Abbreviated MRI and the Dense Breast

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Outline

• History of mammographic screening
• Current landscape of screening
• Re-evaluating our approach to screening
• Concept of AB-MR
• EA1141 Trial and future trials

RCTs of Mammographic Screening

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada NBSS-1</td>
<td>1.06 (0.90–1.40)</td>
</tr>
<tr>
<td>Canada NBSS-2</td>
<td>1.02 (0.78–1.35)</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>0.71 (0.53–0.95)</td>
</tr>
<tr>
<td>HIP</td>
<td>0.77 (0.62–0.97)</td>
</tr>
<tr>
<td>Two-County Trial</td>
<td>0.66 (0.56–0.78)</td>
</tr>
<tr>
<td>Malmo-1</td>
<td>0.82 (0.67–1.00)</td>
</tr>
<tr>
<td>Malmo-2</td>
<td>0.64 (0.50–1.00)</td>
</tr>
<tr>
<td>Stockholm</td>
<td>0.91 (0.65–1.27)</td>
</tr>
<tr>
<td>Gothenburg</td>
<td>0.76 (0.56–1.04)</td>
</tr>
<tr>
<td>UK Age Trial</td>
<td>0.83 (0.66–1.04)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.70 (0.73–0.86)</td>
</tr>
</tbody>
</table>

Figure 3b: Relative risks of breast cancer mortality. The group invited to screening is compared with that receiving usual care in all screening trials. HP = Health Insurance Plan of Greater New York Trial; NBSS-1, NBSS-2 = National Breast Screening Studies of Canada.

2D Analog Screen Mammography

• 8 Randomized clinical trials
• Prior to:
  • Improved high-speed screen film techniques
  • CAD
  • Digital (FFDM)
  • Tomosynthesis

Smith et al www.cancernetwork.com
ACRIN-DMIST

- Digital Mammographic Imaging Screening Trial
- >49,000 women
- Multiple Digital Vendors
- Results presented 9/16/05 show overall no significant difference
- However, benefit for subgroups (age < 50, Dense breasts and peri-menopausal women)

Screening Mammography

- Sensitivity depends on breast density

Mammographic Screening: DMIST Sensitivity

Breast Density Legislation: Where and why did it come about?

- Shortcomings of mammography have led to passage of breast density laws in many states
  - Not results of new data or clinical trial
- Require women be told if they have dense breasts and that they may benefit from supplemental screening
- Type of supplemental screening not specified
Breast Density Legislation

Breast Density: Significance

- Association with increased breast cancer risk
- Decreased sensitivity of mammography (masking effect)

Breast Density: Increased Risk

- “Women with dense breasts are 4-6X more likely to get breast cancer”
  - Comparing 10% with PF and 10% with ED
- Risk relative to average breast density:
  - HD: 1.2X
  - ED: 2.1X

Breast Density: Masking Effect

- Sensitivity depends on breast density
- BCSC data (film screen)
  - PF: 88%
  - SFG: 82%
  - HD: 69%
  - ED: 62%
Digital Breast Tomosynthesis (DBT)

Friedewald et al, JAMA June 2014

- 454,850 patients at 13 sites
- Cancer Detection: 7058 MG
  - MG: 4.2/1000
  - MG+DBT: 5.4/1000
- Recall rate:
  - MG: 10.7%
  - MG+DBT: 9.1%
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

The Current State of Screening

1. For many women with dense breasts, the standard is now annual DM or DBT plus WBUS
2. The combined cancer detection rate is approximately 7-9 cancers per 1000
3. Exact mortality reduction is unknown
4. Limitation of this approach include:
   - Low PPV (8-9%)
   - High frequency of short-term follow recommendations
   - Time consuming
   - Cost

How good is this approach?

What is the sensitivity of Combined DM plus WBUS?

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
Reservoir of Breast Cancer Present in 1000 Women Being Screened

- Is it 30, 40, 50, 60 or more breast cancers per 1000 women?
- Depends on risk of population
- Detection level (size and stage) depends on modality and frequency of screening

Current approach - Mammo plus WBUS

How we choose to screen is somewhat arbitrary

- How many of the cancers in the reservoir we choose to find and at what size is balanced by the cost and harms of the test.

Screening Tests
The Use of MRI for Breast Cancer Screening

- Not limited by breast density
- No ionizing radiation
- Most sensitive test for breast cancer screening
- PPV similar to mammography
- Preferentially detects higher grade lesions

The most sensitive test we have is breast MRI

FFDM and MRI on same patient

Screening Controversies: Limited Sensitivity

- 443 women with negative FFDM
  - 427 with HD/ED breasts also had negative WBUS
  - Mild to moderate risk
- 11/443 (18.2/1000) CA detected
  - 7 invasive CA, 4 DCIS
  - small T1, node negative CA
  - predominantly high-grade tumors
- Ultrasound negative in the 11 CA patients

Abbreviated Breast MRI

Kuhl et al. JCO 2014 Aug 1;32 (22):2304-10
**Supplemental MR Screening in Women at Average Risk**

- 2120 women ages 40-70 with neg mammo +/- WBUS between 2005-2013
  - <15% lifetime risk
- 60 additional CA (supplemental CDR: 16/1000)
  - Invasive: 40, DCIS: 20
  - Median size: 0.8 cm
  - 93% node negative
- No interval CA

Kuhl et al. Radiology 2017 May; 283 (2): 361-370

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

1. Cost
2. Time
3. Perceived low PPV

**Abbreviated MRI (AB-MR)**

- Low cost: $300-$500
- Quick: less than 10 min
- PPV similar to mammography: 20-30%
- 150-200% increase in cancer detection
- Optimal screening interval: 1-3 yrs?
- Potential to preferentially detect higher grade lesions
AB-MR is defined as a breast MRI fulfilling the following requirements:

- Total scan time of less than 10 min (including localizer)
- A localization 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 sequence with in-plane resolution matching the GRE sequences and 3 mm or less slice thickness

Penalty of Abbrev Breast MRI

1. Loss of kinetic info
2. Sensitivity maintained
3. Sensitivity for morphologically benign appearing cancers demonstrating washout may be lower without kinetics

Objectives

Primary Endpoints
1. To compare the rates of detection of invasive cancers between the initial AB-MR and DBT.

Secondary Endpoints
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 short-term quality of life related to diagnostic testing with AB-MR and DBT using the Testing Morbidities Index.
4. To compare willingness to return for testing with AB-MRI vs DBT within the recommended screening interval and explore factors associated with willingness to return for screening.
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.
Tumor Biology

1. Exploration of the differences in the biological detection profiles (BDP) of Tomosynthesis and AB-MR. (PAM50 for invasive CA and DCIS score for DCIS)

Study Design

1. Paired design: All patients undergo both DBT and AB-MR on the same day at year 0 and year 1.
2. Randomization is only done to determine which test is done first. Once randomized, the order of the tests should be done the same at year 0 and year 1.
3. After the year 1 DBT and AB-MR, patients return to their standard screening per site practice and are followed for breast cancer occurrence for 3 years.
4. For patients that consented for tissue submission, tissue from all cancers detected during the study period should be sent for genetic profiling per study protocol.

Schema

- **Women ages 40-75 with dense breasts already scheduled for routine screening DBT**
- **Randomization**
  - **Arm A (DBT first)**
    - Years 0 and 1 DBT followed by AB-MR
    - Year 0 PRO/QOL assessments to be completed approximately 2 weeks after screening
  - **Arm B (AB-MR first)**
    - Years 0 and 1 AB-MR followed by DBT
    - Year 0 PRO/QOL assessments to be completed approximately 2 weeks after screening
- **Return to routine mammographic screening and follow-up for 3 years**

Accrual Goal = 1450
1. Suspicious lesions detected on one or both of the modalities at the Year 0 or 1 time points will be biopsied as per local standard practice
2. Tissue collection and analysis for all cancers detected

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</th>
<th>Sample Size</th>
<th>Difference in invasive cancer rates (AB-MR - DBT)</th>
<th>Proportion of discordant cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.90</td>
<td>1191</td>
<td>0.009</td>
<td>0.010</td>
</tr>
<tr>
<td>0.95</td>
<td>1263</td>
<td>0.009</td>
<td>0.011</td>
</tr>
<tr>
<td>0.90</td>
<td>1502</td>
<td>0.009</td>
<td>0.012</td>
</tr>
<tr>
<td>0.95</td>
<td>1057</td>
<td>0.010</td>
<td>0.011</td>
</tr>
<tr>
<td>0.90</td>
<td>1197</td>
<td>0.010</td>
<td>0.012</td>
</tr>
<tr>
<td>0.95</td>
<td>949</td>
<td>0.011</td>
<td>0.012</td>
</tr>
</tbody>
</table>
Main Eligibility Criteria

1. Patients must be women ages 40 to 75 years and scheduled for routine screening DBT.
2. Patient’s breast density must be known; patients must have mammographically dense breasts (ACR BI-RADS Density categories 3 or 4) on their most-recent prior screening.
3. Patient must be asymptomatic for breast disease and undergoing routine screening.
4. Patient must have no known breast cancer (DCIS or invasive cancer), not currently undergoing treatment for breast cancer, or planning surgery for a high risk lesion (ADH, ALH, LCIS, papilloma, radial scar).
5. Patient must not be taking chemoprevention for breast cancer.
6. Patient must not have undergone breast ultrasound within 12 months prior to randomization.
7. Patient must not have previously had a breast MRI or CEDM.
8. Patient must not be suspected of being at high-risk for breast cancer, as defined by the ACS breast MR screening recommendations (lifetime risk of ≥ 20-25%).
9. Able to undergo breast MRI.
10. Does not have breast implants.

Please see protocol for complete list.

Site Participation

1. AB-MR studies can only be performed on Magnets accredited by the ACR for Breast MRI.
2. Multihance gadolinium contrast agent is a protocol requirement (no substitutes allowed).
3. Readers for the AB-MR studies must be accredited by the ACR in Breast MRI.
4. Readers must have performed the SBMR AB-MR reader training, passed the AB-MR reader certification test and provide their certification number.

Interpretation Guidelines
Interpretation Guidelines

Site Participation

1. Currently about 30 sites open
2. Expect 20-40 sites
3. 1-5 accruals per week per site
4. Approx 1 year accrual window (budgeted for 22 months)
Breast PRISM: PRImary Screening with MRI

In the End

- Access to MRI will be widely expanded
- Women with dense breasts will have a faster, more sensitive and more accurate option to WBUS.
- AB-MR every 2-3 years may prove to be a better stand alone test than mammography and ultrasound every year.

Thank you!