Opto-Acoustics (OA) Correlations with Histopathology

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Background

- Imagio® (Seno Medical Instruments, Inc.) is currently an investigational medical device under FDA review.

- It utilizes dual wavelength laser opto-acoustic (OA) imaging technology co-registered with conventional diagnostic ultrasound to gain both structural (demonstration of neo-angiogenesis) and functional imaging (showing relative degree of de-oxygenation) information of potentially suspicious breast masses without having to administer radioactive contrast agents or expose patients to radiation.

- The purpose of this study is to evaluate which histopathologic correlates can be visualized by OA imaging in malignant masses.

Material and Method (1)

- A prospective series of 31 histologically proven malignant masses underwent Imagio opto-acoustic diagnostic assessment after CDU and prior to biopsy.

- Each mass was blindly evaluated by an expert reader and expert pathologist.

- Three internal OA findings and two external OA findings were assigned score utilizing a 0-5/6 ordinal scale based upon opto-acoustic findings.

    -Internal OA findings: Density of Vascularity (V), Relative Blood Oxygen Saturation (O), and Hemoglobin (H)

    -External OA findings: Boundary Zone (Z) and Peripheral Peri-tumoral Radiating Vessels (R)

Material and Method (2)

- Total internal (IT), total external (ET), and overall (OAT) scores were computed by summing the 3 internal and 2 external scores, respectively. Higher scores were seen in malignant masses relative to benign masses.

- Central nidus, boundary, and peripheral (NBP) zone histopathology measures included BI-RADS assessment, probability of malignancy (POM), estrogen and progesterone receptors, histologic grade with the three components of histologic grading (tubular, mitotic, and nuclear pleomorphism indices), vessel greatest diameter (VGD), and vessel density (VD) metrics.

- Spearman correlations and analysis of variance were used to identify the findings with statistically significant correlations.

Material and Method (3) histopathologic definitions

- Mitotic rate – a component of histologic grading rated 1, 2, or 3
- Vessel greatest diameter:
  - 1 = < 50 microns
  - 2 = 51-150 microns
 - 3 = >150 microns

Results (1)

1. BI-RADS assessment correlated significantly with Boundary Zone, Peripheral Zone, and OA total scores. (Figure 1)

2. There is a statistically significant negative correlation of VGD with probability of malignancy (POM), peripheral zone radiating vessels (R), boundary zone radiating vessels (Z), and total external OA score (ET). (Figure 2)

3. Mitotic rate correlates significantly with density of vascularity (V) and has a statistically significant negative correlation with peripheral zone score. (Figure 3)

4. The feasibility study indicates that evaluation with Imagio provides OA findings that correlate significantly with histopathology in malignant masses. This suggests that Imagio OA evaluation may accurately predict histopathology of malignant breast tumors.

Results (2)

5. In total, 81 Imagio opto-acoustic findings showed statistically significant correlation to histopathology (Table 1).

6. If confirmed in the ongoing 2,100 subject pivotal study, OA may potentially be considered an important non-invasive means of predicting the clinically relevant pathology of breast masses.
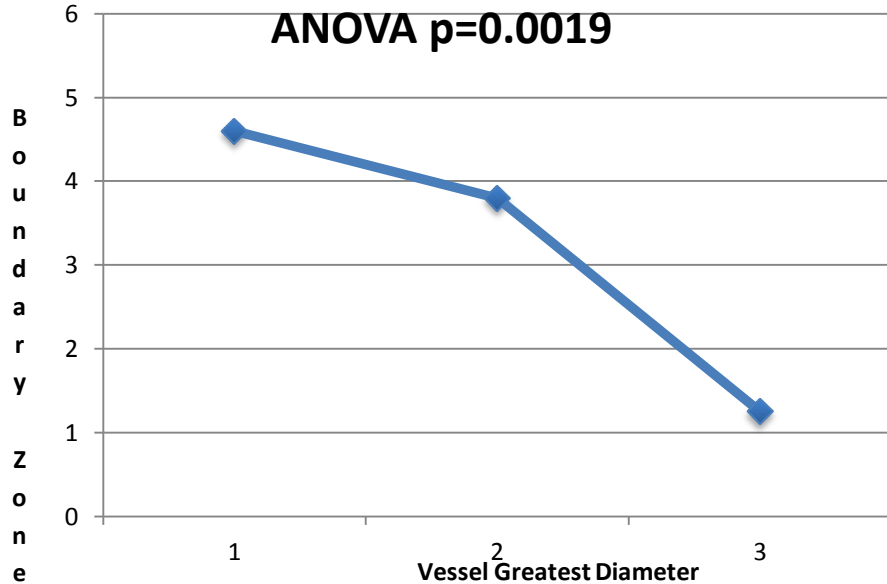
Figure 1
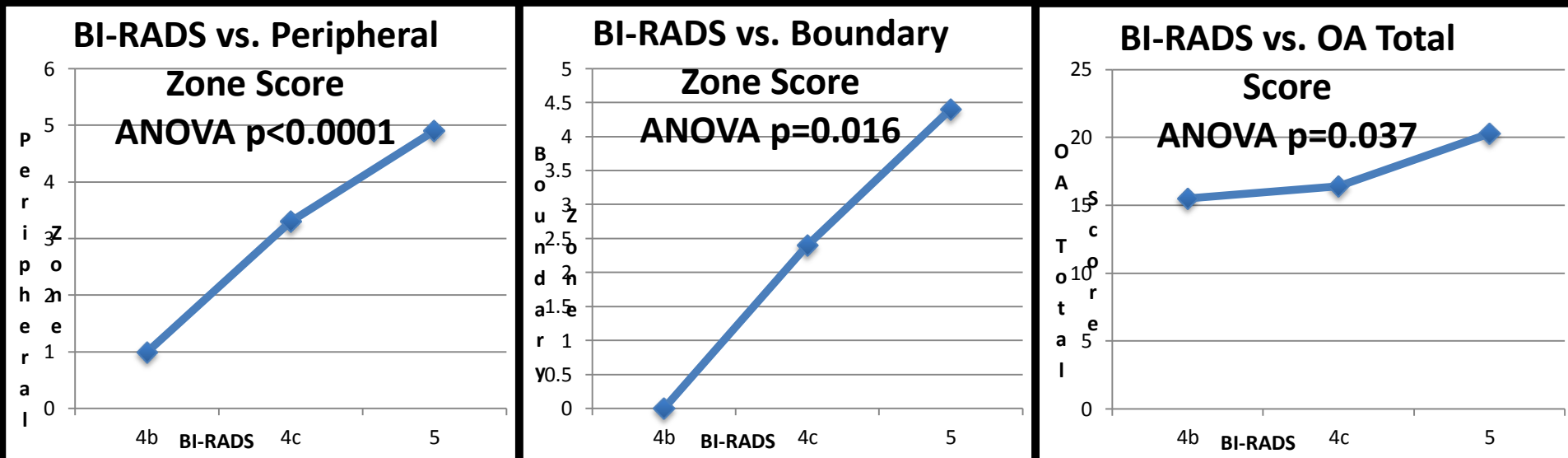
Statistically significant correlation of BI-RADS assessment with Peripheral Zone Score, Boundary Zone Score, and OA Total Score
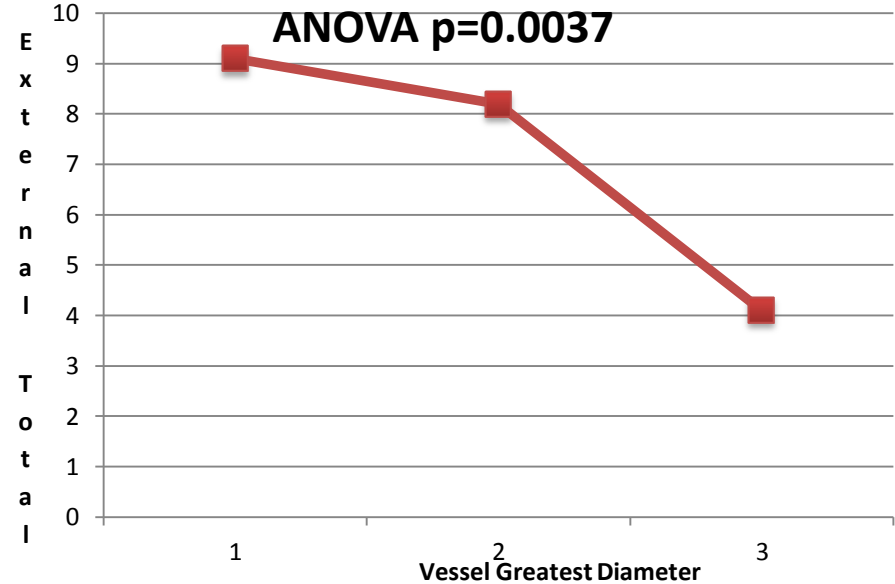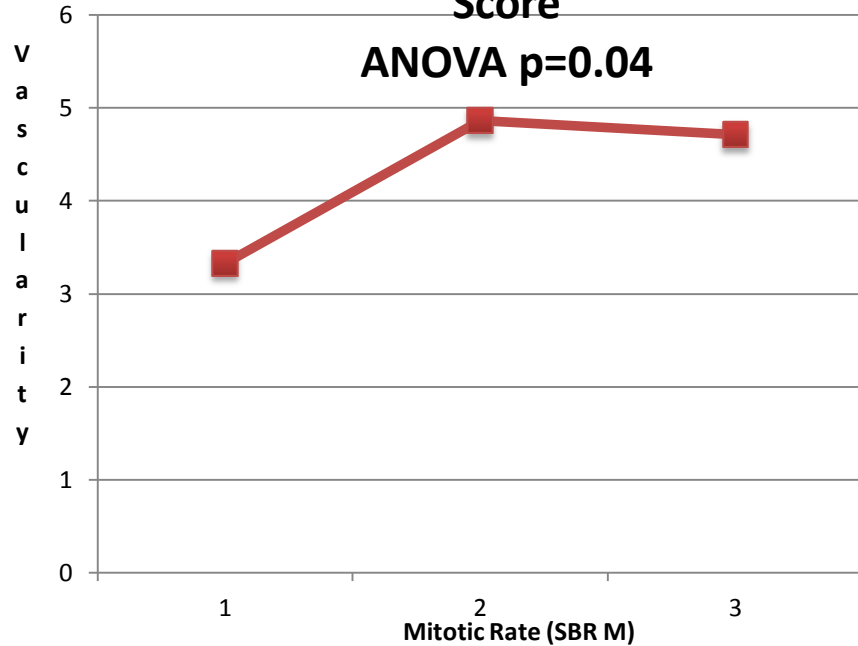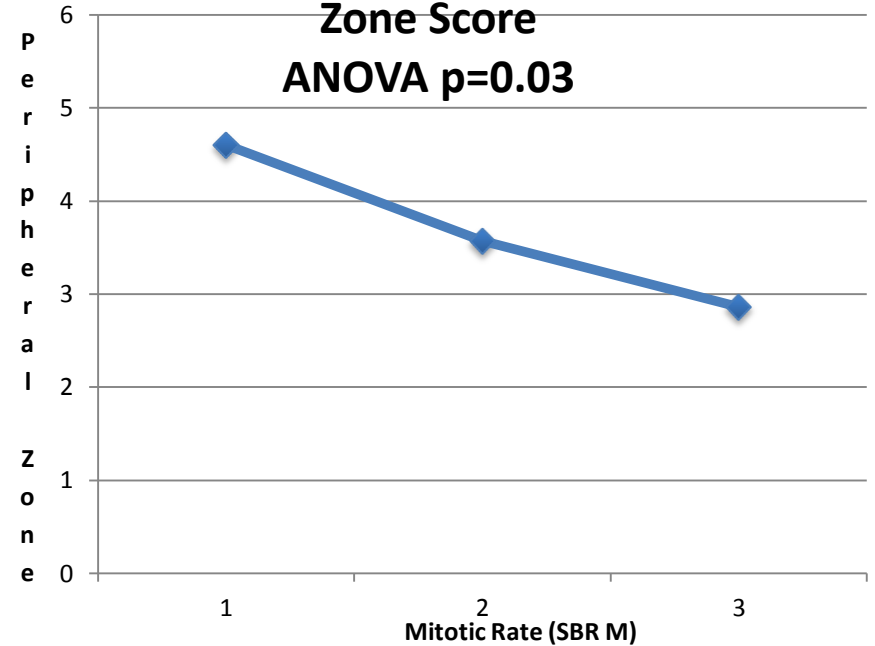
Figure 2

Statistically significant inverse correlation of Vessel Greatest Diameter with Boundary Zone Score and External Total Score

Figure 3

Statistically significant correlation of BI-RADS assessment with Peripheral Zone Score, Boundary Zone Score, and OA Total Score

Table 1

| Region	Histopathology	Feature	Rho	P-value
Nidus	SBR Mitotic	V	0.384	0.04
Nidus	SBR Total	V	0.379	0.043
Nidus	Ki67 Positive	V	0.411	0.033
Nidus	VGD	BZ	-0.559	0.0016
Nidus	SBR Nuclear	R	-0.410	0.027
Nidus	SBR Mitotic	R	-0.525	0.0034
Nidus	SBR Total	R	-0.497	0.0061
Nidus	Tucker Grade	R	-0.485	0.0077
Nidus	Ki67 Positive	R	-0.429	0.026
Nidus	VGD	R	-0.415	0.025
Nidus	SBR Mitotic	ET	-0.407	0.028
Nidus	VGD	ET	-0.522	0.0037
Periphery	X50 VD (mm2)	BZ	0.430	0.018
Periphery	X50 VD (mm2)	ET	0.454	0.012
Boundary	VD (mm2)	OAT	-0.476	0.0091
Boundary	VGD	POM	-0.396	0.034
Boundary	VD (mm2)	POM	-0.476	0.0091

Representative examples of the 81 histopathologic findings and opto-acoustic features with statistically significant correlation by region

# Grade 2 Invasive Ductal Carcinoma – Imagio – Central Nidus with increased Density of Vascularity (V)
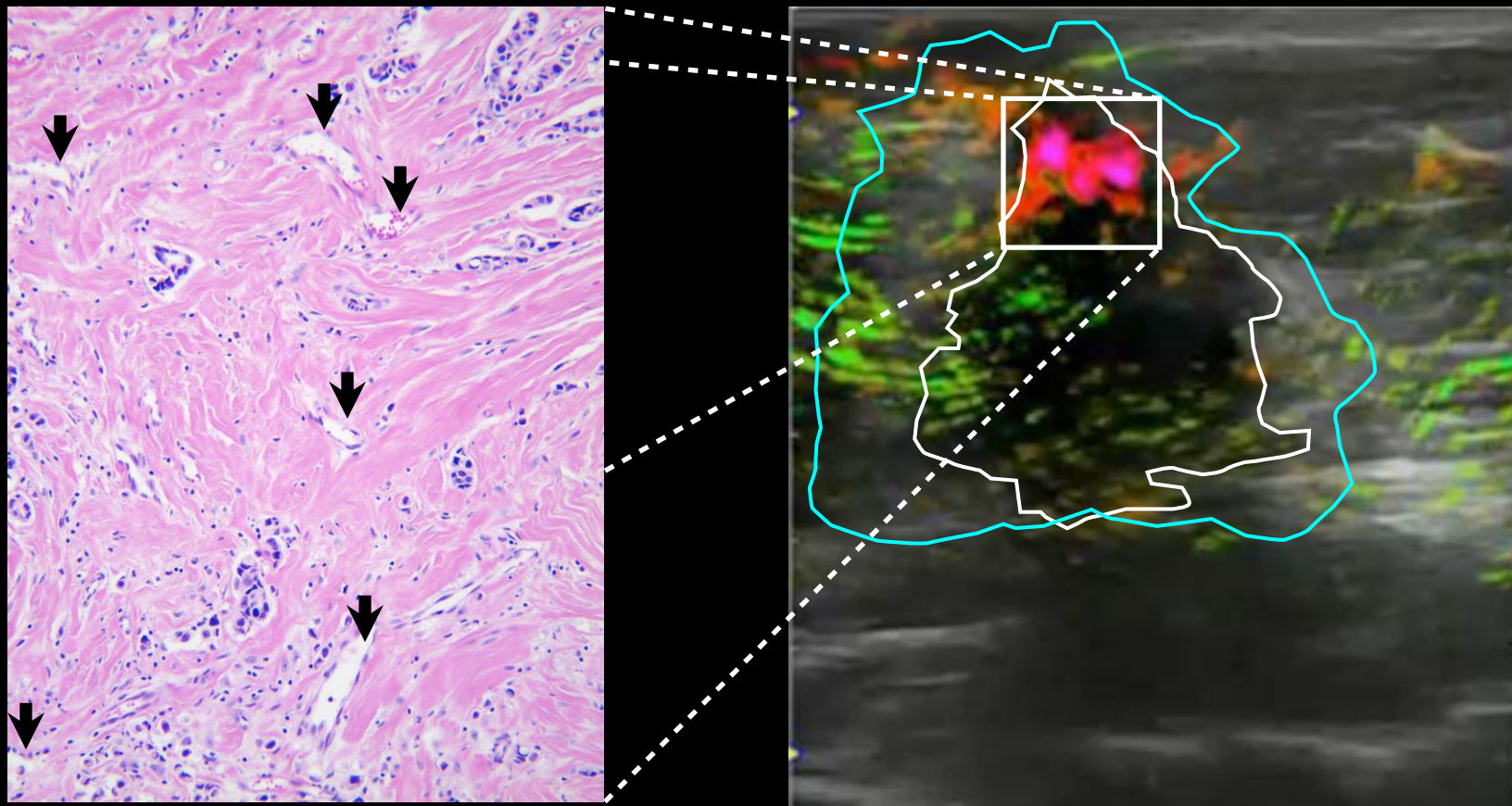
Case 1. White outline denotes central tumor nidus, blue outline represents the boundary zone. Within the central tumor nidus is an intense red blush of deoxygenated hemoglobin corresponding to increased vascular density on histopathology. Black arrows point to numerous small tumor neovessels

Grade 2 Invasive Lobular Carcinoma – Imagio – Boundary Zone with increased Density of Vascularity (V)
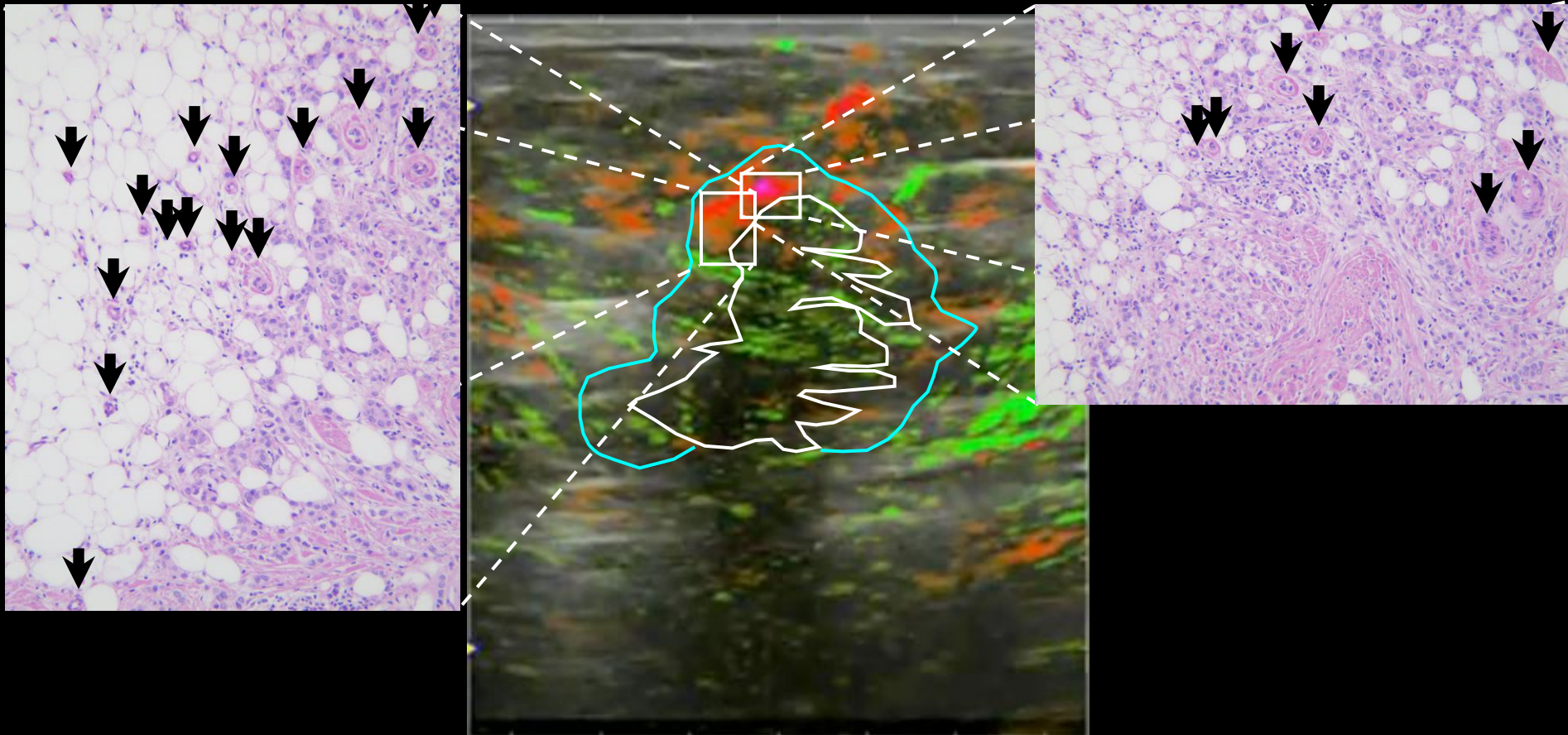
Case 2. White outline denotes central tumor nidus, blue outline represents the boundary zone. Within the boundary zone are two areas of intense red blush compatible with deoxygenated hemoglobin. These areas correspond with numerous small tumor neovessels on histopathology (black arrows)

Grade 2 Invasive Lobular Carcinoma – Imagio - Peripheral Zone Radiating Vessel
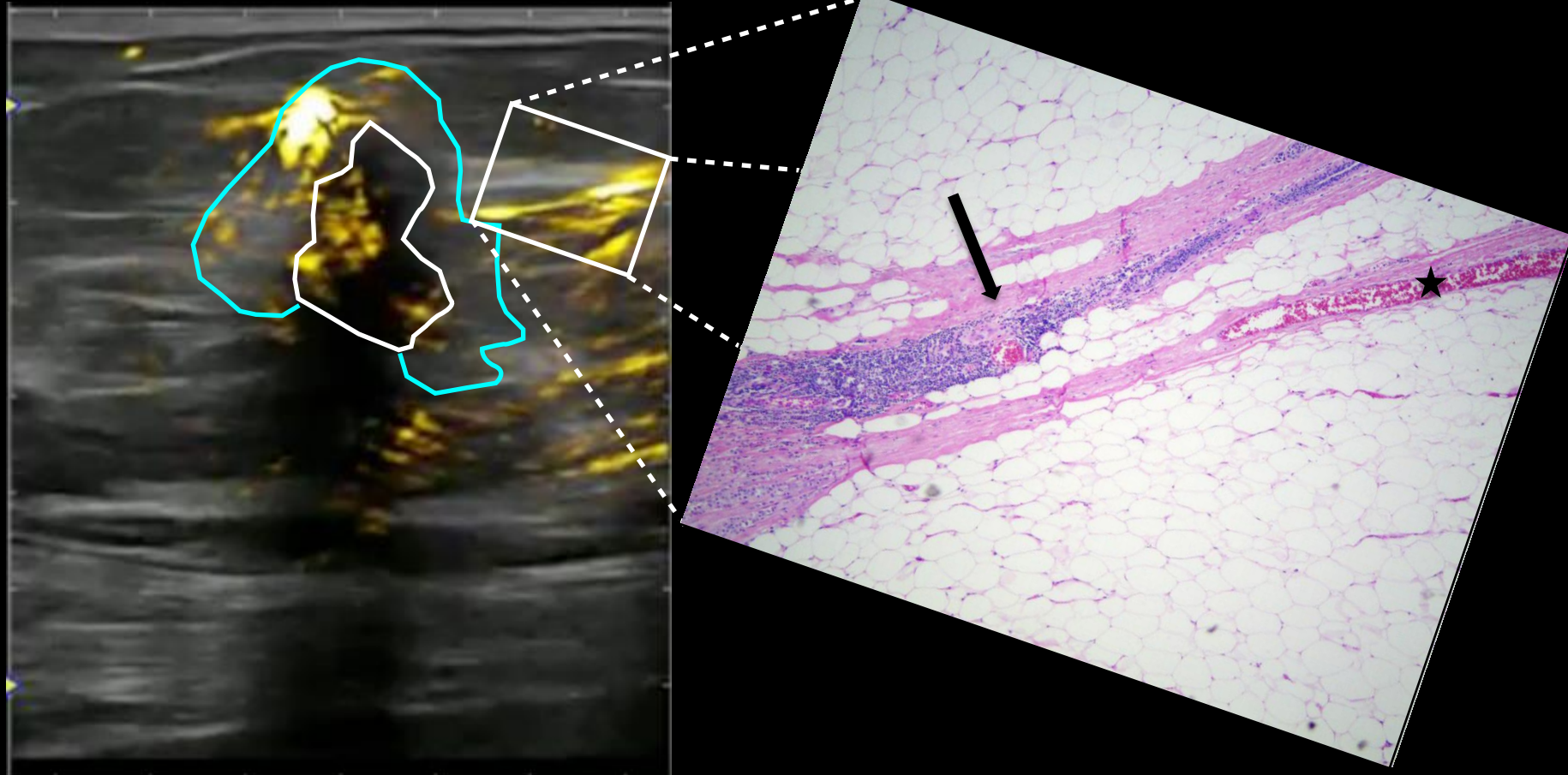
Case 3. White outline denotes central tumor nidus, blue outline represents the boundary zone. Linear yellow signal (total hemoglobin) radiates from the peripheral zone of tumor corresponding to a radiating tumor vessel (*) and tumor infiltrating along Cooper's ligament (arrow).

Conclusion

- Preliminary data suggest that Imagio opto-acoustics has statistical correlation with multiple histopathologic findings and may provide information to help predict cancer histopathology.

- OA potentially offers radiologists, surgeons, and pathologists more information and may help plan treatment.

- Prospective research to evaluate this technology is currently underway for regulatory review.