New developments in Mammographic and MR imaging

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Mammography in Breast Cancer Screening

In 1956 Robert Egan introduced dedicated x-ray film for Mammography

What have we done with breast cancer screening since 1956?

1939 1969 1975 2013

Mammographic Screening: DMIST Sensitivity

Limitations of Mammography

1. 38% sensitivity in women with dense breast
2. 17% interval cancer rate
3. Interval cancers with higher grade histologies

Digital Breast Tomosynthesis (DBT): A little better....

1. 3D mammographic technique
2. Possible increase in cancer sensitivity and reduced call-back rates compared to FFDM

<table>
<thead>
<tr>
<th></th>
<th>MG</th>
<th>MG +DBT</th>
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<tbody>
<tr>
<td>Skaane et al, 2013</td>
<td>6.1/1000</td>
<td>8.0/1000</td>
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<tr>
<td>Ciatto et al, 2013</td>
<td>5.3/1000</td>
<td>8.1/1000</td>
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<tr>
<td>Haas et al, 2013</td>
<td>5.2/1000</td>
<td>5.7/1000</td>
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<tr>
<td>Friedwald et al, 2014</td>
<td>4.2/1000</td>
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Is MRI better than Mammography and US? – The untold story!

From: Detection of Breast Cancer With Addition of Annual Screening Ultrasound or a Single Screening MRI to Mammography in Women With Elevated Breast Cancer Risk

EVA Trial

Why have we ignored MRI except for extremely high-risk women?

1. Cost
2. Time
3. Perceived low PPV
4. Rigid billing system

Breast Density Legislation

1. Shortcomings of mammography has led to passage of breast density legislation in many states
2. Laws recommend women with dense breasts consider supplemental screening
3. Type of supplemental screening not specified

State Bills on Breast Density

Whole Breast Screening Ultrasound

1. Default supplemental screening modality due to relatively low cost and wide availability
2. Supplemental cancer yield: 3-4/1000
3. Limitation of WBUS include:
   - Low PPV (8-9%)
   - High frequency of short-term follow recommendations
   - Time consuming
Current Standard Screening in the USA

- Average to moderate risk women with dense breast
  - 2DFFDM or DBT supplemented with WBUS
  - Cost approx. $400-500

Vascular Based Breast Imaging

- May preferentially detect biologically significant tumors at an earlier stage
- Reduce overdiagnosis/overtreatment
- Reduce interval cancer
- May only need biennial screening

Vascular/Metabolic Based Breast Imaging

1. Abbreviated Breast MRI (AB-MR)
   + Robust platform
   + No radiation or compression
2. Contrast enhanced digital mammography (CEDM)
   - Iodine (16 fold increase in severe reactions)
   - Radiation and compression
   - Non-robust platform
   + Familiar study

Breast MRI

- FFDM and MRI on same patient
- 8 mm IDC

Results: Tumor Histology and Grade by % of CA Seen on Each Modality

Results: CA Detection By Modality
**Abbreviated MRI (AB-MR)**

1. Low cost ($300-$500)
2. Quick (less than 10 min)
3. PPV similar to mammography (20-30%)
4. 150% increase in cancer detection
5. Optimal screening interval 1-3 yrs?
6. Potential to preferentially detect higher grade lesions

**AB-MR**

Total scan time of less than 10 min (including localizer)

1. A localization scan
2. 1 pre- and 30 seconds after contrast injection 1 post-contrast gradient echo (GRE) axial acquisition; fat suppression is highly recommended
3. In-plane resolution of 1 mm or less
4. Slice thickness of 3 mm or less
5. For advanced imaging sites, optional fast temporal scanning at 3 time points between 0-30 seconds after contrast injection
6. Axial T2 weighted sequence with in-plane resolution matching the GRE sequences and 3 mm or less slice thickness

**AB-MR Trial Concept**

*Comparison of Abbreviated Breast MRI and Digital Breast Tomosynthesis in Breast Cancer Screening Women with Dense Breasts*

Primary aim: To compare the invasive cancer detection rate of AB-MR to DBT.

Pis: Drs Comstock, Kuhl and Newstead

**Secondary aims:**

1. To compare the positive predictive value (PPV) of biopsies, call back rates, and short-term follow up rates after AB-MR and DBT on both the initial and 1 year follow up studies.
2. To estimate and compare the sensitivity and specificity of AB-MR and DBT, using the 1 year follow up to define a reference standard.
3. To compare patient-reported test-related disutility of AB-MR and DBT using the Testing Morbidities Index.
4. To assess the most important test-related attribute using individual patient-level utilities elicited by choice-based conjoint-analysis.
5. To compare the tumor biologies of invasive cancers and DCIS detected on AB-MR and DBT.
6. To estimate the incident cancer rate during 3 years following the year 1 AB-MR/DBT when patients return to standard screening.

**Inclusion**

1. Women over the age of 40 and scheduled for screening DBT;
2. Asymptomatic women undergoing routine screening;
3. Does not qualify for high-risk Breast MR screening as defined by the ACS recommendations.
4. No known breast cancer;
5. Have not had a breast US within the prior 12 months.
6. No prior MRI
7. Not on chemoprevention for breast cancer

**Schema**
Statistical Considerations

1. The table shows that 1363 cases with complete data from both tests and pathology are needed to ensure power 90% for a difference in the rates of invasive cancer detection as low as 9/1000.

2. Assuming that inadequate information will be available on up to 6% of cases, a sample size of 1450 will provide power 90% to compare the diagnostic yield in invasive cancer of the two modalities.

<table>
<thead>
<tr>
<th>Power Sample size</th>
<th>Difference in invasive cancer rates (ABMR – DBT)</th>
<th>Proportion of discordant cases</th>
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</thead>
<tbody>
<tr>
<td>0.90</td>
<td>1191</td>
<td>0.008</td>
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<tr>
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<tr>
<td>0.90</td>
<td>949</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Contrast Enhanced Spectral/Digital Mammography

• Intravenous iodinated contrast administered to improve lesion visibility
  – 1.5 ml/kg of Omnipaque

• Dual energy CEDM

Dual Energy CEDM

• K-edge of iodine: 33 keV
• 1 exposure below 33 keV
  – Same as conventional MG
• 1 exposure above 33 keV
  – Captures contrast diffusion
• Areas of contrast uptake highlighted

CEDM: Results

• Bilateral CEDM:
  – First image ~3 minutes post-injection
  – 4 views obtained within 5 minutes of injection
  – Dose: 1.5 cc of Omnipaque-350/kg to max of 150 cc

  • Compared CEDM vs MG vs bilateral breast MRI in 52 patients with newly diagnosed breast cancer

CEDM: Potential Advantages

• Same time as routine mammography
• Low cost
• Only 1.2 x radiation dose if accept the low energy image as equivalent to 2D FFDM
• Improved sensitivity and specificity
• Slightly less sensitive than MRI but slightly fewer false positives

CESM: Screening

• No data supporting use of CEDM as screening modality

• MSKCC prospective study:
  – Comparing CEDM with MRI in intermediate to high risk women
  – Comparing CEDM with WBUS in intermediate risk women
Screening

CEDM: Limitations

• Iodinated contrast administration
• Radiation dose:
  – >20% screening MG
  – Equivalent to single additional view

CEDM

• CEDM FDA intended use as Dx tool
  – Improved sensitivity
  – Reduced recall rates
• Additional studies
  – Tumor biology of cancers detected
  – Frequency of false positives
  – CEDM vs Tomosynthesis vs screening US?
• Role as supplemental screening in women with dense breast?

Vascular Based Screening

CESM vs AB-MR

• Both have injection
• CESM: Compression and radiation
• CESM: Quick and has mammographic screening built in
• Potential replacement to combination of MG + WBUS

Contrast Risk

<table>
<thead>
<tr>
<th>Factors</th>
<th>MR² (Gd)</th>
<th>X-ray¹ (I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard of care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of adverse reaction</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risk of Severe Reaction</td>
<td>15/100,000</td>
<td>3/300,000</td>
</tr>
<tr>
<td>Risk of Death</td>
<td>2/100,000</td>
<td>2/200,000</td>
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</tbody>
</table>

Future Direction of Screening

- Comparison of AB-MR to DBT (ACRIN EA1141)
- Comparison of CESM to DBT plus US
- Evaluation of Contrast enhanced Tomosynthesis
- Evaluation of AB-MR as a standalone test (may address issues of overdiagnosis)