Contrast-Enhanced Breast Tomosynthesis

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Andrew D. A. Maidment, Ph.D.
Chief, Physics Section
Department of Radiology
University of Pennsylvania
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- Dr. Maidment is a scientific advisor to the RTT and XCounter.
- Susan Ng Maidment is the President and CEO of RTT.

FDA Statement

- This presentation will include off-label uses and applications and devices not yet approved for human use in the United States.
Digital Mammography
Contrast arises from different attenuation in various paths through an object.

\[ I_a = I_o e^{-\mu_1 t} \]
\[ I_b = I_o e^{-\mu_2 t} \]
\[ C_M = \frac{I_b - I_a}{I_b + I_a} \]
Mammography and Tomosynthesis

Attenuation of breast tissues

Infiltrating ductal carcinoma

Glandular

Fat

Linear attenuation coefficient (cm⁻¹)

20 30 50 70 100

Energy (keV)

1.0

0.5

0.3

0.2

0.1
\[ I = I_0 e^{-\mu x} \]
\ln\left( \frac{I_0}{I} \right) = \bar{\mu}x
\[ \ln\left(\frac{I_0}{I}\right)/x = \bar{\mu} \]
\[ \ln\left(\frac{I_0}{I}\right)/x = \bar{\mu} \]

\[ \ln\left(\frac{I_0}{I}\right)/x = \widetilde{\mu} \]
Vascular Contrast Enhancement Methods

• The development of an independent vasculature is an essential step in the development of a cancer.

• A contrast agent should be able to demonstrate these vessels and the lesion itself.
Vascular Contrast Enhancement Methods

• A variety of approaches have been investigated to elucidate tumor vasculature, including x-rays, tomosynthesis, CT, MRI and ultrasound

• Radiographic techniques are now readily achievable because of the prevalence of digital mammography, the emergence of digital breast tomosynthesis, and the high quantum efficiency and low detector noise of existing technology
Contrast-Enhanced Breast MR

- Today, MR is the most common breast imaging method to use vascular contrast agents.
- MR is used to distinguish benign from malignant tissues on the basis of enhance, washout, temporal characteristics and morphology.
- Tumors will rapidly take up the contrast agent, but it will wash out slowly.
MRI of the Breast

- **First Reports of Breast MRI:**
  - Stelling et al: *Radiology* 1985
  - Dash et al: *AJR* 1986

- **Contrast Enhanced Breast MRI:**

- **Higher Resolution 3D Imaging:**

- **MRI Guided Bx:**
  - Schnall et al: *RSNA* 1993
  - Heywang et al: *RSNA* 1993

150 μm spatial resolution

Courtesy M. Schnall – U of PA
Intraductal Carcinoma
Current ACR MRI Recommendations

A. Screening
   1. High-Risk Patients
   2. Contralateral breast of patients with new malignancies
   3. Patients pre-augmentation and having free injection augmentation
**TABLE 1**  Recommendations for Breast MRI Screening as an Adjunct to Mammography

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
</table>
| **Recommend Annual MRI Screening (Based on Evidence*)** | - BRCA mutation  
- First-degree relative of BRCA carrier, but untested  
- Lifetime risk ~20–25% or greater, as defined by BRCAPRO or other models that are largely dependent on family history |
| **Recommend Annual MRI Screening (Based on Expert Consensus Opinion†)** | - Radiation to chest between age 10 and 30 years  
- Li-Fraumeni syndrome and first-degree relatives  
- Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives |
| **Insufficient Evidence to Recommend for or Against MRI Screening‡** | - Lifetime risk 15–20%, as defined by BRCAPRO or other models that are largely dependent on family history  
- Lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH)  
- Atypical ductal hyperplasia (ADH)  
- Heterogeneously or extremely dense breast on mammography  
- Women with a personal history of breast cancer, including ductal carcinoma in situ (DCIS) |
| **Recommend Against MRI Screening (Based on Expert Consensus Opinion )** | - Women at <15% lifetime risk |

*Evidence from nonrandomized screening trials and observational studies.  
†Based on evidence of lifetime risk for breast cancer.  
‡Payment should not be a barrier. Screening decisions should be made on a case-by-case basis, as there may be particular factors to support MRI. More data on these groups is expected to be published soon.
### TABLE 2  Published Breast MRI Screening Study Results

<table>
<thead>
<tr>
<th></th>
<th>The Netherlands</th>
<th>Canada</th>
<th>United Kingdom</th>
<th>Germany</th>
<th>United States</th>
<th>Italy</th>
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<tbody>
<tr>
<td>No. of centers</td>
<td>6</td>
<td>1</td>
<td>22</td>
<td>1</td>
<td>13</td>
<td>9</td>
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<tr>
<td>No. of women</td>
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<td>236</td>
<td>649</td>
<td>529</td>
<td>390</td>
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<tr>
<td>Age range</td>
<td>25–70</td>
<td>25–65</td>
<td>35–49</td>
<td>≥30</td>
<td>≥25</td>
<td>≥25</td>
</tr>
<tr>
<td>No. of cancers</td>
<td>50</td>
<td>22</td>
<td>35</td>
<td>43</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>MRI</td>
<td>80</td>
<td>77</td>
<td>77</td>
<td>91</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mammogram</td>
<td>33</td>
<td>36</td>
<td>40</td>
<td>33</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>n/a</td>
<td>33</td>
<td>n/a</td>
<td>40</td>
<td>n/a</td>
<td>16</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MRI</td>
<td>90</td>
<td>95</td>
<td>81</td>
<td>97</td>
<td>95</td>
<td>99</td>
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<tr>
<td>Mammogram</td>
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<td>&gt;99</td>
<td>93</td>
<td>97</td>
<td>98</td>
<td>0</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>n/a</td>
<td>96</td>
<td>n/a</td>
<td>91</td>
<td>n/a</td>
<td>0</td>
</tr>
</tbody>
</table>

n/a = not applicable.

### TABLE 3  Rates of Detection and Follow-up Tests for Screening MRI Compared with Mammography

<table>
<thead>
<tr>
<th></th>
<th>MRI</th>
<th>Mammography</th>
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<tbody>
<tr>
<td></td>
<td>The Netherlands</td>
<td>United Kingdom</td>
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<tr>
<td>Positives</td>
<td>13.7%</td>
<td>19.7%</td>
</tr>
<tr>
<td>Recalls</td>
<td>10.84%</td>
<td>10.7%</td>
</tr>
<tr>
<td>Biopsies</td>
<td>2.93%</td>
<td>3.08%</td>
</tr>
<tr>
<td>Cancers</td>
<td>1.04%</td>
<td>1.44%</td>
</tr>
<tr>
<td>False negatives</td>
<td>0.23%</td>
<td>0.43%</td>
</tr>
</tbody>
</table>
Current ACR MRI Recommendations

B. Extent of Disease
   4. Invasive and ductal carcinoma in situ
   5. Invasion deep to fascia
   6. Post lumpectomy with positive margins
   7. Neoadjuvant chemotherapy

Diagnostic imaging of all women with cancer prior to treatment. 15-20% of women will have multifocal or multi-centric breast cancer.
Chemoprevention

Neoadjuvant Chemotherapy

**TREATMENT RESPONSE ASSESSMENT**

- **Pretreatment**
  - Volume = 57.08 cc

- **Early treatment**
  - Volume = 14.2 cc

- **Inter-regimen**
  - Volume = 0.2 cc

- **Presurgery**
  - Volume = 0.03 cc

Specialized MRI software used in the Contrast-Enhanced Breast MRI for Evaluation of Patients Undergoing Neoadjuvant Treatment for Locally Advanced Breast Cancer (ACRIN 6657) trial creates a tumor map that takes into account tumor diameter, volume, and microvasculature. Tumor maps demonstrate correlation with MR images of tumor response to treatment. Nola M. Hylton, Ph.D., principal investigator, presented preliminary study results at the 2008 RSNA meeting.
Current ACR MRI Recommendations

C. Additional Evaluation of Findings
   8. Recurrence of Breast Cancer
   9. Metastatic disease with unknown origin of primary
   10. Lesion characterization
   11. Post-operative reconstruction
   12. MRI guided biopsy
Breast CT

100 mL (3 mL/s) intravenous injection Iopamiron 300 (Nihon Schering, Osaka)
Scanned at 30s and 120s post-injection

M Nishino et al, J CAT, 27(5), 771-8 2003
Multiple Fibroadenomas
Invasive IDC
Papilloma
Dedicated breast CT scanner

pendant geometry

The Breast Tomography Project
University of California, Davis

Slide Courtesy John Boone, Ph.D.
BCT SUBTRACTION IMAGES

Pt 122
“Contrast-Enhanced” Digital Mammography

• The advent of modern digital mammography has led to a renewed interest in breast angiography.

• The field is now called “contrast-enhanced digital mammography”.

• Rather than image blood vessels, the desire is to fractionally increase the contrast of breast lesions by virtue of their slightly increased uptake and retention of contrast media as compared to surrounding tissue.
Temporal Subtraction

• In temporal subtraction angiography, an initial “mask” image is produced and stored prior to the injection of contrast material.
• The contrast media is then injected.
• Finally, a series of post-contrast images are acquired.
• Subtracted images are produced by logarithmically subtracting the initial mask image from each of the post-contrast images.
Temporal Subtraction

Mask

ICRU-44 Breast Tissue
Iodine
0.27 mm Cu

Photon Fluence [# photons/mm²]

Energy [keV]

Mass attenuation [cm²/g]
Jong and Yaffe

- 22 women with mammographic abnormalities underwent CE digital mammography.
- 6 images were obtained with contrast injected intravenously between the 1st and 2nd images.
- Enhancement was observed in 8 of 10 patients with cancer.
- In 2 cancer cases, no enhancement was observed.
- No enhancement was seen in seven of 12 benign cases, which were otherwise suspected as cancer.
- Lesion enhancement kinetics was similar to MRI.

IDC

Papilloma

CC

1 Min

Courtesy M. Yaffe
Patient With Benign Lesion (Fibrocystic Change)

Scout 1 min 5 min

Enhancement Kinetics

Lesion Mean - Tissue Mean in Subtracted Images

Time (minutes)

0 1 2 3 4 5 6 7 8

0 5 10 15 20 25 30

Lesion Mean - Tissue Mean in Subtracted Images

0 5 10 15 20 25 30

0 1 2 3 4 5 6 7 8

Time (minutes)

Courtesy M. Yaffe
Infiltrating Ductal Carcinoma

Scout 1 min

1 min.

7 min.

Kinetics

mg/cm²

Time (minutes)

0 1 2 3 4 5 6 7 8

0 1 2 3

Courtesy M. Yaffe
CE Tomosynthesis Method

- MLO projection with 5-7 dN compression
- 49 kVp, Rh target, 0.27 mm Cu filter
- 9 projections per data set: 50° arc, 6.25° apart
- 1 projection each 30 sec
- Dose per data set ~ mammogram (~2 mGy)
CE Tomosynthesis Method

• 1 ml/kg of Visipaque-320® (320 mg I/ml iodixanol) - Amersham, Princeton, NJ.
• 60 mL saline flush.
• First post-contrast image obtained 90 sec after start of contrast injection.
• Total exam time ~10 minutes.
• 17 patients to date
Patient 1: Digital Mammography

Right breast - 1.4 cm ill-defined asymmetry overlying pectoralis muscle
Patient 1: MRI

Pre Gd T1 –FS

Post Gd FS

Post Gd - sub

1.3 cm enhancing mass at 12:00 in right breast.
Contrast-Enhanced Tomosynthesis

Pre-contrast

Post-contrast

Subtraction

Spiculated mass with rim enhancement.
Image Registration

- The registration algorithm is a multi-scale, globally smooth and locally affine.
- Before registration, pre- and post-contrast images are sampled and averaged to preserve original geometry while reducing computational time, and improving the per pixel signal-to-noise ratio.
38 yo with ductal carcinoma demonstrating strong enhancement. Registration reduced motion artifacts in axilla and inferior breast, resulting in superior visualization of the lesion and vasculature.
Patient 2: Motion Correction

BEFORE

AFTER

43 yo with segmental enhancement in upper half of breast, concordant with MRI. In the pre-registered image, the enhancement was not discernable from motion artifacts.
Temporal Subtraction

• Advantages:
  • Superior separation of pre- and post-contrast images
  • High kVp pre- and post- contrast images
  • Reduced total dose

• Disadvantages:
  • Motion Artifacts
Dual-Energy Imaging

• At diagnostic energies, there are two main x-ray interactions
  • Photoelectric effect
  • Compton effect

• The relative contribution of the two effects depends upon the energy and the atomic number of the material

• Therefore, the attenuation coefficients of different materials have different trends as a function of energy
Mass Attenuation Coefficients for Soft Tissue

![Graph showing mass attenuation coefficients for different processes (Total, Photoelectric, Coherent, Compton, Pair production) across different energy levels (in keV).]
Dual-Energy Radiography

Attenuation of breast tissues

- Infiltrating ductal carcinoma
- Glandular
- Fat

Linear attenuation coefficient (cm⁻¹)

Energy (keV)

20 30 50 70 100
The attenuation of the two materials is given by

\[ I_a = I_o e^{-(\mu_f t_f + \mu_g t_g)} \]
We can define a quantity, $T$, such that

$$T_{18} = \mu_f t_f + \mu_g t_g \quad \text{at 18 keV}$$

and

$$T_{40} = \mu'_f t_f + \mu'_g t_g \quad \text{at 40 keV}$$
Using data from Johns and Yaffe (1987) for fat and glandular tissue gives

\[ T_{18} = 0.6t_f + 1.0t_g \text{ at } 18 \text{ keV} \]

and

\[ T_{40} = 0.2t_f + 0.3t_g \text{ at } 40 \text{ keV} \]
If you multiply $T_{40}$ by 4, and subtract $T_{18}$, you get

$$T_{\text{sub}} = (4 \times 0.2 - 0.6)t_f + (4 \times 0.3 - 1.0)t_g$$

$$= 0.2(t_f + t_g) .$$

Now, fat and glandular tissue have the same attenuation, and thus they lack contrast.
Energy Subtraction

- In energy subtraction, contrast media is injected first
- Then, a series of sequential image pairs is obtained
- Each image pair consists of one high energy and one low energy image
- Images are then processed and subtracted pair-wise
Energy Subtraction

Low

High

Time
Dual-Energy Contrast-Enhanced Imaging

\[ SI_{DE}(x, y) = \ln(SI_H(x, y)) - w_i \cdot \ln(SI_L(x, y)) \]
Lewin et al.

• CE DSM was performed on 26 subjects with mammographic or clinical findings warranting biopsy.
• High-energy (44-49 kVp, + 8mm Al filtration) and low-energy (30-33 kVp) images were obtained pair-wise, following administration of iodinated contrast.
• A weighted logarithmic subtraction of the images was performed to obtain images that preferentially show iodine.
• 13 subjects had invasive cancers, 11 of which enhanced strongly, 1 moderately and 1 weakly.
• 1 case of DCIS demonstrated a weak enhancement.
• In the 12 benign cases, 2 enhanced diffusely and 2 enhanced weakly focally.

Two-View Film Mammogram
(wire on excisional biopsy scar)

(cyst)
Sagittal Post-contrast MRI

Lateral ...

... to Medial
Post-Contrast Dual-Energy Digital Subtraction Mammography
SHORT COMMUNICATION

Dual-energy contrast-enhanced digital breast tomosynthesis — a feasibility study

A-K CARTON, PhD, S C GAVENONIS, MD, J A CURRIVAN, E F CONANT, MD, M D SCHNALL, MD, PhD and A D A MAIDMENT, PhD

Hospital of the University of Pennsylvania, Department of Radiology, 1 Silverstein, 3400 Spruce Street, Philadelphia, PA 19104, USA

ABSTRACT. Contrast-enhanced digital breast tomosynthesis (CE-DBT) is a novel modality for imaging breast lesion morphology and vascularity. The purpose of this study is to assess the feasibility of dual-energy subtraction as a technique for CE-DBT (a temporal subtraction CE-DBT technique has been described previously). As CE-DBT evolves, exploration of alternate image acquisition techniques will contribute to its optimisation. Evaluation of dual-energy CE-DBT was conducted with IRB approval from our institution and in compliance with federal HIPAA guidelines. A 55-year old patient with a known malignancy in the right breast underwent imaging with MRI and CE-DBT. CE-DBT was performed in the medial lateral oblique view with a DBT system, which was modified under IRB approval to allow high-energy image acquisition with a 0.25 mm Cu filter. Image acquisition occurred via both temporal and dual-energy subtraction CE-DBT. Between the pre- and post-contrast DBT image sets, a single bolus of iodinated contrast agent (1.0 ml kg^{-1}) was administered, followed by a 60 ml saline flush. The contrast agent and saline were administered manually at a rate of \sim 2 ml s^{-1}. Images were reconstructed using filtered-back projection and transmitted to a clinical PACS workstation. Dual-energy CE-DBT was shown to be clinically feasible. In our index case, the dual-energy technique was able to provide morphology and kinetic information about the known malignancy. This information was qualitatively concordant with that of CE-MRI. Compared with the temporal subtraction CE-DBT technique, dual-energy CE-DBT appears less susceptible to motion artefacts.
DE-DBT: Patient 1

- **Age:** 55
- **Diagnosis:** Invasive ductal carcinoma
- **Sign:** mass in axillary tail region
Dual Energy Imaging

• Subtraction of images increases noise, and does not alter intrinsic subject contrast
• However, subtraction reduces background structure, increasing conspicuity of residual signals
• Dual energy imaging is sensitive to scatter and beam hardening
• Subtraction works best for “large” objects where the residual signals and noise are distinguishable.
Iodine HE Stepwedge Images

Not corrected

Corrected
Iodine SI

Not corrected

Corrected

$S_{LE}$

$I_{LE}$
Iodine HE Stepwedge Images

Proj images, angle 1, W/Cu, 49 kV, 100mAs – w/Sn, 45kV, 100 mAs
Total Thickness: 25 mm iodine phantom + 40 mm stepwedge
Quantification of Glandularity and Iodine uptake

Corrected
Energy Subtraction

• Advantages:
  • Motion artifacts are rare

• Disadvantages:
  • System modifications are necessary to allow rapid change of filter material and kVp
  • Detector must be suited to rapid readout
  • Poorer separation of tissue and contrast agent
  • Beam hardening artifacts
Molecular Imaging

• Molecular Imaging in a broad sense implies visualizing normal and abnormal cellular functions by utilizing either biochemical or pharmacological probes.

• Ideally, the imaging technique should not perturb the function which is being assessed.
Molecular Imaging

- Molecular Imaging in a broad sense implies visualizing normal and abnormal cellular functions by utilizing either biochemical or pharmacological probes.

- Ideally, the imaging technique should not perturb the function which is being assessed.
## Molecular imaging in intact species: methods and agents

<table>
<thead>
<tr>
<th>Modality</th>
<th>Agents</th>
<th>H</th>
<th>R</th>
<th>Primary uses</th>
<th>Examples</th>
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<tr>
<td><strong>Optical</strong></td>
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<td>FMT</td>
<td>fluorescent proteins</td>
<td>X</td>
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<td>gene expression, tagging superficial structures</td>
<td>GFP, RFP, NIRF probes</td>
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<td>X</td>
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<td>SPECT</td>
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<td>X</td>
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<td>site-selectivity, gene expression, drug dev’mnt</td>
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<td>NAA, Cr, Cho, Glx, ml, $^{31}$P</td>
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<td>Contrast agents</td>
<td>Gd, Mn, FeO</td>
<td>X</td>
<td></td>
<td>cell trafficking, enzymatic activation</td>
<td>poly-L-lysine, dendrimers, MION</td>
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<td>contrast agents</td>
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<td>X</td>
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<td>Cancer</td>
<td>Gold Nanoparticles</td>
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<tr>
<td><strong>Ultrasound</strong></td>
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<td></td>
<td></td>
<td>drug-delivery, gene transfection</td>
<td>human albumin (Optison)</td>
</tr>
</tbody>
</table>

H=human, R=rodent
Nanoparticles are small polymeric colloidal particles with a therapeutic and/or imaging agent(s) either dispersed in polymer matrix or encapsulated in polymer.

Liposome-encapsulated iodine

Karathanasis, et al., Radiology 250(2), 398, 2009
Tumors are targeted *passively* by virtue of the leaky tumor vasculature and *actively* by high affinity binding of NP-antibody conjugates to tumor antigens.
At mammographic energies, ten 100nm gold nanoparticles/cell will result in 5% subject contrast.
Summary

• Contrast-enhanced digital breast tomosynthesis is possible using either temporal subtraction or energy subtraction.
• Early clinical results indicate that CE DBT gives clinical results which are concordant with MRI.
• Technical challenges still exist before CE DBT will be widely available.