Breast biopsy histology relationships with opto-acoustic imaging of breast masses

Marc van de Vijver, Philip T. Lavin, A. Thomas Stavros

Overview

- **Regulatory Status:** The Imagio® breast imaging system, a diagnostic opto-acoustic (OA) imaging device bearing the CE Mark, is in the U.S. FDA Premarket Approval process.

- **Principle:** OA provides both functional (relative oxygenation/de-oxygenation) and anatomic (angiogenesis) information that is co-registered and temporally interleaved in real time with gray-scale ultrasound that may improve distinction between benign and malignant masses.

- **Goals:** OA imaging pathology correlation was performed to elucidate the histologic features of OA features of breast cancers.

Methods and Materials

- A multicenter post-market surveillance study was conducted in five Dutch sites in which 209 women with breast masses underwent OA prior to biopsy.

- Histopathology examination of the biopsies revealed 146 benign masses (mostly fibroadenomas) and 67 malignant masses (mostly invasive ductal carcinomas).

- For invasive ductal carcinomas, histologic grade and the features used to assess histologic grade (nuclear pleomorphism, tubule formation, and mitotic count) were assessed.

- For each mass, 5 pre-determined OA features, 3 internal features, and 2 external features were evaluated.

- Three internal scores (vessels, blush, and hemoglobin) and 2 external features (capsular boundary zone and peripheral boundary zone) were separately and collectively summed for testing relationships with traditional histopathology measures using a one-sided Jonckheere-Terpstra test of ordered outcomes reflecting experience.

- Distribution differences between benign and malignant masses were performed using a Wilcoxon Rank Sum test for each internal, external, and summed total internal, external, and total score.

Results

- **Table 1:** The mean differences in OA feature scores between benign and malignant masses were statistically significant for internal vessels (p=0.0009), internal blush (p=0.0085), external boundary zone (p<0.0001), and external peripheral radiating vessels(p<0.0001), but not internal hemoglobin (p=0.340).

OA Feature P-Values

Table 1. OA Feature P-values for benign vs. malignant distinction	P-value
Feature 1: Internal Vessels	0.0009
Feature 2: Internal Deoxygenated Blush	0.0085
Feature 3: Internal Total Hemoglobin	0.34
Feature 4: External Boundary Zone	<0.0001
Feature 5: External Peripheral Radiating Vessels	<0.0001
Feature 6: Interfering Artifacts	0.43
Total OA Internal	0.009
Total OA External	<0.0001
Total OA **	<0.0001
Strong differentiation between benign and malignant masses	

Table 2. Total OA Feature Scores vs. Histologic Grade of Invasive Carcinomas

	Grade 1 (n=8)	Grade 2 (n=32)	Grade 3 (n=19)	1-sided J-T p-value *
Total OA Internal	6.2	6.2	7.6	0.050
Total OA External	4.2	6.2	6.7	0.064
Total OA	10.5	12.5	14.3	0.034

Table 3.   Total OA Feature Scores vs Tubule Scores Component of Grading

Tubule	1 (n=3)	2 (n=7)	3 (n=49)	1-sided J-T p-value
Total OA Internal	7.3	5.7	6.8	0.270
Total OA External	3.7	5.1	6.4	0.072
Total OA	11.0	10.9	13.2	0.068

Table 4. Total OA Feature Scores vs Nuclear Pleomorphism Component of Grading

Tubule	1 (n=2)	2 (n=32)	3 (n=25)	1-sided J-T p-value
Total OA Internal	8.0	6.0	7.5	0.059
Total OA External	8.5	5.4	6.9	0.109
Total OA	16.5	11.4	14.4	0.065

### Table 5.   Total OA Feature Scores vs Mitotic Score Component of Grading

Tubule	1 (n=39)	2 (n=7)	3 (n=13)	1-sided J-T p-value
Total OA Internal	6.3	6.1	8.2	0.026
Total OA External	5.8	7.1	6.5	0.190
Total OA	12.1	13.3	14.7	0.072

* One-sided Jonckheere-Terpstra doubly ordered exact contingency table test p-values
** Total OA score = Total Internal OA score + Total External OA score

Results (con't.)

- **Table 1:** Mean Total Internal Score, Total External Score, and Total Score were all significantly higher (all p<0.01) for malignant vs. benign.

- **Table 2:** Among invasive carcinomas, Total Internal Score and Total Score were significantly higher for higher histologic tumor grade (p=0.050, 0.034).

- **Table 3:** Higher Total External Score and Total Score for higher tubule score (p=0.072, 0.068).

- **Table 4:** Higher Total Internal Score and Total Score for higher nuclear pleomorphism score (p=0.059, 0.065).

- **Table 5:** Significantly higher Total Internal Score for higher mitotic score (p=0.026).

OA Imaging and Pathology Comparison
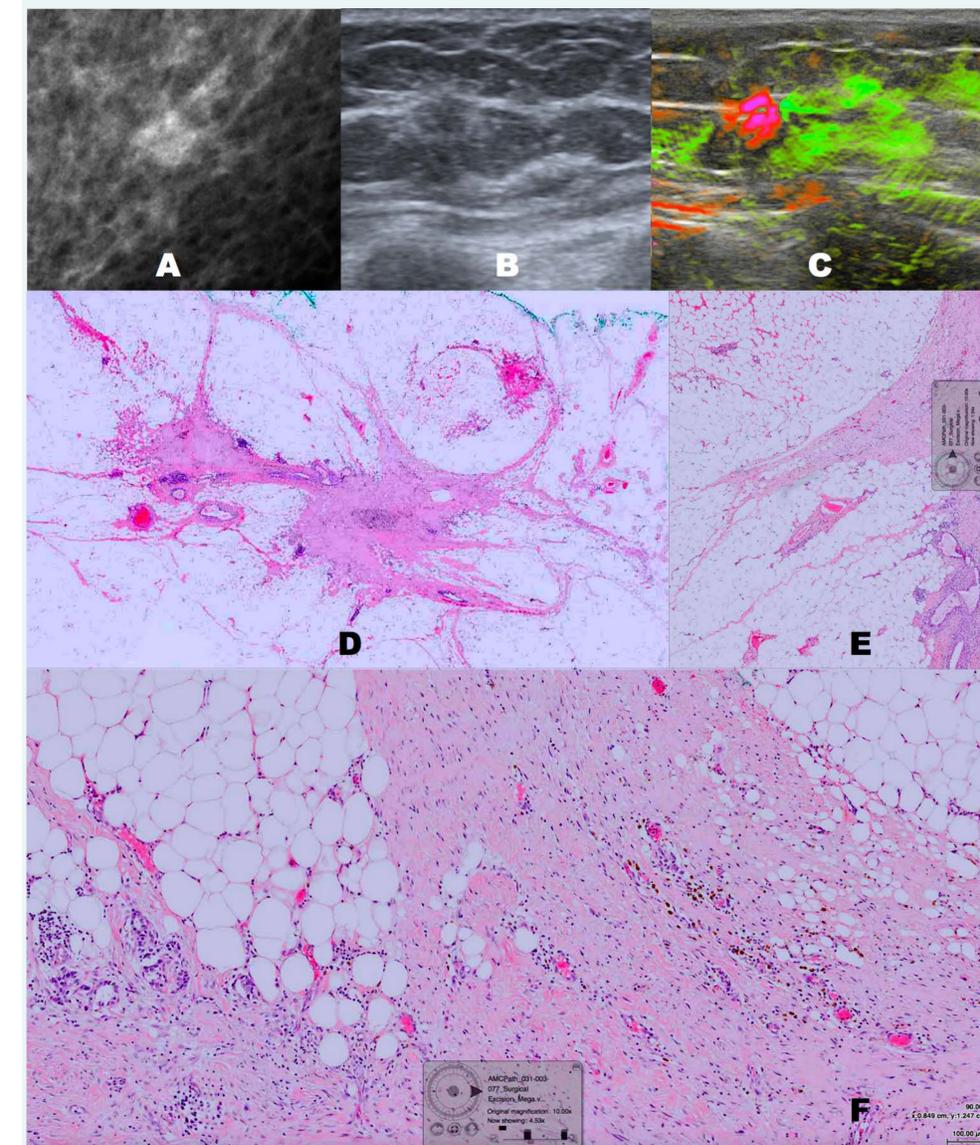
Legend: A) Mammogram showing slightly irregular and indistinctly marginated 5 mm mass. B) Gray scale ultrasound of the mass shows it to be irregular and to have a thick halo. C) OA examination of the mass shows intense deoxygenated (red) blush inside the mass and within the boundary zone. D) 5 x 7 cm megacassette whole mount histopathology shows an irregular mass with angles surrounded by very large blood vessels. E) Low power view of one of the angular margins of the mass shows large vessels around the angular extension of the mass into surrounding tissues. F) medium power histology of one of the angular tumor extensions into surrounding tissues that are too small to be resolved individually, but that together contribute to the deoxygenated blush, despite volume averaging, because of OA's very high contrast resolution.

Conclusions

- OA feature summary scores appear to differentiate between benign vs. malignant and correlate to histologic grade and scoring components of histologic grade.

- The PIONEER pivotal study (n=2,095) may further confirm these results.