AAPM Spring Clinical Meeting

Advanced Mammography Applications

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Disclosures

- Research Contract from Hologic
- Hologic Scientific Advisory Board
- Philips Women's Healthcare Medical Advisory Board

Off-label Use

The use of iodinated contrast agent with digital mammography has not been evaluated by the FDA and is an "off-label" use.

Non-FDA approved devices

Some devices discussed in this presentation have not been approved by the FDA for clinical use in the United States.

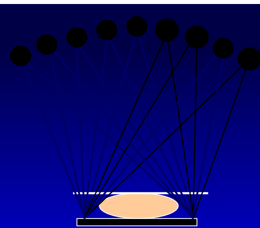
Learning Objectives

- Understand the basic principles of digital breast tomosynthesis
- Understand the clinical strengths and limitations of digital breast tomosynthesis
- Understand the basic principles of contrast enhanced digital mammography
- Understand the clinical strengths and limitations of contrast enhanced digital mammography

Part I - Tomosynthesis

Primer/Refresher: Breast Tomosynthesis

- Mammography is only about 70% sensitive
- One reason cancers are not seen on mammography is that they are obscured by surrounding dense tissue
- Tomosynthesis is a way to separate the cancer from the surrounding dense tissue



- Multiple (10-25) digital images taken at different angles are combined to give an image at a single plane
- Total sweep is typically 15 – 50 degrees
- Each image is acquired at low dose so total ~ standard mammo

Animation courtesy L. Niklason, Hologic Inc

Design Issues

- Arc size
  - Wider arc → better z resolution
    - But… increased dose
- # of images
  - More images → fewer artifacts
    - But… longer acquisition time, more dose or more noise
- Stationary vs moving detector
- Stop and shoot vs continuous imaging

Current Tomo Systems -design

- Hologic – 15º arc / 15 images / 3.7s
- GE – 25º arc / 9 images / 7s
- Siemens – 50º arc / 25 images / 25s
- IMS Giotto – 40º arc / 13 images / 12s
- Planmed – 30º arc / 15 images / 20s
- Philips – 11º arc / 21 images / 3-10s

Source: Sechopoulos. A review of breast tomosynthesis. *Medical Physics* 2013, 40(1)

Current Tomo Systems - Regulatory

- Hologic – FDA approved
- GE – commercial use outside U.S.
- Siemens – commercial use outside U.S.
- IMS Giotto – commercial use outside U.S.
- Planmed – research only
- Philips – research only

Example: Hologic Selenia Dimensions

- Digital Mammography and Tomosynthesis System
- 15 degree tomosynthesis sweep, 15 images, ~5 second tomosynthesis acquisition
- Continuous x-ray tube movement
- 24 x 29 cm detector
- 2D and 3D Imaging under same compression
  - 2D (mammo), 3D (tomo) or Combo modes

video courtesy Hologic

Literature Review

Hologic FDA Study

- Multi-reader study with enriched screening case set
- 7% increase in accuracy (area under ROC curve)
- 15-20% increase in sensitivity for invasive cancers

Rafferty EA, et al. *Radiology* 2013; 266(1): 104-13.

Oslo Tomosynthesis Trial

- 12,631 screening exams in combo mode (2D mammo + tomo)
- 4 readers – 2 for each arm (mammo alone, mammo+tomo)
- RESULTS:
  - Cancer Detection Rate: 6.1/1000 vs. 8.0/1000
    - 27% increase in cancer detection with combo (p=.001)
    - 40% increase for invasive cancers (p<.001)
  - False Positive Rate (recall rate) before arbitration: 8.0% vs. 6.1%
    - 15% decrease in FP rate with combo mode (p<.001)
  - PPV after arbitration similar for mammo and combo, however
    - 29.1% vs 28.5% (p=.72)

Ref: Skaane P, *et al*. *Eur Radiology* 2013; 23(8):2061-71

Italian Tomosynthesis Screening Trial

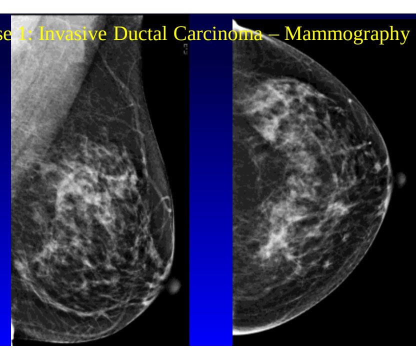
Screening with Tomosynthesis OR Standard Mammography (STORM)

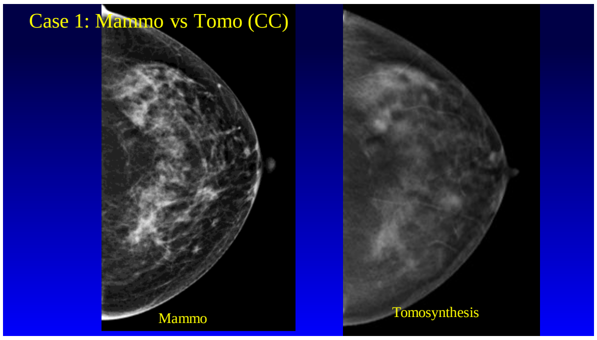
- 7292 screening exams in combo mode (2D mammo + tomo)
- RESULTS:
  - 39 cancers detected on 2D reading; 59 cancers using 2D + tomo
    - Cancer Detection Rate: 5.3/1000 vs. 8.1/1000
  - False Positive Rate: 4.4% vs 3.5%
    - 17.2% decrease in recalls with 2D + tomo

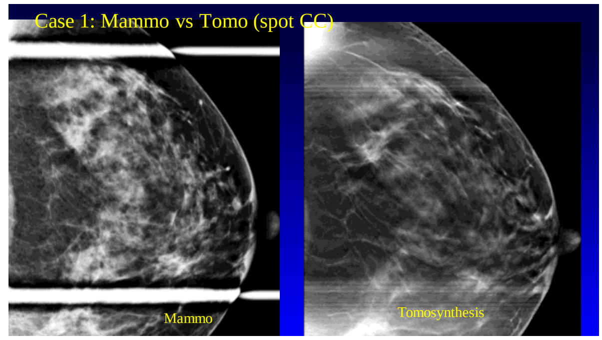
Ref: Ciatto S, *et al*. *Lancet Oncology* 2013; 14(7): 583-9.

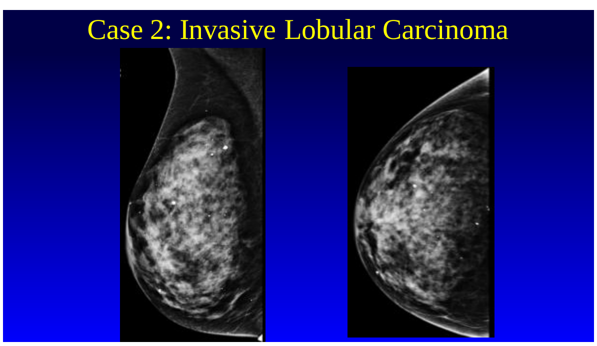
Cases

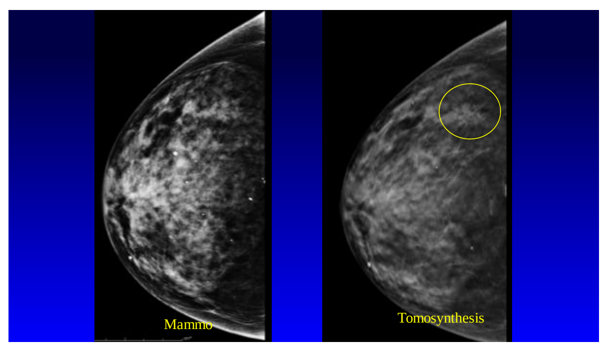
Case 1: Invasive Ductal Carcinoma – Mammography

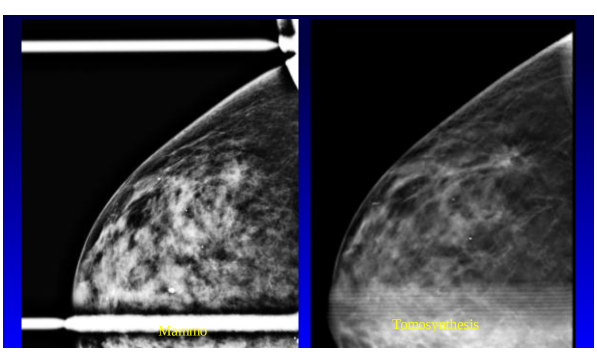


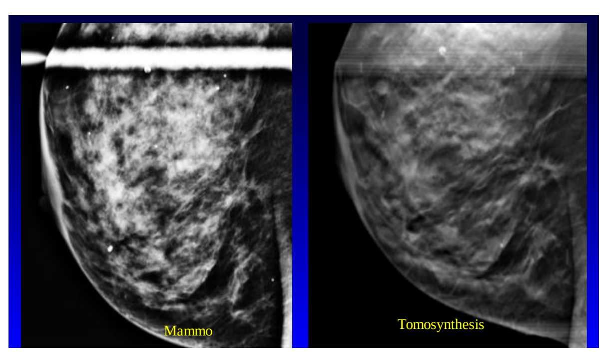

Case 1: Mammo vs Tomo (CC)
Mammo
Tomosynthesis

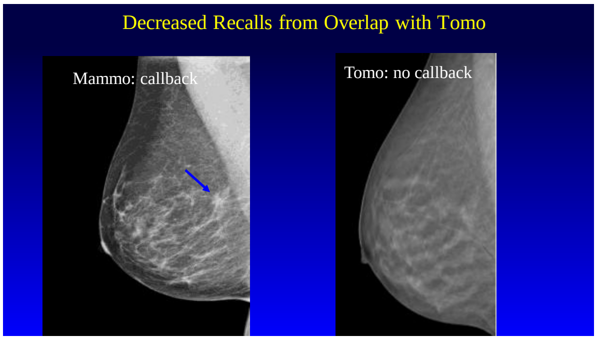

Case 1: Mammo vs Tomo (spot CC)
Mammo
Tomosynthesis

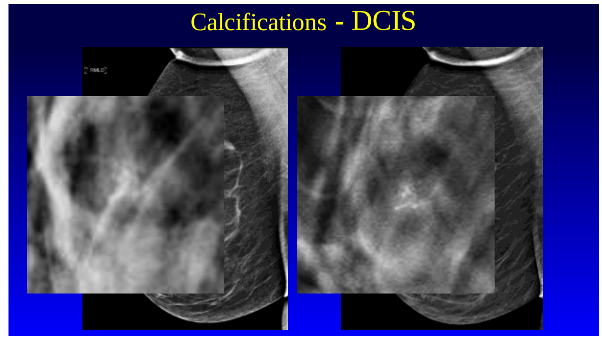

Case 2: Invasive Lobular Carcinoma

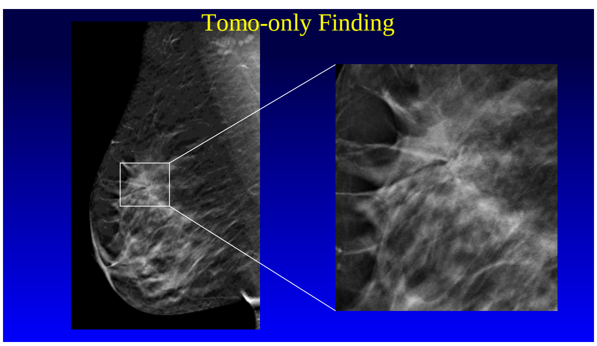

Mammo
Tomosynthesis

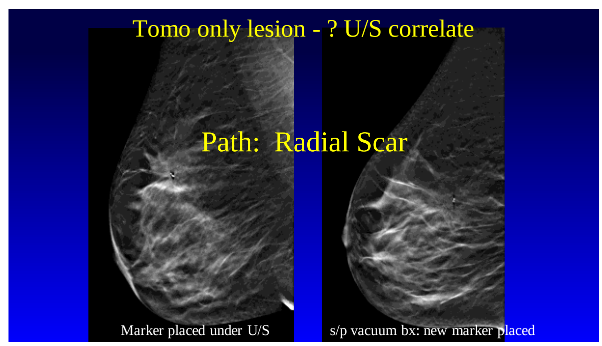

Mammo
Tomosynthesis


Mammo
Tomosynthesis









Upright vacuum-assisted biopsy using tomo is available (and would be good for cases like these)

My experience with screening tomo:

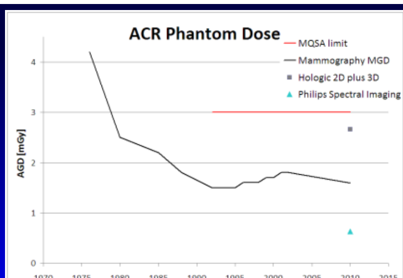
- Year 1 (prevalence year):
  - 3 tomo-only cancers in ~ 2200 exams
    - Better than expected - stopped counting after that
    - All were low grade
    - Also - lots of radial scars
- Year 2 (i.e., year after pt's 1st tomo):
  - All new cancers have been high grade
  - Some have been tomo-only

My experience with diagnostic tomo:

- All spot compression views are now done in combo mode
- Much more reassuring than standard spots
- Replaces straight lateral view, off-angle views, rolled views, etc.
- Several cases where cancers seemed to spot out on 2D but shown on tomo to be true masses

Radiation and Tomosynthesis

- The radiation dose from the Hologic tomo is about 10% higher than a comparable Hologic 2D image
  - So combo mode is more than double a 2D mammogram
- Key tradeoffs:
  - # of images
    - More images = fewer artifacts
    - More images not as dose efficient (more noise/dose)
    - Tomo acquisitions are basically dose-limited



Slide courtesy Philips

Spelic, Ph.D., US Food and Drug Administration, Division of Mammography Quality and Radiation Programs, Dose and Image Quality in Mammography: Trends during the First Decade of MQSA, 9/5/2003

Jennings, PhD, Divison of Imaging and Applied Mathematics, Office of Science and Engineering Laboratories FDA, Center for Devices and Radiological Health, Regulatory Advisory Panel Meeting, September 24, 2010

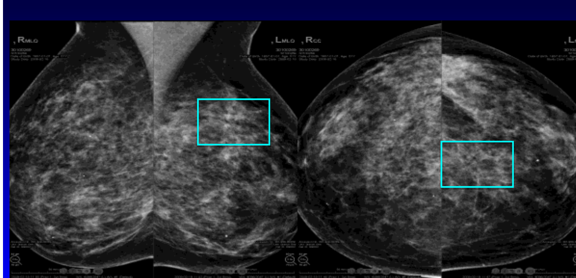
Radiation and Tomosynthesis (cont.)

- But by far the biggest reduction in dose would come from eliminating the 2D views …

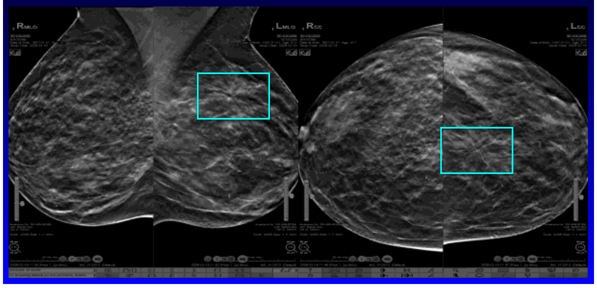
2D Synthetic View

- Uses the tomosynthesis data to create a view that simulates a 2D mammogram
  - Allows one to see calcification distributions that might be difficult to perceive on tomo slices
- Basically a type of MIP image
- Can be made to simulate a 2D image, or improve on it
- Idea is to eliminate requirement for 2D mammo to be done with tomo (Hologic)

Example (courtesy Hologic) : Conventional 2D

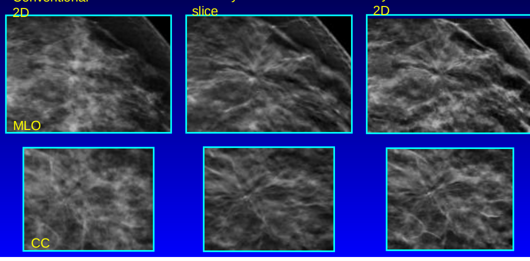


Example (courtesy Hologic): Tomosynthesis Reconstruction Slices (showing one slice)



Example (courtesy Hologic) : Synthetic 2D

Example (courtesy Hologic): Spiculated mass lesion side-by-side



Oslo Trial Synthetic View Study

- 24,901 screening exams (continuation of above trial)
- Combo mode; double reading
- Compared 2D + tomo to tomo with syn. view
- Results (cancer detection rate):
  - A little complicated because syn. view algorithm changed in middle of study
  - Before change: 2D + tomo > tomo with syn. View
  - After change: no difference

Ref: Skaane P, *et al.* *Radiology* 2014; epub ahead of print 1/24/14.

Breaking News

- AMA approved 3 CPT codes for tomosynthesis last week (3/5/14).
  - Doesn’t mean we will actually get paid extra for doing tomo, however (but it is a first step)

Tomosynthesis - summary

- Currently in routine clinical use
- Shown in clinical settings to give <u>both</u> improved sensitivity and improved specificity compared to 2D mammography
- Can be used as an addition to 2D or with a synthetic view
- Additional systems in FDA approval process
- Payment and use of CAD are issues

Part II - Contrast-Enhanced Digital Mammography

CEDM - Outline

- History
- Technique
- Literature Review / Cases
- Clinical Status

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
  - Limited specificity

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)

- 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

CEDM - Hurdles

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

CEDM – Subtraction Techniques

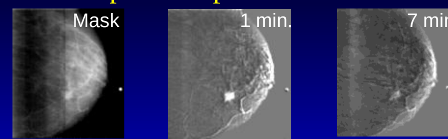
- Temporal Subtraction:

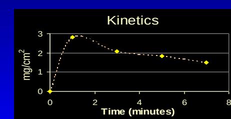
  post-contrast - pre-contrast

- 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

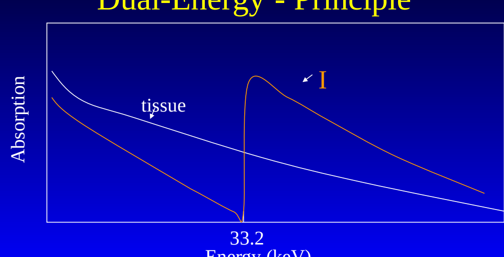
Temporal Subtraction - Limitations

- 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

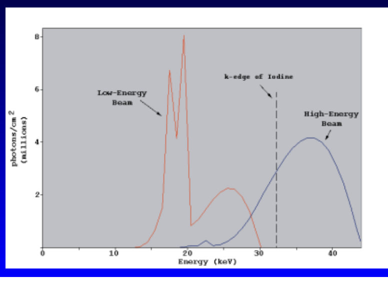
Dual-Energy - Principle

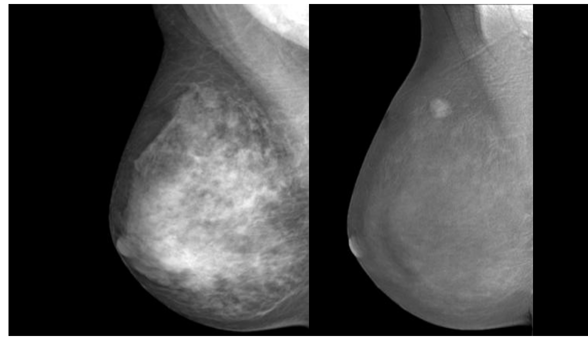


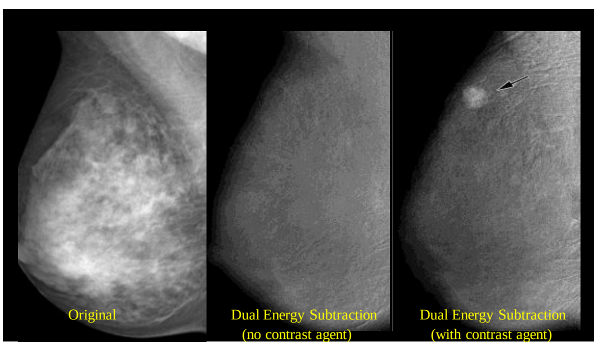
Dual-Energy Subtraction

- 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)

Example: Filtered Spectra on a Mo/Rh Mammo Unit

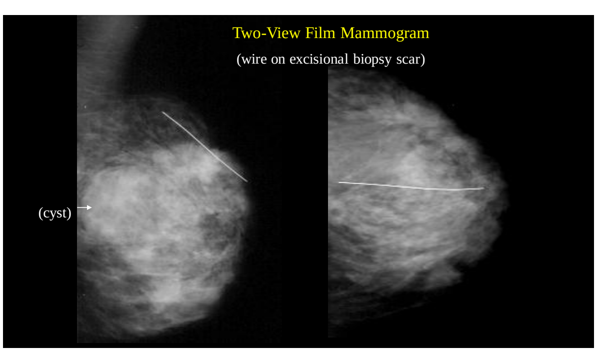


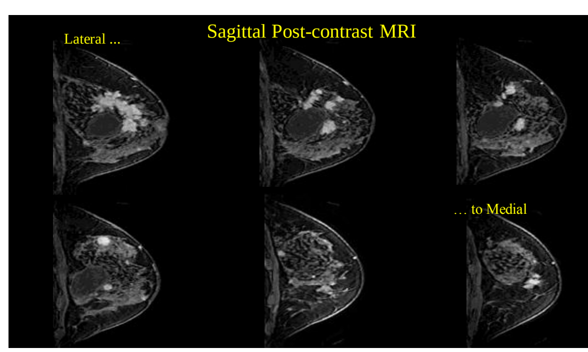




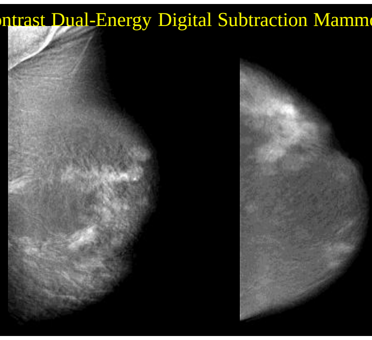
Early Dual Energy Papers

- 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
- Dromain, et al (*Eur Radiol* 2011, *Breast Cancer Res* 2012)
  - 120, 110 subjects (80, 148 cancers)
  - CEDM > mammo and mammo+U/S by ROC
- Schmitzberger, et al (Radiology 2011)
  - 10 subjects (9 cancers) with photon counting tomosynthesis





Post-Contrast Dual-Energy Digital Subtraction Mammography



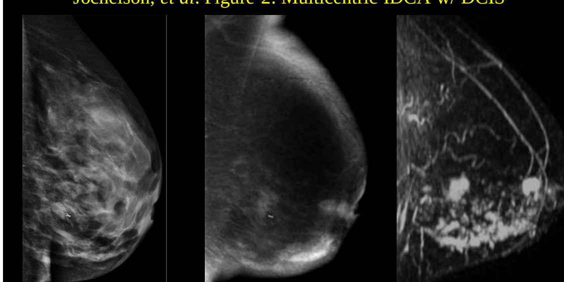
CEDM vs MRI: Recent Literature

- Fallenberg, *et al*. *European Radiology* 2013; *epub* 9/19
  - Bilateral CEDM, MRI, mammo
    - Note: Average rad dose of CEDM sl. < mammo (1.72 vs 1.75 mGy)
  - 80 subjects with new CA at 1 site
  - Single reader of CEDM; clinical read of MRI
  - CEDM > MRI sensitivity for index lesion (100% vs. 97%)
    - 80/80 vs 78/80
  - CEDM correlated best with path in terms of size of lesion
    - MRI and mammo both underestimated size

CEDM vs MRI: Recent 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

Jochelson, *et al*. Figure 2: Multicentric IDCA w/ DCIS



Additional CEDM Papers of Note

Clinical Papers:

Thibault F, *et al*. Contrast enhanced spectral mammography: better than MRI? *Eur J Radiol* 2012

Badr S, *et al*. Dual-energy contrast-enhanced digital mammography in routine clinical practice in 2013. *Diagn Interv Imaging* 2013

Physics Papers:

Hill ML, et al. Anatomical noise in contrast-enhanced digital mammography. Parts I and II in *Med Phys* 2013

Allec N, et al. Evaluating noise reduction techniques while considering anatomical noise in dual-energy contrast-enhanced mammography. *Med Phys* 2013

Allec N, et al. Including the effect of motion artifacts in noise and performance analysis of dual-energy contrast-enhanced mammography. Phys Med Biol 2013

CEDM - Current Clinical Status

- June 2010 – CEDM product introduced in Europe
- October 2011 – CEDM product receives U.S. FDA 510k approval
- Currently – being incorporated into routine practice, esp. outside U.S.
- At least one additional company has attained 510k approval for a CEDM product

What is next?

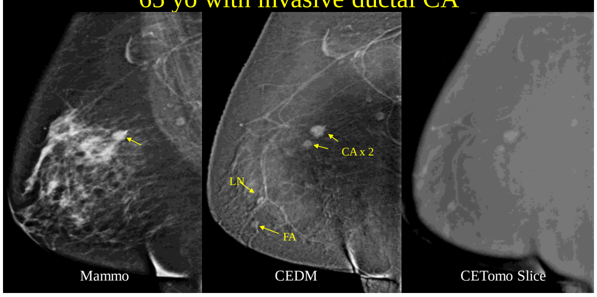
- ✓ Compare CEDM to MRI
- Optimize the technique
  - Beam energies (target, filter, kVp)
  - Image processing
  - ???
- Combine CEDM with tomosynthesis

CEDM/CET Research Study

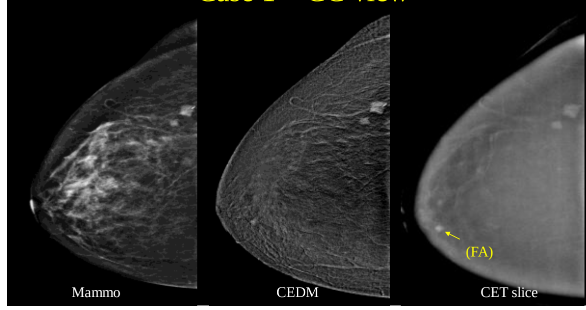
- CEDM and CE Tomosynthesis vs MRI
  - Subjects with newly diagnosed cancers
- CEDM and CET performed in single compression
  - Prototype device allowing dual energy combo-mode imaging (2D and tomo)
  - < 1 sec between LE and HE images
  - Tomo with 22 source images (alt HE and LE)
  - Affected breast only

Research project funded by Hologic

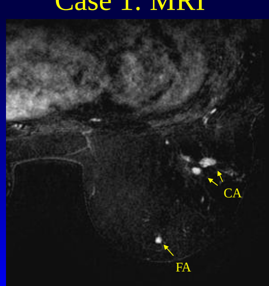
CEDM / CET Case 1: 65 yo with invasive ductal CA



Case 1 – CC view

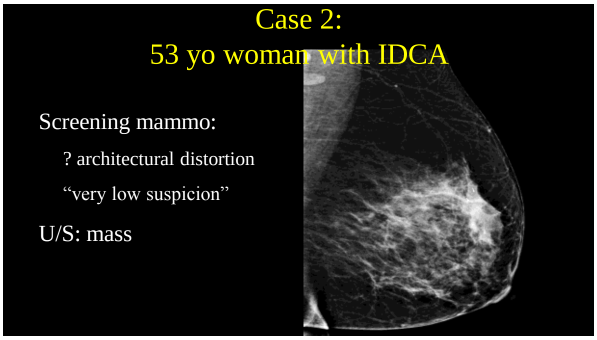


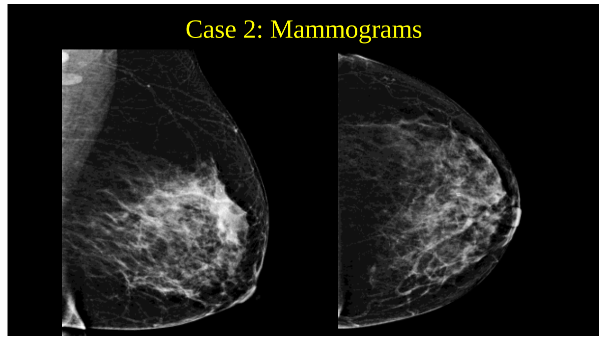
Case 1: MRI

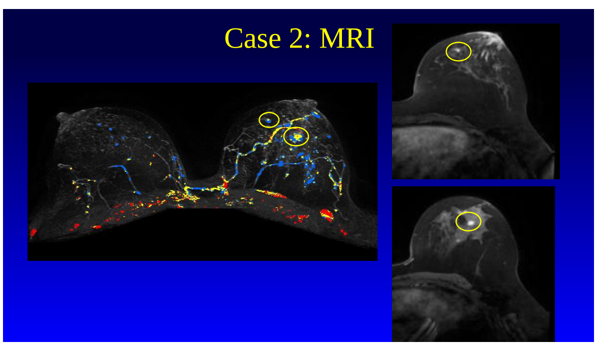


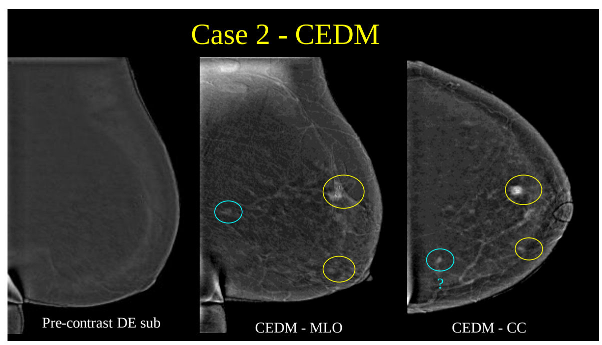
Lessons…

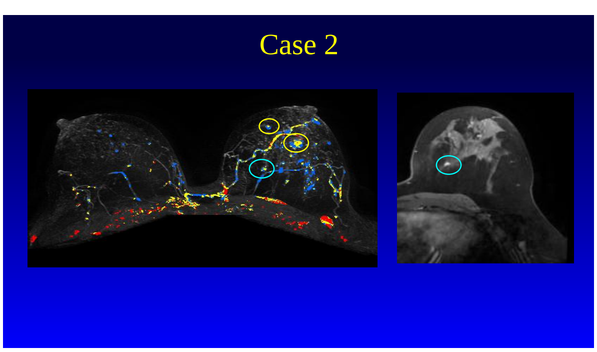
- Benign masses that light up on MRI also light up on CEDM (e.g. FAs, LNs)
- Sometimes you see things better on CEDM and other times on CET

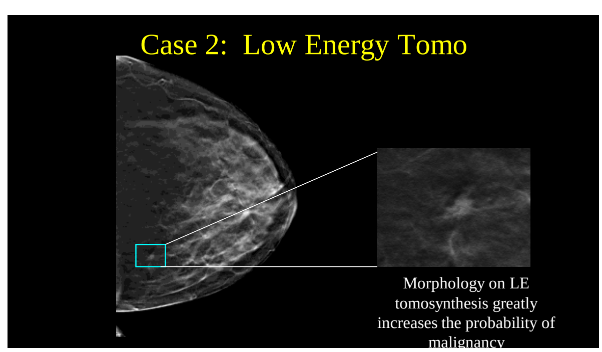

Case 2:
53 yo woman with IDCA
Screening mammo:
? architectural distortion
"very low suspicion"
U/S: mass


Case 2: Mammograms


Case 2: MRI


Case 2 - CEDM
Pre-contrast DE sub
CEDM - MLO
CEDM - CC


Case 2


Case 2: Low Energy Tomo
Morphology on LE tomosynthesis greatly increases the probability of malignancy

Case 2: Lesson

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

CEDM vs MRI

- CEDM
  - Lower cost
  - Easier on patient (noise, claustrophobia)
  - Faster
  - More specific (?esp. with tomo)
  - Single exam for high risk screening (shows calcs)
  - ? Upright stereo biopsy easier than MR biopsy
- 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

Summary

- CEDM has gone from research to clinical use
  - Cancers reliably enhance with this technique
  - Morphology helps with specificity
- Potential to reduce costs by decreasing need for MRI
- Very early in life cycle → expect improvements in image quality and interpretation
  - Early results indicate MRI is more sensitive, less specific
- Addition of tomo has potential to further improve results
- Continued research is needed…