

OPTO-ACOUSTIC BREAST IMAGING

*A Novel Fusion of Functional and
Morphologic Imaging*

Reni S. Butler, MD

A. Thomas Stavros, MD

F. Lee Tucker, MD

Michael J. Ulissey, MD

PURPOSE

1. Explain opto-acoustic (OA) imaging and its potential role in the assessment of breast masses
 2. Illustrate OA findings within tumor zones and their histopathologic basis
 3. Present data and case examples showing strong correlation between OA features and likelihood of malignancy
 4. Present data and case examples showing strong correlation between OA features in malignant tumors and their histologic grade and molecular subtype
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FUNDAMENTAL PRINCIPLES

WHAT IS OA IMAGING?

- Fusion of B-mode ultrasound with functional information about level of oxygenation of hemoglobin (Hgb) within tumors
- Based on concept that malignant tumors are more metabolically active and, therefore, deoxygenate Hgb to a greater degree than benign tumors or normal tissue



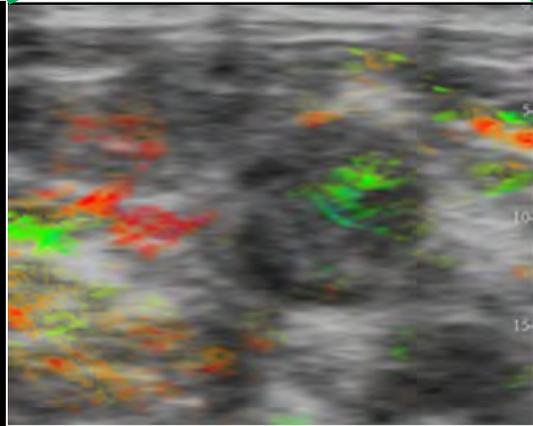
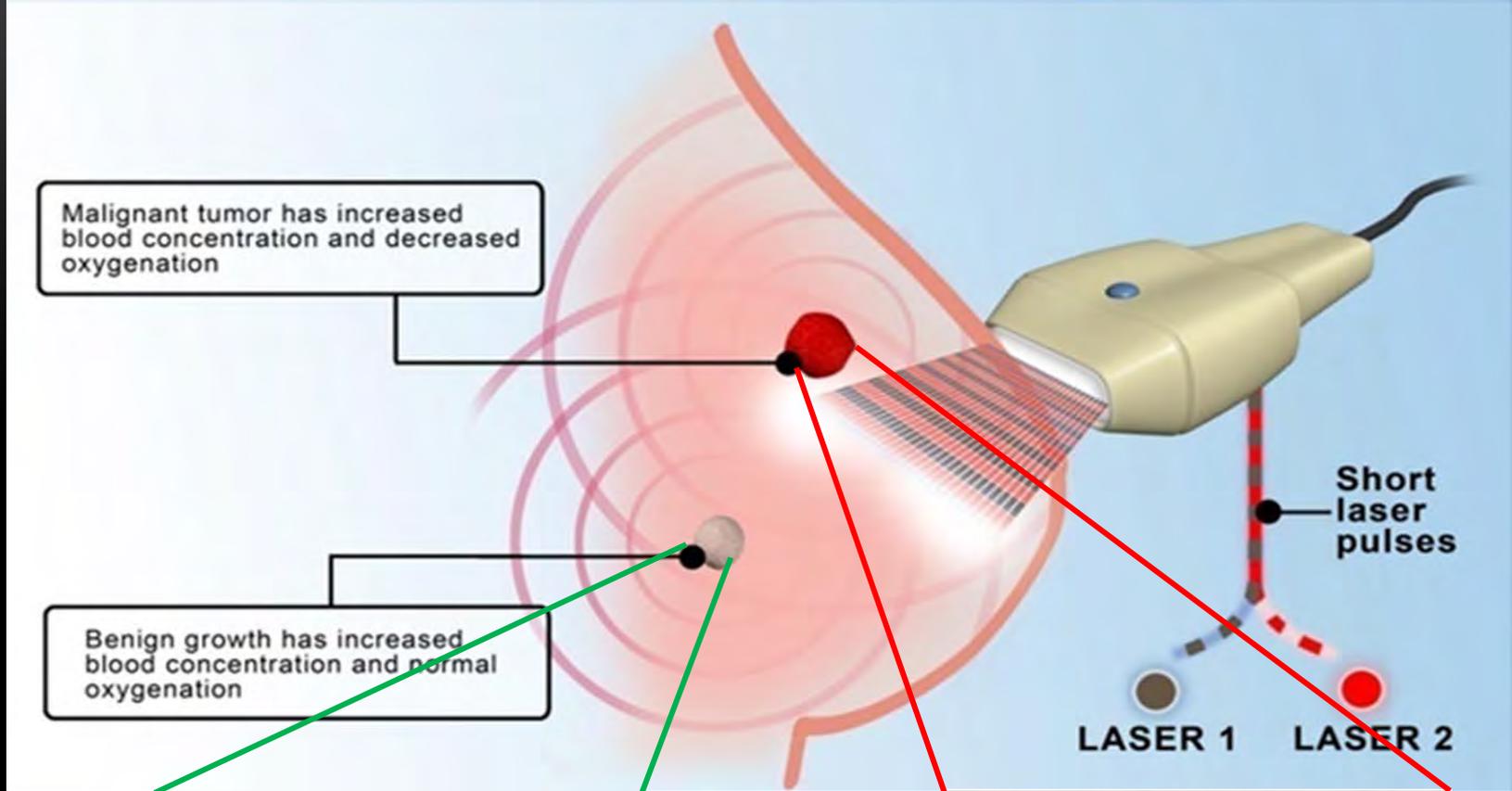
Seno Medical Instruments, Inc.

FUNDAMENTAL PRINCIPLES

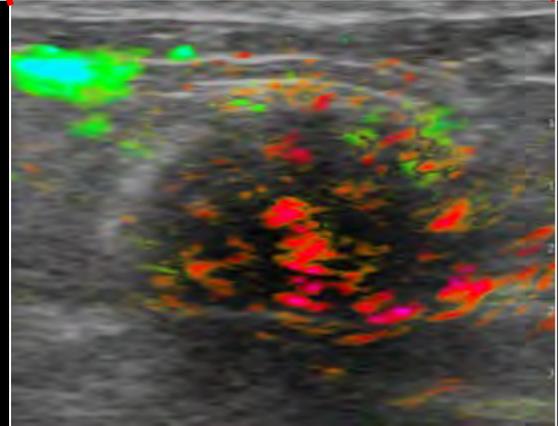
HOW IS OA IMAGING PERFORMED?

- Transducer emits short laser light pulses at two different wavelengths corresponding to absorption peaks of oxygenated and deoxygenated Hgb
- Laser light pulses in nanoseconds cause expansion of tissues
- Opto-acoustics detects heating and expansion of tissues at each wavelength and color codes it
 - Oxygenated Hgb – green
 - Deoxygenated Hgb – red
- Color coded opto-acoustic data is co-registered with gray scale ultrasound image in real time

LASER LIGHT IN - ULTRASOUND OUT



Fibroadenoma with oxygenated Hgb (green)



Grade 3 invasive ductal carcinoma with deoxygenated Hgb (red)

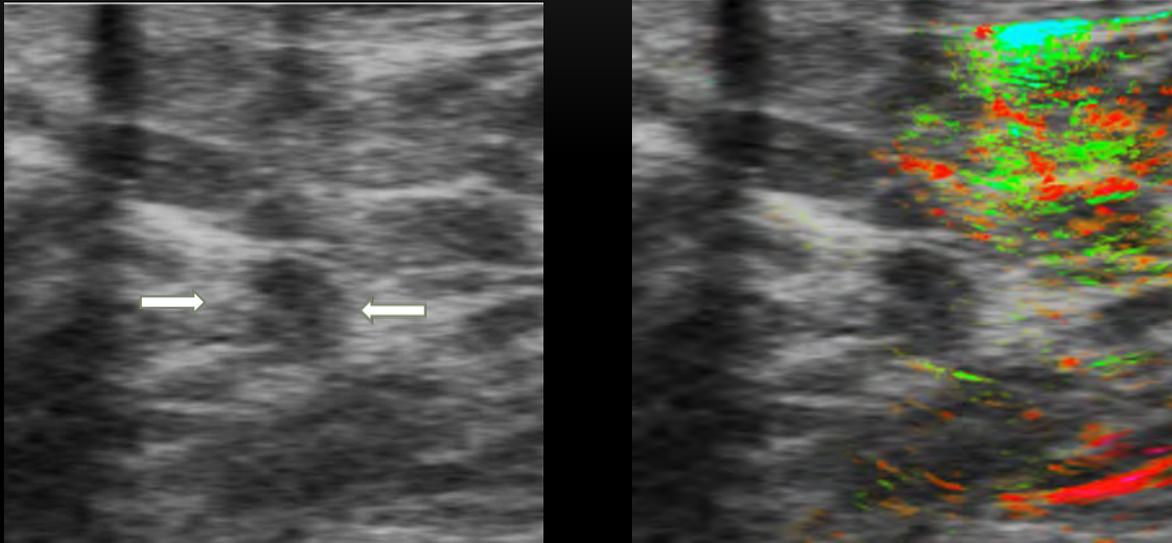
FUNDAMENTAL PRINCIPLES

WHY IS OA IMAGING OF INTEREST?

- **Positive** predictive value for biopsies performed (PPV3) is between 25 and 40% according to current acceptable performance criteria*, i.e. majority of biopsies are benign
- Additional functional information about tumors may improve specificity and reduce the number of negative biopsies
- Additional functional information may also help detect cancers with deceptively benign morphology, such as many high-grade, triple negative invasive ductal carcinomas (IDCs)

CASE EXAMPLE #1

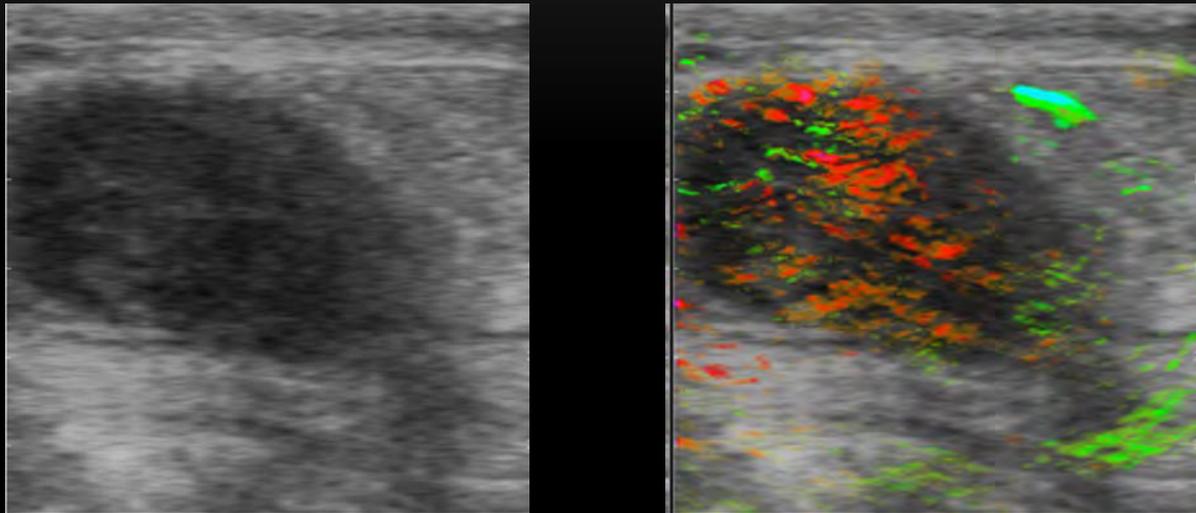
POTENTIAL FOR IMPROVED SPECIFICITY



- Conventional B-mode image: irregular mass (arrows) with angular margins and anti-parallel orientation consistent with a BI-RADS 4 lesion
- OA: absence of internal vascularity or deoxygenation, consistent with a BI-RADS 2 lesion
- Biopsy: fibroadenoma

CASE EXAMPLE #2

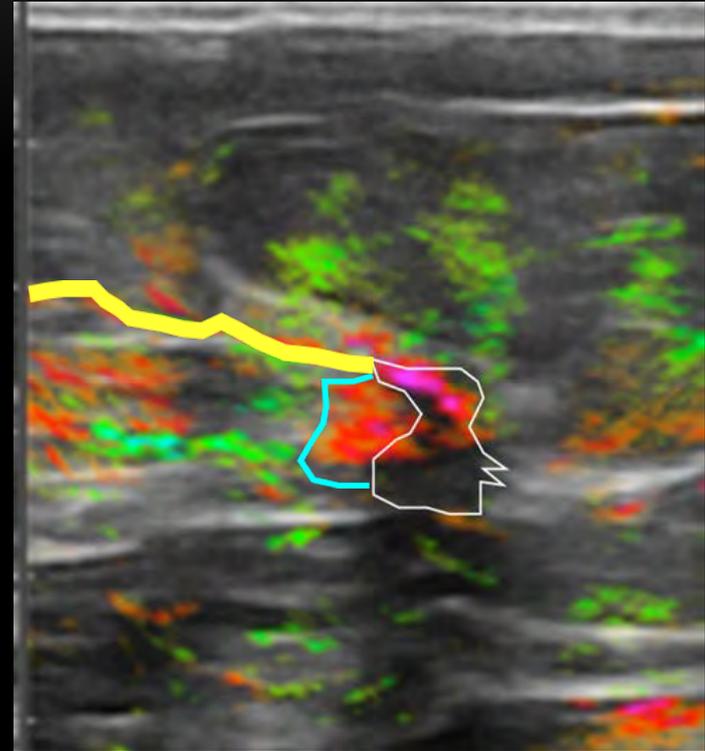
POTENTIAL FOR IMPROVED SENSITIVITY



- Conventional B-mode image: oval mass with partially circumscribed, partially indistinct margins and parallel orientation which could be misinterpreted as a BI-RADS 3 lesion
- OA map: increased internal vascularity with deoxygenation (red), consistent with a BI-RADS 4 lesion
- Biopsy: Grade 3 IDC, triple negative subtype

TUMOR ZONES AND HISTOPATHOLOGY

- In OA interpretation, tumors are divided into 3 zones which are independently assessed
 1. Tumor Interior
 2. Boundary Zone
 3. Tumor Periphery



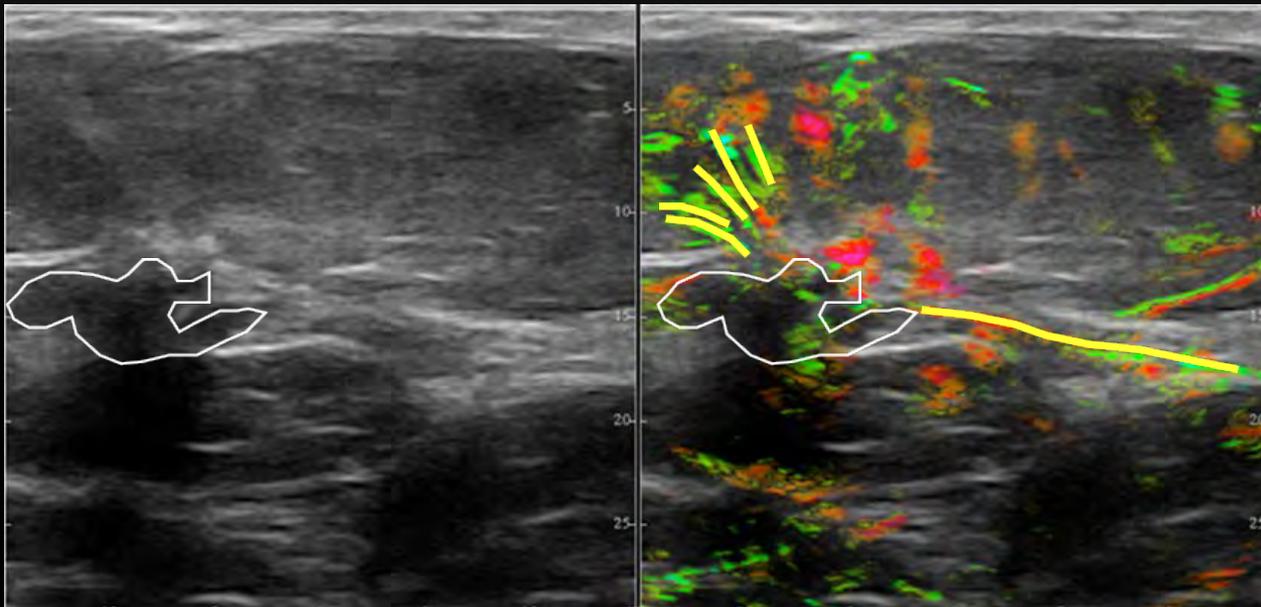
White outline shows tumor interior with deoxygenated (red) and intensely deoxygenated (pink) Hgb; aqua outline shows boundary zone with deoxygenated (red) vascularity; yellow line shows tumor periphery with prominent draining vein (pink)

TUMOR ZONES AND HISTOPATHOLOGY

- The predominance of OA features in each zone correlates with histologic grade
 - Grade 1 IDC – characterized primarily by external OA findings in tumor boundary zone and periphery
 - Grade 2 IDC – characterized by a mixture of OA findings in all 3 zones
 - Grade 3 IDC – characterized primarily by OA findings in tumor interior

CASE EXAMPLE #3

GRADE 1 INVASIVE DUCTAL CARCINOMA – MAINLY EXTERNAL FINDINGS



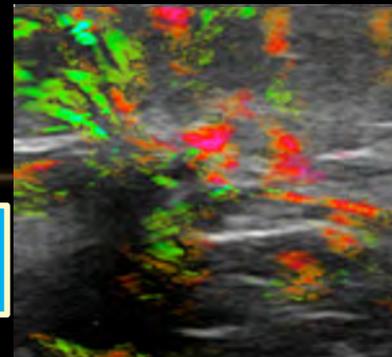
Tumor interior shows minimal vascularity with no deoxygenated Hgb; however, tumor periphery demonstrates prominent radiating vessels analogous to architectural distortion on mammography

DOES IT MAKE BIOLOGIC SENSE THAT GRADE 1 IDC SHOWS MAINLY EXTERNAL SUSPICIOUS FINDINGS?

Yes, OA findings correlate with histopathology

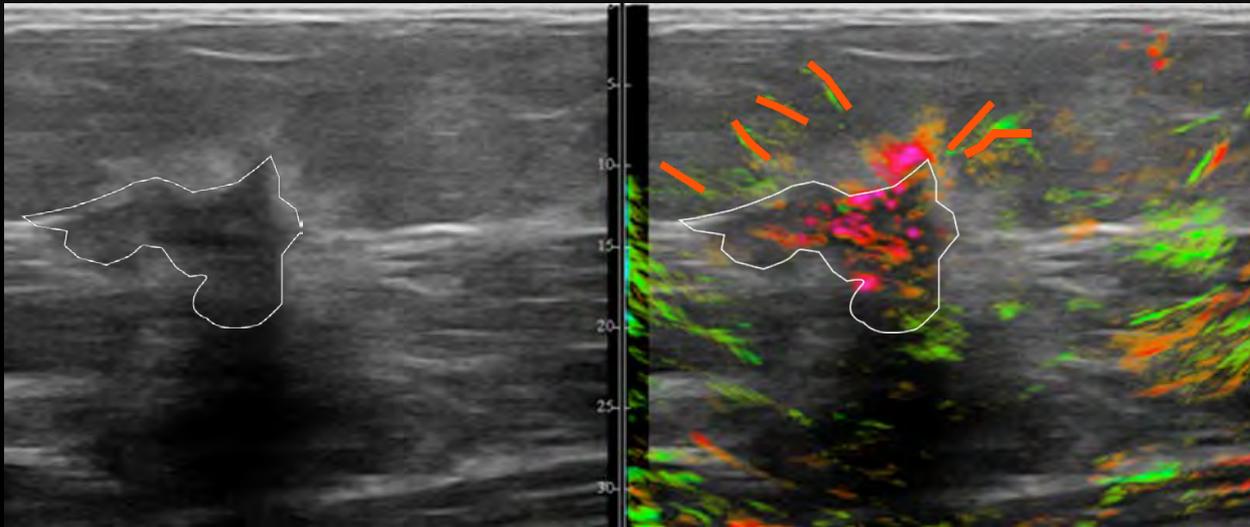
- Grade 1 IDCs have low internal cellularity and de-oxygenation
 - Paucicellular; most of internal tumor volume is extracellular matrix
 - Tumor cells only mildly de-differentiated with few biologically active immune cells
- Grade 1 IDCs show peri-tumoral radiating vessels
 - Associated with hypocellular peri-tumoral desmoplasia
 - Spiculated masses on mammography

Radiating peripheral vessels are key finding



CASE EXAMPLE #4

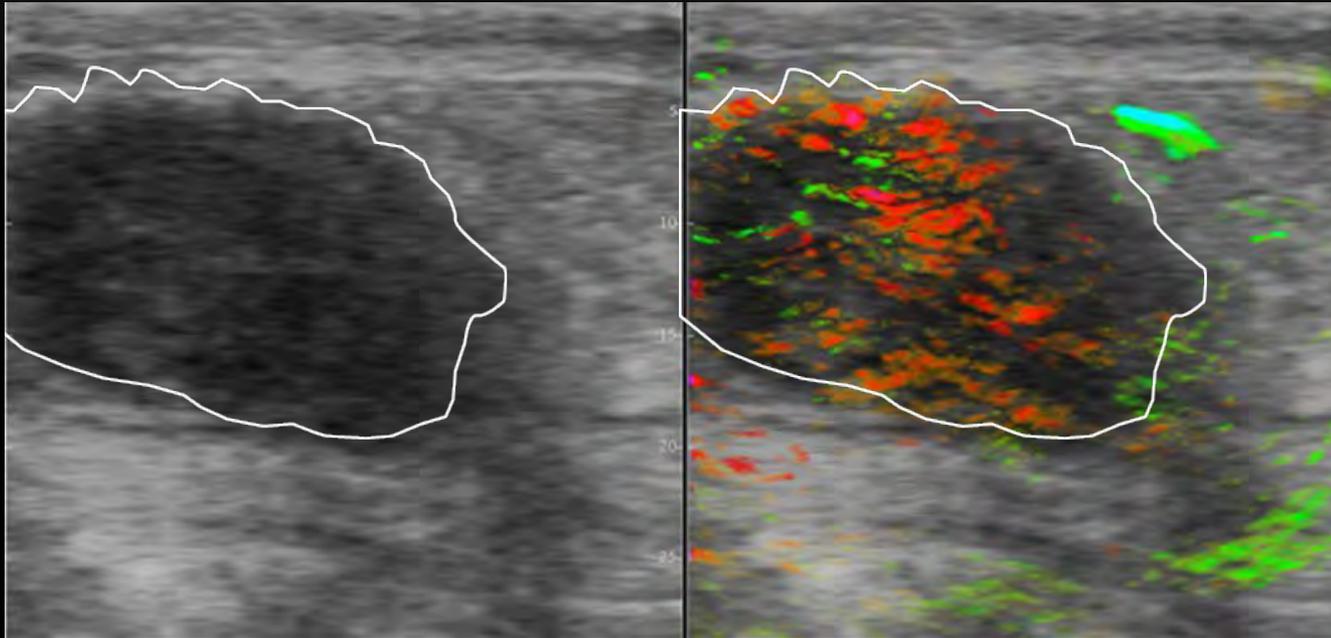
GRADE 2 INVASIVE DUCTAL CARCINOMA – MIXTURE OF INTERNAL AND EXTERNAL FINDINGS



Tumor interior shows increased vascularity with deoxygenated Hgb (red and pink), and tumor periphery shows radiating vessels

CASE EXAMPLE #5

GRADE 3 INVASIVE DUCTAL CARCINOMA – MAINLY INTERNAL FINDINGS



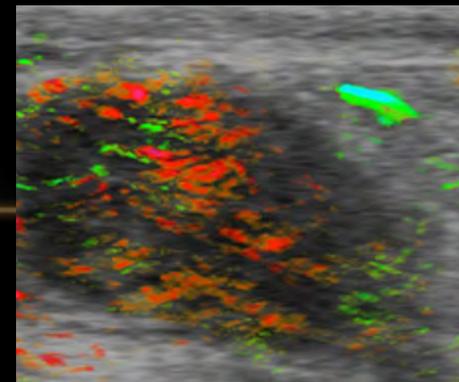
Tumor interior shows increased vascularity with deoxygenated Hgb;
no OA findings are seen in boundary zone and tumor periphery

DOES IT MAKE BIOLOGIC SENSE THAT GRADE 3 IDC SHOWS MAINLY INTERNAL SUSPICIOUS FINDINGS?

Yes, OA findings correlate with histopathology

- Grade 3 IDCs have high internal vascularity and deoxygenation
 - Highly cellular tumors
 - Tumor cells are very de-differentiated
 - Many biologically active immune cells
- Grade 3 IDCs have few peri-tumoral radiating vessels
 - More often circumscribed with less desmoplasia and spiculation than grade 1 or 2 lesions

Morphology overlaps that of benign lesions
but OA features are malignant



CLINICAL PHASE II TRIAL

FEASIBILITY STUDY

- 155 subjects with solid breast masses imaged with conventional diagnostic ultrasound underwent Imagio scans at two IRB approved sites
- 79 lesions biopsied
 - 39 benign
 - 34 malignant
 - 6 excluded
- Images retrospectively interpreted by 5 independent readers blinded to biopsy results

CLINICAL PHASE II TRIAL

FEASIBILITY STUDY

- Probability of malignancy (POM) assigned by readers to each lesion based on OA vs. conventional diagnostic US (CDU)
- ROC area under the curve (AUC) derived from POM compared to biopsy results and sensitivity and specificity calculated

	OA	CDU
POM for all malignant lesions	73.6	62.1
Sensitivity	0.99	1.0
Specificity	0.237	0.161

OA had same sensitivity as CDU, but 40% better specificity

DATA: CORRELATION OF OA AND HISTOPATHOLOGIC FEATURES

- OA provides the following functional information about each tumor zone:
 1. Vessel score – number of individually resolved internal vessels
 2. Hgb score – total amount of detected Hgb
 3. Blush score – degree of tumor blush representing vessels too small to resolve
 4. Total score – sum of above

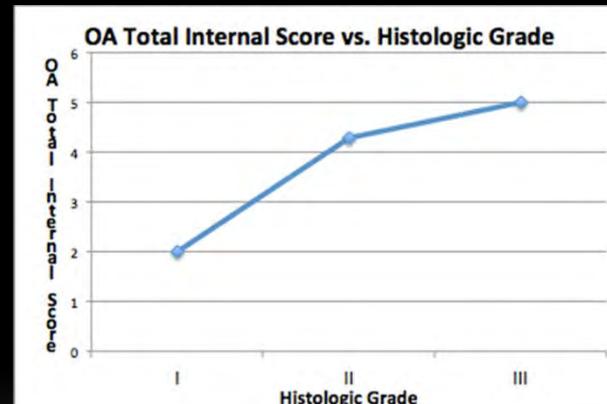
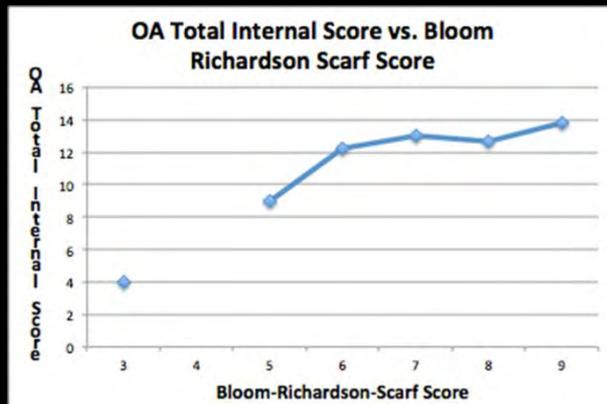
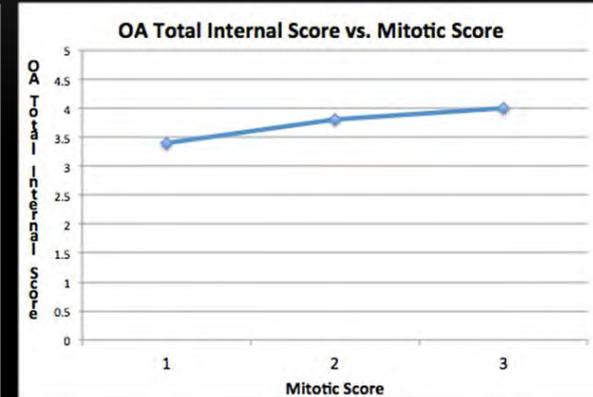
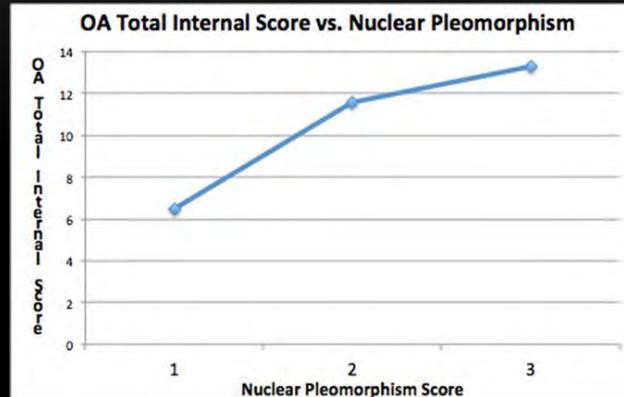
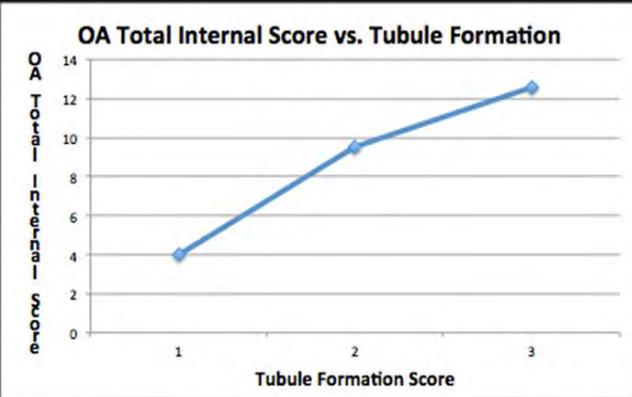
DATA: CORRELATION OF OA AND HISTOPATHOLOGIC FEATURES

TUMOR INTERIOR – INTERNAL FEATURES

- We correlated the OA functional data with the following internal histopathologic features based on core needle biopsy:
 - Histologic grade, including tubule formation, nuclear pleomorphism, mitotic count, and Scarff-Bloom-Richardson score
 - Tumor cellularity - tumor cell/stroma ratio
 - Vessel density
 - Maximum vessel diameter
- We present the correlation of total **internal** OA score (sum of individual internal OA features) with the above histopathologic measures

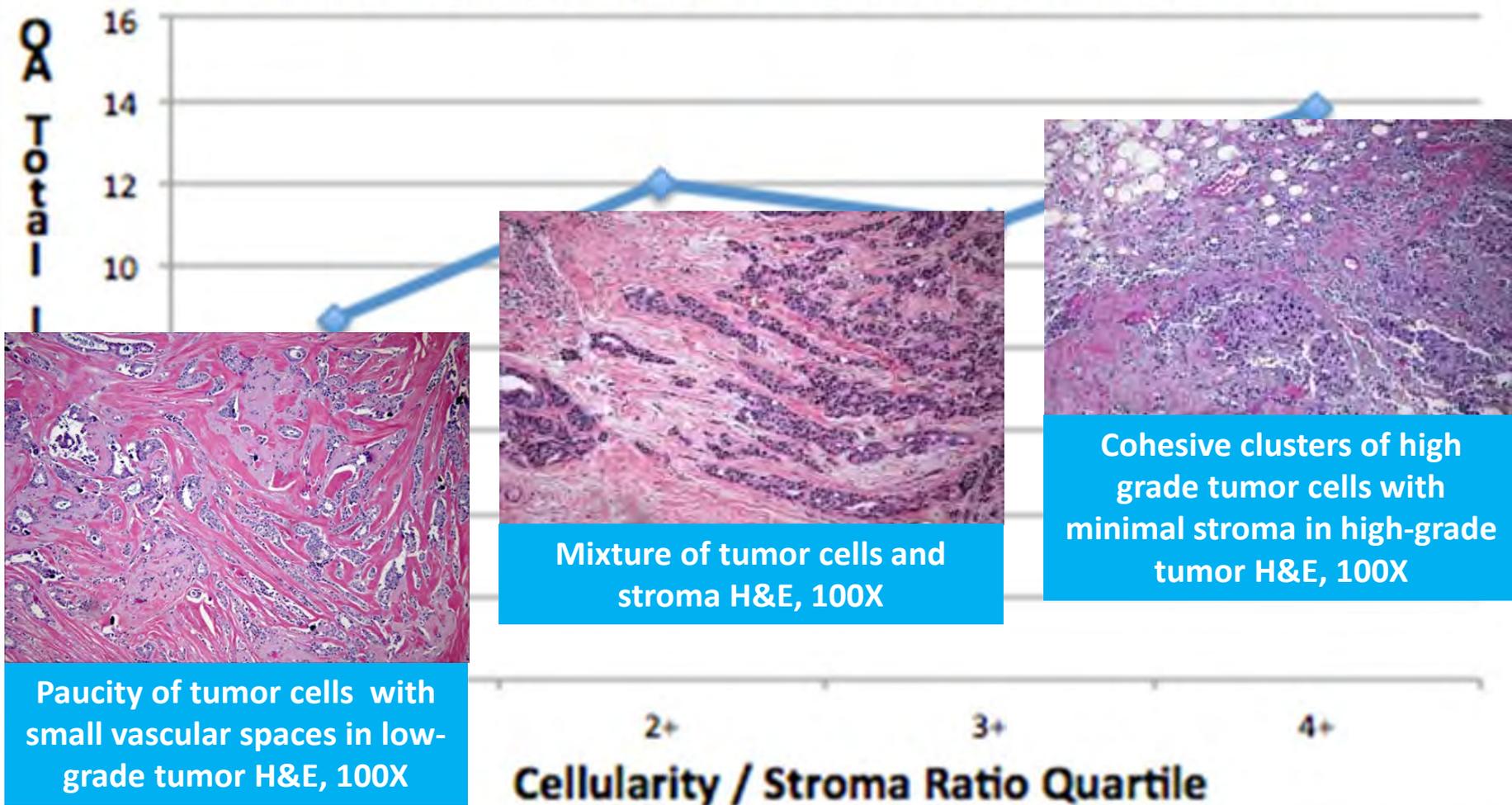
RESULTS

OA TOTAL INTERNAL SCORE VS. HISTOLOGIC GRADE



All histopathologic measures of tumor grade correlate positively with OA total internal score indicative of malignancy

OA Total Internal Score vs. Tumor Cellularity/Stroma Ratio



Tumor cellularity / stroma ratio increases with increasing internal OA score, reflecting higher grade tumors

CONCLUSIONS ABOUT SIGNIFICANCE OF OA FEATURES IN TUMOR INTERIOR

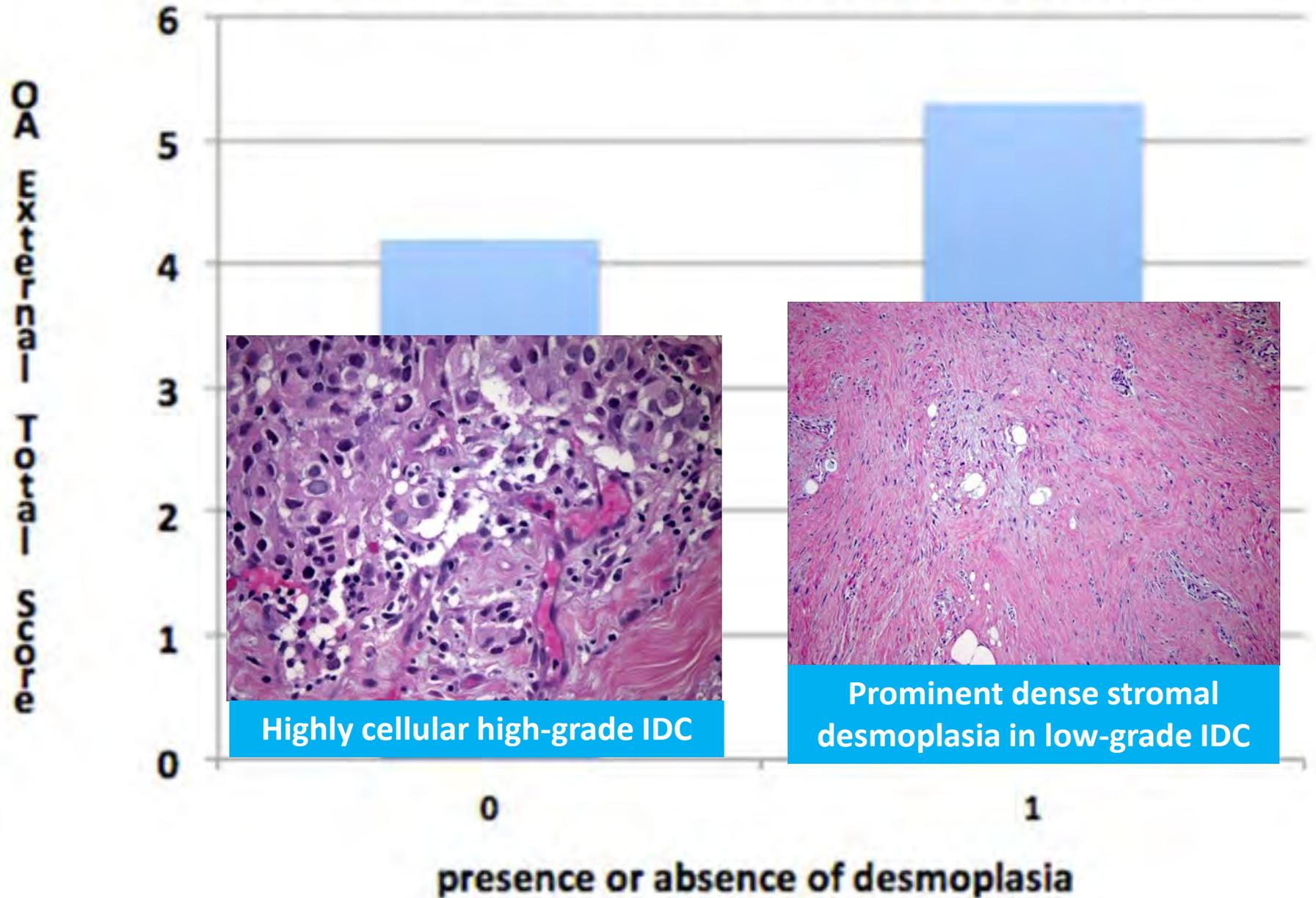
- Functional information provided by OA imaging reflects underlying histologic grade of tumor interior, as measured by tubule formation, nuclear pleomorphism, mitotic count, and Scarff-Bloom-Richardson score
- High-grade tumors demonstrate prominent internal deoxygenated vessels and a paucity of external features
- Functional information provided by OA imaging does not correlate with vessel density within tumor interior, a surprising finding that may be related to the low number of cases in this initial study

DATA: CORRELATION OF OA AND HISTOPATHOLOGIC FEATURES

BOUNDARY ZONE AND TUMOR PERIPHERY – EXTERNAL FEATURES

- We correlated the OA functional data with the following external histopathologic features based on excisional biopsy:
 - Tumor cellularity - tumor cell/stroma ratio
 - Stromal desmoplasia
- We present the correlation of total **external** OA score with the above histopathologic measures

OA External Total Score vs. Desmoplasia



CONCLUSIONS ABOUT SIGNIFICANCE OF OA FEATURES IN TUMOR BOUNDARY ZONE AND PERIPHERY

- Functional information provided by OA imaging reflects underlying cellularity and desmoplasia
- Low-grade tumors demonstrate prominent external deoxygenated vessels and a paucity of internal features, while intermediate grade tumors demonstrate a mixture of internal and external OA features
- High grade lesions grow too fast for the slow forming desmoplasia to develop. Thus, higher external OA scores occur in low grade lesions that have more desmoplasia.

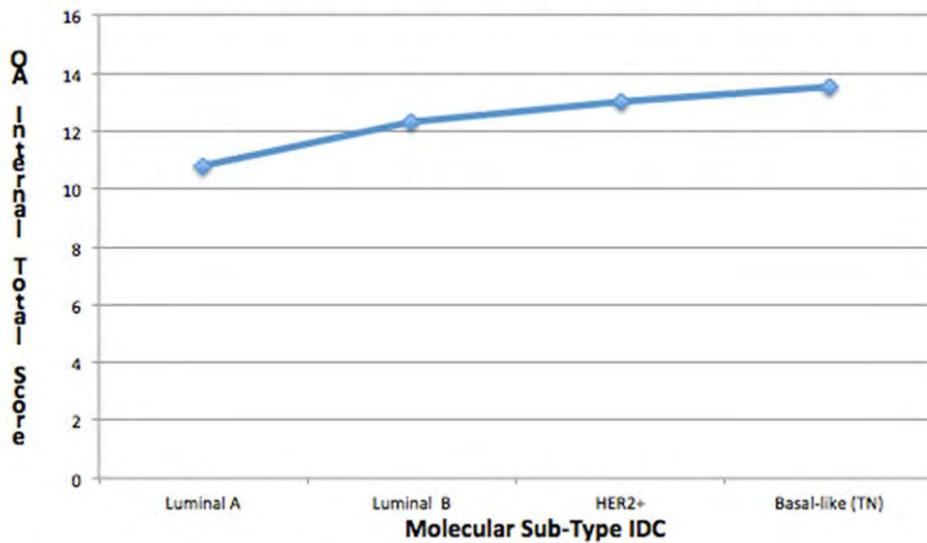
MOLECULAR SUBTYPES

- Interest in understanding genetic signature of breast cancer subtypes and tailoring therapy accordingly continues to rise
- Four major molecular subtypes are recognized which direct treatment and correlate with prognosis
 1. Luminal A – ER+ PR+ Her2-, 90% 5 year survival (5YS)
 2. Luminal B – ER+ PR+ Her2- (30% Her2+), higher grade, 40% 5YS
 3. Her2-enriched – ER- PR- Her2+, 30% 5YS
 4. Basal-like – ER- PR- Her2- (Triple negative) – lowest 5YS

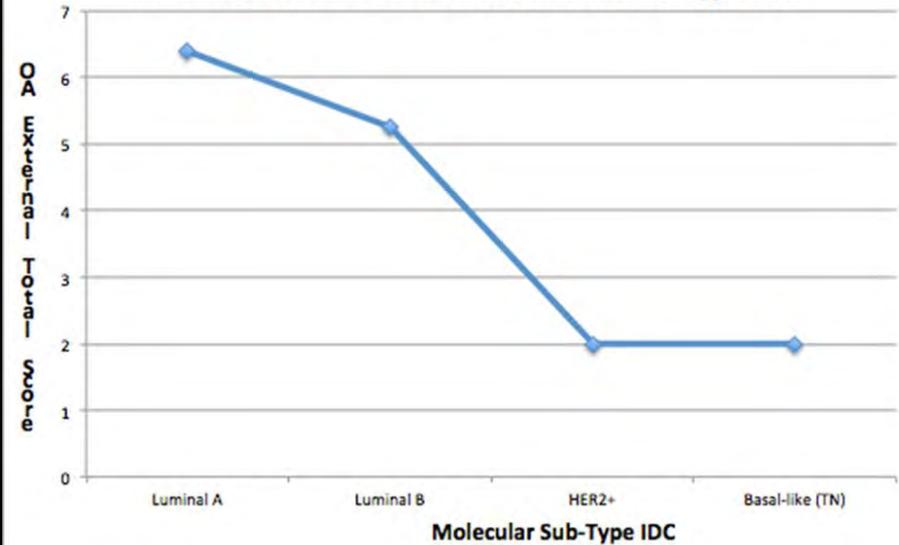
OA features correlate with molecular subtypes, potentially contributing to pre-operative tumor assessment

DATA: CORRELATION OF OA AND MOLECULAR SUBTYPES

OA Internal Total Score vs. Molecular Sub-Type IDC



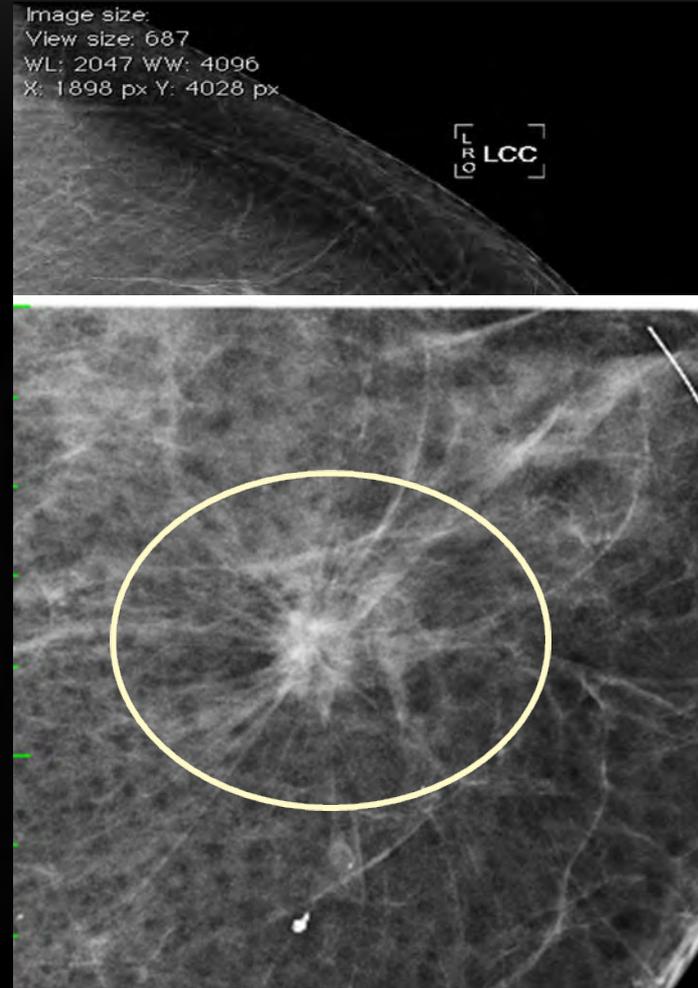
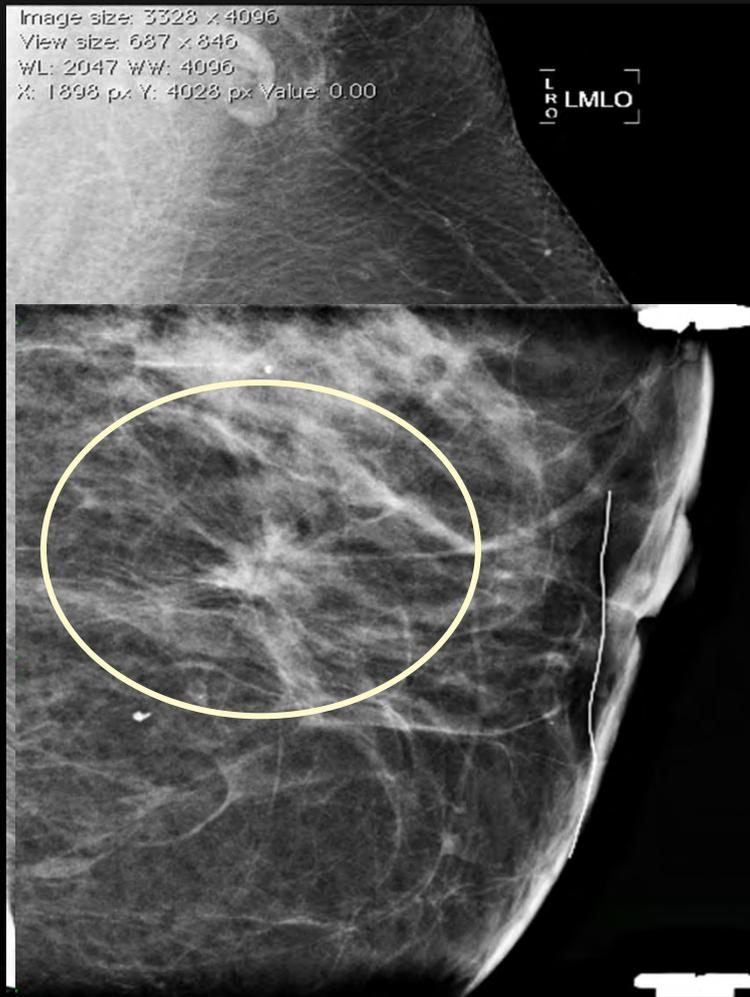
OA External Total Score vs. Molecular Sub-Type IDC



Molecular sub-types with worse prognoses have higher internal OA scores, while molecular sub-types with better prognoses have higher external OA scores

CASE EXAMPLE #6

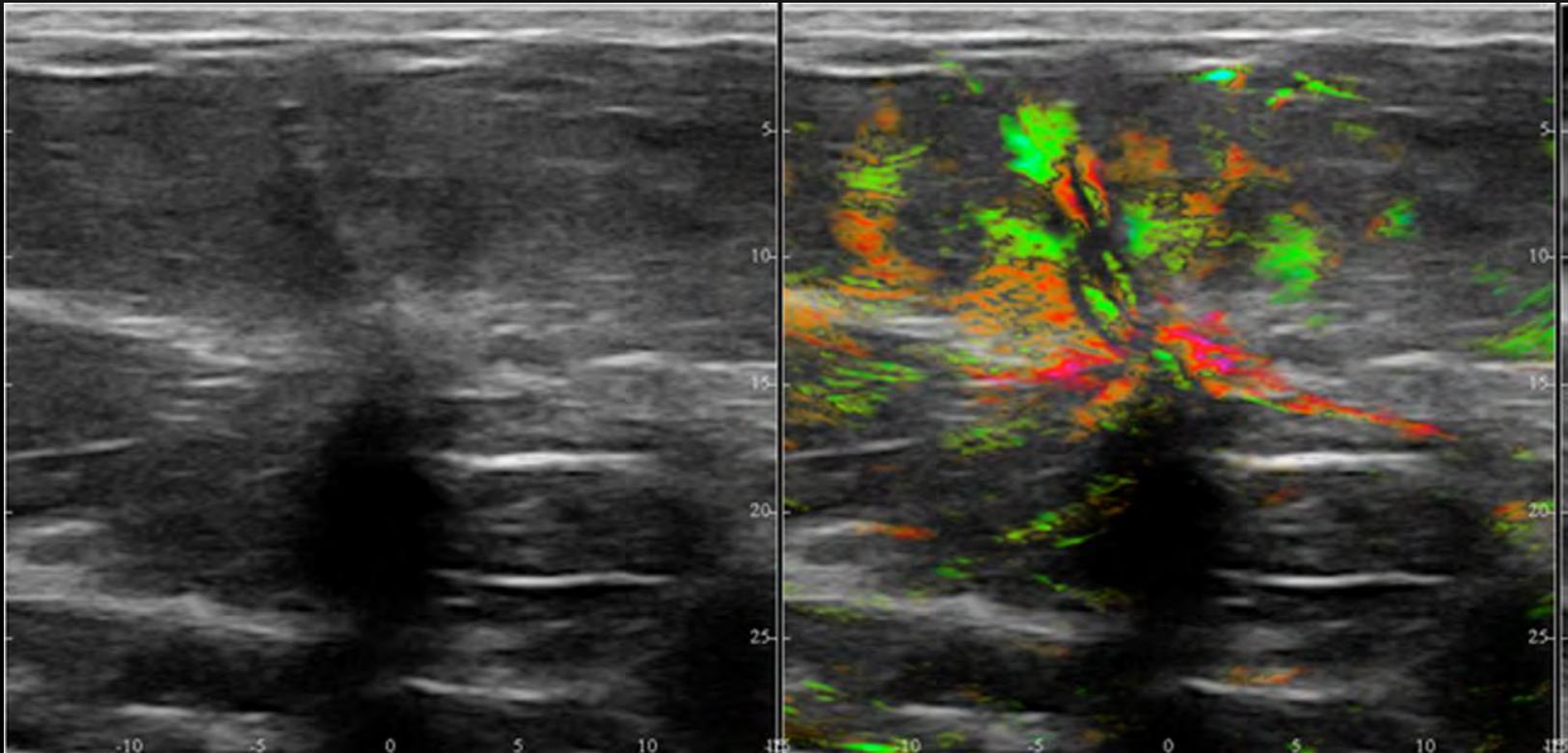
LUMINAL A INVASIVE DUCTAL CARCINOMA, ER+PR+HER2-



Mammogram - spiculated mass with prominent architectural distortion

CASE EXAMPLE #6

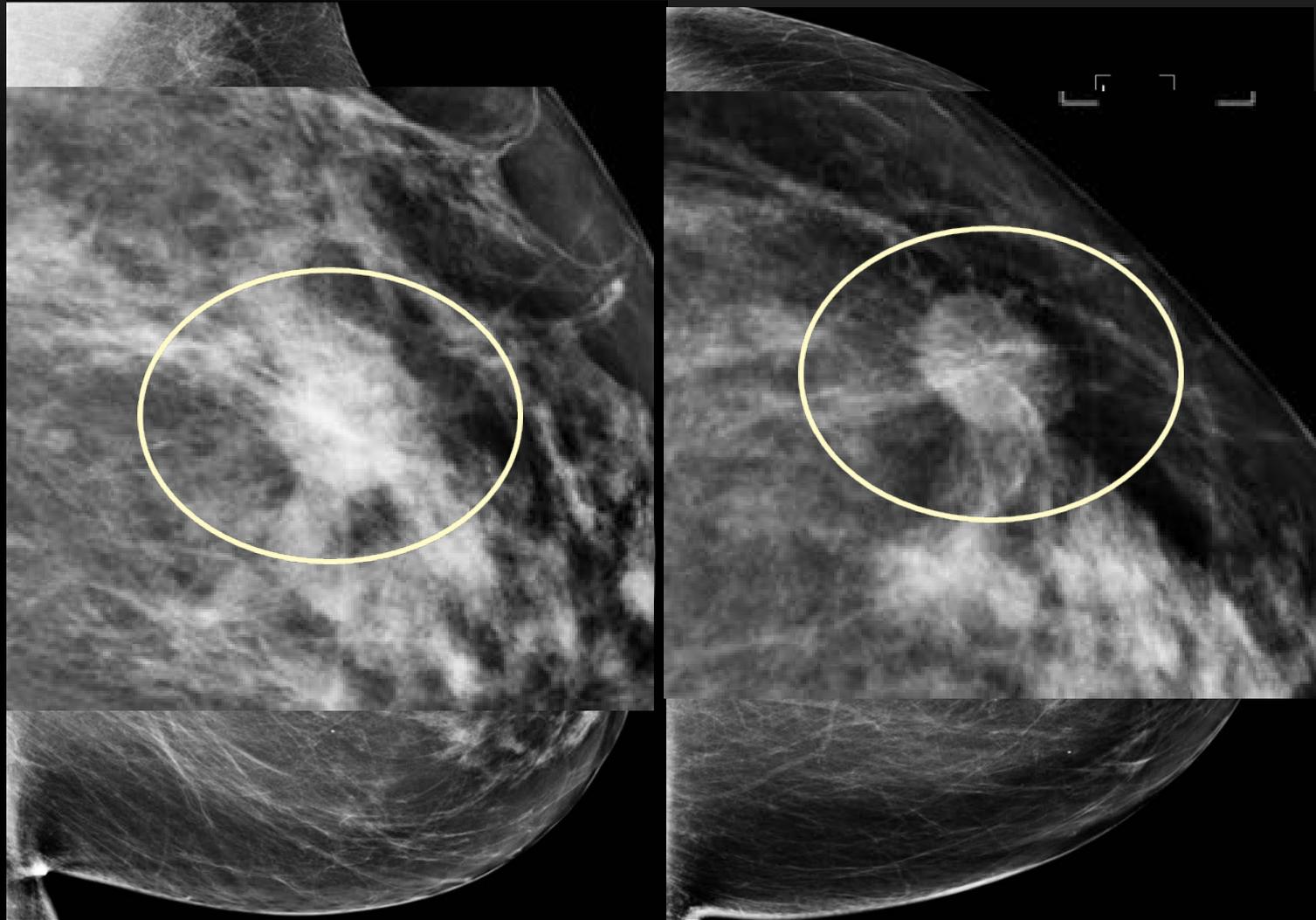
LUMINAL A INVASIVE DUCTAL CARCINOMA, ER+PR+HER2-



Ultrasound: intensely hypoechoic anti-parallel lesion with posterior acoustic shadowing; OA: malignant EXTERNAL features of prominent peripheral vascularity and deoxygenation (red, pink and orange peripheral vessels)

CASE EXAMPLE #7

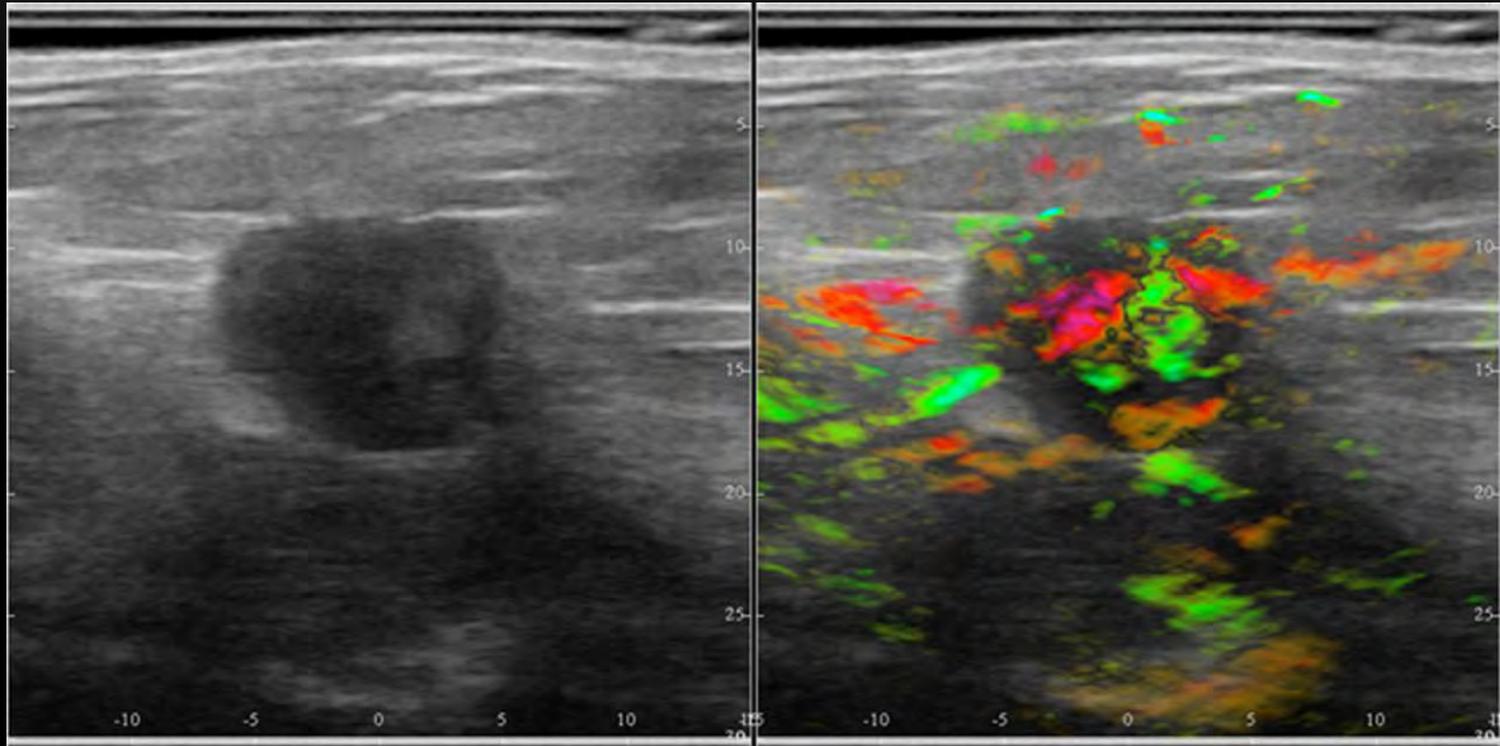
LUMINAL B INVASIVE DUCTAL CARCINOMA, ER+PR+HER2+



Mammography: Lobulated mass with partially circumscribed, partially obscured margins

CASE EXAMPLE #7

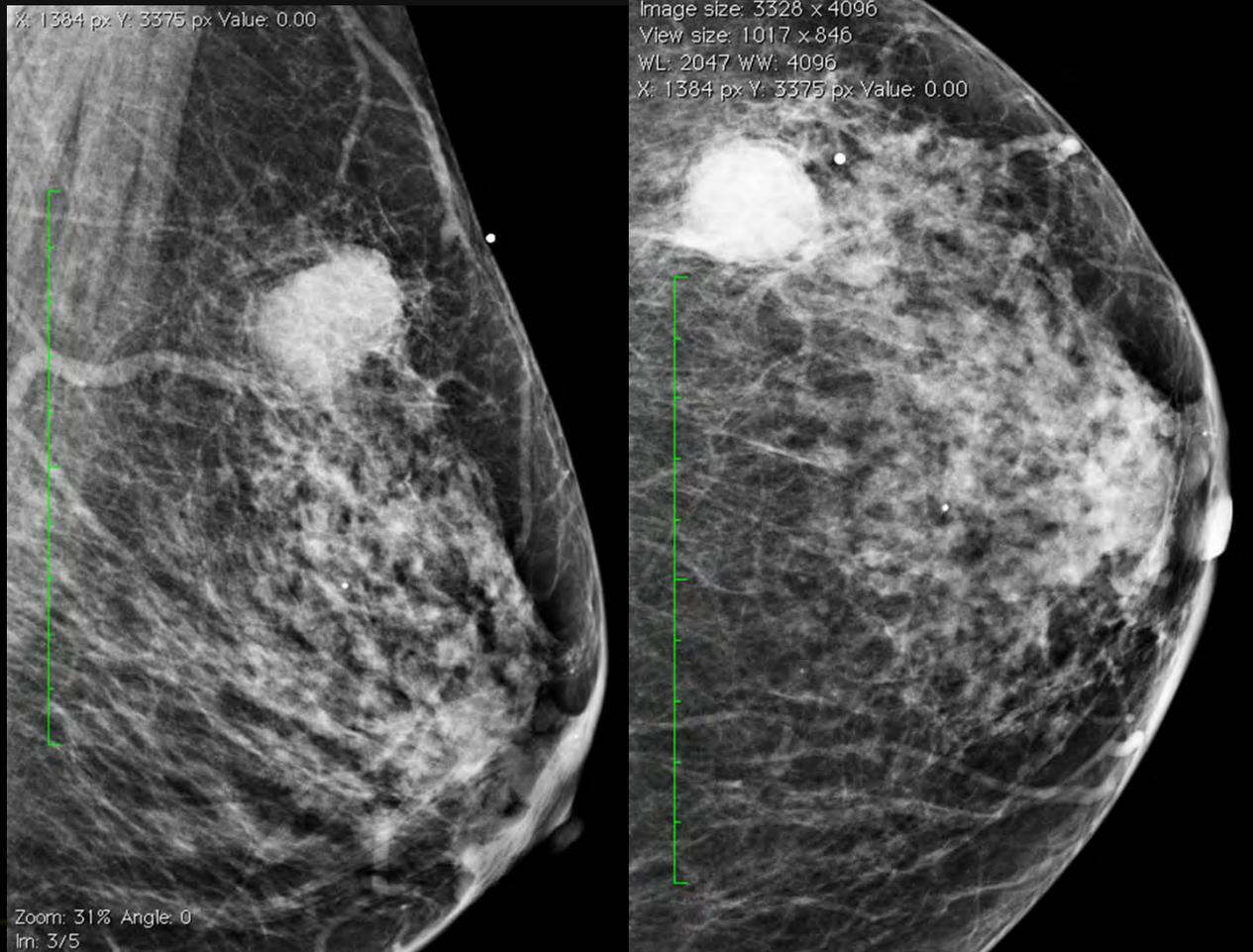
LUMINAL B, INVASIVE DUCTAL CARCINOMA, ER+PR+HER2+



Ultrasound: lobulated hypoechoic mass with circumscribed and indistinct margins; OA: malignant INTERNAL AND EXTERNAL features of prominent internal vascularity and deoxygenation (red, pink and orange internal vessels)

CASE EXAMPLE #8

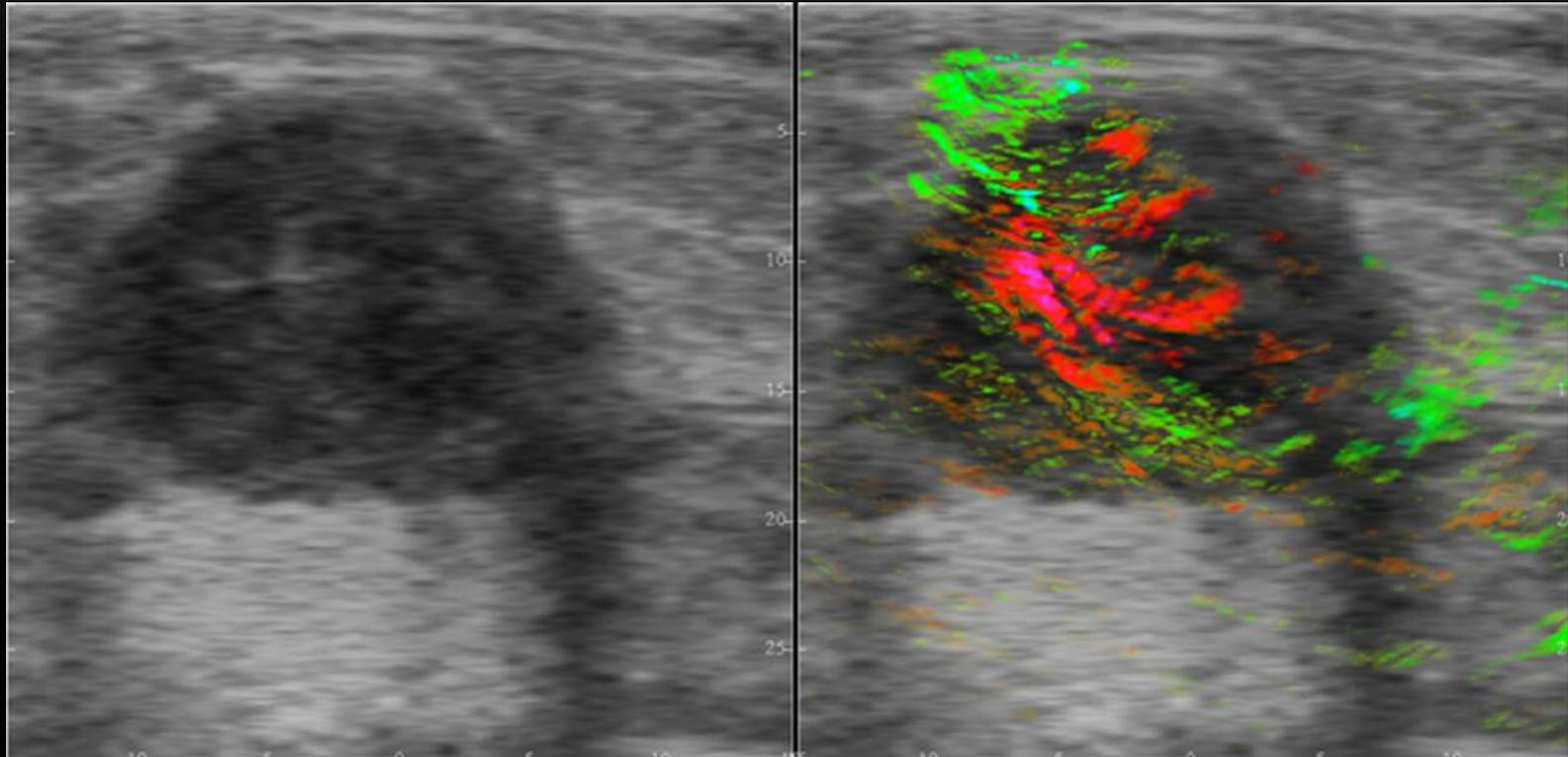
BASAL-LIKE, TRIPLE NEGATIVE INVASIVE DUCTAL CARCINOMA, ER-PR-HER2-



Mammography: Dense mass with partially circumscribed, partially obscured margins

CASE EXAMPLE #8

BASAL-LIKE, TRIPLE NEGATIVE INVASIVE DUCTAL CARCINOMA, ER-PR-HER2-



Ultrasound: oval hypoechoic mass with microlobulated margins; OA: malignant INTERNAL features of prominent internal vascularity and deoxygenation (red, pink and orange internal vessels)

LIMITATIONS

- Initial study of novel technology with small number of cases
- Analysis of histopathologic features based primarily on H&E stains
 - It is possible, for example, that correlation with vessel density may be revealed if vessel-specific stains used
- Images interpreted by formally trained readers blinded to mammography and histopathology – results may be difficult to generalize

CONCLUSIONS

- OA Imaging is a promising new ultrasound technology that adds functional information about tumor deoxygenation without the need for contrast injection or ionizing radiation
- The presence of suspicious OA features correlates with likelihood of malignancy
- The distribution of suspicious OA features, i.e. internal vs. external, correlates with the histologic grade and molecular subtype of malignant tumors
- Further study in a large patient population is underway