Emerging Techniques in Breast Imaging: Contrast-Enhanced Mammography and Fast MRI

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Overview

• Rationale for new imaging techniques
  – Contrast enhanced mammography (CEM)
  – Fast (abbreviated) MRI (AB-MR)

• Current data
Screening Mammography

• Widely available
• Low cost
• Only modality shown to reduce breast cancer mortality
  – 30% reduction
Limitations of Mammography

- Less sensitive in women with dense breasts
  - Mammographic sensitivity 62% in extremely dense vs. 88% in fatty breasts
- Interval cancers
- Recall rate and false positive biopsies
- Overdiagnosis (~1-10% est. from RCT)
Alternative Modalities

- Tomosynthesis
- Ultrasound
- Molecular breast imaging
- MRI
- Contrast-enhanced mammography (CEM)
Alternative Modalities

• Tomosynthesis
• Ultrasound
• Molecular breast imaging
• MRI
• Contrast-enhanced mammography (CEM)

→ vascular or functional based imaging
CONTRAST ENHANCED MAMMOGRAPHY (CEM)
Contrast-Enhanced Mammography

- Relies on abnormal blood flow related to neovascularity
- IV injection of iodinated contrast
- Performed using adaptation to standard DM unit
- Dual energy or temporal technique
CEM – Temporal Technique

• Temporal subtraction technique
  – Baseline high-energy image with breast mildly compressed
  – Multiple images of single view of one breast over 5-7 minutes
  – Generate subtractions
• Advantage: Kinetic analysis
• Disadvantage
  – Only 1 view of 1 breast
  – Motion artifact
# CEM: Temporal Technique

<table>
<thead>
<tr>
<th></th>
<th>Cancers (SN)</th>
<th>Benign (FP)</th>
<th>Missed CA (FN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jong et al. 2003</td>
<td>8/10 (80%)</td>
<td>5/12</td>
<td>1 IDC, 1 DCIS</td>
</tr>
<tr>
<td>Diekmann et al. 2005</td>
<td>14/14/ (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dromain et al. 2006</td>
<td>16/22 (73%)</td>
<td></td>
<td>4 IDC (0.5-1.6 cm), 2 not included on film</td>
</tr>
</tbody>
</table>
Diekmann et al., Eur J Radiol 2011.
CEM: Temporal Technique

- Prospective study CEM vs 2D FFDM
- 70 pts, 80 lesions on MG, US, or MR
  - 30 cancers, 50 benign
- Improves diagnostic accuracy
  - Sensitivity increased from 0.43 FFDM to 0.62 with CEM
  - Significant improvement in AUC

Diekmann et al., Eur J Radiol 2011.
CEM: Temporal Technique

Limitations

• Patient motion
• Kinetics do not differentiate between benign and malignant lesions
• Single view only
CEM: Dual Energy

- Two images performed in CC, MLO:
  - a low-energy image (below the k edge of iodine, same as conventional MG)
  - a high-energy image (above the k edge).
- Uses algorithm to suppress background breast to highlight iodine-enhanced areas.
Fig. 1 Schema of the technique of dual-energy CEDM examination
CEM: Dual Energy vs Temporal

• Dual energy:
  – Less motion
  – Can be prone to “rim” artifact from radiation scatter
  – No kinetic info
### CEM: Cancer Detection

<table>
<thead>
<tr>
<th>Study</th>
<th># CA</th>
<th>% seen CEM</th>
<th>% seen DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dromain (2011)</td>
<td>80</td>
<td>92%</td>
<td>78%</td>
</tr>
<tr>
<td>Jochelson (2013)</td>
<td>26</td>
<td>96%</td>
<td>85%</td>
</tr>
<tr>
<td>Fallenberg (2014)</td>
<td>107</td>
<td>95%</td>
<td>78%</td>
</tr>
<tr>
<td>Cheung (2014)</td>
<td>89</td>
<td>93%</td>
<td>72%</td>
</tr>
<tr>
<td>Lobbes (2014)</td>
<td>113</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td>Lalji (2016)</td>
<td>199</td>
<td>97%</td>
<td>93%</td>
</tr>
</tbody>
</table>

CEM finds more cancer than FFDM.
CEM: Cancer Detection

Identification of multifocal carcinoma

Dromain et al., Eur Radiol 2011
23 multifocal cancer cases
- 100% seen with CEM
- 70% seen with FFDM

Jochelson et al., Radiology 2013
25 additional ipsilateral cancers
- 56% (14/25) seen with CEM
- 88% (22/25) seen with MR
- 25% (4/25) seen with DM
## CEM vs. MRI: Cancer Detection

<table>
<thead>
<tr>
<th>Study</th>
<th>CEM</th>
<th>MRI</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jochelson Radiology 2013</td>
<td>92% (50/52)</td>
<td>92% (50/52)</td>
<td>81% (42/52)</td>
</tr>
<tr>
<td>Fallenberg Eur Radiol 2013</td>
<td>100% (80/80)</td>
<td>97.4% (78/80)*</td>
<td></td>
</tr>
<tr>
<td>Fallenberg Eur Radiol 2014</td>
<td>100% (80/80)</td>
<td>97% (77/79)</td>
<td>83% (66/80)</td>
</tr>
<tr>
<td>Lee-Felker Radiology 2017</td>
<td>94% (66/70)</td>
<td>99% (69/70)</td>
<td></td>
</tr>
</tbody>
</table>

* MR missed 8 mm IDC w 12 mm DCIS, 16 mm ILC
Of all enhancing lesions seen, those which were true cancers were:

- CEM 30/30 = 100%
- MRI 30/37 = 81%

Of 52 pts, FP findings in 4% (2/52) CEM vs. 25% (13/52) for MRI.

An abnormality seen on CEM was significantly more likely to be cancerous than one seen on MRI (97% vs. 85%, p<.01).
CEM vs. MRI: Lesion Specificity

Lee-Welker et al., Radiology 2017

52 women with 120 breast lesions

• CEM and MRI had similar sensitivity
  – 66/70 (94%) for CEM vs 69/70 (99%) MRI

• CEM and MRI had equal sensitivity for detecting additional disease
  – CEM 11/11 (100%) and MRI 10/11 (91%)

• CEM had significantly higher PPV than MR
  – 66/71 (93%) vs 69/115 (60%)

• CEM had fewer false positives than MR
  – 5 vs 45

CEM and MRI have similar sensitivity, but CEM has greater specificity
CEM: False positives

• Fibroadenomas
• Papillomas
• Hamartomas
• Intramammary lymph nodes
• Fat necrosis
CEM: False Positives

CEM: False negatives

- Lesion not included on mammographic field of view
- ILC (infiltrative nature)
  - Thibault et al., 4/6 false negatives
- DCIS
  - Subtle or no enhancement
- Mucinous carcinomas
  - No enhancement or “eclipse” sign: misinterpreted as cyst
Background Parenchymal Enhancement

MRI

CEM

Minimal  Mild  Moderate  Marked
CEM: Palpable Abnormality

- Improved performance with CEM vs. low-energy images alone
  - AUC 0.93 vs 0.83
- Improved sensitivity
  - 84% to 95%
- Improved specificity
  - 63% to 81%

Tennant et al., Clin Radiol 2016.
611 women with intermediate breast cancer risk and dense breasts

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>52.4%</td>
<td>90.5%</td>
<td>16.4%</td>
<td>98.2%</td>
</tr>
<tr>
<td>CEM</td>
<td>90.5%</td>
<td>76.1%</td>
<td>11.9%</td>
<td>99.6%</td>
</tr>
</tbody>
</table>

CEM significantly more sensitive than standard DM for detecting cancer – role for supplemental screening

Sorin et al. AJR 2018.
CEM: Limitations

- Additional radiation dose ~43-81%, but well within dose recommendations for mammography
- Contrast reactions to iodinated contrast (occur <1%, mostly mild)
- Interpretation can be affected by BPE
- No CEM bx capability
CEM: Summary

Benefits:
- Good diagnostic accuracy: more sensitive than DM and fewer FP than MRI
- Reproducible without operator dependency
- Fast imaging technique
- Direct correlation with conventional DM
- Uses current DM system with software and hardware adaptations
- Less expensive, faster, and more comfortable than MRI

Limitations:
- Radiation
- Need for IV
- Iodine allergy
- Artifact near edge of images (scattered radiation)
- Artifact from patient motion
- No dedicated biopsy system
- Interpretation may be limited by BPE
• Potential applications:
  – Screening intermediate risk patients
  – EOD evaluation if no access to MR
  – Diagnostic setting: palpable abnormality, etc.
ABBREVIATED BREAST MRI
Breast MRI

• Most sensitive imaging modality for breast cancer detection

• Currently recommended as supplemental screening for women with >20% lifetime risk of breast cancer
  – BRCA mutation, history of chest irradiation before age 30, Li Fraumeni, etc.
MRI for Breast Cancer Screening

- Not limited by breast density
- No ionizing radiation
- Most *sensitive* test for breast cancer detection
- PPV similar to mammography
- Preferentially detects higher grade lesions
Efficacy of MRI and Mammography for Breast-Cancer Screening in Women with a Familial or Genetic Predisposition

Compare efficacy of MRI vs. MG in high-risk women
1909 women screened, incl. 358 carriers germ-line mutations
51 cancers identified (44 invasive, 6 DCIS, 1 lymphoma)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical breast exam</td>
<td>17.9%</td>
<td>98.1%</td>
</tr>
<tr>
<td>Mammography</td>
<td>33.3%</td>
<td>95.0%</td>
</tr>
<tr>
<td>MRI</td>
<td>79.5%</td>
<td>89.8%</td>
</tr>
</tbody>
</table>

MRI significantly better than MG in detecting tumors, but MG had higher sensitivity for DCIS (83% vs. 17%, p=0.22).

Mammography, Breast Ultrasound, and Magnetic Resonance Imaging for Surveillance of Women at High Familial Risk for Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>MG</th>
<th>US</th>
<th>MG+US</th>
<th>MRI</th>
<th>MG+MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>32.6%</td>
<td>39.5%</td>
<td>48.8%</td>
<td>90.7%</td>
<td>93.0%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>96.8%</td>
<td>90.5%</td>
<td>89.0%</td>
<td>97.2%</td>
<td>96.1%</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>23.7%</td>
<td>11.3%</td>
<td>11.9%</td>
<td>50.0%</td>
<td>42.1%</td>
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19 cancers seen only on MRI – 5 DCIS and 14 invasive

Comparison of Diagnostic Yield of Different Imaging Modalities Regarding Prognostically Relevant Tumor Features

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<thead>
<tr>
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<th>Detected by MG</th>
<th>Detected by US</th>
<th>Detected by MG + US</th>
<th>Detected by MRI</th>
<th>Only MRI Detected*</th>
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<tbody>
<tr>
<td># Primary invasive CA</td>
<td>10</td>
<td>12</td>
<td>16</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>Node + inv. CA (%)</td>
<td>4/10 (40)</td>
<td>5/12 (42)</td>
<td>5/16 (31)</td>
<td>5/31 (16)</td>
<td>0/14 (0)</td>
</tr>
<tr>
<td>Mean Size inv. (mm)</td>
<td>13.2</td>
<td>15.1</td>
<td>13.9</td>
<td>12.4</td>
<td>9.0</td>
</tr>
<tr>
<td># Minimal cancers (%)</td>
<td>5/25 (20)</td>
<td>3/25 (12)</td>
<td>6/25 (24)</td>
<td>23/25 (92)</td>
<td>18/25 (72)</td>
</tr>
<tr>
<td># Intraductal Ca (%)</td>
<td>3/9 (33)</td>
<td>0/9 (0)</td>
<td>3/9 (33)</td>
<td>8/9 (89)</td>
<td>5/9 (56)</td>
</tr>
</tbody>
</table>

*not detected with MG+US

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<th>Detected by MRI</th>
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<td>5/9 (56)</td>
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</table>

*not detected with MG+US

Node + rate 16% vs. 35-44% published for MG screening
Rate of interval CA 2% vs. 43-60% with MG surveillance

Prospective Multicenter Cohort Study to Refine Management Recommendations for Women at Elevated Familial Risk of Breast Cancer: The EVA Trial

Fig 1. Cancer yield of the different imaging methods, used alone or in combination. Number of true-positive diagnoses per 1,000 complete screening rounds. Mx, mammography; US, ultrasound; MRI, magnetic resonance imaging.

Prospective Multicenter Cohort Study to Refine Management Recommendations for Women at Elevated Familial Risk of Breast Cancer: The EVA Trial

**Fig 1.** Cancer yield of the different imaging methods, used alone or in combination. Number of true-positive diagnoses per 1,000 complete screening rounds. Mx, mammography; US, ultrasound; MRI, magnetic resonance imaging.

## Table 4. Screening Performance in 612 Participants Screened by Magnetic Resonance Imaging After 3 Annual Mammography and Ultrasound Screenings

<table>
<thead>
<tr>
<th></th>
<th>Combined Mammography Plus Ultrasound</th>
<th>Combined Mammography Plus Ultrasound Plus MRI</th>
<th>Difference of (Mammography Plus Ultrasound Plus MRI) and (Mammography Plus Ultrasound)</th>
<th>Difference of (Mammography Plus Ultrasound Plus MRI) and Mammography Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yield (95% CI), per 1000</strong></td>
<td>11.4 (4.6 to 23.4)</td>
<td>26.1 (15.0 to 42.1)</td>
<td>14.7 (3.5 to 25.9)</td>
<td>.004</td>
</tr>
<tr>
<td><strong>AUC (95% CI)</strong></td>
<td>0.69 (0.55 to 0.83)</td>
<td>0.95 (0.91 to 0.99)</td>
<td>0.26 (0.11 to 0.42)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Sensitivity (95% CI), %</strong></td>
<td>43.8 (19.8 to 70.1)</td>
<td>100.0 (79.4 to 100.0)</td>
<td>56.3 (25.7 to 68.6)</td>
<td>.004</td>
</tr>
<tr>
<td><strong>Specificity (95% CI), %</strong></td>
<td>84.4 (81.2 to 87.2)</td>
<td>65.4 (61.5 to 69.3)</td>
<td>-19.0 (-22.3 to -15.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Recall rate (95% CI), %</strong></td>
<td>16.3 (13.5 to 19.5)</td>
<td>36.3 (32.5 to 40.2)</td>
<td>19.9 (16.6 to 23.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>PPV1 (95% CI), %</strong></td>
<td>7.0 (2.9 to 13.9)</td>
<td>7.2 (4.2 to 11.4)</td>
<td>0.2 (-3.8 to 4.0)</td>
<td>.92</td>
</tr>
<tr>
<td><strong>Short-term follow-up rate (95% CI), %</strong></td>
<td>4.6 (3.1 to 6.5)</td>
<td>19.6 (16.5 to 23.0)</td>
<td>15.0 (12.0 to 18.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Biopsy rate (95% CI), %</strong></td>
<td>6.2 (4.4 to 8.4)</td>
<td>13.2 (10.7 to 16.2)</td>
<td>7.0 (4.8 to 9.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>PPV3 (95% CI), %</strong></td>
<td>18.4 (7.7 to 34.3)</td>
<td>18.5 (10.8 to 28.7)</td>
<td>0.1 (-8.8 to 8.8)</td>
<td>.98</td>
</tr>
</tbody>
</table>

### MRI Alone

- **Yield (95% CI), per 1000**: 22.9 (12.6 to 38.1)
- **AUC (95% CI)**: 0.87
- **Sensitivity (95% CI), %**: 87.5
- **Specificity (95% CI), %**: 75.7
- **Recall rate (95% CI), %**: 26.0
- **PPV1 (95% CI), %**: 8.8
- **Short-term follow-up rate (95% CI), %**: 15.8
- **Biopsy rate (95% CI), %**: 8.5
- **PPV3 (95% CI), %**: 23.1

---

Supplemental Screening: Cancer Yield

- US: 3-4/1,000 screened
- MRI: 10-24/1,000 screened

*Why not screen everyone with MRI?*
Limitations of MR for Screening Average Risk Women

- Cost
- Time
- IV contrast
- Availability
- Perceived low specificity
Abbreviated MRI (AB-MR)

• Total scan time <10 minutes
• Localizer scan
• 1 pre- and 1 post-contrast gradient echo (GRE) axial acquisition; in-plane resolution of 1 mm or less
• Slice thickness of 3 mm or less
• (+/-) Axial T2 weighted sequences with in-plane resolution matching GRE sequences and ≤3 mm slice thickness
Benefits AB-MR

• Low cost: $300-$500
• Quick: <10 minutes
• PPV similar to MG: 20-30%
• 150-200% increase in cancer detection
• Potential to preferentially detect higher grade lesions
Benefits AB-MR

- Shorter acquisition time
- Shorter interpretation time

→ higher volume of patient throughput
→ more cost-effective

while maintaining high diagnostic accuracy
Limitations of AB-MR

• Loss of kinetic information
• Sensitivity for morphologically benign appearing cancers demonstrating washout may be lower without kinetics (rare)
Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximum-intensity projection—a novel approach to breast cancer screening with MRI.

- 443 women with negative FFDM
  - 427 with dense or extremely dense breasts also had negative WBUS
  - Mild to moderate risk
- Radiologists reviewed:
  - MIP and FAST images for significant enhancement
  - complete AP (MIP, FAST images, and nonsubtracted source images)
  - Regular full diagnostic protocol

Kuhl et al., J Clin Oncol 2014.
AB-MR

Acquisition time:
- AP: 3 minutes
- Full protocol: 17 minutes

Kuhl et al., J Clin Oncol 2014.
Pre-contrast

Post-contrast

FAST (subtraction)

MIP

Kuhl et al., J Clin Oncol 2014.
AB-MR

- 11 cancers detected (18.2/1000)
  - 7 invasive, 4 DCIS
  - Small T1, node negative cancers
  - Predominantly high-grade tumors
- US negative in 11 cancers

Kuhl et al., J Clin Oncol 2014.
Intermediate grade IDC

Kuhl et al., J Clin Oncol 2014.
AB-MR

• Sensitivity
  – MIP only: 90.9% (10/11 cancers)
  – 1st post contrast: 100% (11/11)

• Specificity
  – 1st post: 94.3%
  – Full protocol 93.9%

• Interpretation time
  – MIP only: 3 seconds
  – 1st post: 28 seconds

• NPV MIP only: 99.8%

Kuhl et al., J Clin Oncol 2014.
AB-MR

• MIP image interpretation time of 3 s
• NPV 99.8%
• reading time <30 seconds for complete AP
• diagnostic accuracy equivalent to FDP with cancer yield of 18.2/1000
→ batch read AB-MR for general screening like screening mammography?

Kuhl et al., J Clin Oncol 2014.
AB-MR

- Study of 100 consecutive MRs in patients with biopsy proven unicentric breast CA
  - 79 invasive, 21 DCIS
- Four readers
- AP: 1st post, 1st subtraction, MIP
- Compared AP to FDP (13 pre-contrast, post-contrast, and post-processed sequ)

Mango et al., Eur J Radiol 2015
AB-MR

- **Sensitivity:**
  - 1\textsuperscript{st} post-contrast: 96%
  - 1\textsuperscript{st} post-contrast subtraction: 96%
  - MIP: 93%

- **Mean interpretation time:**
  - 44 s (11-167 s)

- **Acquisition time:**
  - AP: 10-15 min
  - FDP: 30-40 min

Mango et al., Eur J Radiol 2015
AB-MR

• Elimination of sequences from FDP may limit interpretation:
  – T1 non-fat saturated images for fat necrosis, lymph nodes
  – T2 weighted images to enable benign assessment
  – Lack of kinetic information
  – Increase unnecessary recalls
AB-MR

- Compared two AP to standard FDP
- 48 MRIs (24 normal, 12 benign, 12 CA)

<table>
<thead>
<tr>
<th>Protocol</th>
<th>T2</th>
<th>Pre</th>
<th>1st post</th>
<th>2nd post</th>
<th>3rd/4th post</th>
<th>Non-FS T1</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP1</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP2</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>FDP</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Grimm et al., Acad Radiol 2015
AB-MR

• No significant difference in sensitivity:
  – AP 1: 86%
  – AP2: 89%
  – FDP: 95%

• No significant difference in specificity:
  – AP 1: 52%
  – AP2: 45%
  – FDP: 52%
  – Lesion kinetics did not affect specificity

• Similar interpretation times:
  – AP1: 2.98 minutes
  – FDP: 2.95 minutes

Grimm et al., Acad Radiol 2015
AB-MR: Protocols

- Moschetta et al.: STIR, T2W, pre-, single post
- Dogan et al.: T2W, single pre- and post
- Choi et al.: fat-suppressed T2, single pre- and post, subtracted MIPs
- Petrillo et al.: single pre- and post T1W
- Romeo et al.: pre- and three post

Studies show comparable diagnostic accuracy to full protocol
Comparison of Abbreviated Breast MRI and Digital Breast Tomosynthesis in Breast Cancer Screening in Women with Dense Breasts

Christopher Comstock M.D.
Christiane Kuhl M.D.
Gillian Newstead M.D.
ECOG-ACRIN 4112

- All patients undergo DBT and AB-MR on the same day at year 0 and year 1
- Randomization as to which test is performed first
- After year 1, patients return to standard screening and are followed for 3 years
ECOG-ACRIN 4112

• Primary endpoint:
  – Compare rates of detection of invasive cancers between initial AB-MR and DBT.

• Secondary endpoints:
  – Compare PPV of biopsies, callback rates, and short-term follow-up rates after AB-MR and DBT on initial and 1 year follow-up
  – Estimate and compare sensitivity and specificity of AB-MR and DBT
  – Compare patient-reported short-term quality of life related to diagnostic testing with AB-MR and DBT
  – Comparative cost analysis of both exams
AB-MR: Goal

• Expand access to MRI
• Allow women with dense breasts to have a faster, more sensitive, and more accurate option to screening US
• AB-MR every 2-3 years may prove to be a better stand alone test than mammography and US every year
AB-MR: Future Directions

- Standardize protocol across sites
- Determine financial cost: cost-effective enough to be first-line exam?
- Establish screening interval
- Multihead scanners to increase patient throughput
- Improving specificity: DWI, Ultrafast, CAD
- Non-contrast MR imaging
Summary

• Reviewed rationale for development of new imaging techniques
• Discussed CEM and AB-MR
  – Applications
  – Current data
  – Future directions