AAPM Annual Meeting
7/17/19

Contrast-Enhanced Digital Mammography

John Lewin, M.D.
The Women's Imaging Center
Denver, Colorado

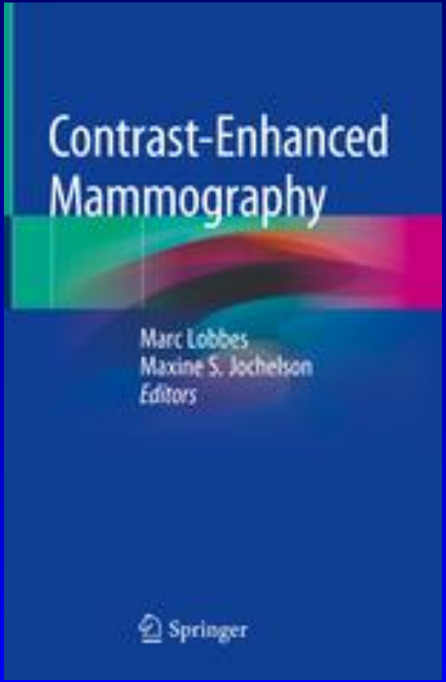
The Women's Imaging Center

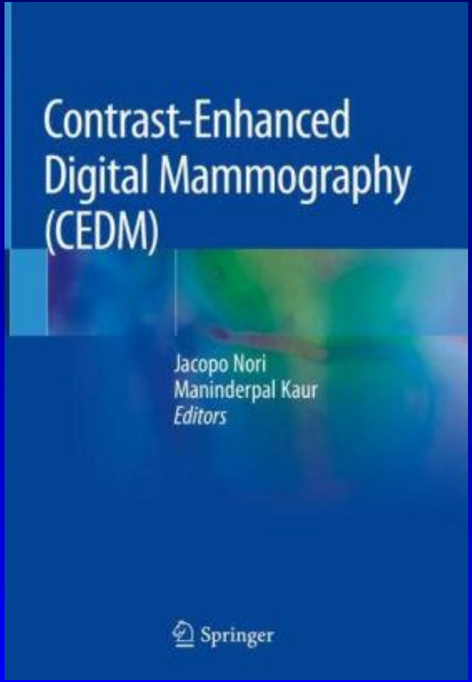
Outline

- 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

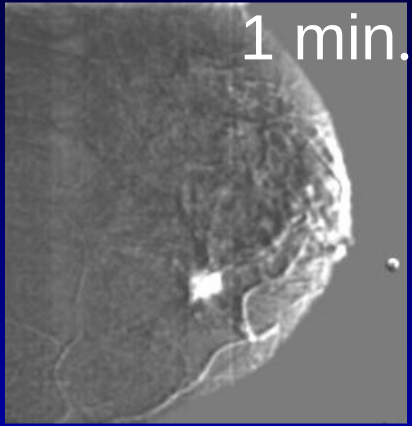
- Temporal Subtraction:

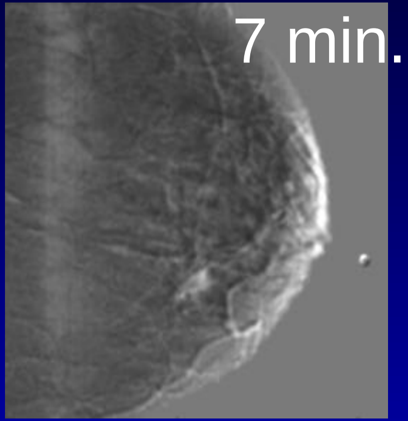
  post-contrast - pre-contrast

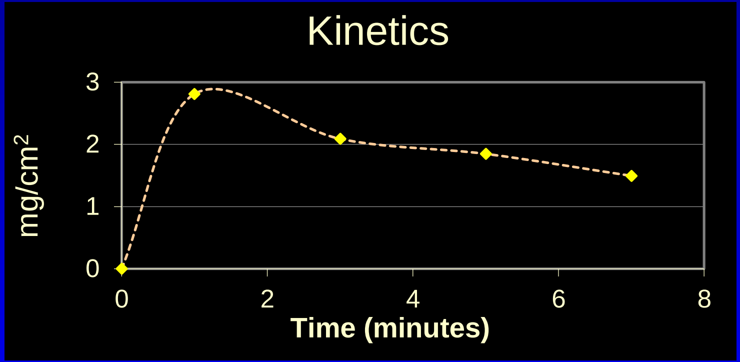
- Dual-Energy Subtraction:

  high-energy - k*low-energy

Example: Temporal Subtraction







Ref: Jong RA, et al. Radiology 2003;228:842-50

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

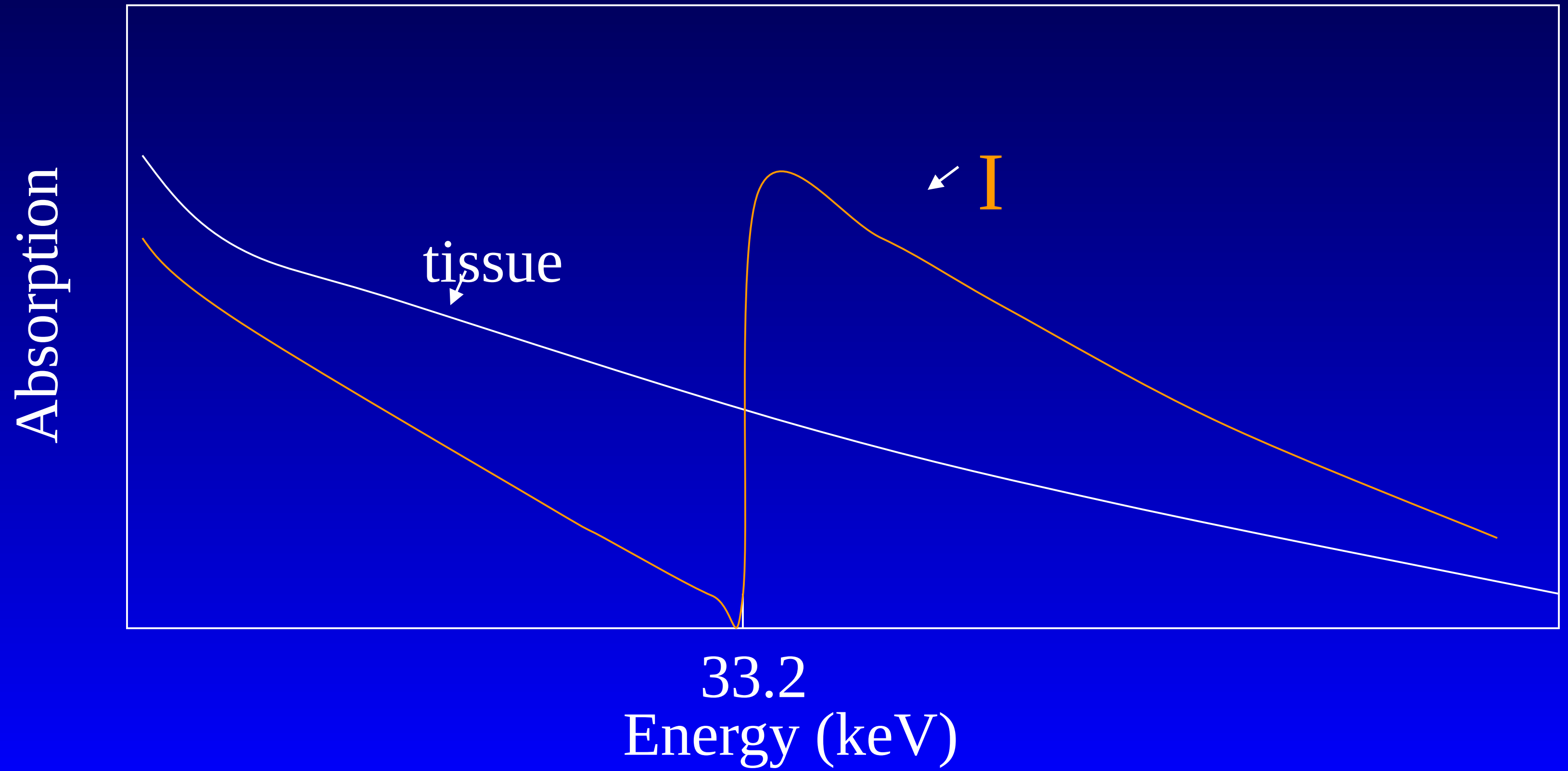
Dual-Energy Subtraction

- 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)

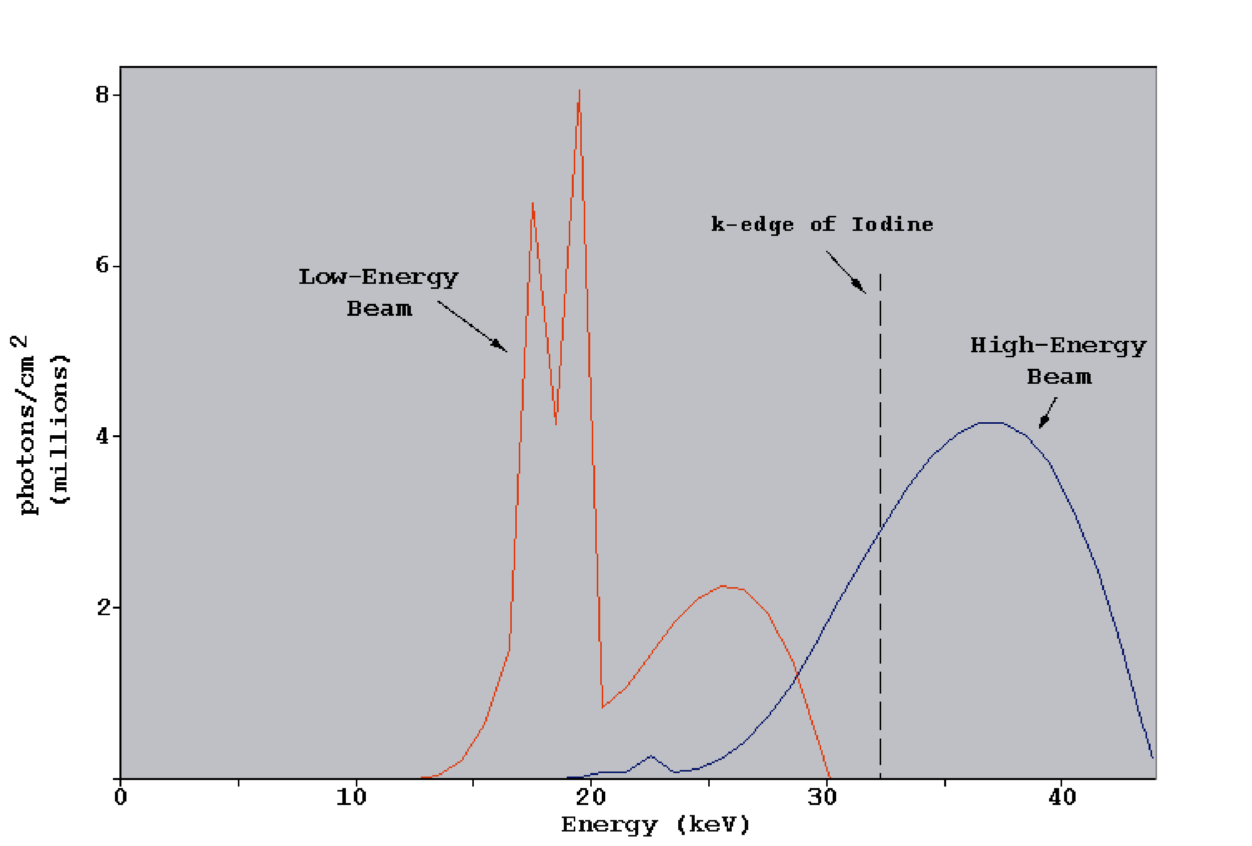
Dual-Energy k-edge Subtraction - Principle



Beam Shaping

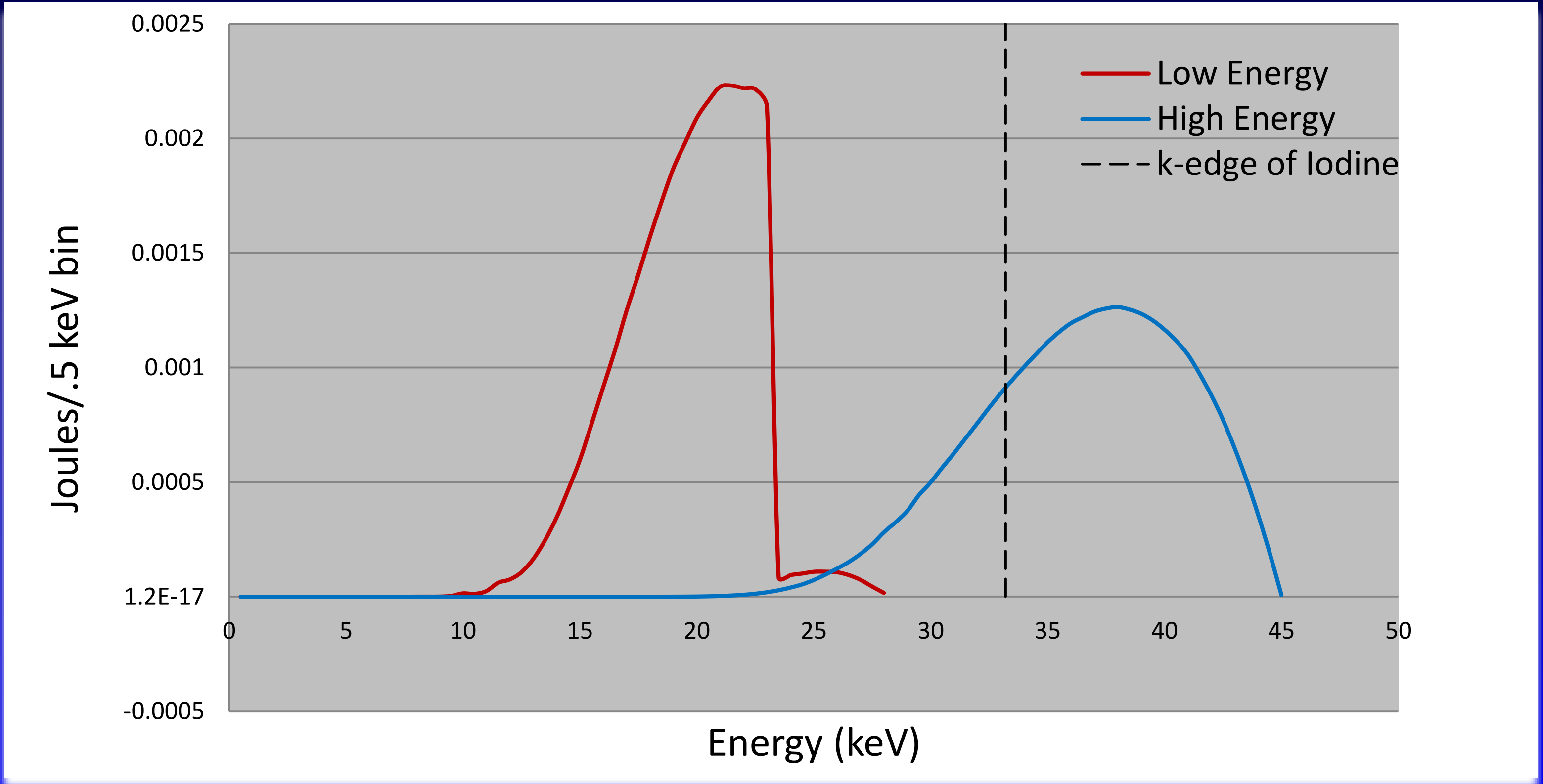
- The difference in beam energy is achieved by changing the kVp (e.g., from 28 to 45) and by using different filtration (e.g., Rh or Ag vs Cu)

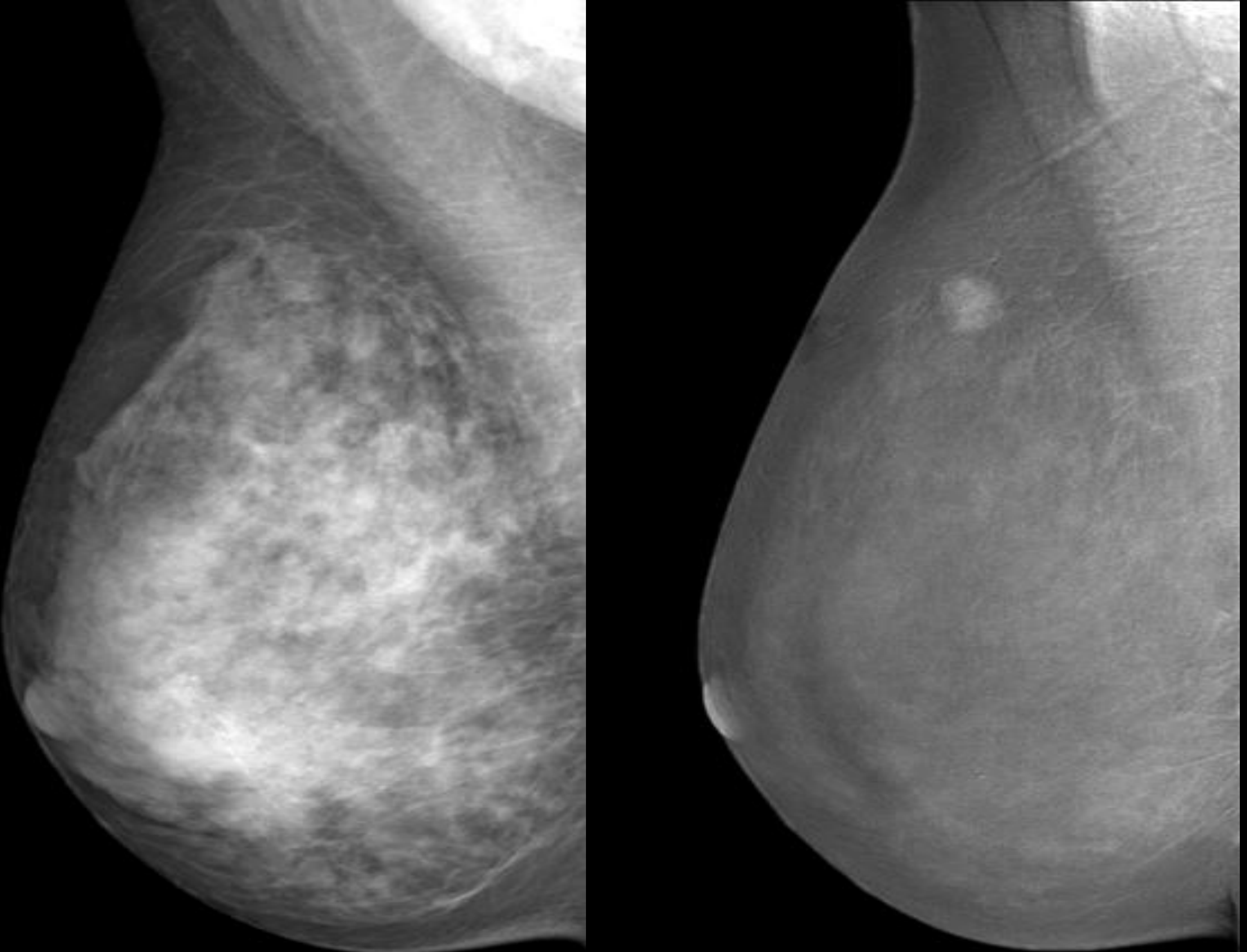
Example: Filtered Spectra on a Mo/Rh Mammo Unit

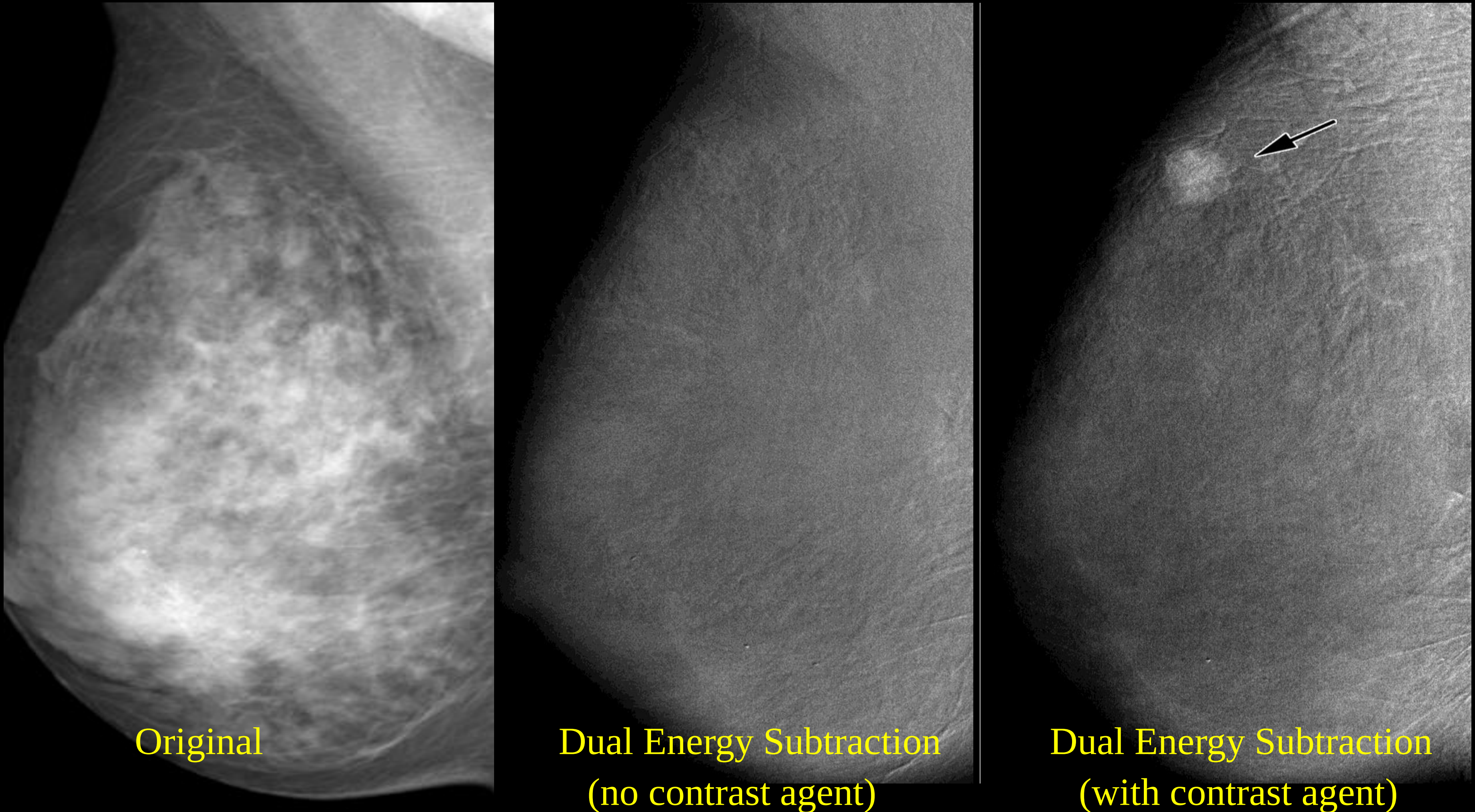


Example: Filtered Spectra on a W Mammo Unit

(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

- Lewin, et al (*Radiology* 2003)
  - 26 subjects (13 cancers)
  - All cancers enhanced
- Diekmann, et al (*Invest Radiol* 2005)
  - 25 lesions (14 cancers)
  - All cancers enhanced

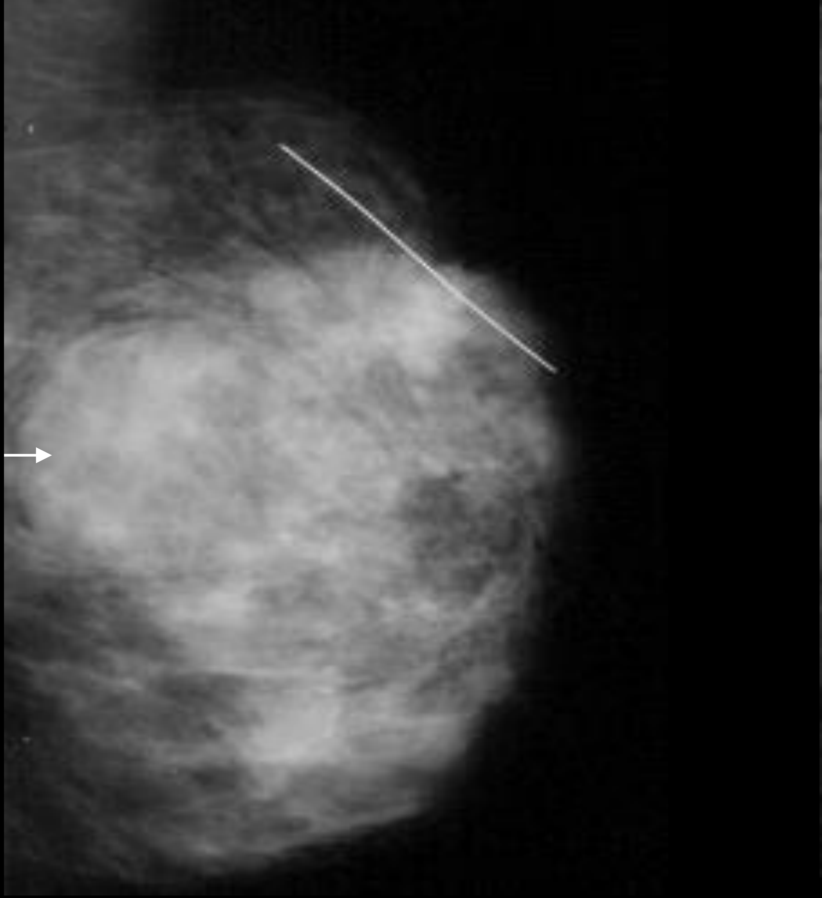
DE CEDM vs Mammo

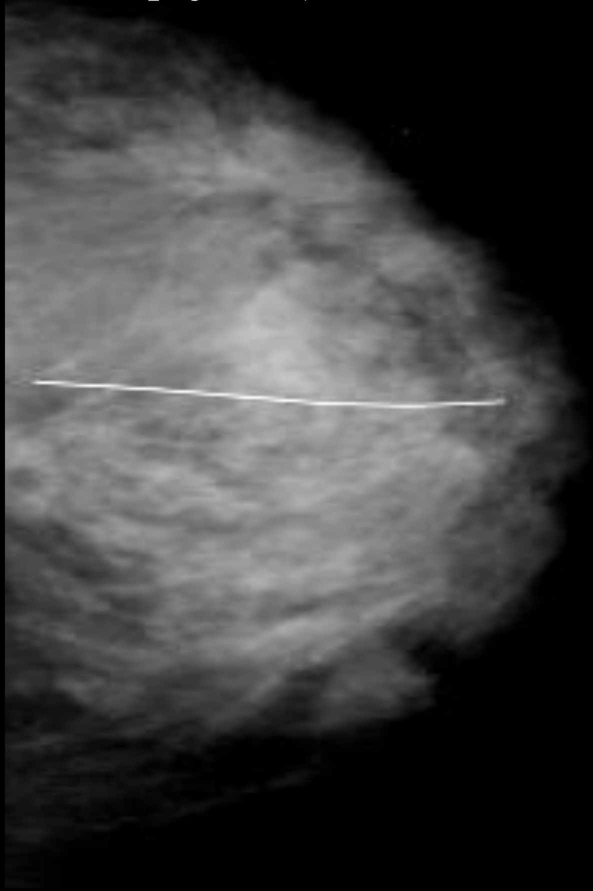
- Dromain, et al (*Eur Radiol* 2011, *Breast Cancer Res* 2012)
  - 120, 110 subjects (80, 148 cancers)
  - CEDM > mammo and mammo+U/S by ROC
- Cheung, et al. (*Eur Radiol* 2014)
  - 89 subjects (72 cancers)
  - CEDM > mammo in both sensitivity (92.7 vs 71.5) and specificity (67.9 vs 51.8)
- + Several more

Not surprising it is better than mammo. Is it as good as MRI?

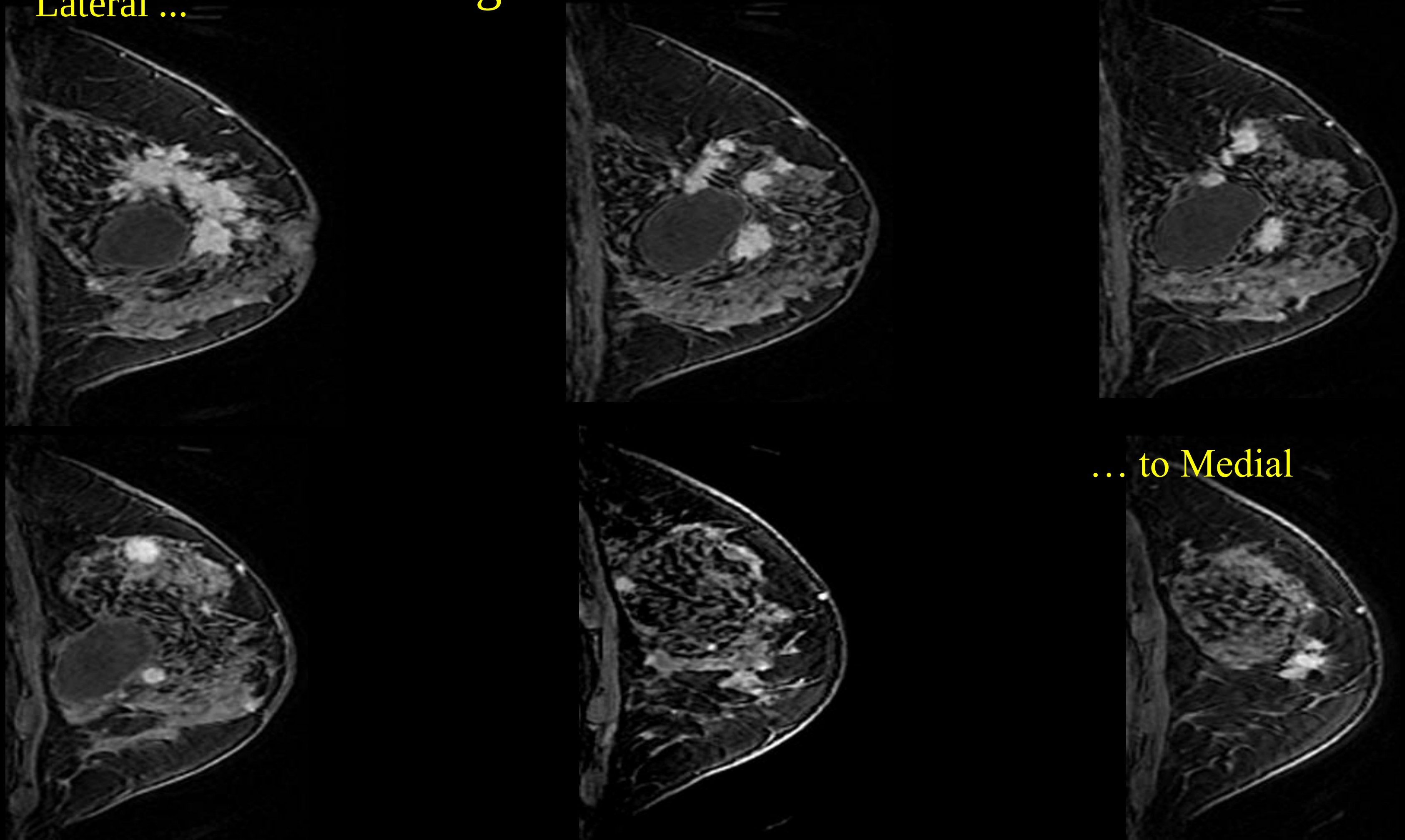
Two-View Film Mammogram

(wire on excisional biopsy scar)

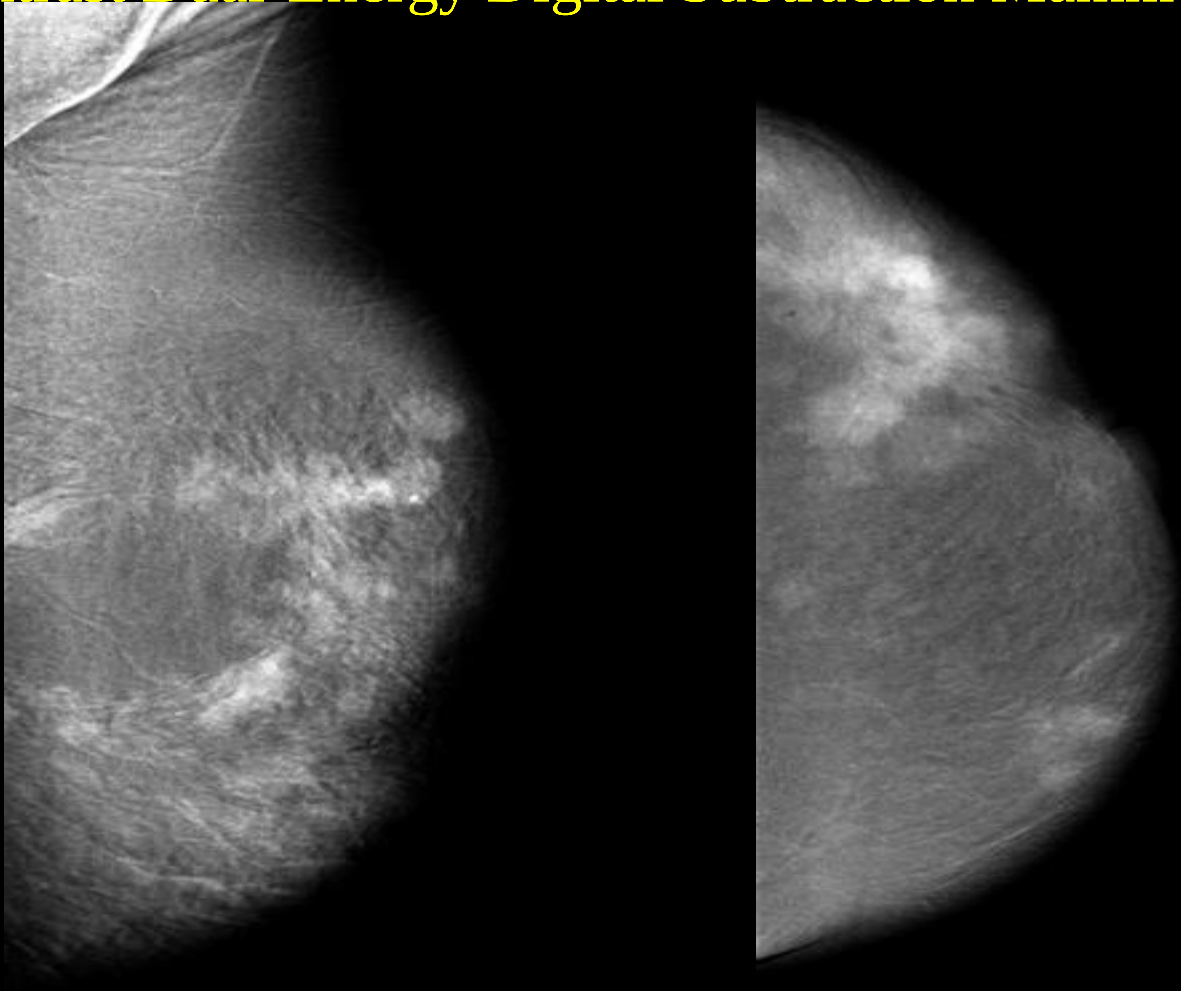




Sagittal Post-contrast MRI



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.)

- Jochelson, *et al*. *Radiology* 2013; 266:743-51
  - 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.)

- Chou, *et al*. *Eur J Radiol*. 2015; 84:2501-8.
  - 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.)

- Łuczyńska E, et al. *Med Sci Monit* 2015; 21:1358-67.
- 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

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

Fallenberg EM, Dromain C, Diekmann F, et al. *European radiology.* 2014;24(1):256-264.
Jochelson MS, Pinker K, Dershaw DD, et al. *European journal of radiology.* 2017;97:37-43.
Chou CP, Lewin JM, Chiang CL, et al. *European journal of radiology.* 2015;84(12):2501-2508
Li L, Roth R, Germaine P, et al. *Diagnostic and interventional imaging.* 2017;98(2):113-123.
Luczynska E, Heinze-Paluchowska S, Hendrick E, et al. *international medical journal of experimental and clinical research.* 2015;21:1358-1367.

Selected Papers – Diagnostic Use

- Work-up after abnormal screening
  - Houben, Lalji, Lobbes, et al (Maastricht) (*Eur J Radiol* 2016, 2017)
- Background Parenchymal Enhancement
  - Sogani, et al (Sloan Kettering) (*Radiol* 2017)
  - Savaridas, et al (Perth) (*Clin Radiol* 2017)
- Response to neoadjuvant chemotherapy
  - Barra, et al (Brasilia) (*Radiol Bras* 2017)
  - Iotti, et al (Reggio Emilia, Italy) (*Breast Cancer Res* 2017)
- Patient preference for CEM
  - Hobbs, et al (Perth) (*J Med Imaging Radiat Oncol* 2015)
  - Phillips, et al (Beth Israel Deaconess) (*Clin Imaging* 2017)

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 mammo and CEDM
- 21 Cancers
  - Mammography found 11/21 (52%)
  - CEDM found 19/21 (91%) (2 interval cancers)
  - Specificity better for mammo: 91% vs 76%
  - PPV better for mammo: 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)
  - Jeukens CR, *et al.* *Invest Radiol* 2014 :

    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 breas
  - 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.

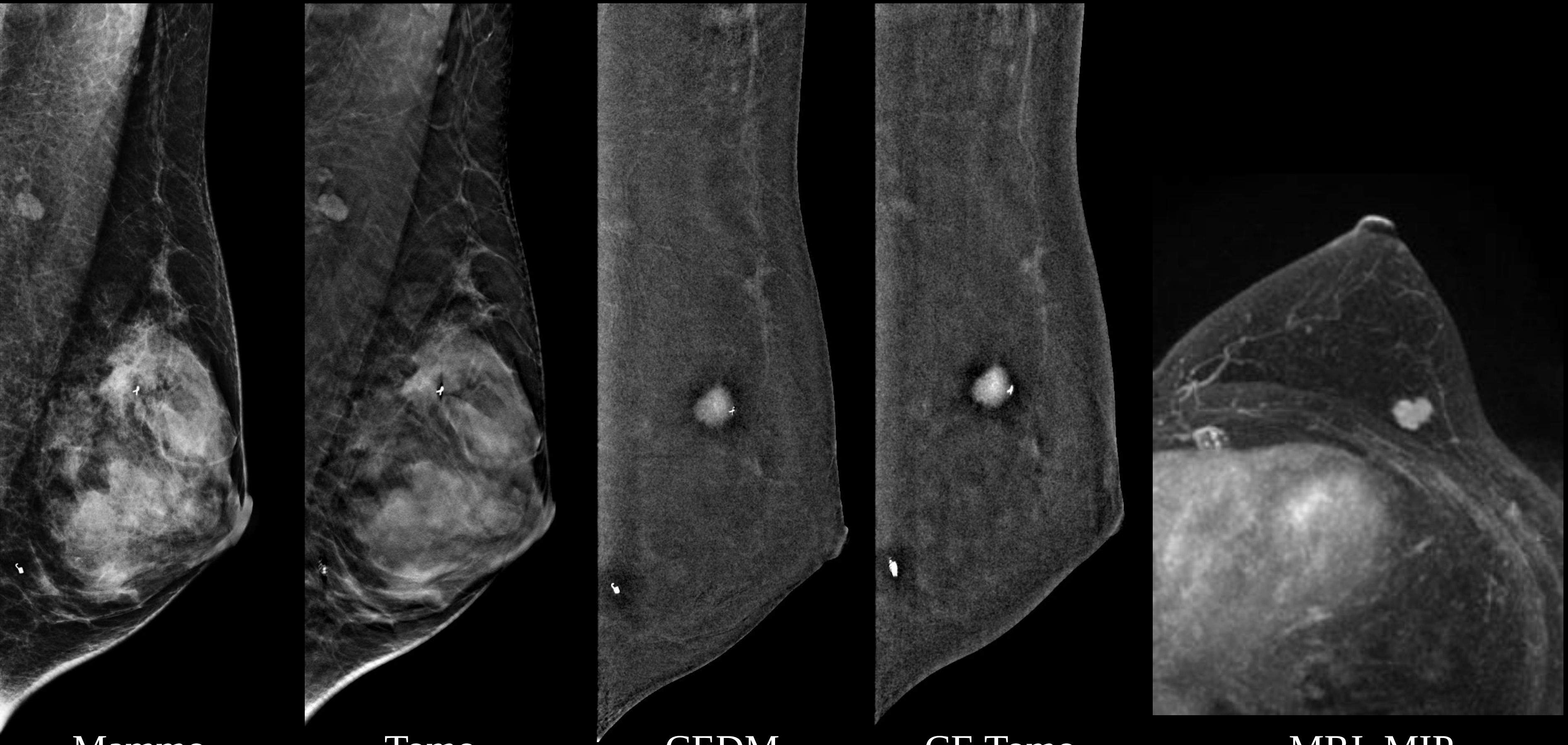
- Device automatically performs the subtraction and other processing.
- Low-energy (“non-contrast”) and subtracted images are available on the acquisition station and are sent to the review station.

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

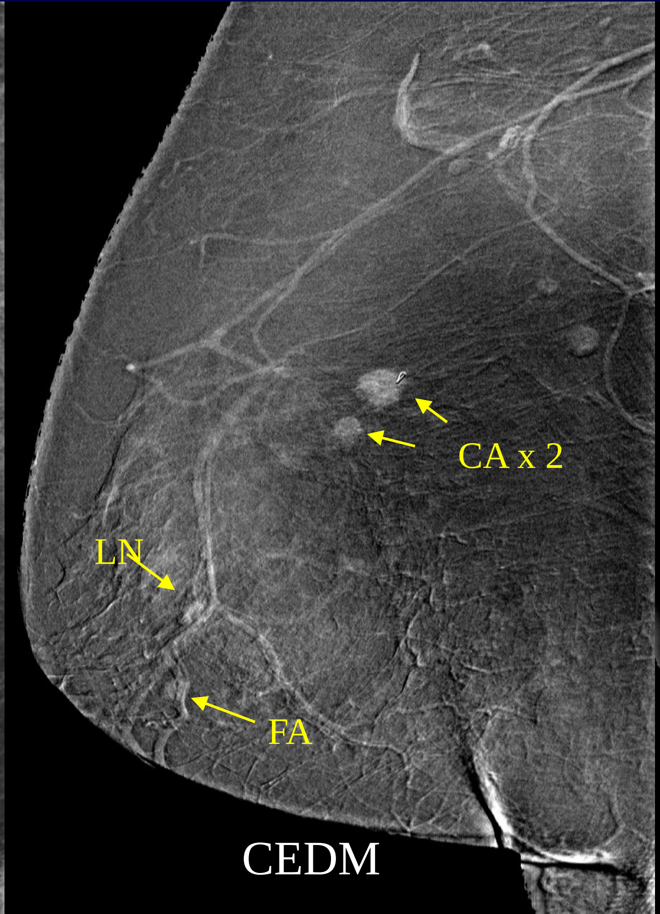


Mammo Tomo CEDM CE Tomo MRI MIP

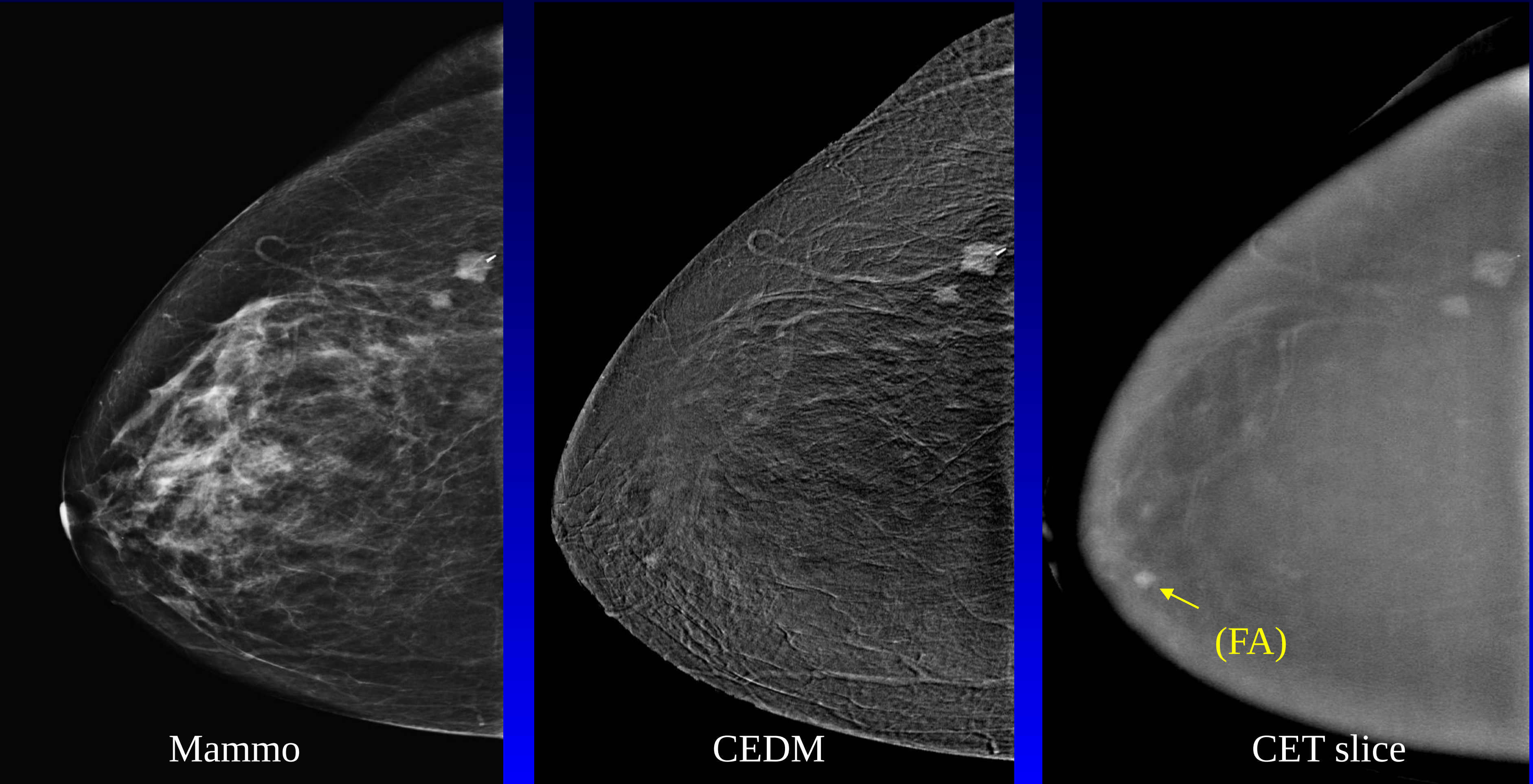
Case 1 -- Lessons…

- 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

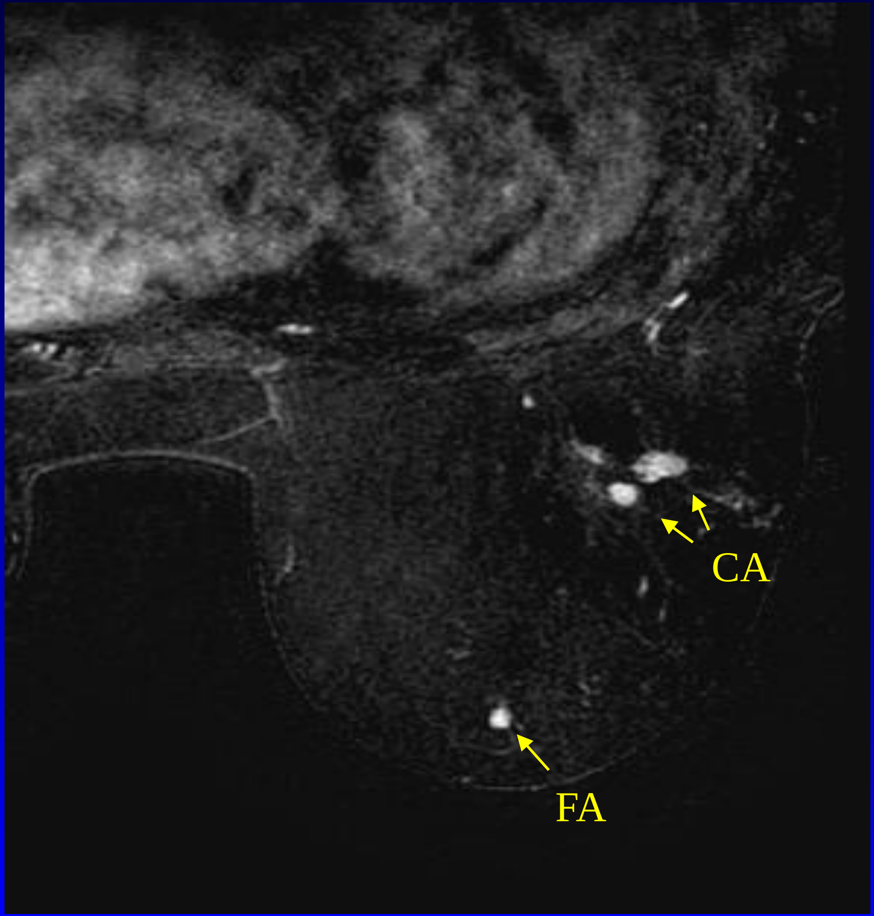
Case 2: Multifocal IDCA w/ add'l lesions



Case 2 – CC view



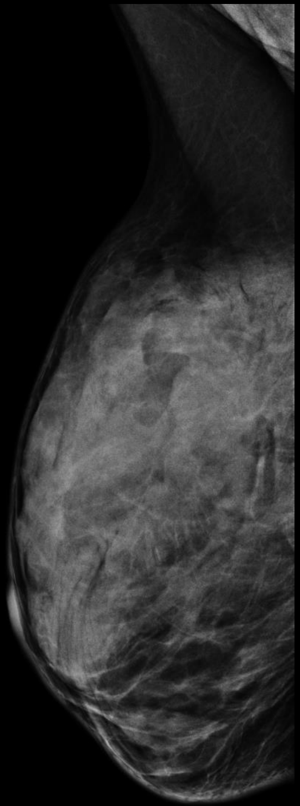
Case 2: MRI



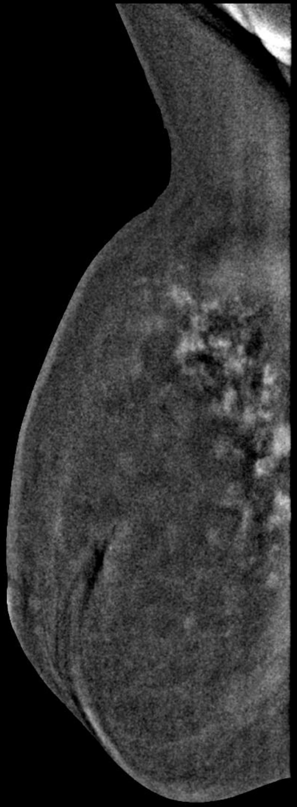
Lessons…

- 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

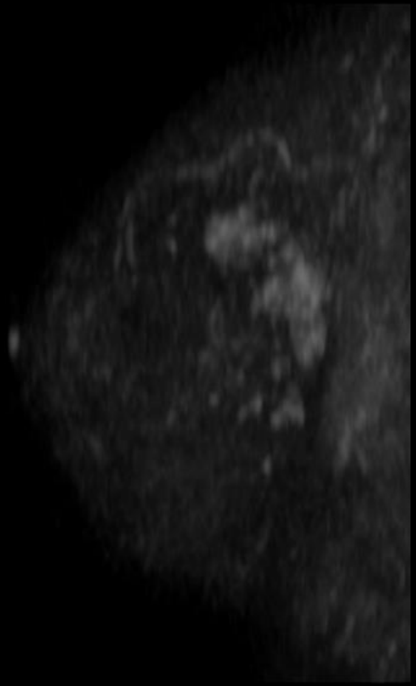
CEDM/CET Case 3: Invasive Lobular CA



Mammo

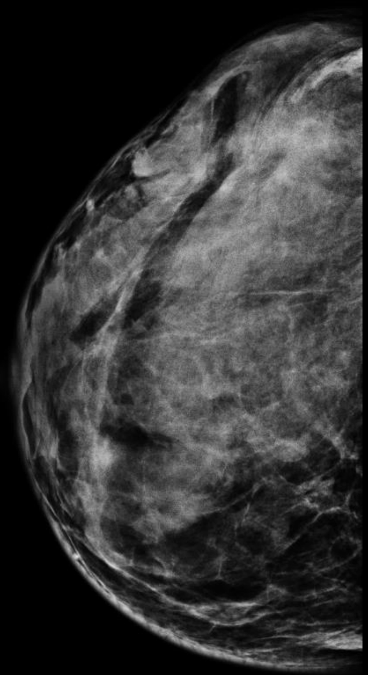


CEDM

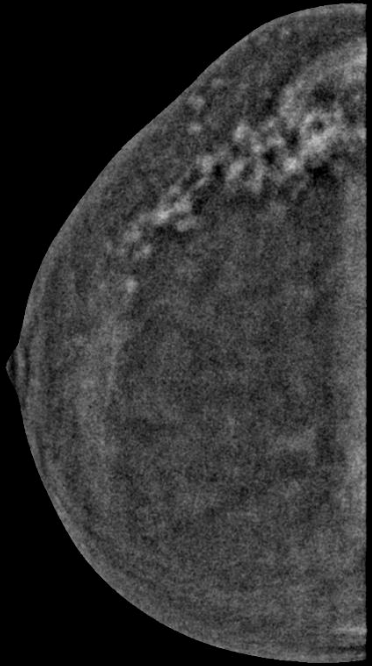


MRI MIP

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)

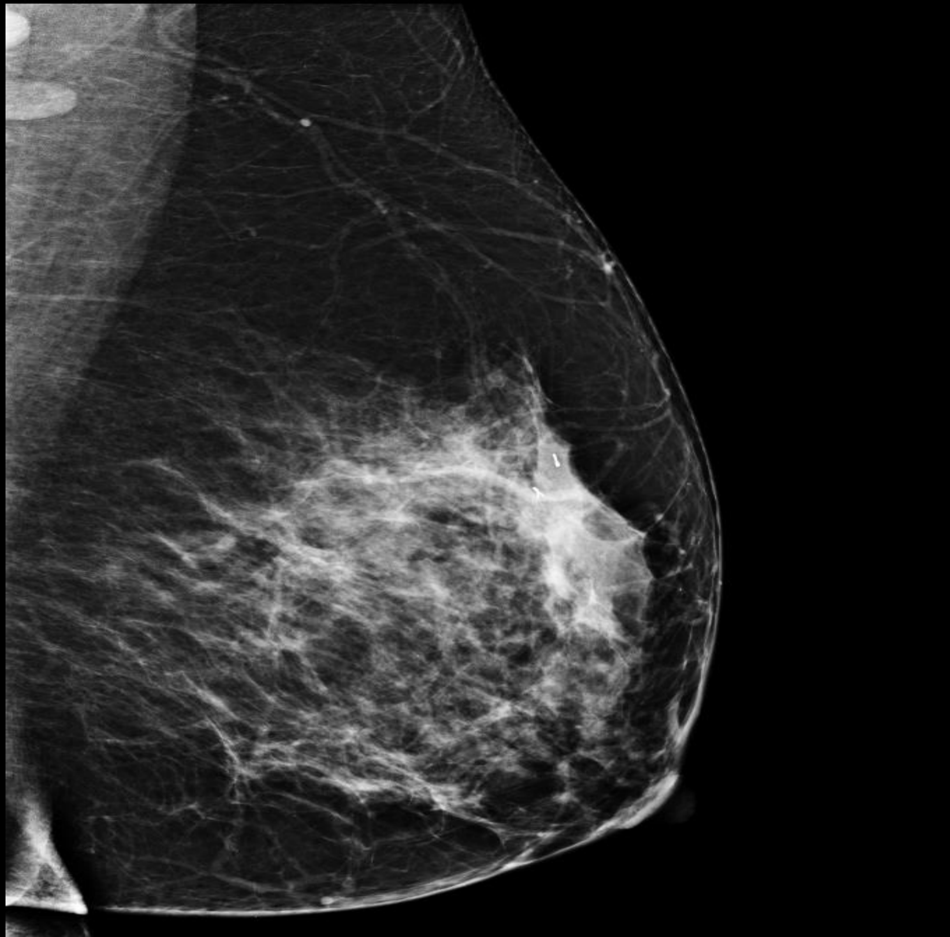
CEDM/CET Case 4: multifocal IDCA

Screening mammo:

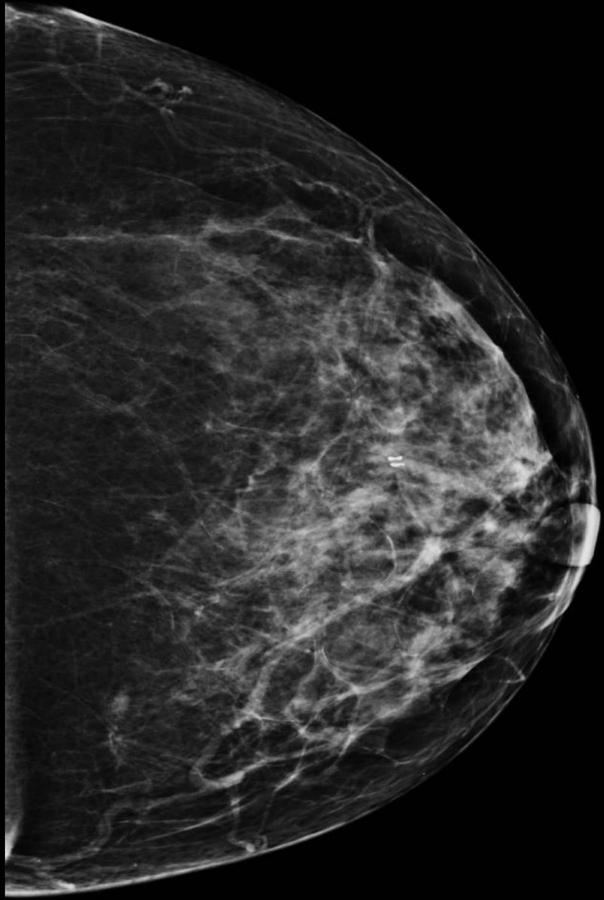
? architectural distortion

"very low suspicion"

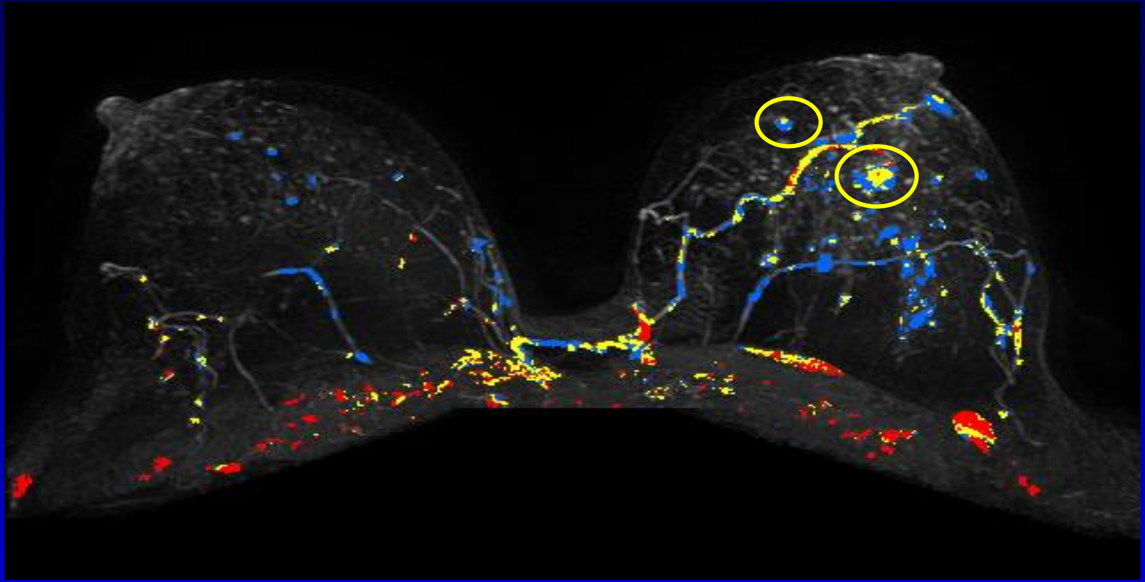
U/S: mass

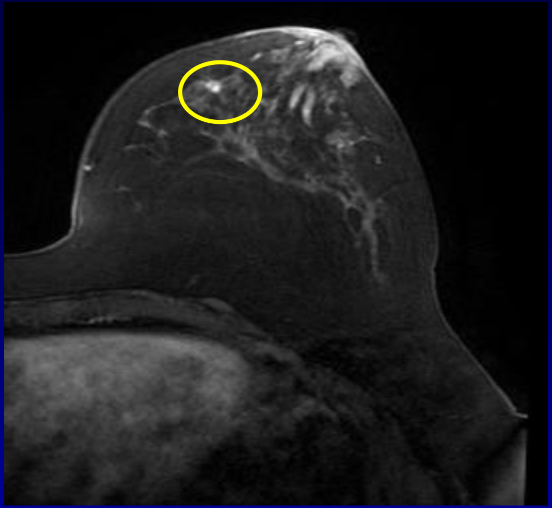


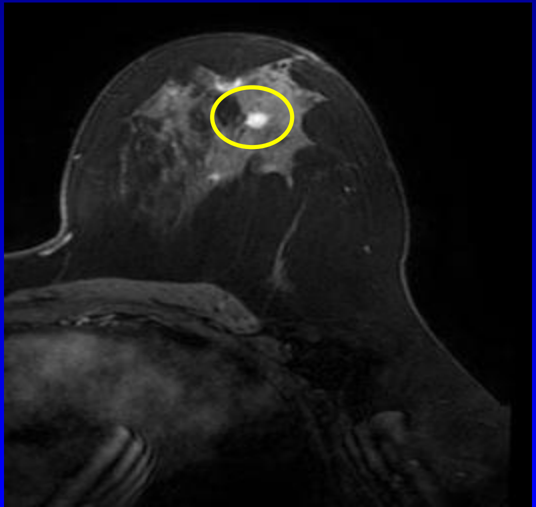
Case 4: Mammograms



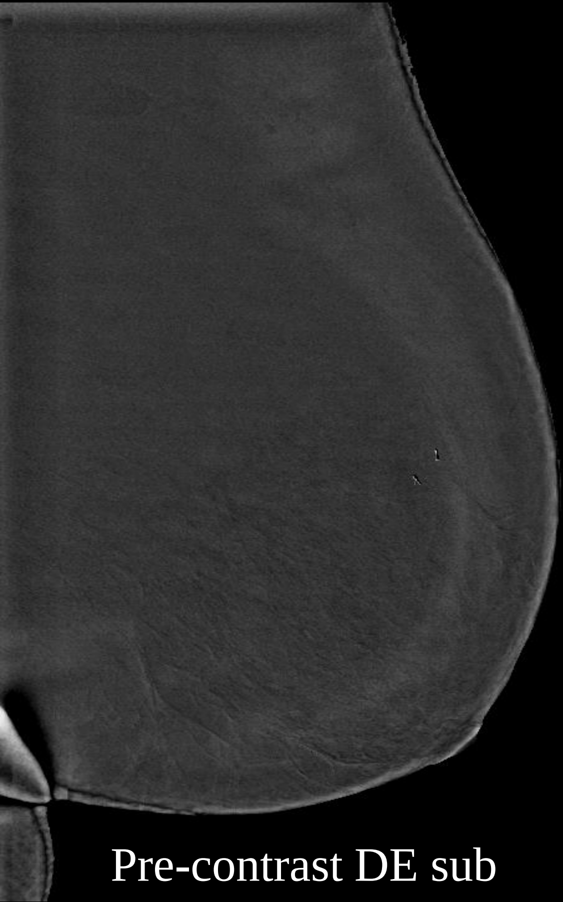
Case 4: MRI



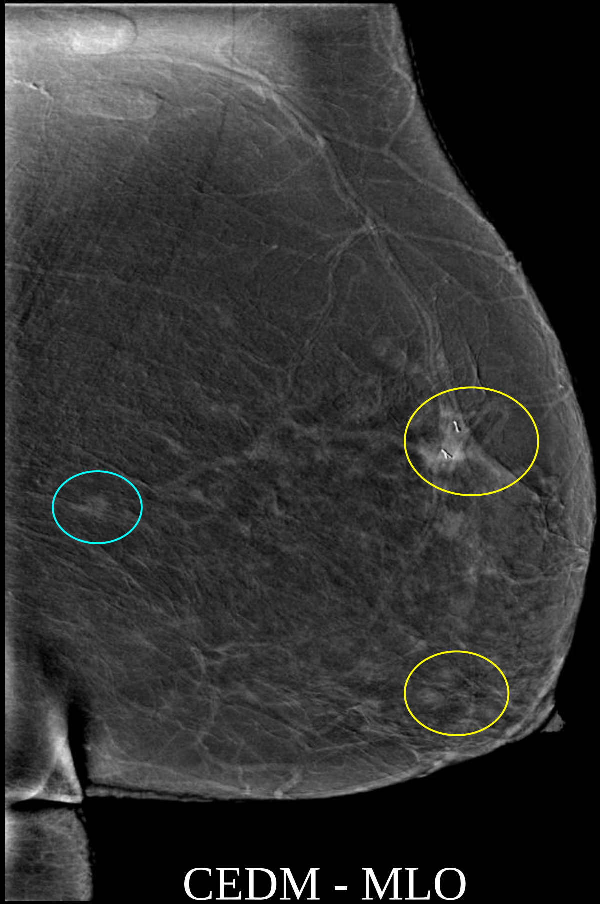




Case 4: CEDM



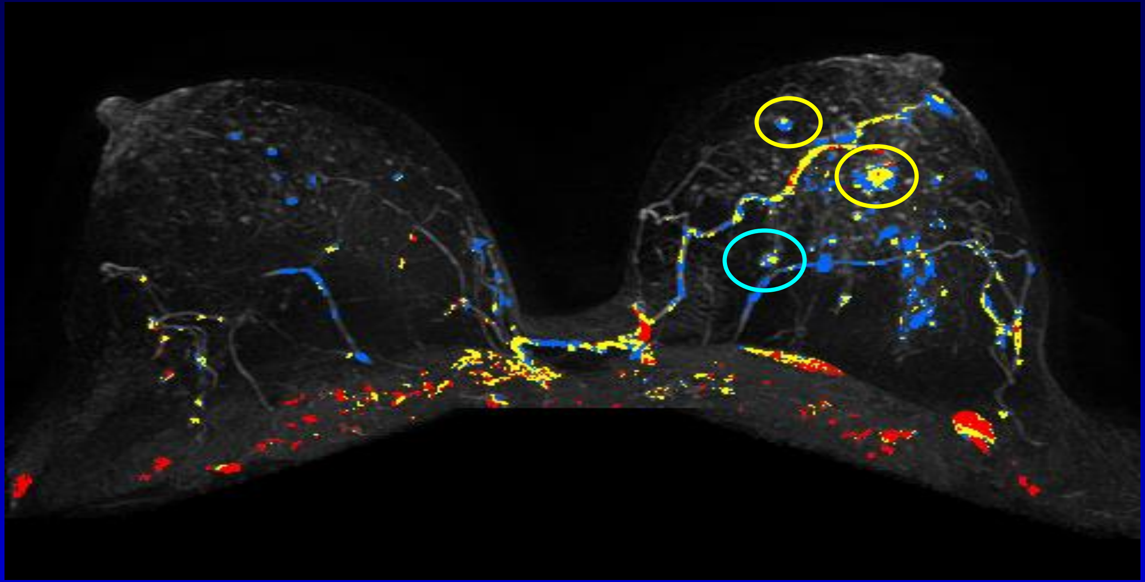
Pre-contrast DE sub

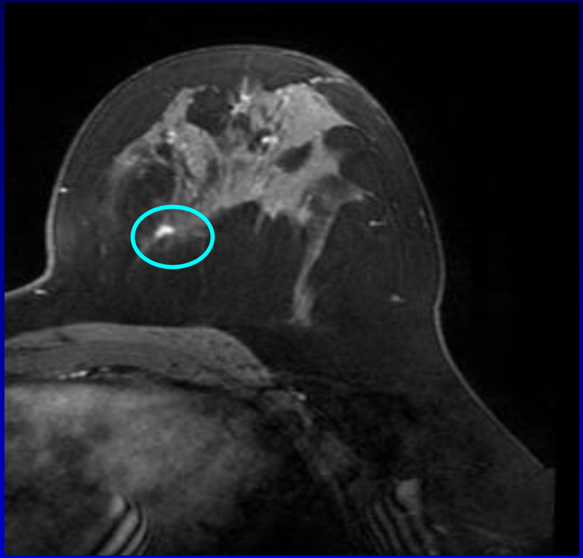


CEDM - MLO

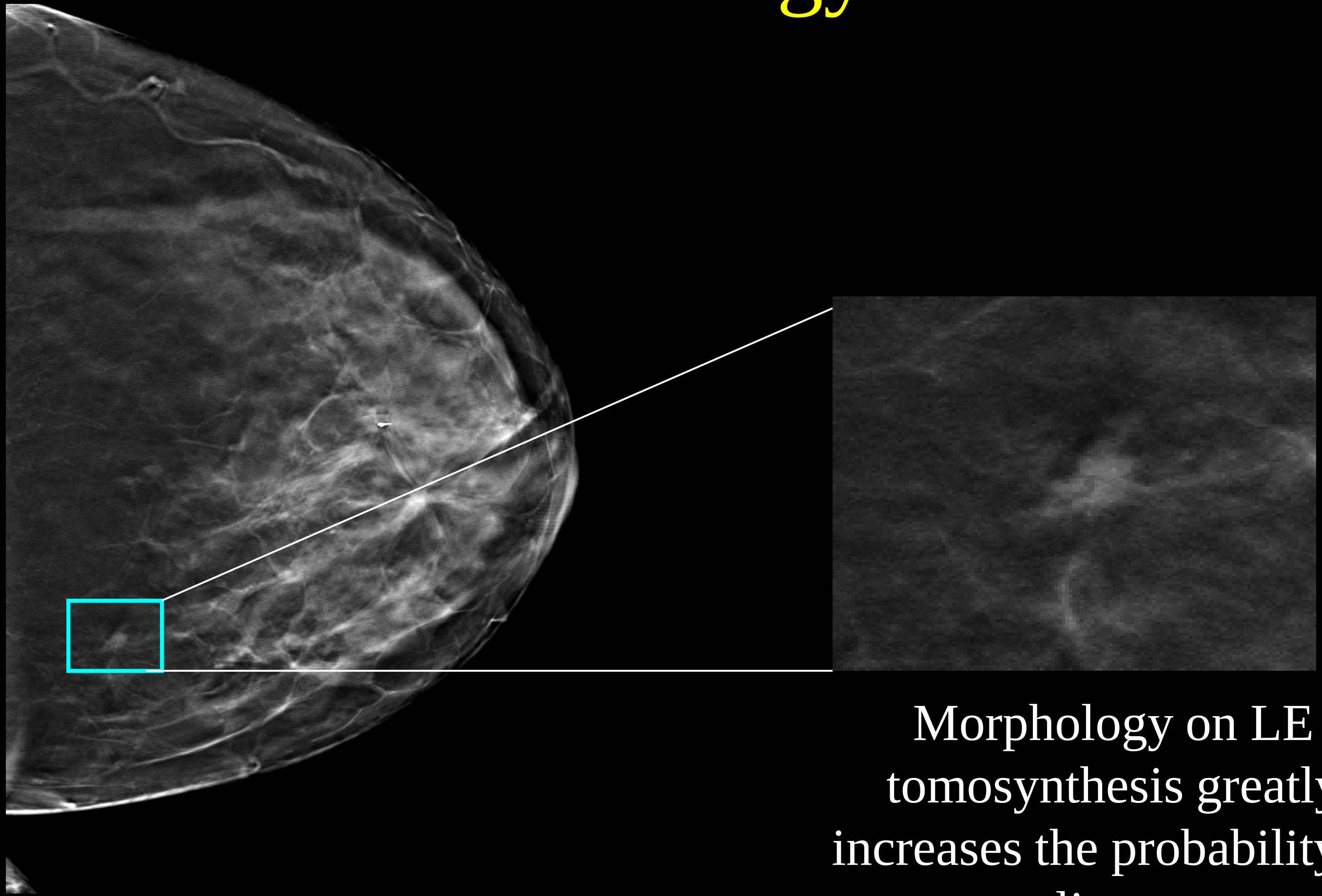
CEDM - CC

Case 4: MRI





Case 4: Low Energy Tomo

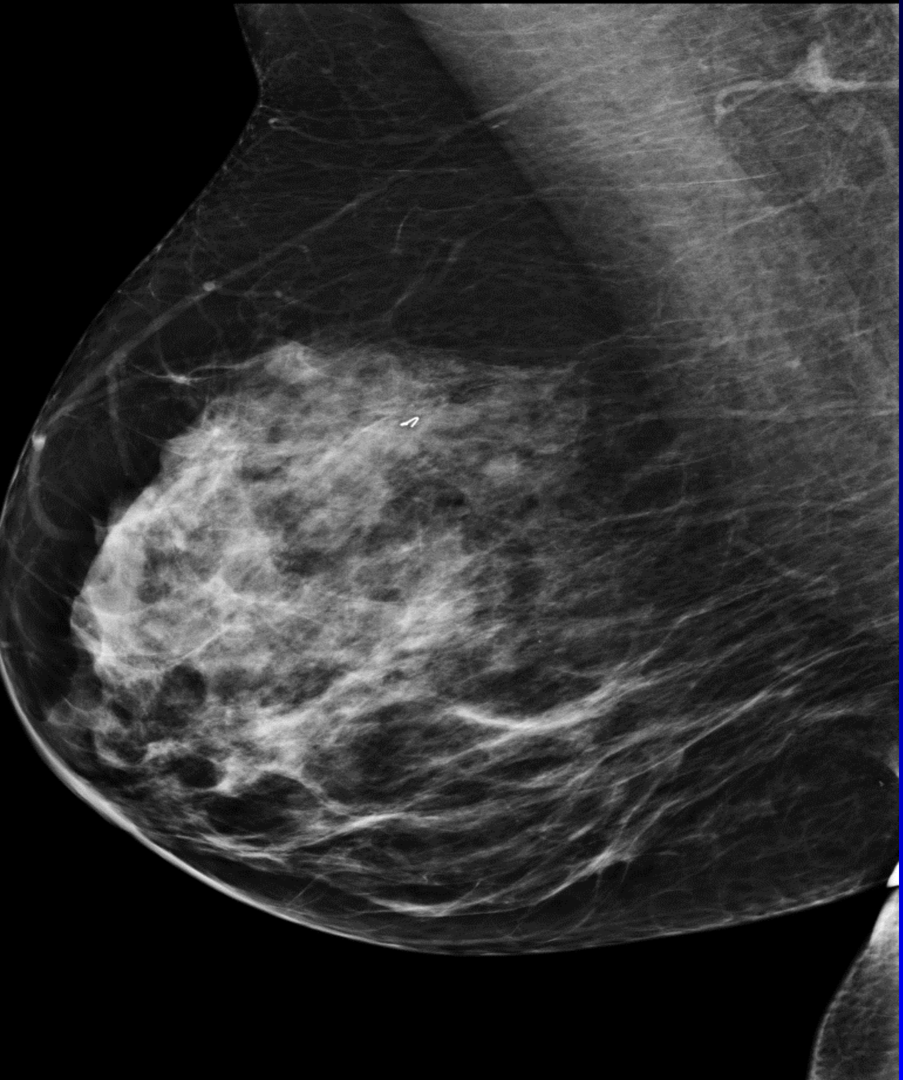
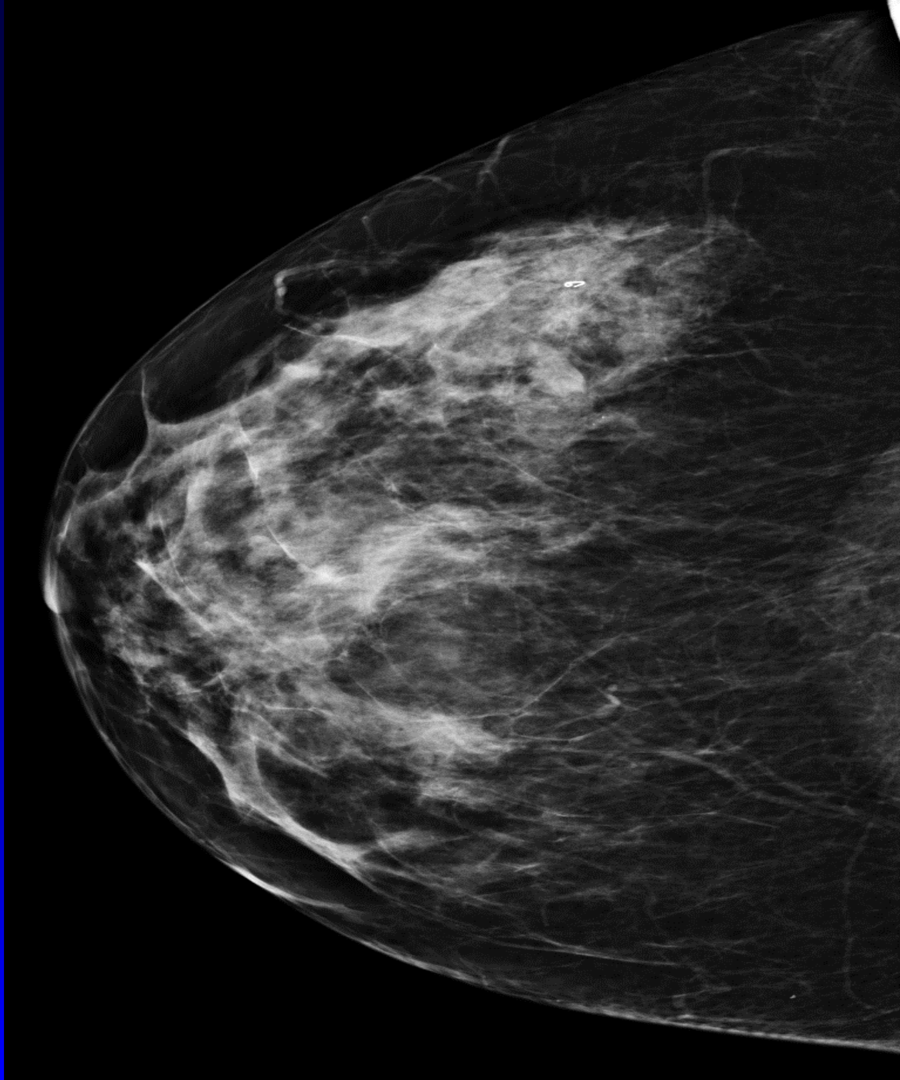


Morphology on LE tomosynthesis greatly increases the probability of malignancy

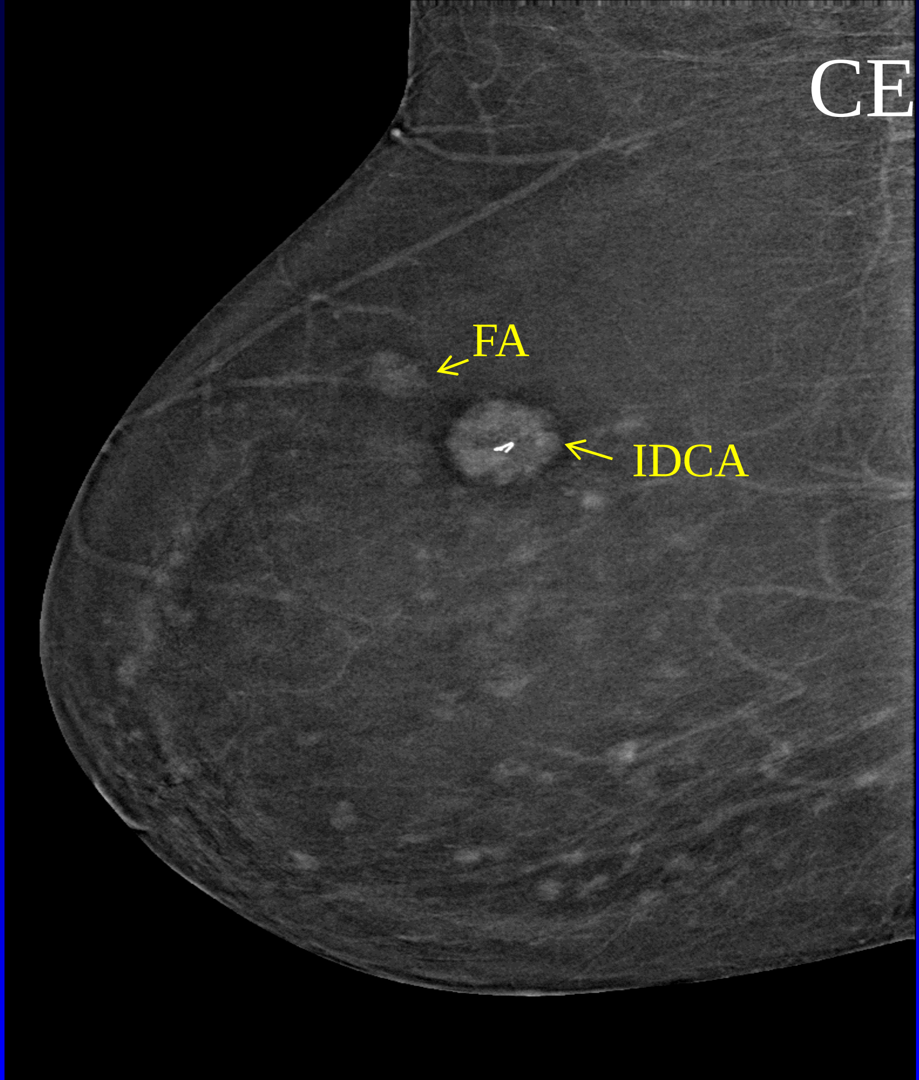
Case 4: Lessons…

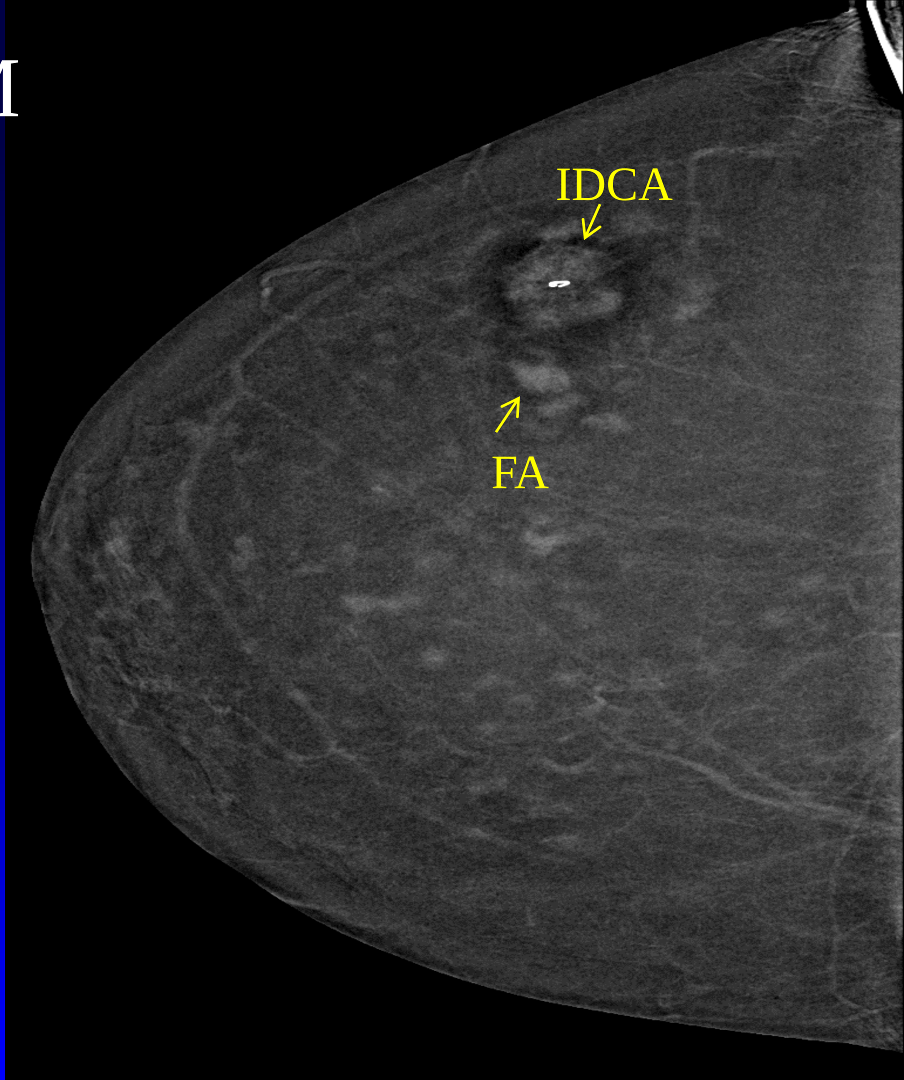
- Low energy tomo images can add useful information on morphology – changing the assessment of the lesion

Example 5:

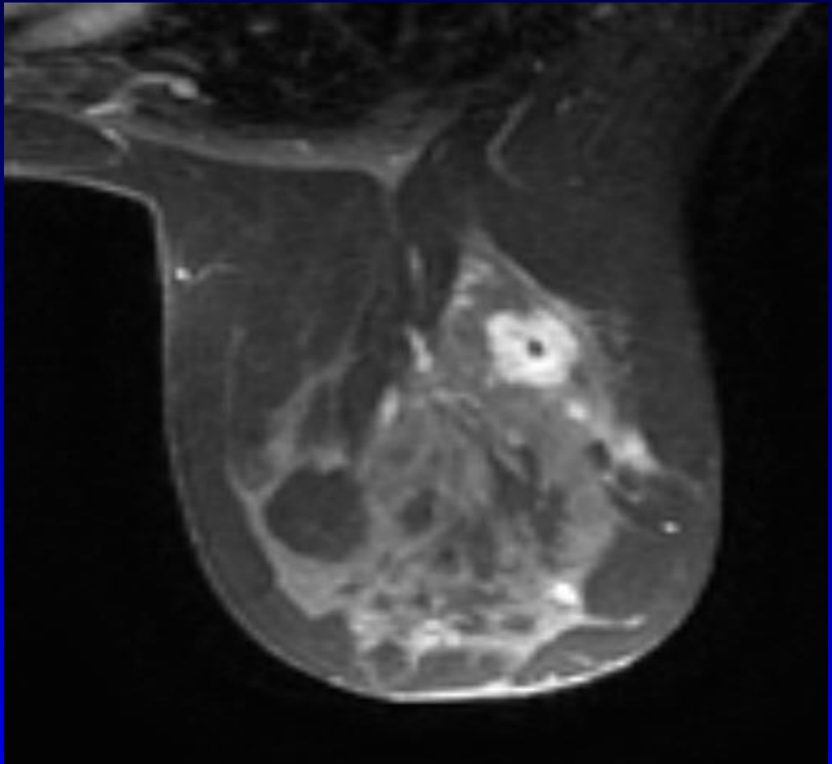



CEM

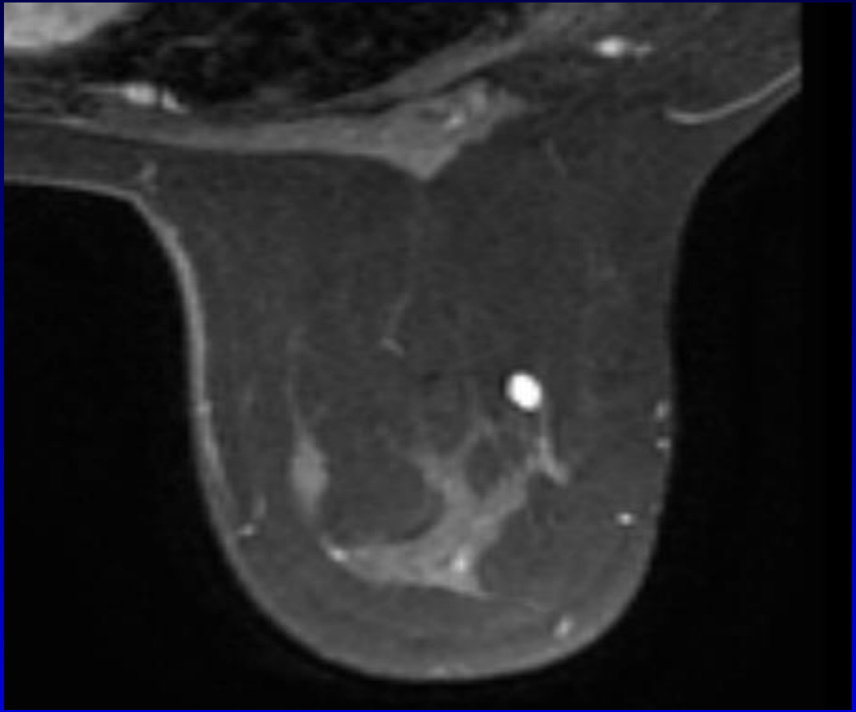




MRI



IDCA



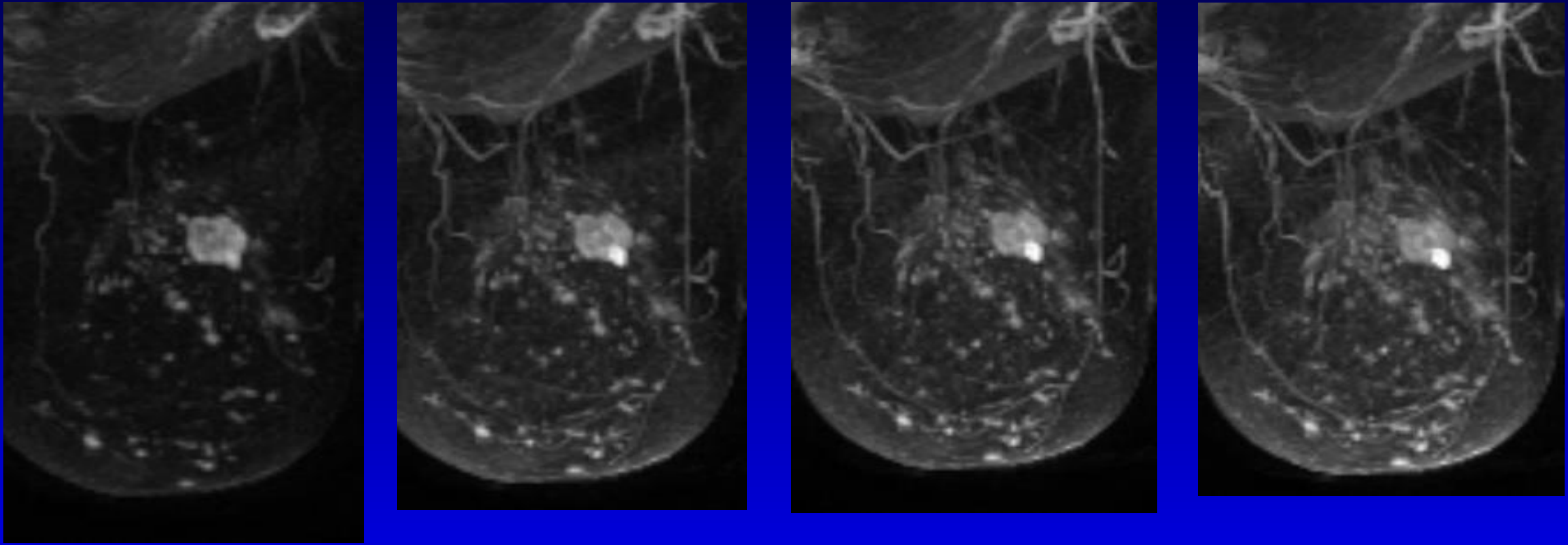
Fibroadenoma

CEM

2 minutes

5 minutes

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