MAESTRO TRIAL – FINAL RESULTS

Gisela L.G. Menezes, MD, PhD
MAESTRO
Angiogenesis

Somatic mutation

Metastasis
How does OA work?

Malignant:
- de oxy Hb

Benign:
- O₂
- oxy Hb
How does OA work?
How does OA work?

**OPTO-ACOUSTIC TECHNOLOGY**
Laser light energy converted to ultrasound energy = the "Opto-acoustic Effect".
"Light in = Sound out"

- Malignant tumor has increased blood concentration with decreased oxygen content
- Benign growth has variable blood concentration with normal oxygen content
- Laser light transmitted in alternating, short pulses
- Returned ultrasound signals
- Two colors of laser light enable the evaluation of both the relative blood concentration and the relative oxygen content of that blood
Optoacoustic Imaging

- Fibroadenoma
- IDC Grade 2
MAESTRO - Primary Objectives

• To assess OA/US’s ability to correctly downgrade benign masses classified as BI-RADS 4a and 4b to BI-RADS 3 or 2.

• Sensitivity, specificity, PPV, NPV, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of CDU and OA/US.
## Why BI-RADS 4a and 4b?

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
<th>Probability of Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Needs additional imaging evaluation</td>
<td>NA</td>
</tr>
<tr>
<td>1</td>
<td>Normal mammography – back to screening program</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>Benign findings – back to screening program</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>Probably benign – 6-month interval follow-up</td>
<td>≤ 2%</td>
</tr>
<tr>
<td>4</td>
<td>Suspicious abnormality – tissue diagnosis (biopsy)</td>
<td>4a. Low POM (&gt;2% to ≤ 10%)&lt;br&gt;4b. Moderate POM (&gt;10% to ≤ 50%)&lt;br&gt;4c. High POM (&gt;50% to &lt;95%)</td>
</tr>
<tr>
<td>5</td>
<td>Highly suggestive of malignancy – tissue diagnosis (biopsy)</td>
<td>≥ 95%</td>
</tr>
<tr>
<td>6</td>
<td>Known biopsy-proven malignancy</td>
<td>NA</td>
</tr>
</tbody>
</table>
Study Design

• Prospective, multicenter, and observational study.

• Based on images obtained with OA/US, investigators estimated the probability of malignancy (POM) on a scale from 0% to 100% and, when appropriate, adjusted the BI-RADS classification.
Study Design

- Five OA features were scored (downgrade or upgrade the lesion classification).
- 140 benign and 70 malignant masses were projected.
- Power > 80% (2% Type I error).
- Sensitivity and specificity for CDU and OA were calculated. PLR and NLR were also calculated.
### Results: BI-RADS classification of benign lesions according to CDU and OA (n=146)

<table>
<thead>
<tr>
<th>OA BI-RADS</th>
<th>CDU BI-RADS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4a (N=119)</td>
</tr>
<tr>
<td>2</td>
<td>8 (6.7%)</td>
</tr>
<tr>
<td>3</td>
<td>49 (41.2%)</td>
</tr>
<tr>
<td>4a</td>
<td>44 (37.0%)</td>
</tr>
<tr>
<td>4b</td>
<td>18 (15.1%)</td>
</tr>
<tr>
<td>4c</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

**Downgrade CDU BI-RADS (4a, 4b) to OA BI-RADS (2, 3):**

- **Downgrade [n/N (%)]**: 60/146 (41.1%)
- **96% CI**: (32.7, 49.4)
- **P-value [null hypothesis is ≤ 15%]**: < 0.0001
### Results: BI-RADS classification of malignant lesions according to CDU and OA (n=67)

<table>
<thead>
<tr>
<th>OA BI-RADS</th>
<th>CDU BI-RADS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4a (N=7)</td>
</tr>
<tr>
<td></td>
<td>4b (N=60)</td>
</tr>
<tr>
<td>3</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td></td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>4a</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td></td>
<td>6 (10.0%)</td>
</tr>
<tr>
<td>4b</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td></td>
<td>21 (35.0%)</td>
</tr>
<tr>
<td>4c</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>30 (50.0%)</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2 (3.3%)</td>
</tr>
</tbody>
</table>

Downgrade CDU BI-RADs (4a, 4b) to OA BI-RADs (2, 3):

- Downgrade [n/N (%)]: 3/67 (4.5%)
- 96% CI: (0.9, 13.0)
- p-value [null hypothesis is ≥ 10%]: 0.0872
Results

• CDU sensitivity = \[ \frac{TP}{TP + FN} = \frac{67}{67} = 100\% \]

• CDU Specificity = \[ \frac{TN}{TN + FP} = \frac{0}{146} = 0\% \]

• OA sensitivity = \[ \frac{TP}{TP + FN} = \frac{64}{67} = 95.5\% \]

• OA Specificity = \[ \frac{TN}{TN + FP} = \frac{60}{146} = 41.1\% \]

• OA without the estimator: PPV was 42.7% and NPV was 95.2%. PLR was 1.61 and NLR was 0.11
Discussion

• NLR of 0.11 - post-test probability lower than the pre-test probability.
• BI-RADS 3 (benign) has a very low POM (≤ 2%).
• The POM of BI-RADS 4a varies from >2% to ≤10%.
• A NLR of 0.11 shows that a pre-test probability at the upper end of a 4a lesion (≈10%) can be reduced to a post-test probability of 1.1% by a negative OA examination, allowing the lesion to be downgraded from BI-RADS 4a to 3.
Discussion

• BI-RADS lexicon: Categories 1 or 2 are typically benign (virtually 0% chance of malignancy).
• In 8 cases benign masses were downgraded from BI-RADS 4a to BI-RADS 2.
• The lower end of BI-RADS 4a range (≈2%) can be reduced to a post-test probability of only 0.22%.
• The PPV of category 4b varies from from >10% to ≤50%.
• Considering category 4b, a mass with a pre-test probability of 15.6% could be downgraded to BI-RADS 3 (2 categories downgrade). However, lesions with a higher probability of malignancy cannot be downgraded without increasing the FN rates.
Conclusions

- 41.1% of benign masses could be downgraded in BIRADS category using OA/US.
Conclusions

- **49.2%** of malignant masses could be upgraded with OA/US.
Conclusions - Implications for patient care

- **OA improves the distinction between benign and malignant masses compared to CDU alone.**

- Benign masses classified as BI-RADS 4a can be downgraded to BI-RADS 3 or 2, potentially minimizing negative biopsies and short interval follow-up imaging exams.

- Potential to lower overall costs related to interventional procedures and short-interval follow-up imaging studies.

- Limitations: 3 false-negatives.
First false-negative mass: an IDC grade 1 which was downgraded from BI-RADS 4b to BI-RADS 2
Second false-negative mass: an IDC grade 3 which was downgraded from BI-RADS 4a to BI-RADS 2
Third false-negative mass: an ILC grade 2 (alveolar variant) which was downgraded from BI-RADS 4a to BI-RADS 3
Inclusion Criteria

- Females ≥ 18 years.
- Have a suspicious finding classified by CDU as BI-RADS 4a or 4b.
- Have received recommendation for an image-guided biopsy.
Exclusion Criteria

- Has a condition that could interfere with the intended field of view (breast implants or tattoos).

- Prior surgery within the same quadrant as the mass to be biopsied.

- Have had prior excisional biopsy within the vicinity of the suspicious mass within the past 18 months.
Exclusion Criteria

• More than 3 masses recommended for biopsy.

• Mass to be biopsied is greater than 3.0 cm in maximum diameter.

• Patient currently has mastitis.

• Patient is pregnant or lactating or planning to become pregnant during study participation.
Likelihood Ratios

- Likelihood ratios are important to assess the value of performing a diagnostic test.
- \( \text{PLR} = \frac{\text{sensitivity}}{1-\text{specificity}} \)
- \( \text{NLR} = \frac{1-\text{sensitivity}}{\text{specificity}} \)
- The larger the PLR, the greater the likelihood of disease; the smaller the NLR, the lesser the likelihood of disease.
- These rates are less likely to change with the prevalence of the disorder.
- To use this measure a nomogram (estimators) should be employed or pre-test probabilities should be converted into Odds.