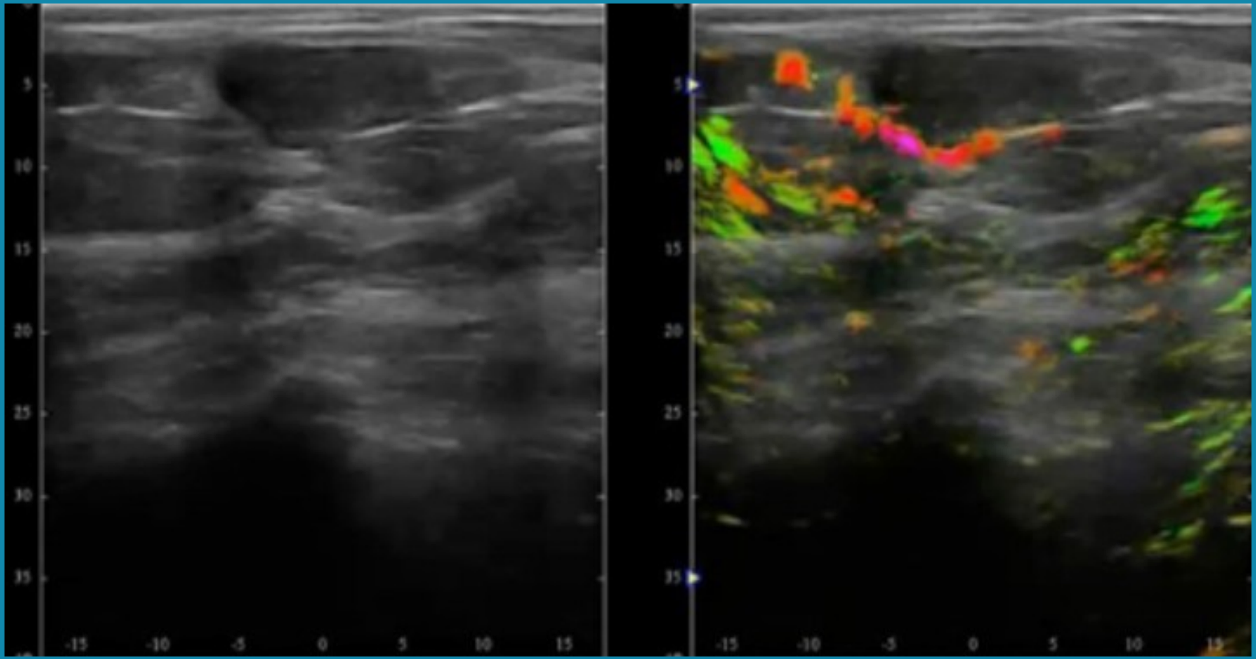


OA often shows vessels and deoxygenation when Doppler findings are absent or minimal

Images proprietary to Seno Medical Instruments, Inc.

Courtesy Dr. Michael J. Ulissey

FIBROADENOMA



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Courtesy Dr. Michael J. Ulissey

OA/US CLINICAL RESULTS

Radiology

A Pivotal Study of Optoacoustic Imaging to Diagnose Benign and Malignant Breast Masses: A New Evaluation Tool for Radiologists[1]

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 EV, Parris TM, Schilling KJ, Tucker FL, Dogan BE.
Radiology. 2018 May;287(2):398-412.

PIONEER PIVOTAL STUDY

- HIPPA compliant and IRB-approved prospective, controlled, multicenter observational study.
- Purpose was 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 which were evaluated for the potential ability of OA/US to downgrade BI-RADS categories in benign masses and upgrade BI-RADS categories of malignant masses.

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*. 2018 May;287(2):398-412.

PIONEER PIVOTAL STUDY

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

7 academic and 9 private institutions

THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER
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NORTHWESTERN UNIVERSITY

Yale University School of Medicine

RADNET, inc.

Cleveland Clinic

ATLANTA Breast Care

Weinstein Imaging Associates
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ARA 60 YEARS
DIAGNOSTIC IMAGING

EWbc Elizabeth Wende Breast Care

INVISION SALLY JOBE
Imaging by RIA and HealthONE

NewYork-Presbyterian
The University Hospital of Columbia and Cornell

2,191 masses	12,283 mass reads

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 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

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*. 2018 May;287(2):398-412.

IMAGING PROTOCOL

- 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

- Standardized imaging protocol used at all sites

- 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

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*. 2018 May;287(2):398-412.

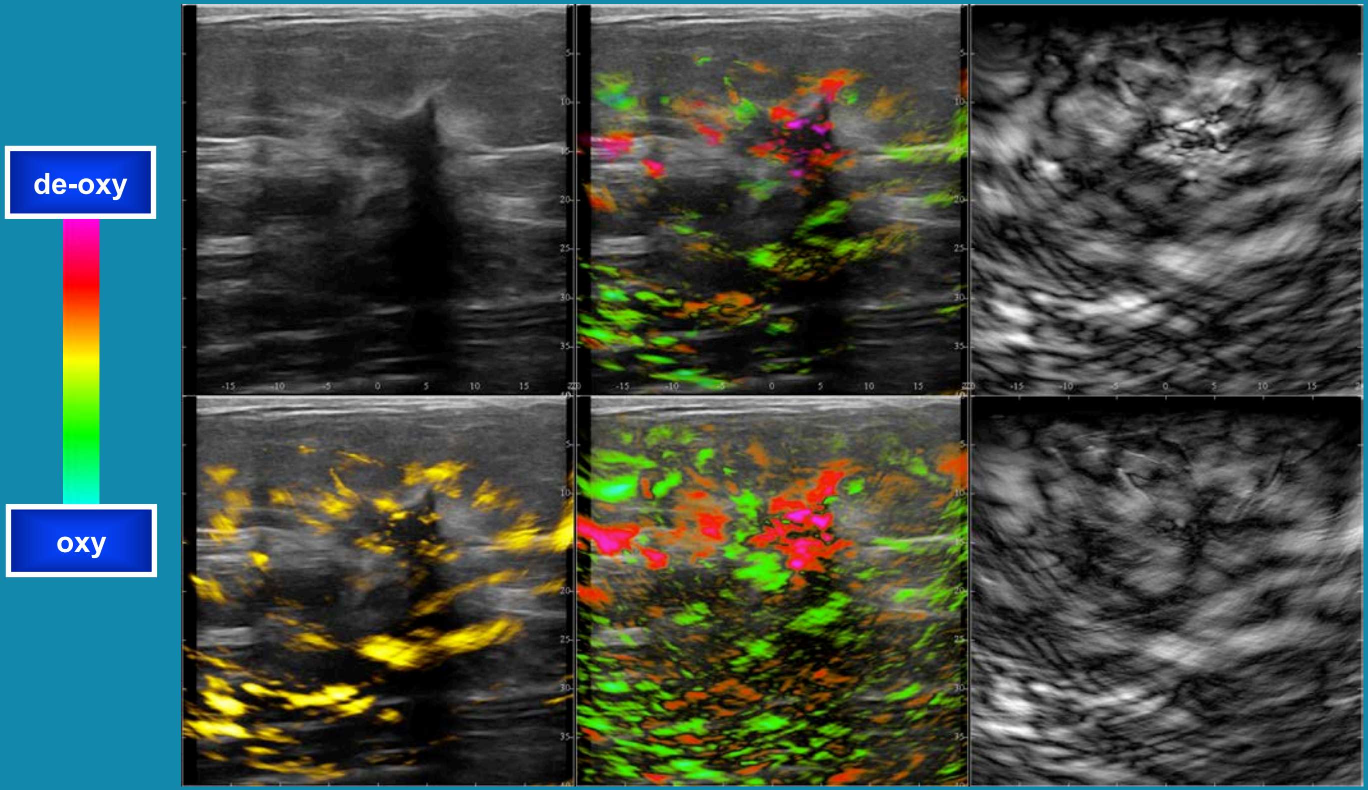
READER STUDY

- 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

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*. 2018 May;287(2):398-412.

OA/US 6-on-1 Real Time Display

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



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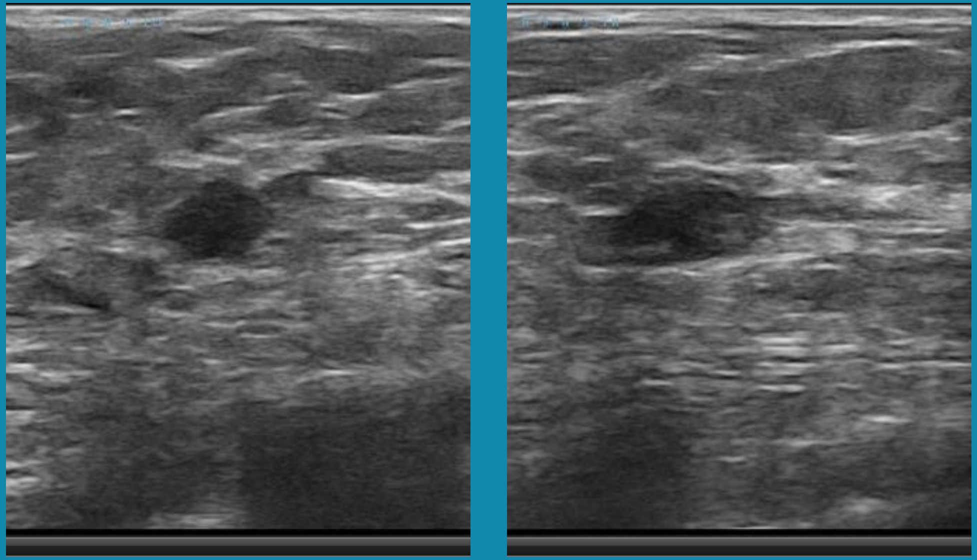
PILOT CASE

1.1 cm mass in right breast at 9:00, 5 cm from the nipple

- IUS: BI-RADS 4A

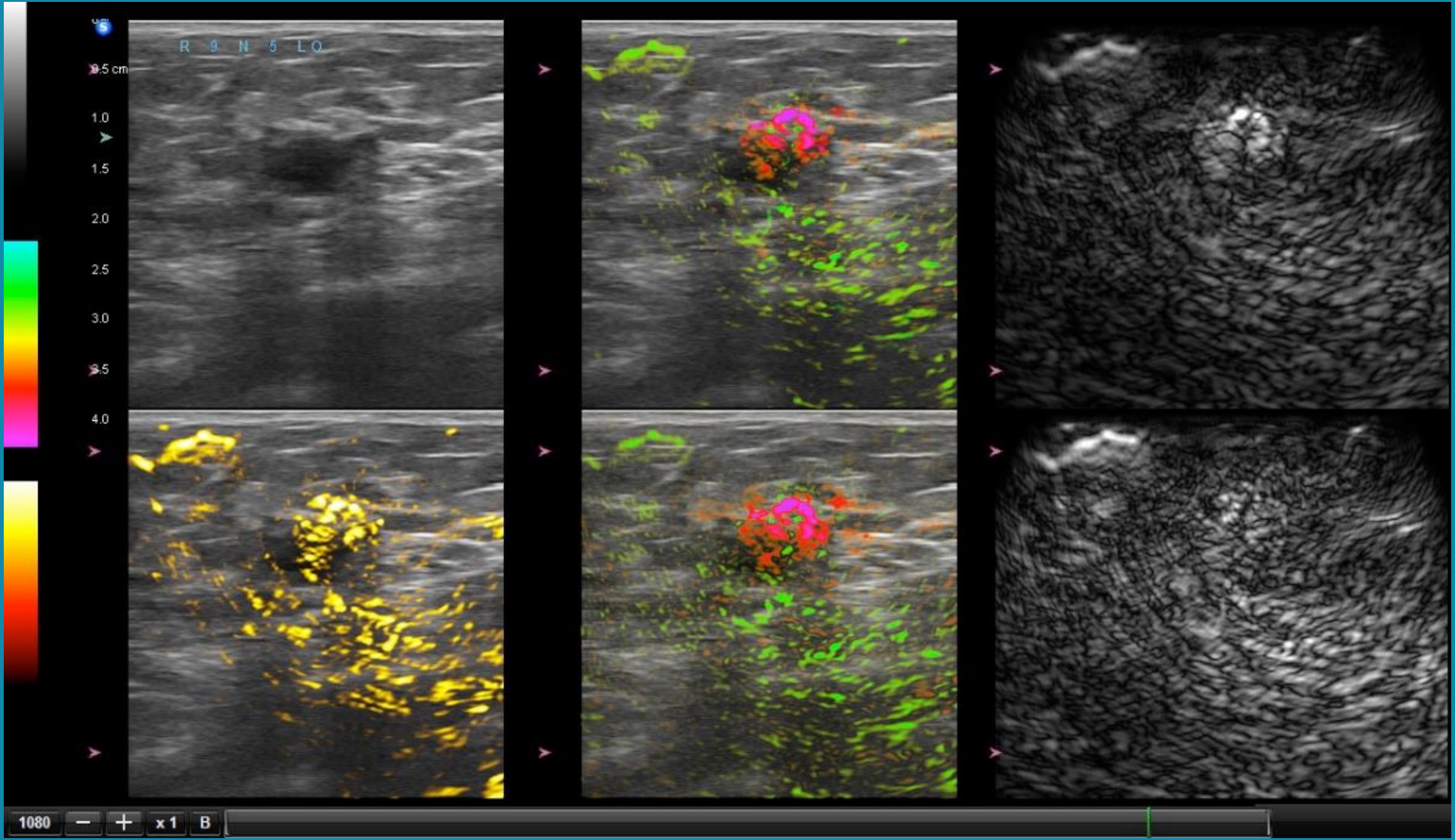


RAD **ARAD**

Images proprietary to Seno Medical Instruments, Inc.

Neuschler EI, Lavin PT, Tucker FL et al. Downgrading and Upgrading Gray-Scale Ultrasound BI-RADS Categories of Benign and Malignant Masses With Optoacoustics: A Pilot Study. AJR 2018; 211:689–700.

OA/US



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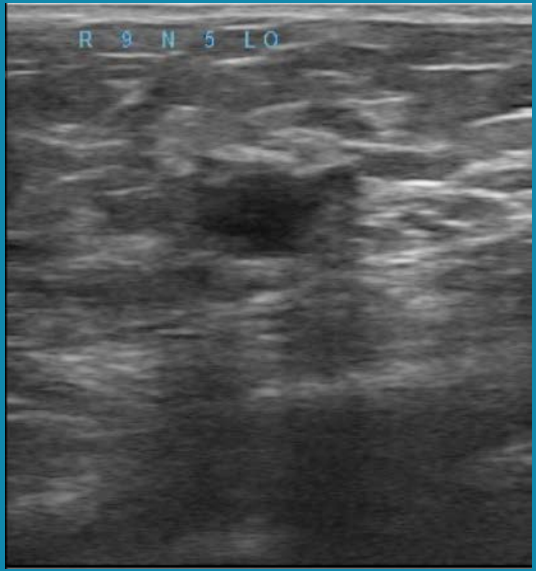
DCIS GRADE 2 (SOLID TYPE)

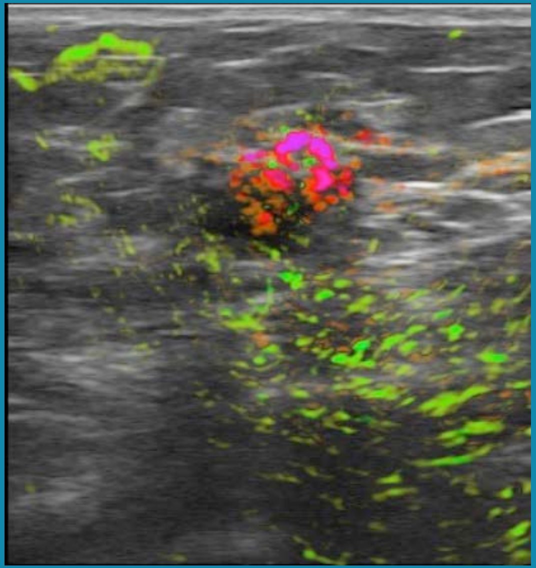
1.1 cm mass in right breast at 9:00, 5 cm from the nipple

IUS: BI-RADS 4A

OA/US: BI-RADS 4C



IUS



OA

Images proprietary to Seno Medical Instruments, Inc.

Neuschler EI, Lavin PT, Tucker FL et al. Downgrading and Upgrading Gray-Scale Ultrasound BI-RADS Categories of Benign and Malignant Masses With Optoacoustics: A Pilot Study. AJR 2018; 211:689–700.

RESULTS – 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		

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*. 2018 May;287(2):398-412.

SENSITIVITY AND SPECIFICITY

- Independent readers had a mean sensitivity of 98.6% for internal 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 internal device US was established relative to a 5% non-inferiority margin ($p<0.01$)

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*. 2018 May;287(2):398-412.

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

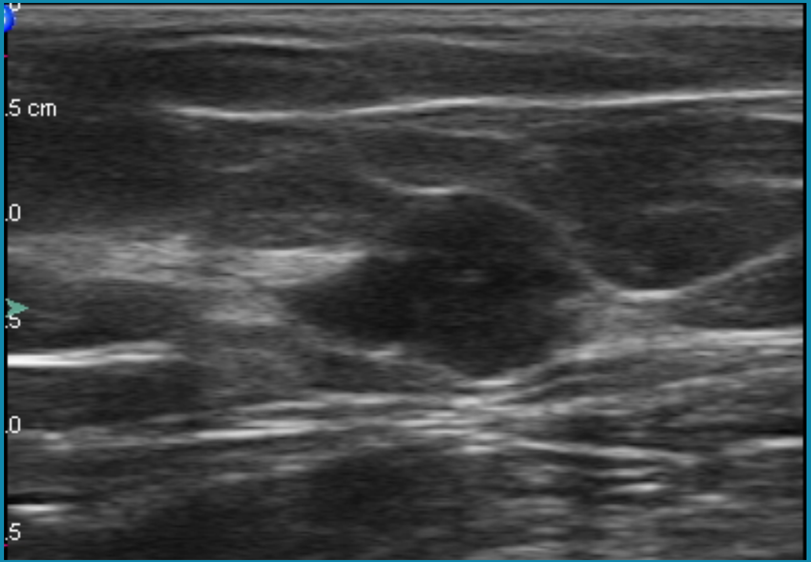
Neuschler EI, Butler R, Young CA et al. A Pivotal Study of Optoacoustic Imaging to Diagnose Benign and Malignant Breast Masses: A New Evaluation Tool for Radiologists. *Radiology*. 2018 May;287(2):398-412.

UPGRADES AND DOWNGRADES

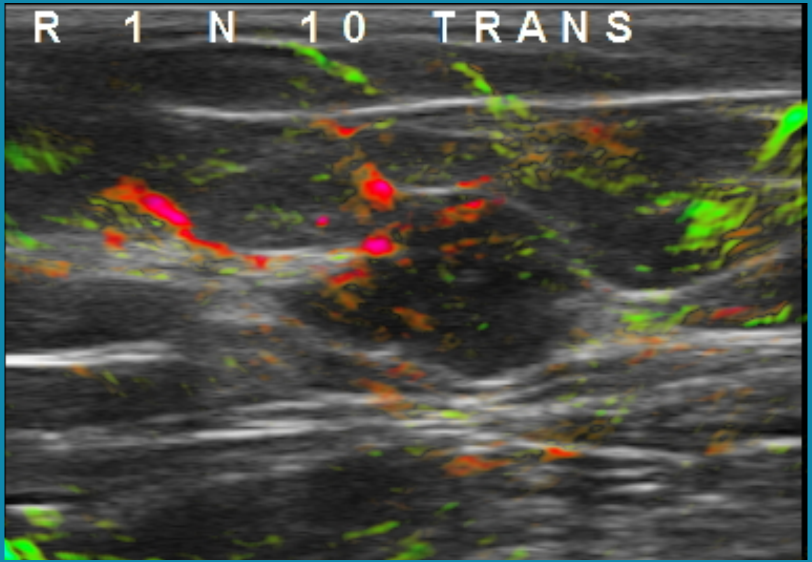
- 12,283 OA/US reads and 12,289 internal gray-scale US reads compared with diagnostic outcomes of biopsied malignant and biopsied benign plus truth panel benign masses
- Correct downgrades (2,601 reads) was significantly higher than the number of incorrect upgrades (453 reads) with OA/US ($p<0.0001$)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

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*. 2018 May;287(2):398-412.

UPGRADE – IDC GRADE 3

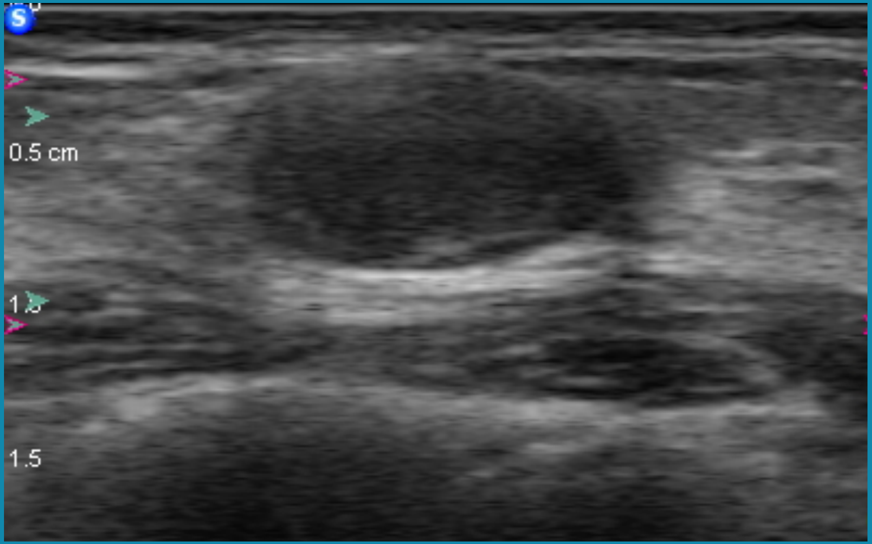


IUS: BI-RADS 3

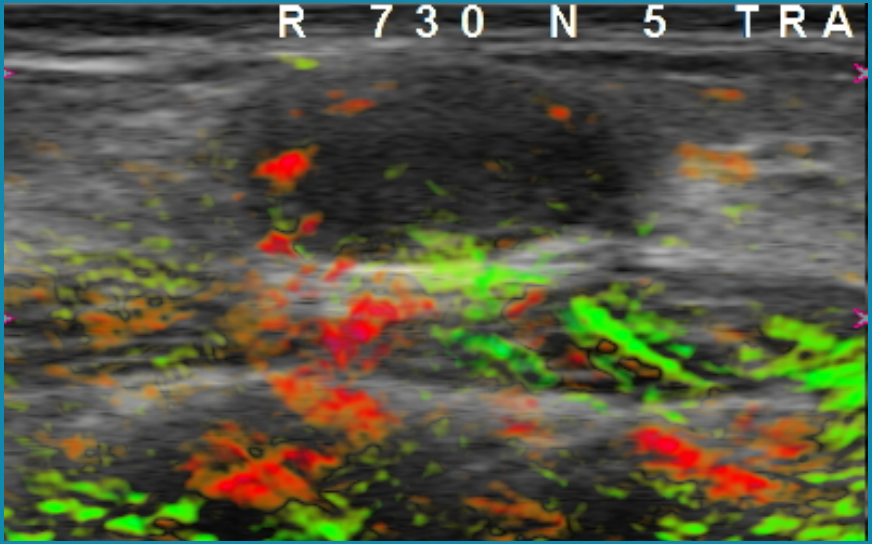


OA/US: BI-RADS 4C

DOWNGRADE - FIBROADENOMA



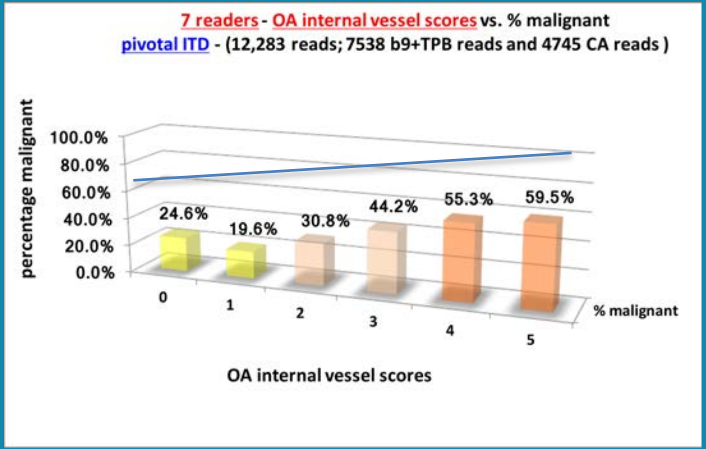
IUS: BI-RADS 4A

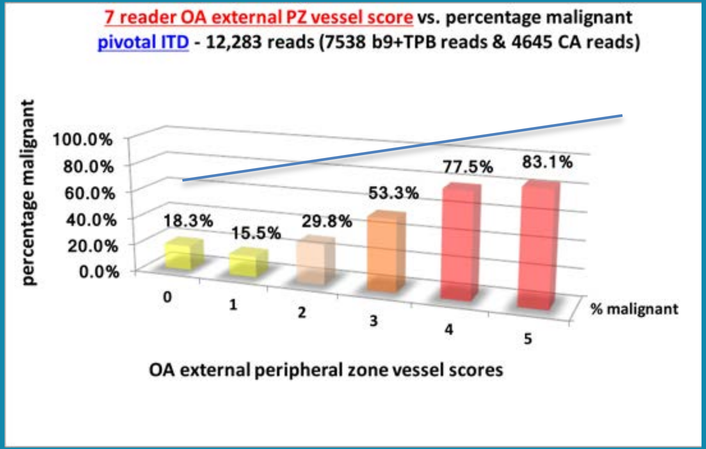


OA/US: BI-RADS 3

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 $p < 0.0001$)

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*. 2018 May;287(2):398-412.

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.

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*. 2018 May;287(2):398-412.

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
- No severe adverse events

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*. 2018 May;287(2):398-412.

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

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*. 2018 May;287(2):398-412.

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 trial but is not considered standard of care

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*. 2018 May;287(2):398-412.

OA/US CLINICAL RESULTS

Downgrading of Breast Masses Suspicious for Cancer by Using Optoacoustic Breast Imaging

Gisela L. G. Menezes, MD, PhD • Ruud M. Pijnappel, MD, PhD* • Carla Meeuwis, MD, PhD • Robertus Bisschops, MD, PhD • Jeroen Veltman, MD, PhD • Philip T. Lavin, PhD • Marc J. van de Vijver, MD, PhD • Ritse M. Mann, MD, PhD*

Menezes GLG, Pijnappel RM, Meeuwis C, Bisschops R, Veltman J, Lavin PT, van de Vijver MJ, Mann RM. Radiology. 2018 Aug;288(2):355-365.

MAESTRO TRIAL

- Prospective Multicenter European Study
- Purpose to assess ability of OA/US to help correctly downgrade masses classified as 4a and 4b to 3 or 2
- 209 patients with 215 breast masses
- Masses were first evaluated with US with knowledge of mammography and clinical information. Then assigned probability of malignancy (POM) and BI-RADS category.
- Re-evaluated with OA/US, scored five OA/US features and assigned an OA/US-based POM and BI-RADS category for each mass[17]

Menezes GLG, Pijnappel RM, Meeuwis C et al. Downgrading of Breast Masses Suspicious for Cancer by Using Optoacoustic Breast Imaging. Radiology. 2018 Aug;288(2):355-365.

MAESTRO VS. PIONEER

- Not a reader study
- Radiologists scanned and interpreted the studies themselves
- When OA/US suggested a downgrade a biopsy was still performed
- OA/US then compared to final histopathology

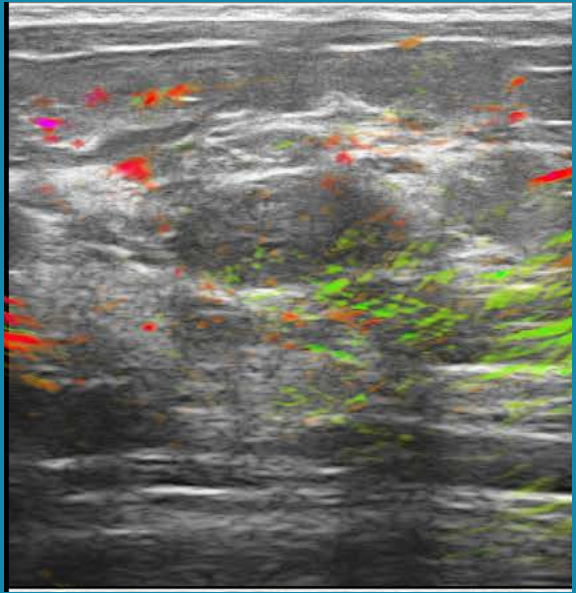
MAESTRO RESULTS

- 47.9% of benign masses classified as BI-RADS 4a were correctly downgraded to 3 or 2
- 11.1% of masses classified as BI-RADS 4b were correctly downgraded to BI-RADS 3 or 2.
- Two of seven malignant masses classified as BI-RADS 4a at US were incorrectly downgraded
- 1 of 60 malignant masses classified as BI-RADS 4b at US was incorrectly downgraded for a total of 4.5% false-negative findings.

Menezes GLG, Pijnappel RM, Meeuwis C et al. Downgrading of Breast Masses Suspicious for Cancer by Using Optoacoustic Breast Imaging. Radiology. 2018 Aug;288(2):355-365.

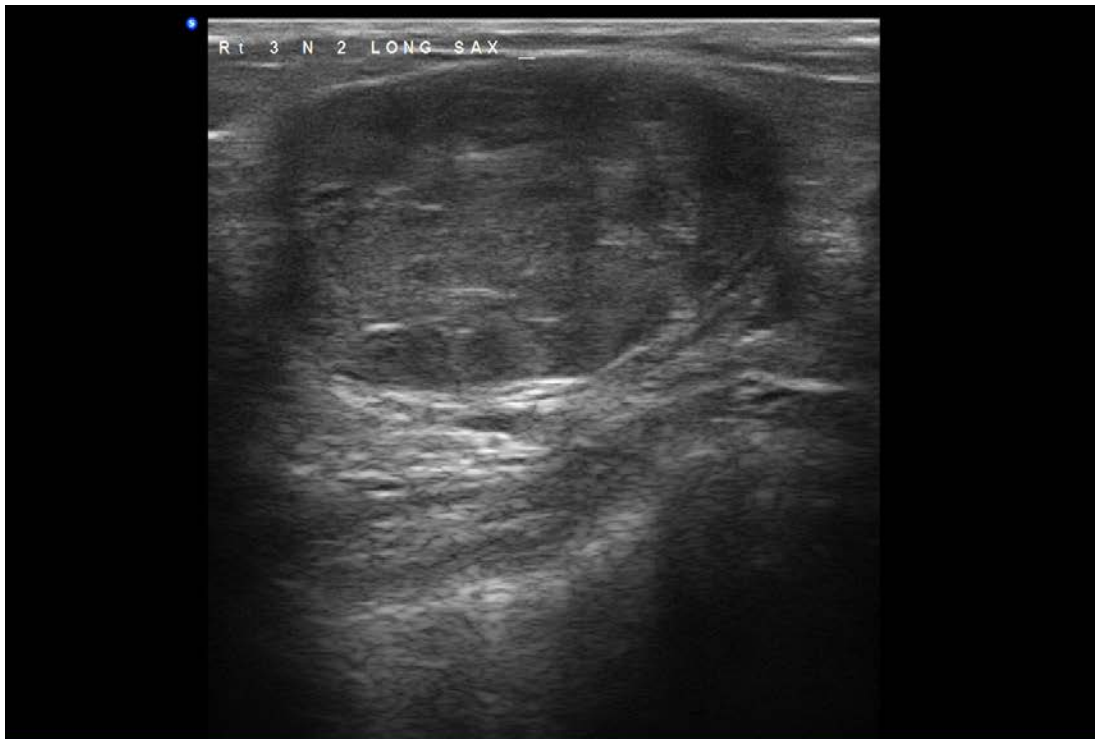
DOWNGRADE

IUS: BI-RADS 4A

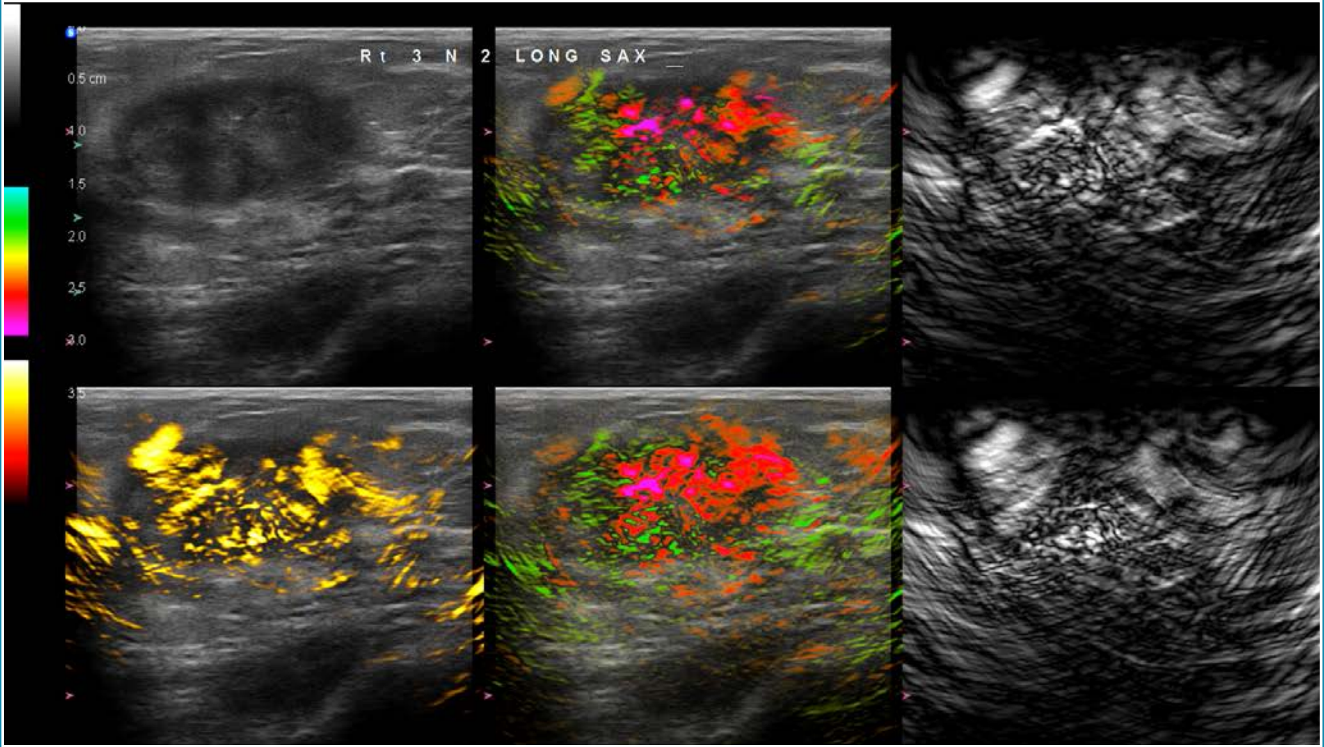


OA/US: BI-RADS 3

Images proprietary to Seno Medical Instruments, Inc.


Rt 3 N 2 LONG SAX

FIBROADENOMA



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ORIGINAL RESEARCH • BREAST IMAGING

Radiology

Optoacoustic Imaging and Gray-Scale US Features of Breast Cancers: Correlation with Molecular Subtypes

Basak E. Dogan, MD • Gisela L. G. Menezes, MD, PhD* • Reni S. Butler, MD • Erin I. Neuschler, MD • Roger Aitchison • Philip T. Lavin, PhD • F. Lee Tucker, MD • Stephen R. Grobmyer, MD • Pamela M. Otto, MD • A. Thomas Stavros, MD*

Dogan BE, Menezes GLG, Butler RS et al. Radiology. 2019 Sep;292(3):564-572.

MOLECULAR SUBTYPES

- Purpose was to investigate whether OA/US feature scores correlated with breast cancer molecular subtypes
- 1972 women with a total of 2055 breast masses
  - 653 invasive cancers in 629 women
  - 532 cancers in 519 women had molecular markers available
- Seven readers scored gray-scale US and OA/US features of known cancers
- Analyzed the relationship between feature scores and molecular subtypes

Dogan BE, Menezes GLG, Butler RS et al. Optoacoustic Imaging and Gray-Scale US Features of Breast Cancers: Correlation with Molecular Subtypes. Radiology. 2019 Sep;292(3):564-572.

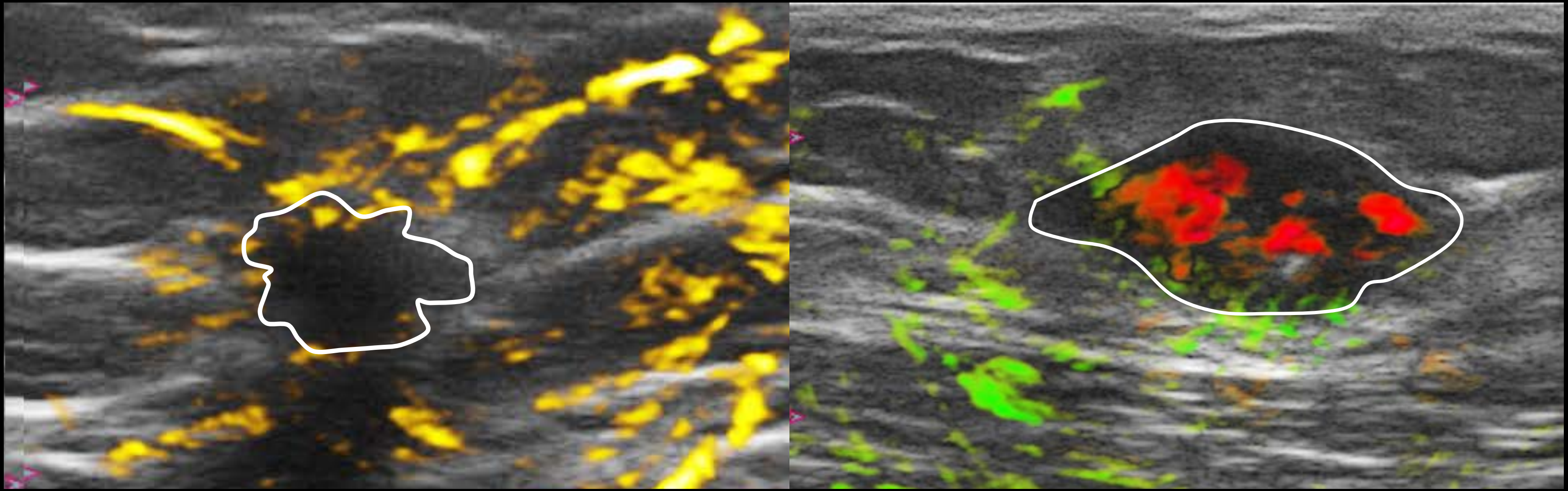
MOLECULAR SUBTYPES

Molecular Subtypes	LUMA vs. LUMB p-values	LUMA vs TNBC p-values	LUMA vs. HER2-E p-values	LUMB vs. TNBC p-values	LUMB vs. HER2-E p-values	TNBC vs. HER2-E p-values
IUS and OA Scores Combined	1.6062×10^{-7}	1.5435×10^{-18}	3.2953×10^{-7}	2.7366×10^{-9}	0.003160	0.193116
US Sound and OA	8.4689×10^{-9}	1.1563×10^{-18}	0.000001	1.7741×10^{-8}	0.011655	0.198652
US Sound/BZ and OA	1.8434×10^{-8}	6.0246×10^{-19}	1.6953×10^{-7}	1.1369×10^{-8}	0.006252	0.260493
US Sound/Sum US Int and OA	3.6214×10^{-9}	5.7902×10^{-17}	9.5325×10^{-7}	2.7895×10^{-7}	0.006868	0.393699
US Sound/Sum US Ext and OA	9.3776×10^{-9}	2.0586×10^{-18}	2.4624×10^{-7}	2.6041×10^{-8}	0.005078	0.281403
US Sound/Sum Int and Ext and OA	1.6062×10^{-7}	$p = 1.5435 \times 10^{-18}$	3.2953×10^{-7}	2.7366×10^{-9}	0.003160	0.193116

Courtesy of Dr. Gisela Menezes

Dogan BE, Menezes GLG, Butler RS et al. Optoacoustic Imaging and Gray-Scale US Features of Breast Cancers: Correlation with Molecular Subtypes. Radiology. 2019 Sep;292(3):564-572.

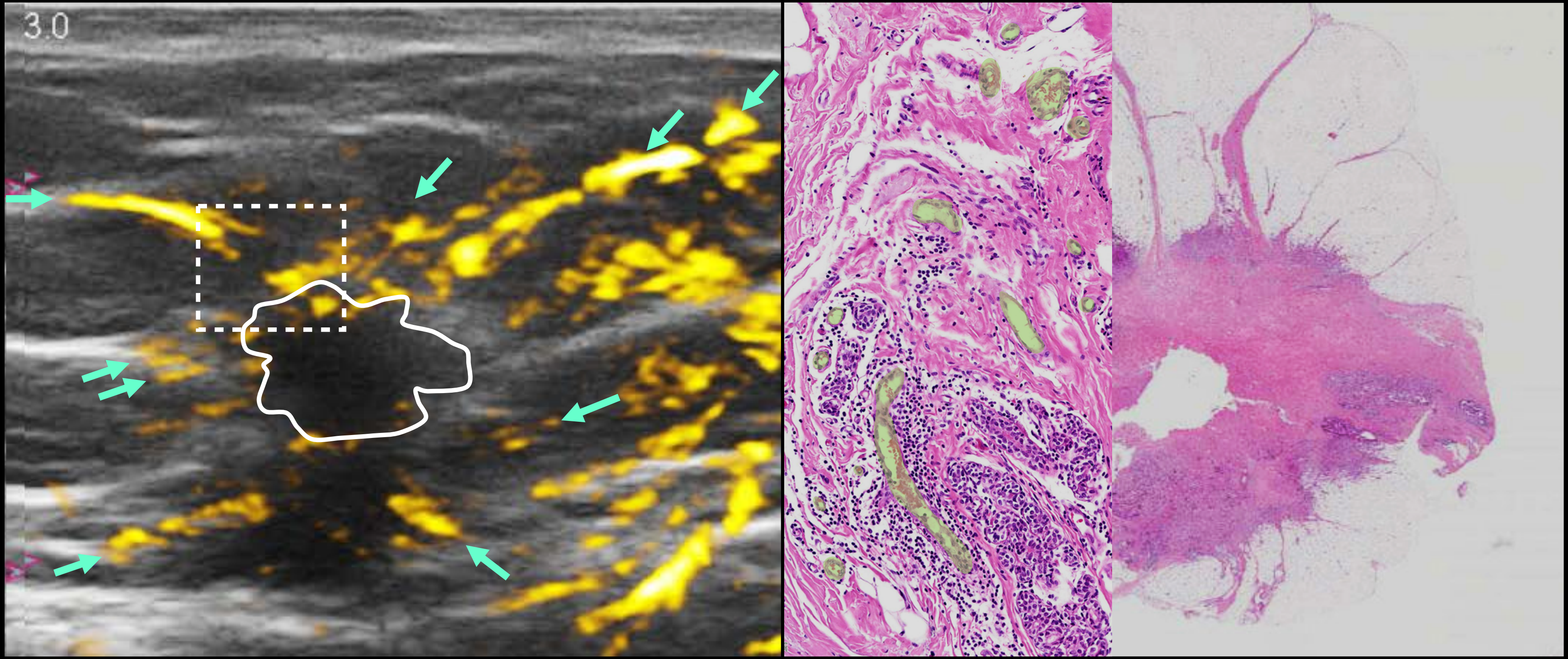
LUMINAL A (LUMA) VS. TRIPLE NEGATIVE BREAST CANCER (TNBC)



Images proprietary to Seno Medical Instruments, Inc.

Courtesy of Dr. Gisela Menezes

LUMA – PREDOMINANTLY EXTERNAL FINDINGS



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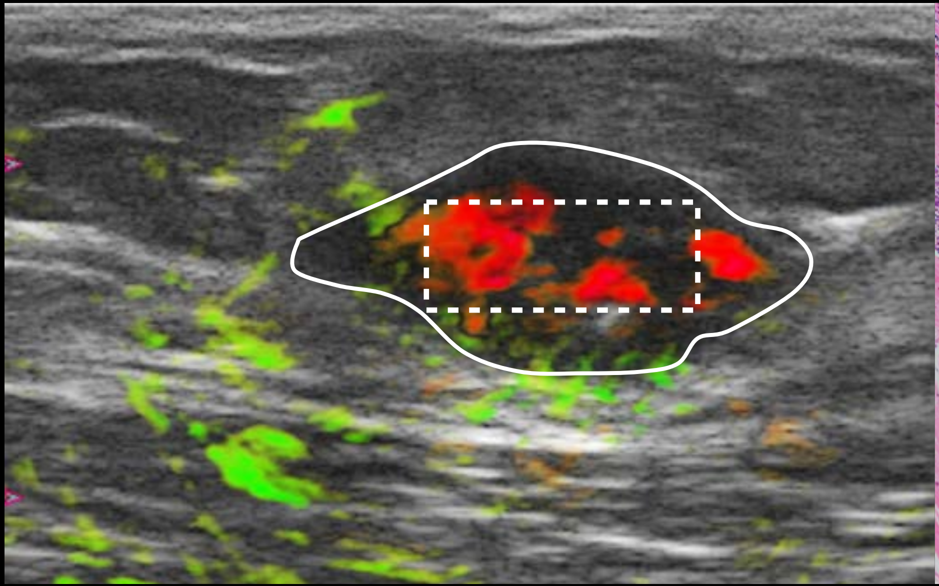
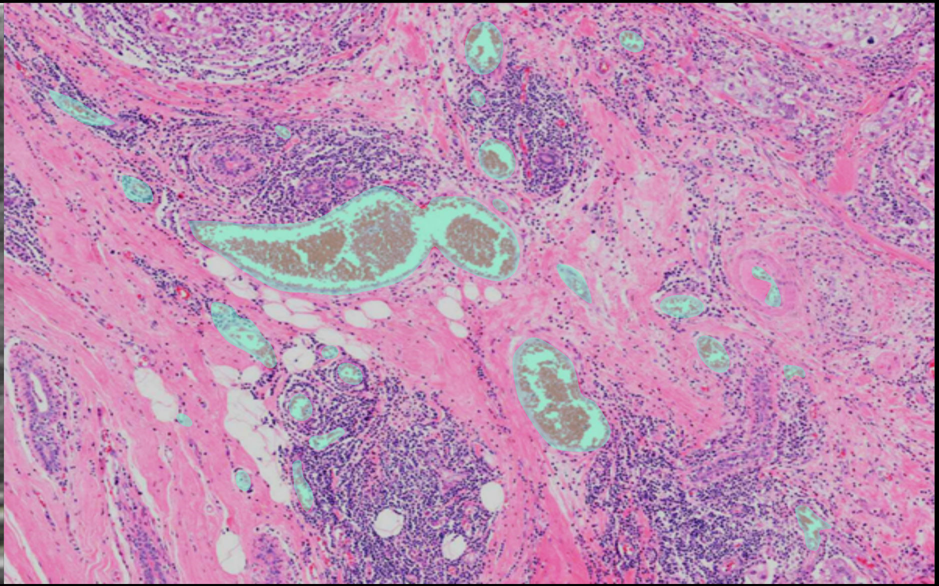
TNBC – PREDOMINANTLY INTERNAL FINDINGS





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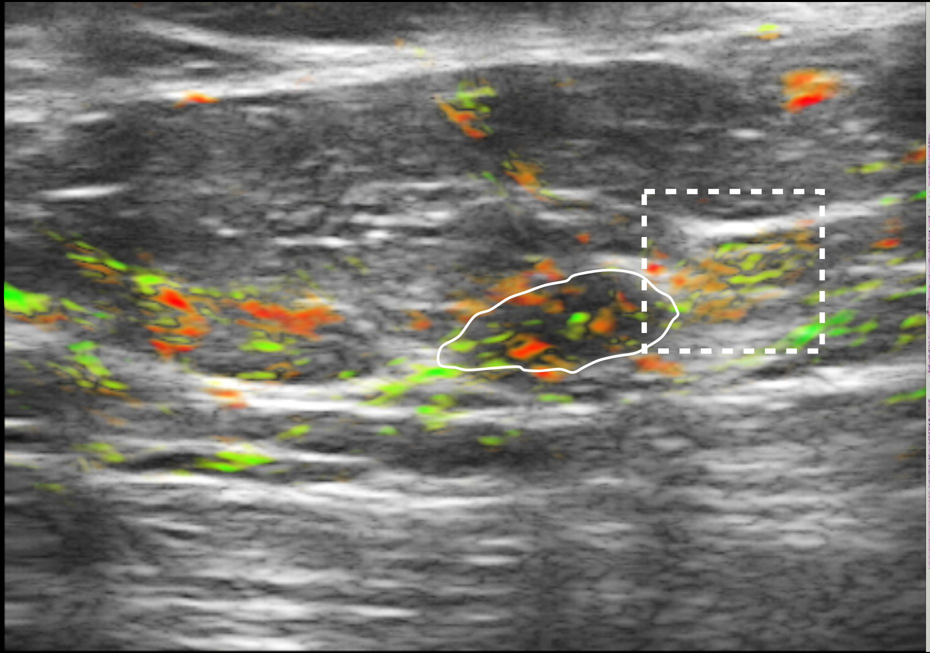
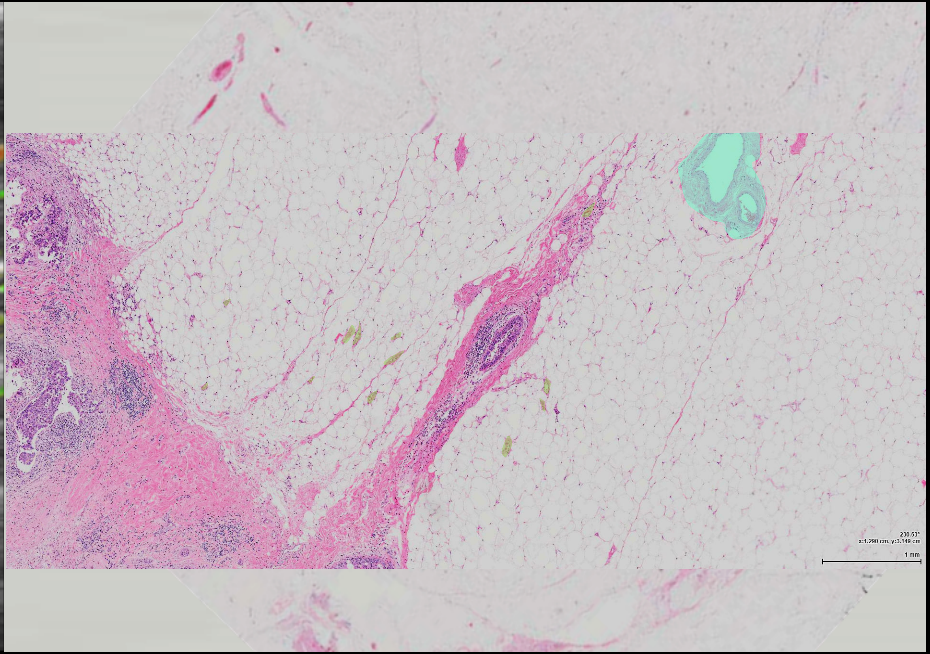
Courtesy of Dr. Gisela Menezes

HER2-ENRICHED





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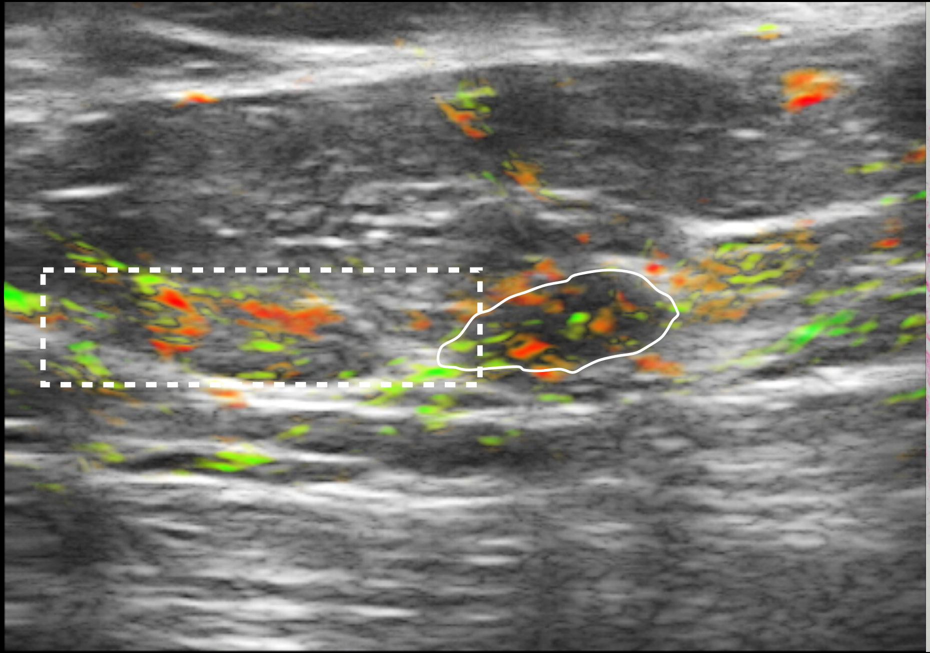
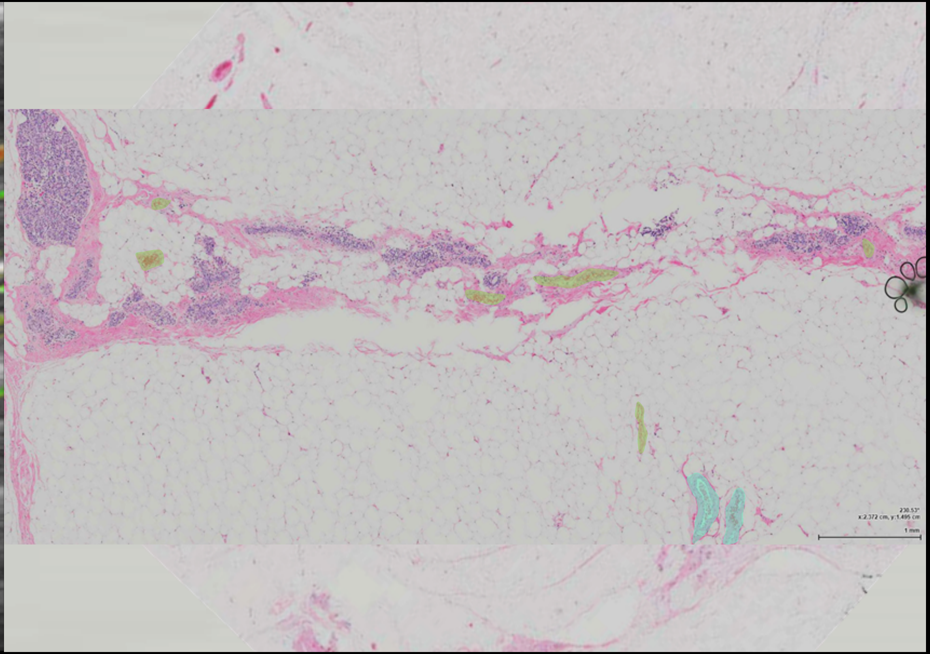
Courtesy of Dr. Gisela Menezes

HER2-ENRICHED





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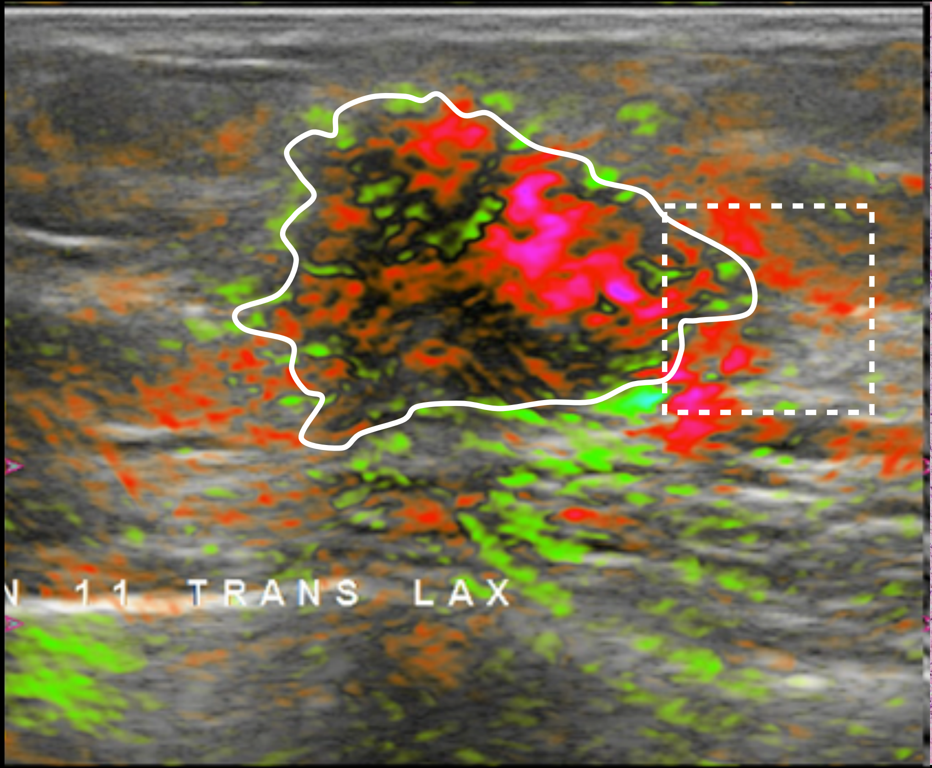
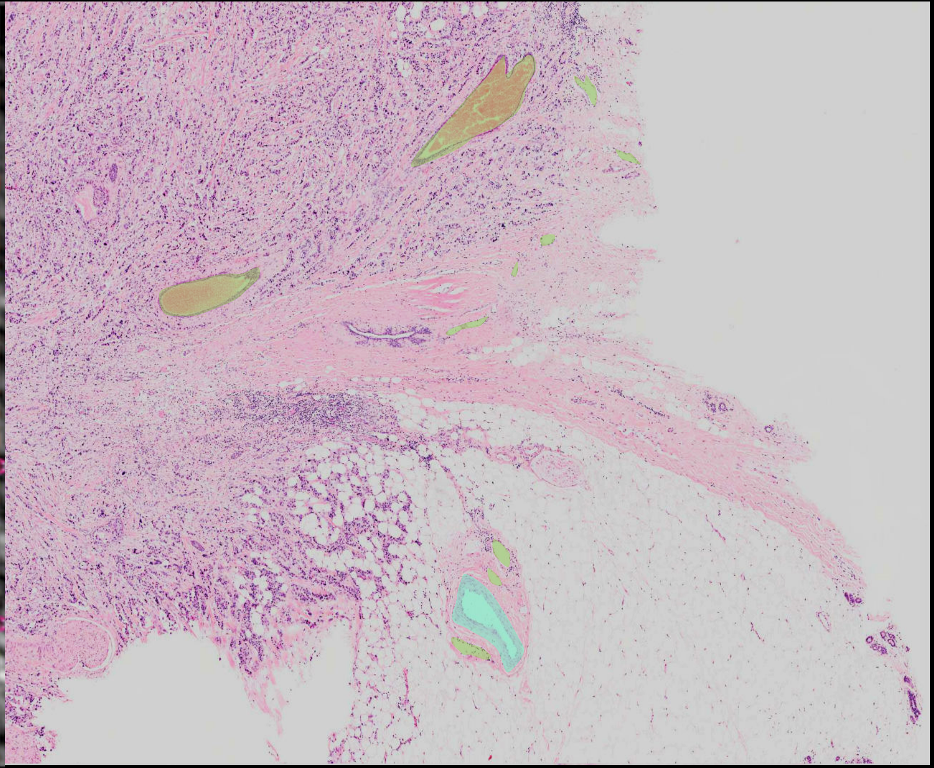
LUMINAL B





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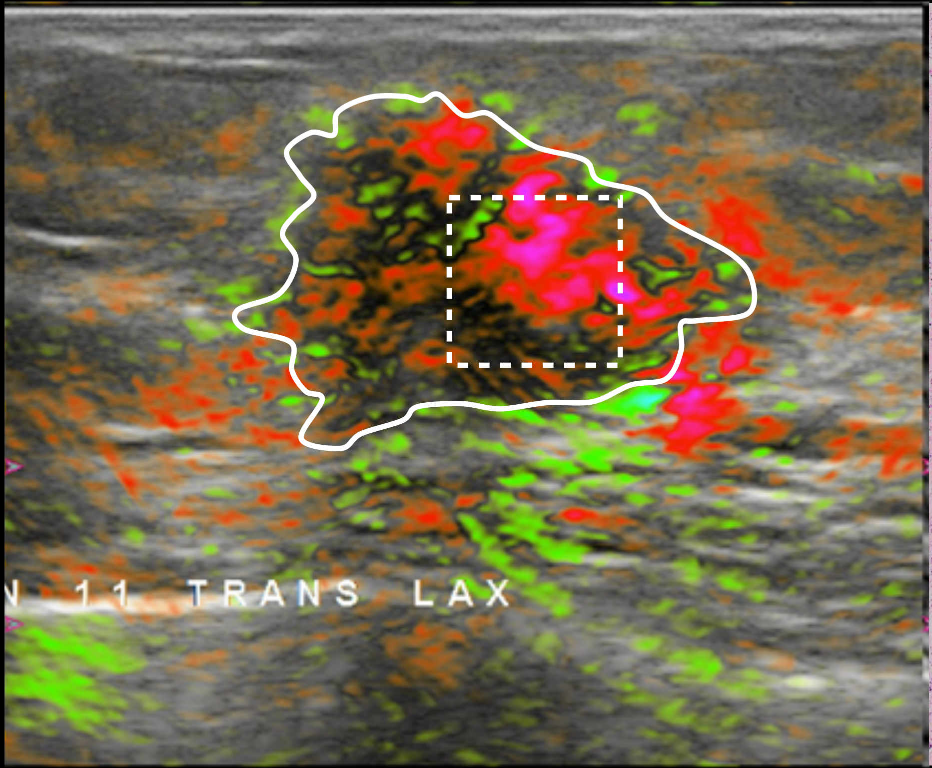
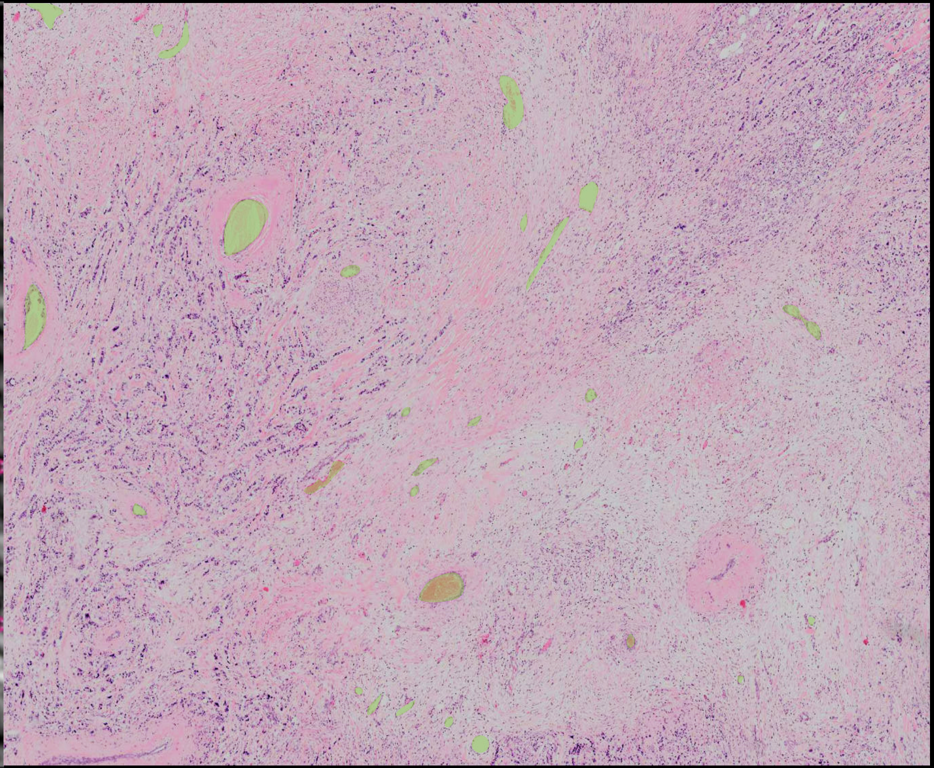
LUMINAL B





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Courtesy of Dr. Gisela Menezes

DISCUSSION

- 678 malignant masses in the study, but only 532 (78%) masses had molecular subtyping available.
- Small number of TNBCs (79) and HER2-E (23).
- Breast tumors are usually heterogeneous and biopsy may be insufficient to assess intra-tumoral heterogeneity.
- OA/US may demonstrate the dominant feature of the whole tumor.
- If OA/US features do not match the biopsy findings, it might indicate the need for more extensive histopathologic inspection.

Dogan BE, Menezes GLG, Butler RS et al. Optoacoustic Imaging and Gray-Scale US Features of Breast Cancers: Correlation with Molecular Subtypes. Radiology. 2019 Sep;292(3):564-572.

CONCLUSIONS

- OA/US findings may 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
- It is unlikely that OA/US or any other imaging technique will make histologic biomarker analysis unnecessary.
- Nevertheless, OA/US features might help non-invasively distinguish breast cancer molecular subtypes and might facilitate management decisions.

CONTRAST-ENHANCED ULTRASOUND (CEUS)

CONTRAST-ENHANCED ULTRASOUND (CEUS)

- Malignant tumors produce abnormal neovasculature to support growth once they reach about 2-mm in size[1,2]
- Power and color doppler imaging are limited to image vasculature due to low sensitivity for detection of slow blood flow
- Low sensitivity for detection of small neovessels
- CEUS is an alternative to doppler imaging to image vascularity[3]

1. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971; 285:1182-1186
2. Folkman, J. Clinical applications of research on angiogenesis. N Engl J Med 1995; 333:1757-1763.
3. Sridharan A1,2, Eisenbrey JR1, Dave JK1, Forsberg F1.Quantitative Nonlinear Contrast-Enhanced Ultrasound of the Breast. AJR 2016 Aug;207(2):274-81.

CONTRAST-ENHANCED ULTRASOUND

- Intravenous injection of gas-filled microbubbles
- Shell-stabilized microbubbles which have diameters between 1 and 8 μm[1]
- When compared to surrounding blood and tissue they are different in terms of compressibility and density[2]
- Produces an acoustic impedance difference which results in an increase of ultrasound signal enhancement (up to 25 dB)[3]

1. Sridharan A1,2, Eisenbrey JR1, Dave JK1, Forsberg F1.Quantitative Nonlinear Contrast-Enhanced Ultrasound of the Breast. AJR Am J Roentgenol. 2016 Aug;207(2):274-81.
2. Leighton TG. The acoustic bubble. London, UK: Academic Press, 1994
3. Goldberg BB, Raichlen JS, Forsberg F, eds. Ultrasound contrast agents: basic principles and clinical applications. London, UK: Martin-Dunitz, 2001

CONTRAST-ENHANCED ULTRASOUND

- Contrast agents are more echogenic than RBCs[1]
- Increases imaging sensitivity such that there is angiogenic vascular enhancement[2]
- Given microvascular flow seen in both benign and malignant masses, enhancement characteristics can overlap[3]
- Qualitative and quantitative analysis is possible
- However, qualitative and quantitative CEUS parameters are not well defined

1. Zhao H, Xu R, Ouyang Q, et al. Contrast-enhanced ultrasound is helpful in the differentiation of malignant and benign breast lesions. Zhao H, Xu R, Ouyang Q, et al. Eur J Radiol. 2010 Feb: 73(2):288-93
2. Sridharan A1,2, Eisenbrey JR1, Dave JK1, Forsberg F1. Quantitative Nonlinear Contrast-Enhanced Ultrasound of the Breast. AJR Am J Roentgenol. 2016 Aug;207(2):274-81.
3. Lee SC, Tchelepi H, Grant E, et al.Contrast-Enhanced Ultrasound Imaging of Breast Masses: Adjunct Tool to Decrease the Number of False-Positive Biopsy Result. J Ultrasound Med. 2019 Sep;38(9):2259-2273.

CEUS ENHANCEMENT PATTERNS

- Benign masses
  - Hypovascular or homogeneously enhancing
- Malignant masses
  - Rapid hyperenhancement
  - Enlarged size on CEUS
  - Peripheral enhancement
  - Heterogeneous enhancement

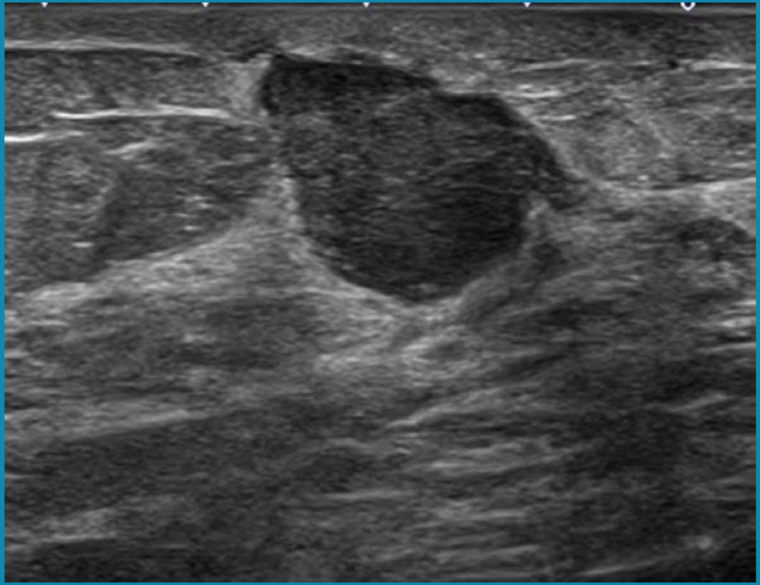
Lee SC, Tchelepi H, Grant E, et al.Contrast-Enhanced Ultrasound Imaging of Breast Masses: Adjunct Tool to Decrease the Number of False-Positive Biopsy Result. J Ultrasound Med. 2019 Sep;38(9):2259-227
Liu H, Jiang YX, Liu JB, Zhu QL, Sun Q, Evaluation of breast lesions with contrast-enhanced ultrasound using the microvascular imaging technique: initial observations. Breast 2008; 17:532–539.
Wang Y, Fan W, Zhao S, et al. Qualitative, quantitative and combination score systems in differential diagnosis of breast lesions by contrast-enhanced ultrasound. Eur J Radiol 2016; 85:48–54.

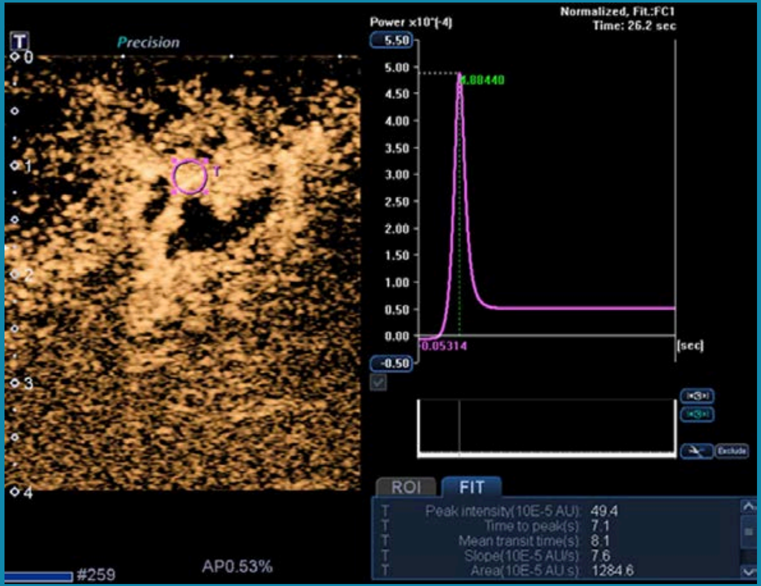
CEUS QUANTITATIVE PARAMETERS

- Following contrast administration, different perfusion phases
- Early (0 – 1 min), middle (1 – 4 min) and late (4 – 6 min)[1]
- Produce time-signal intensity curves that can be analyzed
- Quantitative parameters of the time-intensity curve[2]
  - Time to peak
  - Peak intensity – maximum intensity of time-intensity curve
  - Area under the curve

1. Zhao H1, Xu R, Ouyang Q, Chen L, Dong B, Huihua Y. Contrast-enhanced ultrasound is helpful in the differentiation of malignant and benign breast lesions. Eur J Radiol. 2010 Feb;73(2):288-93.
2. Lee SC, Tchelepi H, Grant E, et al.Contrast-Enhanced Ultrasound Imaging of Breast Masses: Adjunct Tool to Decrease the Number of False-Positive Biopsy Result. J Ultrasound Med. 2019 Sep;38(9):2259-2273.

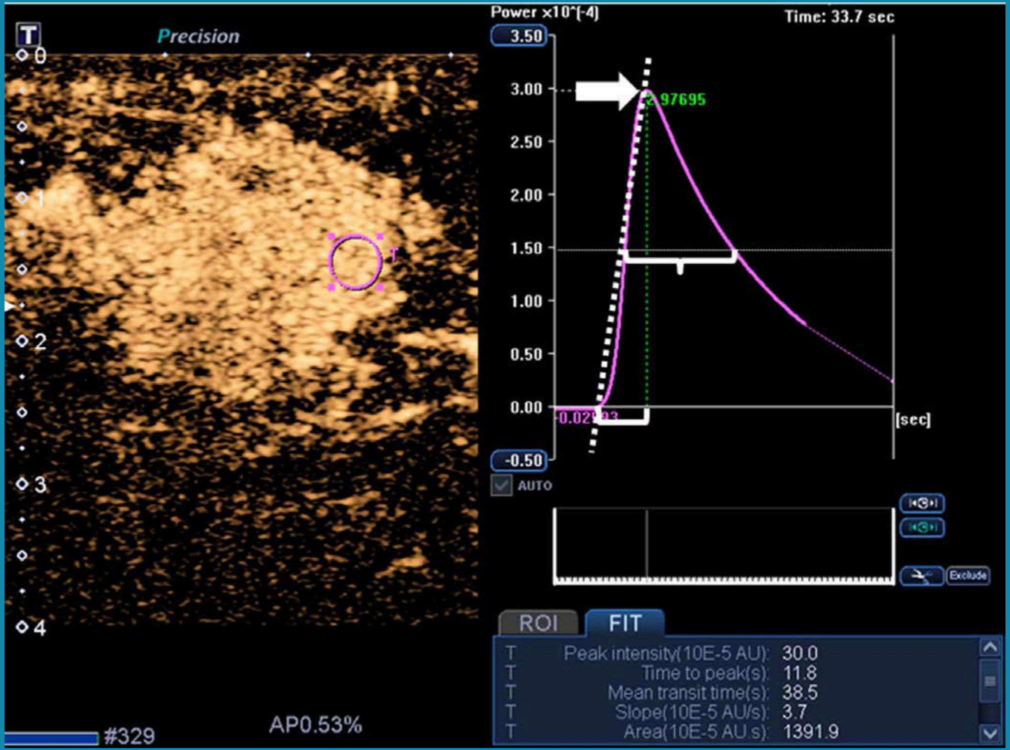
INVASIVE DUCTAL CARCINOMA





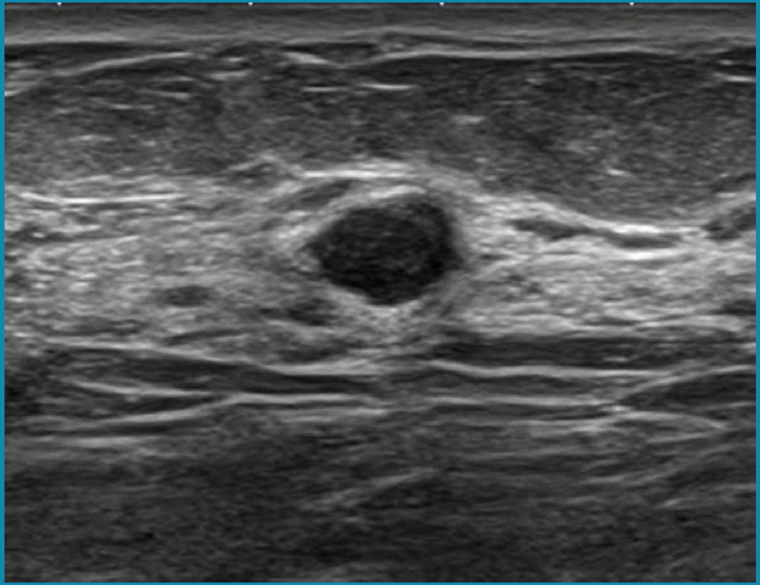
Park AY, Seo BK. Up-to date Doppler techniques for breast tumor vascularity: superb microvascular imaging and contrast-enhanced ultrasound. Ultrasonography. 2018 Apr;37(2):98-106.

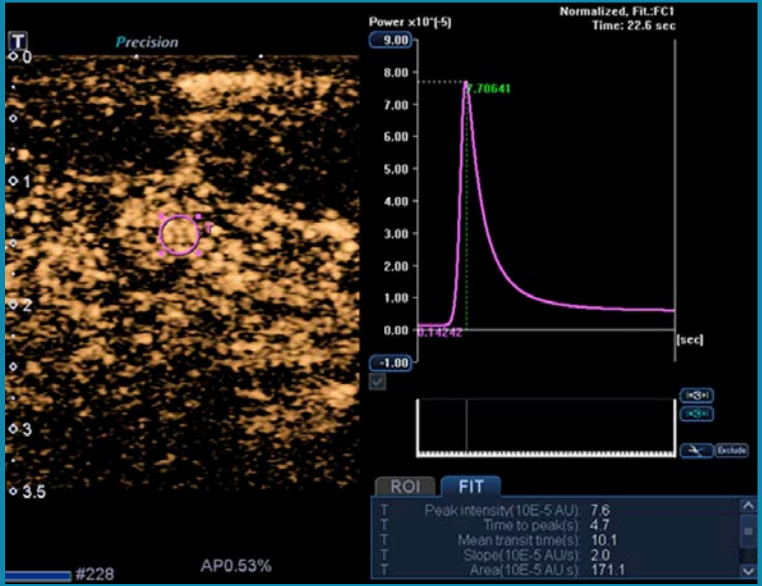
TIME-INTENSITY CURVE ANALYSIS



Park AY, Seo BK. Up-to date Doppler techniques for breast tumor vascularity: superb microvascular imaging and contrast-enhanced ultrasound. Ultrasonography. 2018 Apr;37(2):98-106. https://creativecommons.org/licenses/by-nc/3.0/legalcode

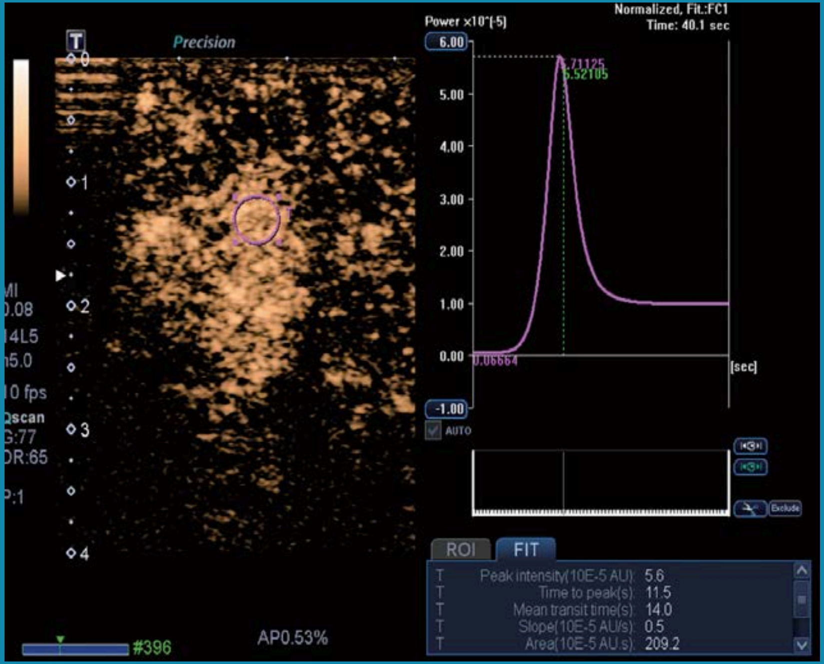
FIBROADENOMA





Park AY, Seo BK. Up-to date Doppler techniques for breast tumor vascularity: superb microvascular imaging and contrast-enhanced ultrasound. Ultrasonography. 2018 Apr;37(2):98-106. https://creativecommons.org/licenses/by-nc/3.0/legalcode

FIBROADENOMA



Park AY, Kwon M, Woo OH et al. A Prospective Study on the Value of Ultrasound and Microflow Assessment to Distinguish Malignant from Benign Solid Breast Masses: Association between Ultrasound Parameters and Histologic Microvessel Densities. Korean J Radiol. 2019 May; 20(5):759-772.

REDUCING FALSE POSITIVES

- Pilot study recently performed by Lee et al. to determine if CEUS can reduce the number of benign breast masses recommended for biopsy
- 131 women with BI-RADS 4 masses either detected by mammography, US or both
- CEUS exams performed before biopsy
- Qualitative and quantitative CEUS parameters were compared with histopathology

Lee SC, Tchelepi H, Grant E et al. Contrast-Enhanced Ultrasound Imaging of Breast Masses: Adjunct Tool to Decrease the Number of False-Positive Biopsy Results. J Ultrasound Med. 2019 Sep;38(9):2259-2273.

REDUCING FALSE POSITIVES

- Study demonstrated that CEUS could be used to downgrade BI-RADS 4 masses
- Parameters - Presence or absence of enhancement, mass margin, mass shape
- Potential for a 31% reduction of biopsies
  - Non-enhancing mass with circumscribed margin
  - Oval homogeneously enhancing mass
- Overlap between benign and malignant features in enhancing masses

Lee SC, Tchelepi H, Grant E et al. Contrast-Enhanced Ultrasound Imaging of Breast Masses: Adjunct Tool to Decrease the Number of False-Positive Biopsy Results. J Ultrasound Med. 2019 Sep;38(9):2259-2273.

REDUCING FALSE POSITIVES

- Proposed algorithm for evaluation with CEUS
- Determine if contrast uptake
- If no enhancement then margin analysis
- No enhancement with circumscribed margin characterized as probably benign
  - Algorithm applied to 29 of 38 nonenhancing masses
- In algorithm no enhancement with noncircumscribed margin requires biopsy
  - 7 out of 9 masses with noncircumscribed masses had benign pathology
  - 2 out of 9 had malignant pathology

Lee SC, Tchelepi H, Grant E et al. Contrast-Enhanced Ultrasound Imaging of Breast Masses: Adjunct Tool to Decrease the Number of False-Positive Biopsy Results. J Ultrasound Med. 2019 Sep;38(9):2259-2273.

CONCLUSIONS

- CEUS may be helpful when used in conjunction mammography and grayscale US to downgrade BI-RADS 4 masses
- Advantages of being able to be used in patients with renal failure, pacemakers and claustrophobia
- Small field of view
- Further studies necessary

Lee SC, Tchelepi H, Grant E et al. Contrast-Enhanced Ultrasound Imaging of Breast Masses: Adjunct Tool to Decrease the Number of False-Positive Biopsy Results. J Ultrasound Med. 2019 Sep;38(9):2259-2273.

Thank you!

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