Contrast-Enhanced Digital Mammography

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Outline

• History
• Technique
• Literature Review / Cases
• Clinical Status
Spoiler: CEDM is no longer new

- There are now (at least) two textbooks on CEM
So Why CEDM?

Mammography

• Inexpensive, fast
• But…
  – Only about 75% sensitive
    • ~60% in dense breasts; 90% in fatty breasts

MRI

• Very high sensitivity
• But…
  – Expensive
  – Inconvenient – long, noisy, claustrophobic
Question: What makes MRI so good at showing cancers?

Answer: The contrast agent

- Despite 3-D capability and excellent contrast sensitivity, non-contrast MRI has not been shown to work for cancer detection

To get the best of both mammography and MRI…
Contrast-Enhanced Digital Mammography (CEDM, aka CESM, aka CEM)

• Hypothesis
  – By using intravenous iodinated contrast with digital mammography, occult cancers can be made visible

  – Rationale: Breast cancers have been shown to enhance on MRI and CT

(see our History chapter in Lobbes textbook)
CEDM - Hurdles

- Contrast resolution of digital mammography is far lower than CT and MRI
- Breast compression inhibits blood flow
CEDM – Subtraction Techniques

• Temporal Subtraction:
  \[ \text{post-contrast} - \text{pre-contrast} \]

• Dual-Energy Subtraction:
  \[ \text{high-energy} - k\times\text{low-energy} \]
Example: Temporal Subtraction


Courtesy M. Yaffe and R. Jong
Temporal Subtraction - Limitations

- Breast must be immobilized during contrast administration
  - Limited to one view of one breast
    - Bilateral exam requires 2nd injection
    - Only light compression can be used
      - Increases motion (misregistration), scatter
Dual-Energy Subtraction

• Images are acquired at two X-ray energies after contrast injection
  – Iodine absorbs high-energy beam better than low energy beam
  – Breast tissue absorbs low-energy beam better than high-energy beam
  – In practice, energies straddle the k-edge of iodine
  – Final image is weighted logarithmic subtraction (more or less)
Dual-Energy Subtraction

• Advantages
  – Image both breasts in multiple projections
  – Can image with full compression
  – Images obtained only seconds apart
    • Minimal misregistration
    • Improved morphology information

• Disadvantage
  – Weighted subtraction is imperfect (magnitude of effect depends on beam quality)
Dual-Energy k-edge Subtraction - Principle
Beam Shaping

• The difference in beam energy is achieved by changing the kVp (e.g., from 28 to 45) and by using different filtration (e.g., Rh or Ag vs Cu)
Example: Filtered Spectra on a Mo/Rh Mammo Unit

- Low-Energy Beam
- High-Energy Beam
- k-edge of Iodine
Example: Filtered Spectra on a W Mammo Unit
(28 kVp W/Rh ; 45 kVp W/Cu)
Original

Dual Energy Subtraction (no contrast agent)

Dual Energy Subtraction (with contrast agent)
Early Dual Energy Papers

  • 26 subjects (13 cancers)
  • All cancers enhanced

  • 25 lesions (14 cancers)
  • All cancers enhanced
DE CEDM vs Mammo

  - 120, 110 subjects (80, 148 cancers)
  - CEDM > mammo and mammo+U/S by ROC

- Cheung, et al. (Eur Radiol 2014)
  - 89 subjects (72 cancers)
  - CEDM > mammo in both sensitivity (92.7 vs 71.5) and specificity (67.9 vs 51.8)

- + Several more
Not surprising it is better than mammo. Is it as good as MRI?
Two-View Film Mammogram

(wire on excisional biopsy scar)
Sagittal Post-contrast MRI

Lateral ...

... to Medial
Post-Contrast Dual-Energy Digital Subtraction Mammography
CEM vs MRI: Selected Literature

- Fallenberg, *et al.* *Eur Radiol* 2014;24:256-64.
  - Bilateral CEDM, MRI, mammo
  - 80 subjects with new CA at 1 site
  - CEDM > MRI sensitivity for index lesion (100% vs. 97%)
    - 80/80 vs 77/79
CEM vs MRI: Literature (cont.)

  - Bilateral CEDM vs MRI
  - 52 subjects with new cancer
  - CEDM = MRI sensitivity for index lesion (96%)
    - 50/52
  - MRI > CEDM in detection rate for additional foci
    - 22/25 (88%) vs 14/25 (56%)
  - CEDM had fewer false positives than MRI
    - 2 vs 13
CEM vs MRI: Literature (cont.)

  – Mammo, DBT, CEM, CE Tomo, MRI
  – 81 cancers; 144 benign lesions; 3 readers
  – ROC analysis – no difference between CEM, CET, MRI
    • all 3 better than unenhanced DM, DBT
  – Sensitivities: 93-98% for CEM; 86%-93% for MRI
CEM vs MRI: Literature (cont.)

- 102 patients with suspicious mammographic lesions
- 118 lesions identified
  - 81 malignant (37 benign)
    - 72 invasive / 9 in situ
- Sensitivity 100% for CEM vs 93% for MRI
- Accuracy 79% for CEM vs 73% for MRI
  - ROC using BIRADS: .83 vs .84
## Selected Studies of CEDM vs MRI

<table>
<thead>
<tr>
<th>Study</th>
<th># of subjects/lesions</th>
<th>Primary Outcome</th>
<th>Result: CEDM vs MRI</th>
<th>Statistical Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fallenberg, et al.</td>
<td>80</td>
<td>Sensitivity</td>
<td>100% vs 98%</td>
<td>No difference</td>
</tr>
<tr>
<td>Jochelson, et al.</td>
<td>52</td>
<td>Sensitivity</td>
<td>96% vs 96%</td>
<td>No difference</td>
</tr>
<tr>
<td>Chou, et al.</td>
<td>185</td>
<td>Accuracy (AUC)</td>
<td>0.878 vs 0.897</td>
<td>No difference</td>
</tr>
<tr>
<td>Li L, et al.</td>
<td>48</td>
<td>Sensitivity</td>
<td>100% vs 100%</td>
<td>No difference</td>
</tr>
<tr>
<td>Luczynska et al, 2015</td>
<td>102/118</td>
<td>Sensitivity</td>
<td>100% vs 93% 79% vs 73%</td>
<td>Statistically significant No difference</td>
</tr>
</tbody>
</table>

Selected Papers – Diagnostic Use

• **Work-up after abnormal screening**

• **Background Parenchymal Enhancement**

• **Response to neoadjuvant chemotherapy**

• **Patient preference for CEM**
CEDM for Screening

• Potentially the most important application
  – Life-saving
  – Realize the cost-advantages
  – Probably not for average risk, but maybe
    • Risk of contrast and cost outweighed by benefit of higher sensitivity?
  – Well accepted by patients / fast
Only 2 Published Studies:

1. Sloan Kettering (USA):
   - 307 high risk patients
   - Each subject received both CEDM and MRI
   - Only 3 cancers: 2 invasive lobular CA’s found by both CEDM and MRI and 1 DCIS found by MRI
   - Why the low yield? Many of the subjects had been screened by MRI the previous year

Jochelson M, et al. (12 authors total) EJR 2017;97: (37-43)
2. Tel Aviv University (Israel):

- 611 intermediate risk patients with dense breasts
- Each subject had mammography and CEDM
- 21 Cancers
  - Mammography found 11/21 (52%)
  - CEDM found 19/21 (91%) (2 interval cancers)
  - Specificity better for mammography: 91% vs 76%
  - PPV better for mammography: 16% vs 12%
Dual Energy CEDM Radiation Dose

• Taking dual energy images does not double the radiation dose
  – The high-energy image has less dose than the low-energy image.
  – The LE beam is equivalent to a standard mammogram, but can be taken at a lower dose if only the subtraction image is important.

  • e.g., you have an unenhanced mammo for seeing calcs
Dual Energy CEDM Radiation Dose (cont.)

• Literature shows variability – These papers both used the GE system:
  – Fallenberg, et al. European Radiology 2013:
    Avg dose of CEDM ~ FFDM (1.72 vs 1.75 mGy)
    Avg dose of CEDM > FFDM by 81% (2.80 vs 1.55 mGy)

Most of difference is in technique factors for the low energy image
Practical Aspects: How to do a CEM Procedure
Step 0. Get the Equipment

• Can upgrade newer GE or Hologic device
  – Add copper filter to filter wheel
  – Software modification

• If machine has capability to do both 2D and tomo under the same compression, can add a “non-contrast” tomo sequence to each view
  – Note: The tomosynthesis is performed after the contrast is in, but is single-energy, so the contrast is not visible
1. Contrast Agent Administration

- Standard non-ionic CT contrast agent
  - 300 mgI/ml or higher (300, 350, 370)
  - IV injection (forearm or antecubital)
  - 1.5 ml/kg body weight
  - 2.5 - 3 ml/sec via power injector

- Patient is seated during injection

- Wait 2 minutes post injection before starting to position patient
Why wait 2 minutes? (why not 90 seconds like for MRI?)

• Extra 30 seconds is primarily the extra time needed for contrast administration
  – For example:
    • MRI – 15 ml @ 2ml/sec = 8 s
    • CEDM – 100 ml @ 3ml/sec = 33 s
    • so 25 extra seconds

• With CEDM it is better to err on the side of being a little late rather than too early
  – First compression affects all subsequent images of that breast
  – Start positioning at 2 minutes so that compression occurs at about 10-15 seconds later
2. Dual Energy 2D Imaging

- Devices set exposure parameters automatically
- Two exposures are made in rapid sequence:
  1. Low kV (normal mammogram)
  2. High kV (~45-49 kV, Cu filter)
- MLO, CC views are performed in any order
- Repeat as desired (can add add’l views)
  - Imaging window ends after ~6-12 minutes due to contrast redistribution
3. After Imaging

• Remove the IV. Patient is done.

• Device automatically performs the subtraction and other processing.

• Low-energy (“non-contrast”) and subtracted images are available on the acquisition station and are sent to the review station.
Examples

Example cases from:

• John Lewin, MD, Rose Medical Center, Denver
• Chen-pin Chou, MD, Kaohsiung Veterans General Hospital, Taiwan
CEDM/CET Study Case 1: Unifocal IDCA
Case 1 -- Lessons...

- In some cases, CEDM shows spiculations and general morphology better than MRI.
- In our study (Hologic prototype) no measurable improvement in morphology depiction with CE Tomo.
- Non-con tomo is best for morphology, esp spiculations.
Case 2: Multifocal IDCA w/ add’l lesions
Case 2 – CC view

Mammo

CEDM

CET slice

(FA)
Case 2: MRI
Lessons...

- Benign masses that light up on MRI also light up on CEDM (e.g. FAs, LNs)

- Sometimes you see things better on CEDM and other times on CET
Same case -- CC Views

Mammo

CEDM
Case 3 -- Lessons…

- CEDM shows lesion extent similar to an MRI MIP
  - More helpful to surgical planning than was the 2D MRI slices (not shown)
CEDM/CET Case 4: multifocal IDCA

Screening mammo:

? architectural distortion

“very low suspicion”

U/S: mass
Case 4: Mammograms
Case 4: MRI
Case 4: CEDM

Pre-contrast DE sub

CEDM - MLO

CEDM - CC
Case 4: MRI
Case 4: Low Energy Tomo

Morphology on LE tomosynthesis greatly increases the probability of malignancy.
Case 4: Lessons…

• Low energy tomo images can add useful information on morphology – changing the assessment of the lesion
Example 5:
MRI

IDCA

Fibroadenoma
MRI

Time
Teaching Points

• Shape and margin are key for distinguishing benign from malignant enhancing lesions, but…

• When available, CEM kinetics appear to be analogous to MRI kinetics (as would be expected)
  – Kinetics more difficult to obtain in typical CEM exam than in MRI due to need for multiple separate acquisitions
CEDM – Clinical Implementation

• Two FDA and CE approved devices in clinical use worldwide
  – GE (2011)
  – Hologic (2012)

• Two additional companies with devices
  – Siemens, Philips

• Well over 100,000 CEDM examinations have been performed worldwide (no accurate count)
What is the FDA Approved Use?

• CEDM is approved as an adjunct to mammography and ultrasound when those studies are inconclusive
What is hindering adoption in the U.S.?

1. No billing code!
   - MRI is very profitable; CEDM is not.

2. Concerns about contrast reactions

3. Not “approved” for high-risk screening
   - Note that breast MRI is not labeled for that either
   - But MRI is covered by insurance and is accepted by the medical community

We need more screening data!
CEDM Guided Biopsy

• No major technical obstacles
• Combine existing upright stereo biopsy techniques with CEDM software/filter
• Companies have not felt the market is big enough to justify
• GE is supposedly close to announcing
• Current practice is to do MRI for CEDM-only findings
CEDM vs MRI

- **CEDM**
  - Lower cost
  - Easier on patient (noise, claustrophobia)
  - Faster
  - More specific (maybe)
  - Single exam for high risk screening (shows calcs)

- **MRI**
  - Includes all of breast and chest wall
  - Signal to noise for enhancement very good / more sensitive
  - ? Gad safer than iodinated contrast
  - No radiation
Where will CEDM/CET fit in?

• Possible indications:
  – Cancer Staging
  – High Risk Screening
  – Moderate Risk Screening

• Must compete against MRI, nuc med, unenhanced tomo
  – Cheaper, easier and faster than MRI
  – Faster than Nucs – no systemic radiation
  – Shows lesions that tomo misses
Opportunities for Physics Research

• Improved dual energy physics
  – Improved beam shaping
    • Novel anodes
    • Elements other than iodine (Zn, Gd)
  – Energy selective detectors
    • Hyperspectral imaging
    • Photon-counting
Opportunities for Physics Research

• Improved Image Processing
  – Iterative methods; A.I.–based methods?
    • Maximize lesion contrast
    • Decrease background contrast
    • Reduce inhomogeneity artifacts
    • Skin edge processing
    • Scatter reduction
Opportunities for Chemistry Research

- Even safer iodinated contrast agents
Summary

• CEDM has gone from research to clinical use
• Tons of literature (and 2 textbooks)
• Potential to reduce costs by decreasing MRIs
• Acceptance by breast surgeons, patients and rads
  – Contrast reactions have not been a factor, at least so far
• Still limited adoption, at least partly due to financial disincentives