Canadian Society of Breast Imaging
Société canadienne de l'imagerie mammaire

Digital Tomosynthesis: State of Clinical Practice in Canada

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Outline

- Advantages of tomosynthesis
  - Screening
  - Diagnostic
  - Biopsy
- Requirements of tomosynthesis
  - Cost
  - PACS
  - DBT biopsy
  - Time
  - CARMAP
- Current state in Canada
  - Number of units, Health Canada approved
    - Hologic 90-110 units
    - GE ??
  - TMIST sites in Canada 5: Ottawa, London, Quebec, Toronto, Vancouver
  - DBT biopsy capability (GE?, Siemens?)

Objectives

- Review the evidence of tomosynthesis in screening and diagnostic settings
- Discuss the current use of tomosynthesis in Canada

DBT in the screening environment

- Multiple DBT screening trials in the US and Europe demonstrated for DBT+DM compared with DM alone
  - reduction in screening recalls
  - increase in cancer detection rate

Lower FPs and Higher Cancer Detection Rates for DBT +DM vs DM in 2 Prospective European Studies

	Country	Machine	# Sites #Women	Δ FP rate (TM+DM, Rate DM)	Δ Cancer Detection Rates/1000 (Rate TM+DM, rate DM)
Ciatto 2013	Italy	Hologic	2 7292	**Reduced FPs from 322 to 254 17% decrease**	**2.8 (8.1, 5.3) Bigger cancers 53% increase**
Skaane 2013	Norway	Hologic	1 12631	**Reduced by 1.2% (5.3/6.1) 15% decrease**	**1.9 (8.0, 6.1) More invasive Ca 31% increase**

3 US retrospective studies-↓recalls,↑CDR

All of these studies were on DBT+TM vs DM, none on Synthetic DM+DBT vs DM

	Machine	# Sites #Women	Δ % recalls (rate DBT+DM, rate DM)	Δ Cancer Detection Rates/1000 (Rate DBT+DM, rate DM)
Friedewald 2014	Hologic	**13** **454,850**	**15%*** **(9.1%, 10.7%)**	**1.2** **(5.4, 4.2)** **29% increase**
Lourenco 2014	Hologic	1 12,577	**31%** **(6.4%,9.3%)**	0.8 (5.4,4.6) 17% decrease (NS)
Rose 2013	Hologic	1 13,856	**37%** **(5.5%, 8.7%)**	1.4 (5.4, 4) 35% increase

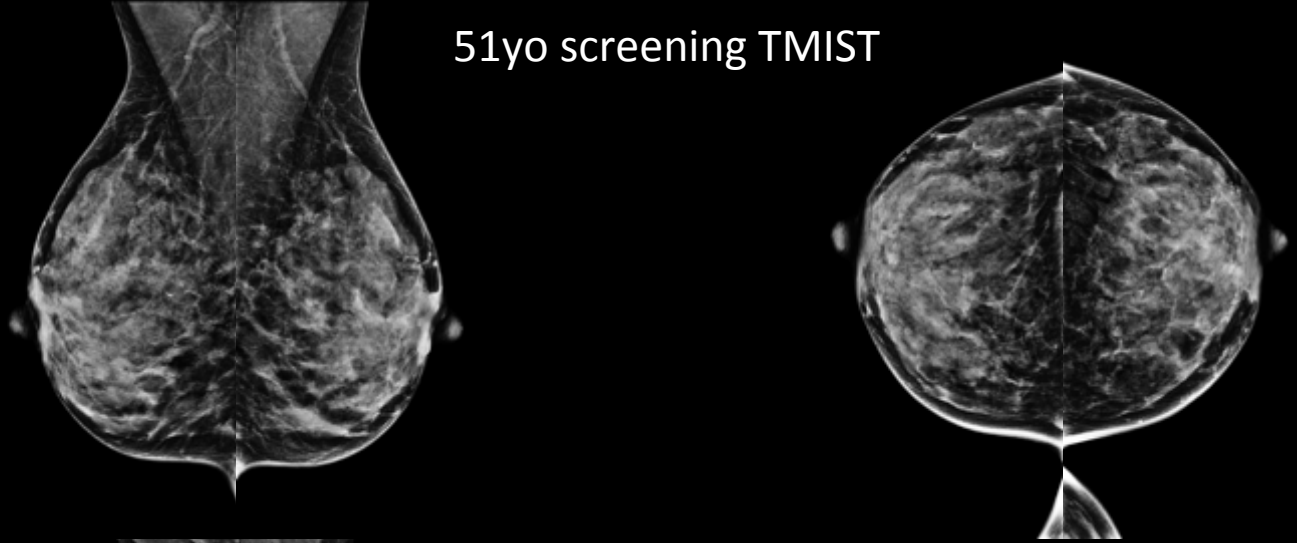
Cancer outcomes for digital breast tomosynthesis in combination with digital mammography (DBT) compared to digital mammography (DM) alone

Cancer Outcomes	**DM 113,061**	**DBT 25,268**	**P-value**
Invasive cancer rate per 1000	3.7	4.7	0.0252
PPV1 % (cancers/recall)	4.1	6.4	<0.0001
Sensitivity %	90.6	90.9	1.0
Specificity %	89.7	91.3	< 0.0001
False negative rate per 1000	0.46	0.60	0.347

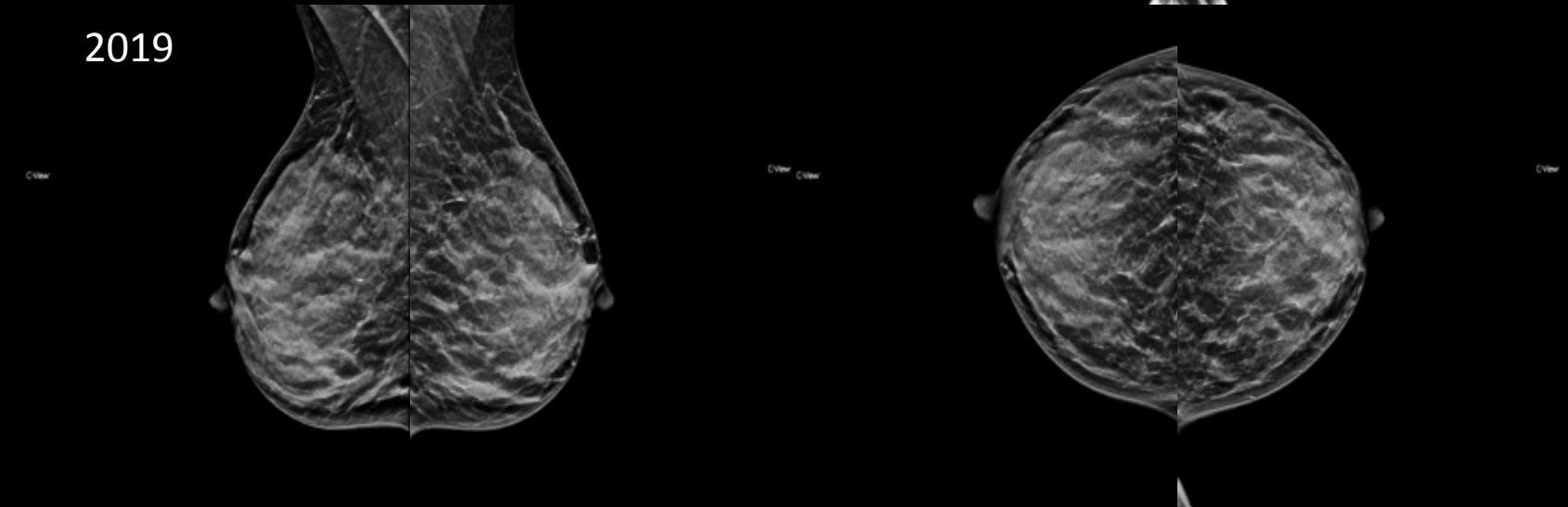
Conant E et al, Breast Cancer Res Treat 2016 Feb 156

51yo screening TMIST

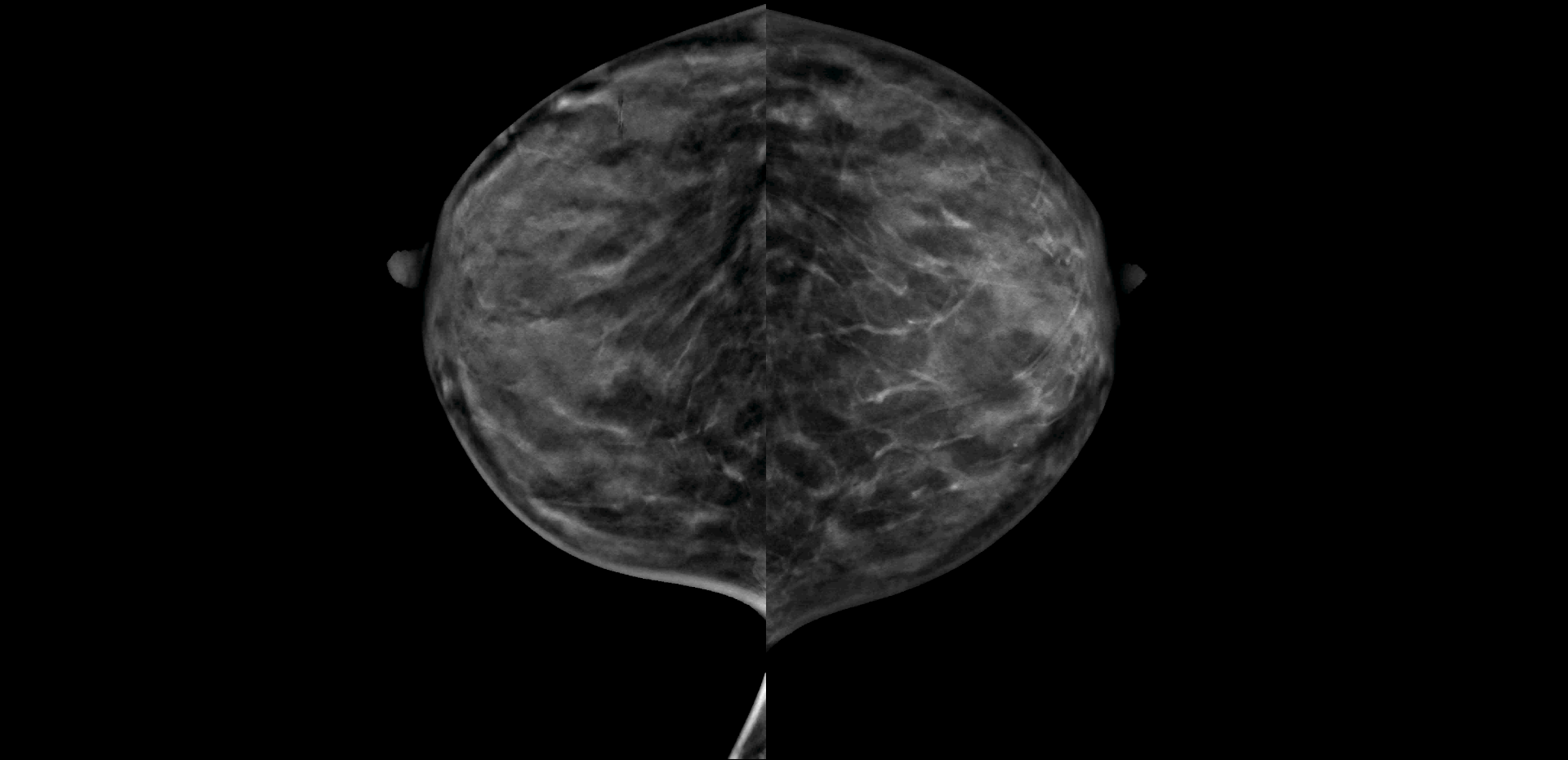
2018

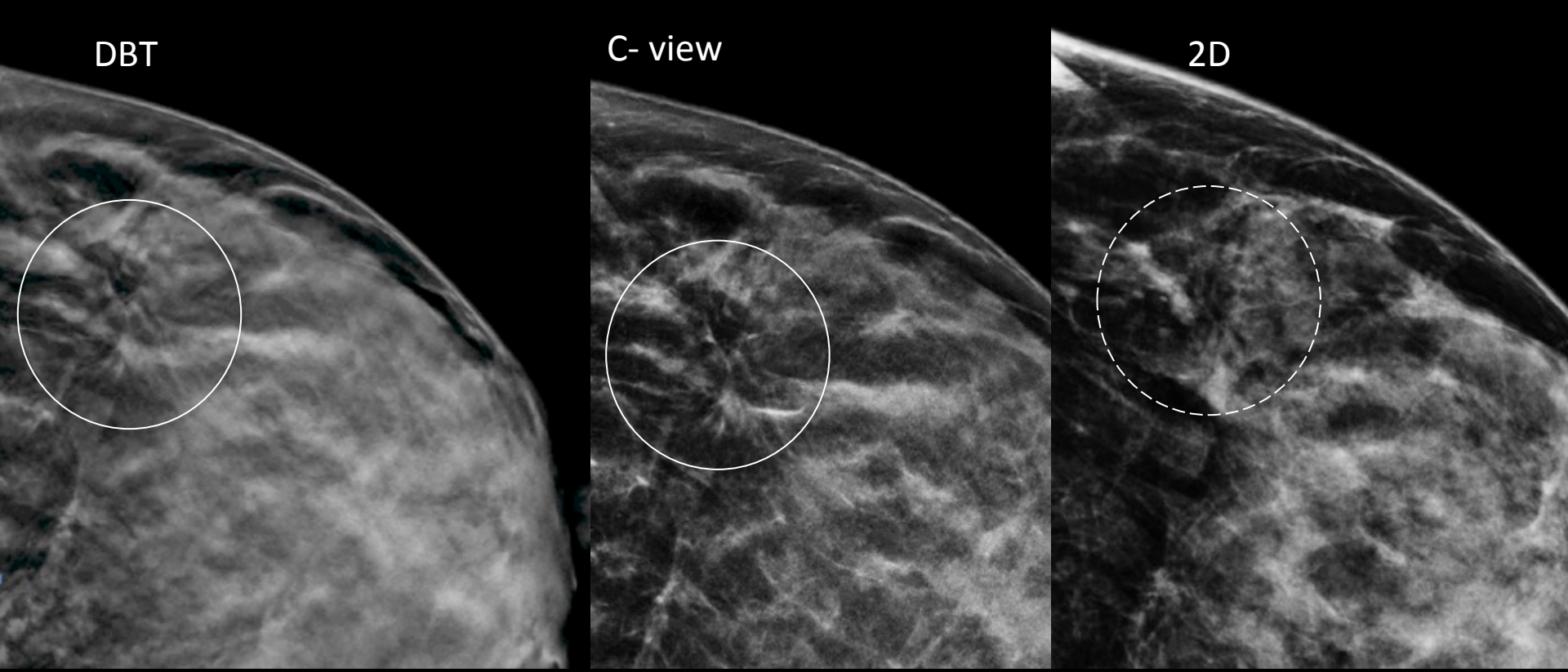


2019

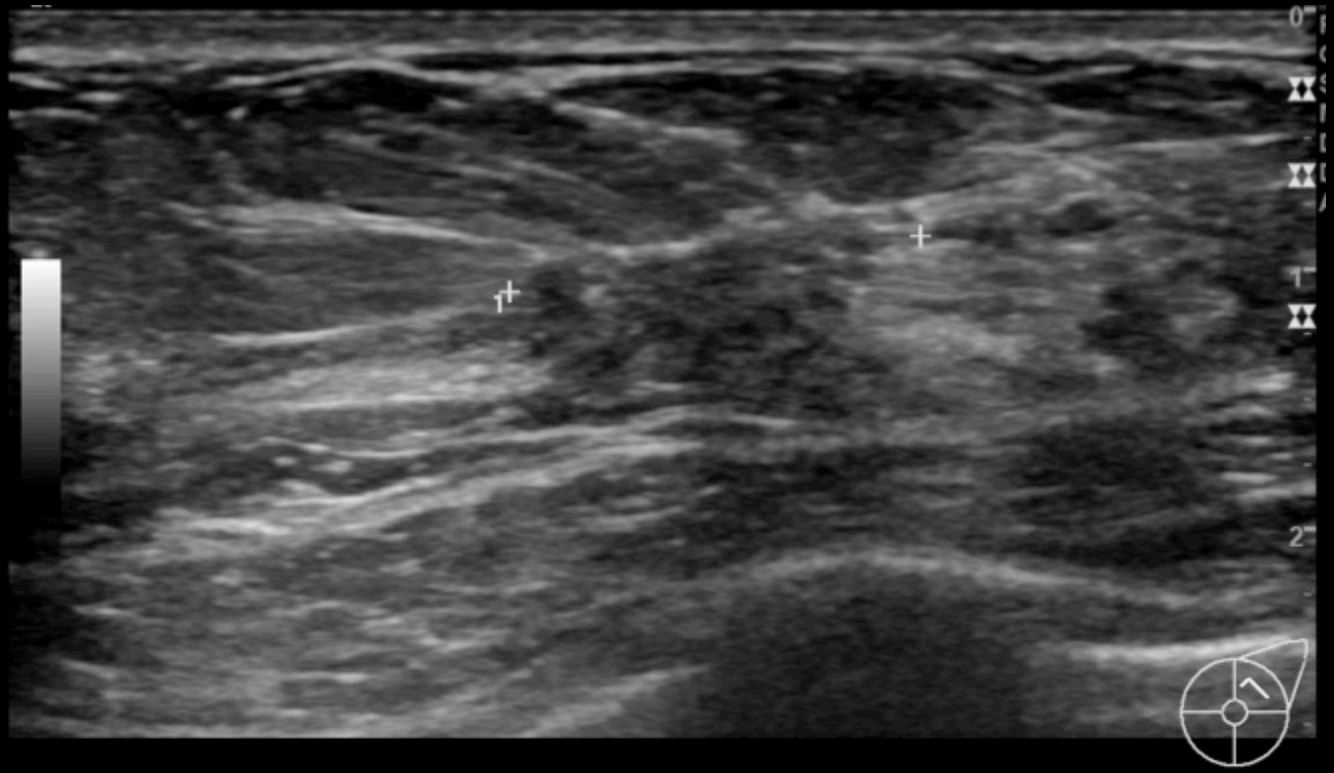


Right and left CC DBT




DBT
C- view
2D

1.5 cm low grade invasive ductal carcinoma with DCIS



DBT Increased CDR Invasive Ca

- The Increased CDR with DBT favors invasive carcinoma over DCIS
  - Skaane: 40% of invasive carcinomas alone
  - Ciatto: 34% of invasive carcinomas alone
  - Friedewald: 40% of invasive carcinomas alone

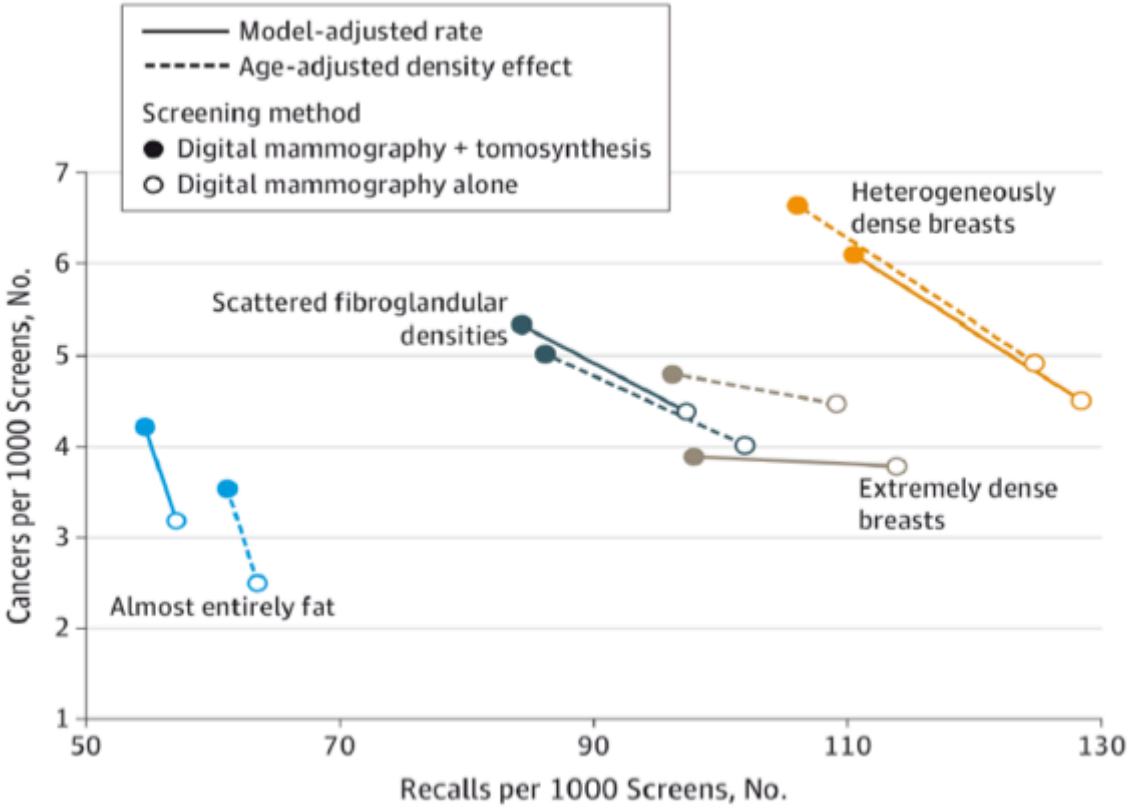
Tumor Size, Stage and Histologic Subtypes of DBT-detected Cancers

- Cancers smaller (0.6 cm vs 1 cm)
- Grade 1 (70% vs 27%)
- Luminal A characteristics (ER/PR pos, HER2Neg, Ki-67< 14%)
- Fewer lymph nodes involved (15% vs 31%)
- Improved detection of invasive lobular ca

Breast Tissue Density and DBT

- All breast tissue density categories benefit from DBT
- In dense breast tissue, heterogeneously dense (ACR C) benefit more from DBT compared with extremely dense breast tissue (ACR D)

Combined Change in Recall and Cancer Detection Rates for DM vs DM+DBT for Each Breast Tissue Density



- Reduced recall rates for all densities
- Increased CDR for densities ACR A, B, and C, but not D

Friedewald SM et al, JAMA 2014

ASTOUND Trial

Adjunct Screening with Tomosynthesis Or US in women with mammography Negative Dense breasts

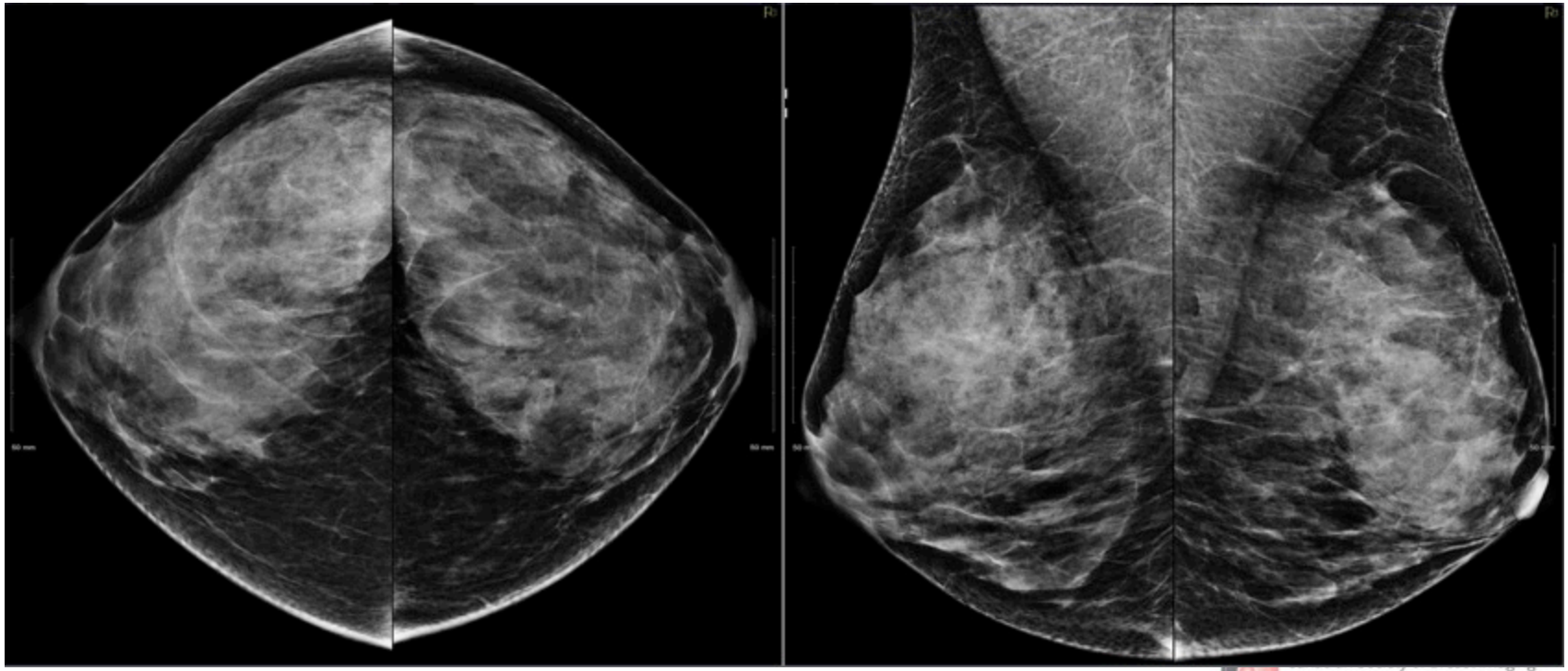
- 3,231 women Heterogeneous or Extremely dense
- Negative /benign 2D
- Had DBT and US

- 24 additional cancers (23 invasive)
  - 13 DBT (4.0 ICDR)
  - 23 US (7.1 ICDR)
- FPs not different
- FP biopsy not different

Tagliafico AS. JCO; 2016

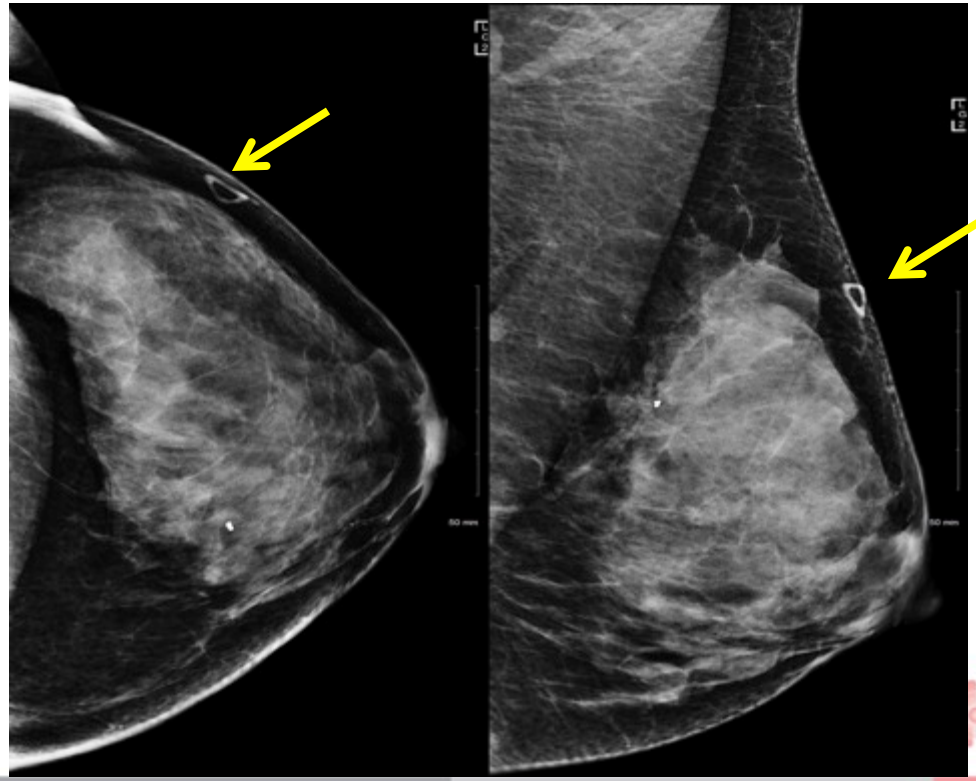
50 yr old woman

negative screening mammogram



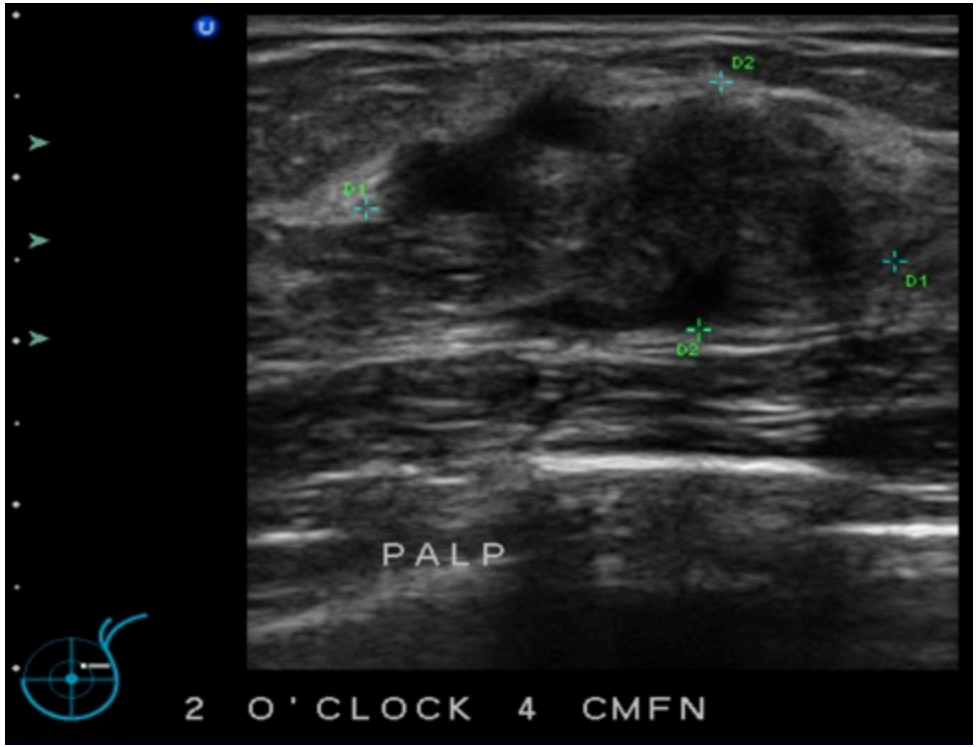
8 Months Later Palpable Mass

Mammogram Still Negative – even with DBT



3.2 cm cancer, Missed in Dense Breast

Seen Easily on Ultrasound



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DBT in Routine Screening Practice

Metric	DMo (N=10728)	DBT1 (N=11007)	DBT2 (N=11157)	DBT3 (N=11576)
Recall Rate	10.4%	8.8% (p<0.001)	9.0% (p<0.001)	9.2% (p<0.001)
Cancer Detection Rate	4.6/1000	5.5/1000 (p=0.37)	5.8/1000 (p=0.20)	6.1/1000 (p=0.11)
PPV1 (ca/recall)	4.4%	6.2% (p=0.063)	6.5% (p=0.034)	6.7% (p=0.020)
Interval Cancer Rate	0.7/1000	0.5/1000 (p=0.60)	N/A	N/A
Invasive ca	3.2/1000	3.8 (p=0.420)	4.1 (p=0.243)	4.1 (p=0.269)

McDonald, E et al, JAMA 2016 Oncol

Interval Cancers

- STORM trial showed slight decrease in interval cancer rate: 1.23/1000 with DBT+DM vs 1.6/1000 for DM
- TMIST will determine long-term outcomes

Screening with DBT

- Sustained benefits of increased cancer detection, reduced recalls and improved PPV
- Mild reduction in interval cancer rate

DBT Average Glandular Dose

Metric	FFDM mean[range]	DBT mean[range]	Difference P-Value
Mean AGD	1.63 mGy (0.68-7.41 mGy)	1.7 mGy (0.93-5.02 mGy)	<0.001*

Shin et al. Eur Radiol. 2014 Sep 3

Oslo Tomosynthesis Screening Trial

Average system computed mean fibro-glandular doses:

- 2-D only 1.58 ± 0.61 mGy
- 2D plus CAD
- 2-D plus 3D 3.52±1.08 mGy
- Synthetized 2-D plus 3D 1.95±0.58 mGy

($P<0.001$)

Skaane P, Bandos AI, Gulien R, et al. Eur Radiol 2013 August; 23(8): 2061-2071

Replacement of 2D with 3D

- 24 301 women (59.1 years, 50–69 years) biennial screening Oslo
- Sensitivity 70.5% vs 54.1%, P = 0.001
- Specificity 95.0% vs 94.2%, P <0.001
- Synthetic + DBT had no differences in sensitivity 69.0% vs 70.5% and specificity 95.4% vs 95%

Skaane P et al. Radiology 2019; 291:23–30

Oslo Tomosynthesis Screening Trial (OTST)

- Screening accuracy improved with the addition of DBT vs DM alone
- Synthetic mammograms had similar performance to mammography when combined with DBT
- CAD did not improve performance of mammography

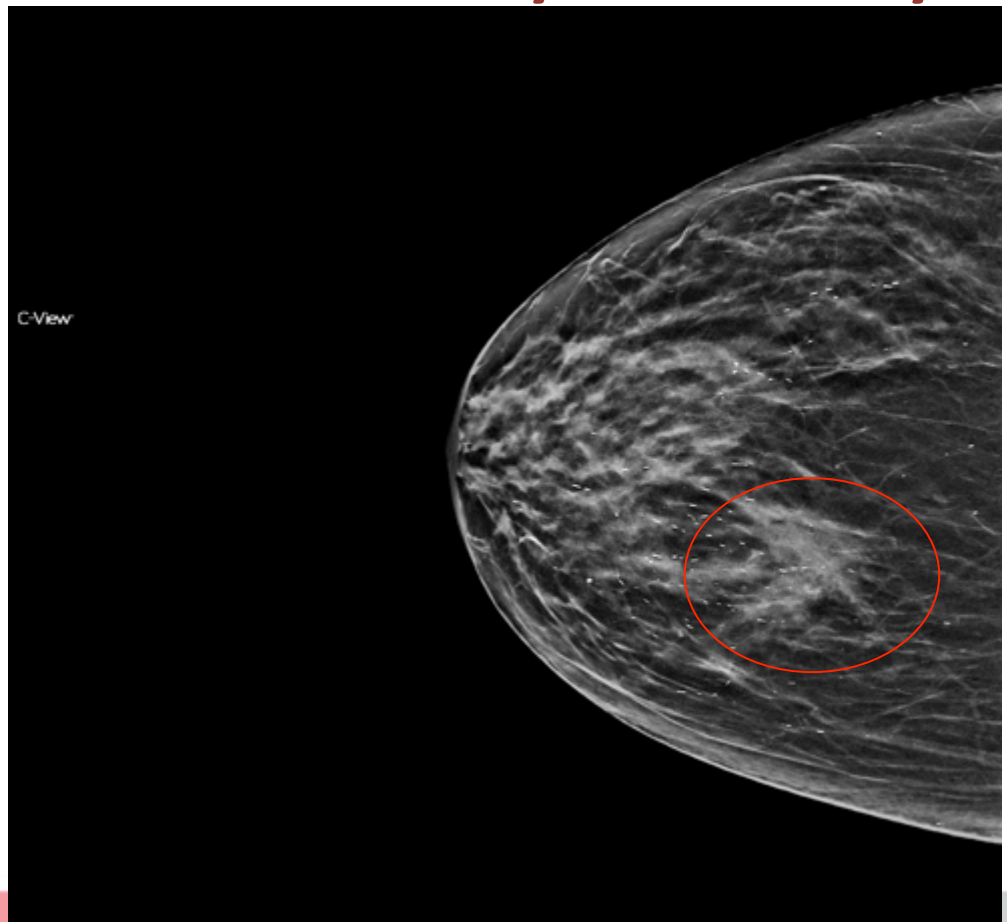
Skaane P et al. Radiology 2019; 291:23–30

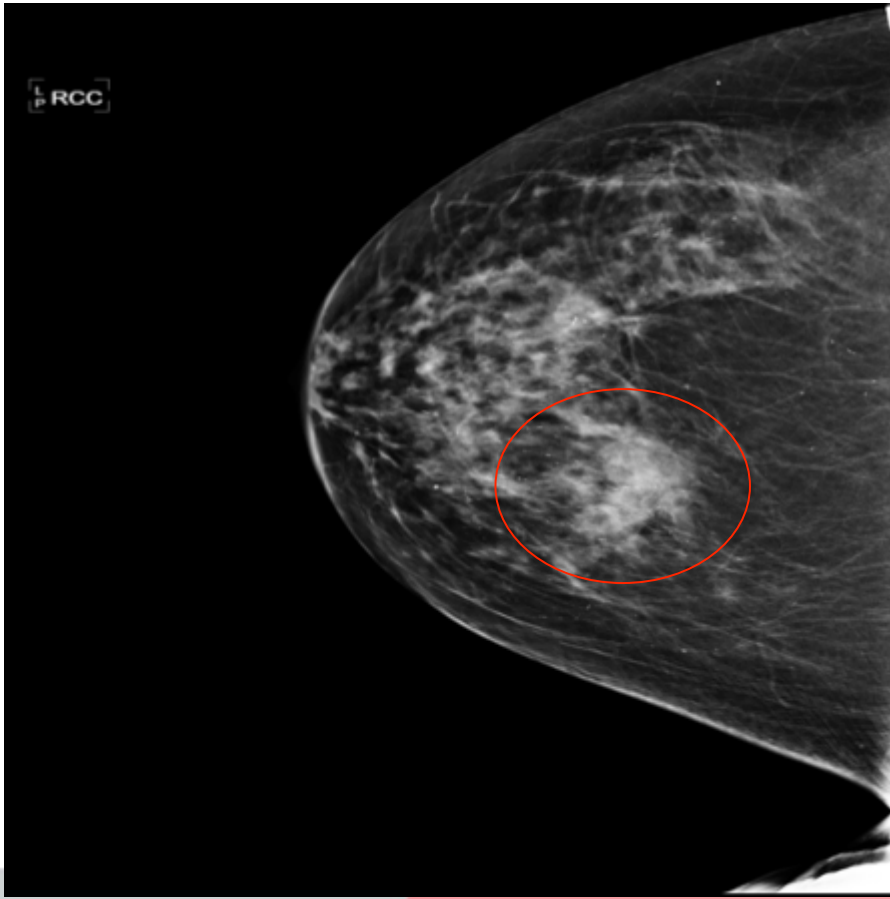
Breast tissue density and modality

- Breast density downgraded with FFDM+DBT or synthetic M+DBT vs DM alone (31% and 57%)
- Lower likelihood of high breast density assignments after replacement of DM by synthetic M (reduced by 38%)

Gastounioti A et al. Radiology 2019; 291:320–327

Focal asymmetry with C-view





DBT Screening in Canada

- In some centers, DBT+SM has replaced 2D screening
- Some centers use DBT+DM for baseline screens
- Screening programs have not adopted DBT screening
- Permitted in some screening programs when DBT used with DM

Reasons for lack of widespread use in organized programs

- Fear of increasing costs of high-volume programs
- Radiology concerns about increasing workload
- Providers and screening opponents concerns about “overdiagnosis”
- Lack of evidence of long-term effect on reduction of interval cancer rates and reduction of advanced cancers

DBT in the Diagnostic Environment

- Improved diagnostic accuracy
- Abbreviated diagnostic work-up
- Shift in BI-RADS assessment categories and increase in positive predictive values

Improved diagnostic accuracy

- DBT could replace conventional work-up in 90% of screening-recalled abnormalities without calcifications
- DBT replaces conventional work-up with improved accuracy

Comparison of performance metrics with digital 2D versus tomosynthesis mammography in the diagnostic setting.

	Total DM	Total DBT +DM	P value
Number	22,883	22,824	
CDR per 1000	31.3	38.2	0.14
Invasive to in situ	72.3% (518/716)	83.7% (731/873)	<0.01
AIR	10.4	10.3	<0.01
PPV2	30%	37%	0.01
PPV3	33.8%	39.6%	0.01
Specificity	92.4%	93.2%	<0.01

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Bahl M et al, Eur Radiol. 2019 Feb;29(2):477-484

DBT on Benign Biopsy Rate in UK NHS

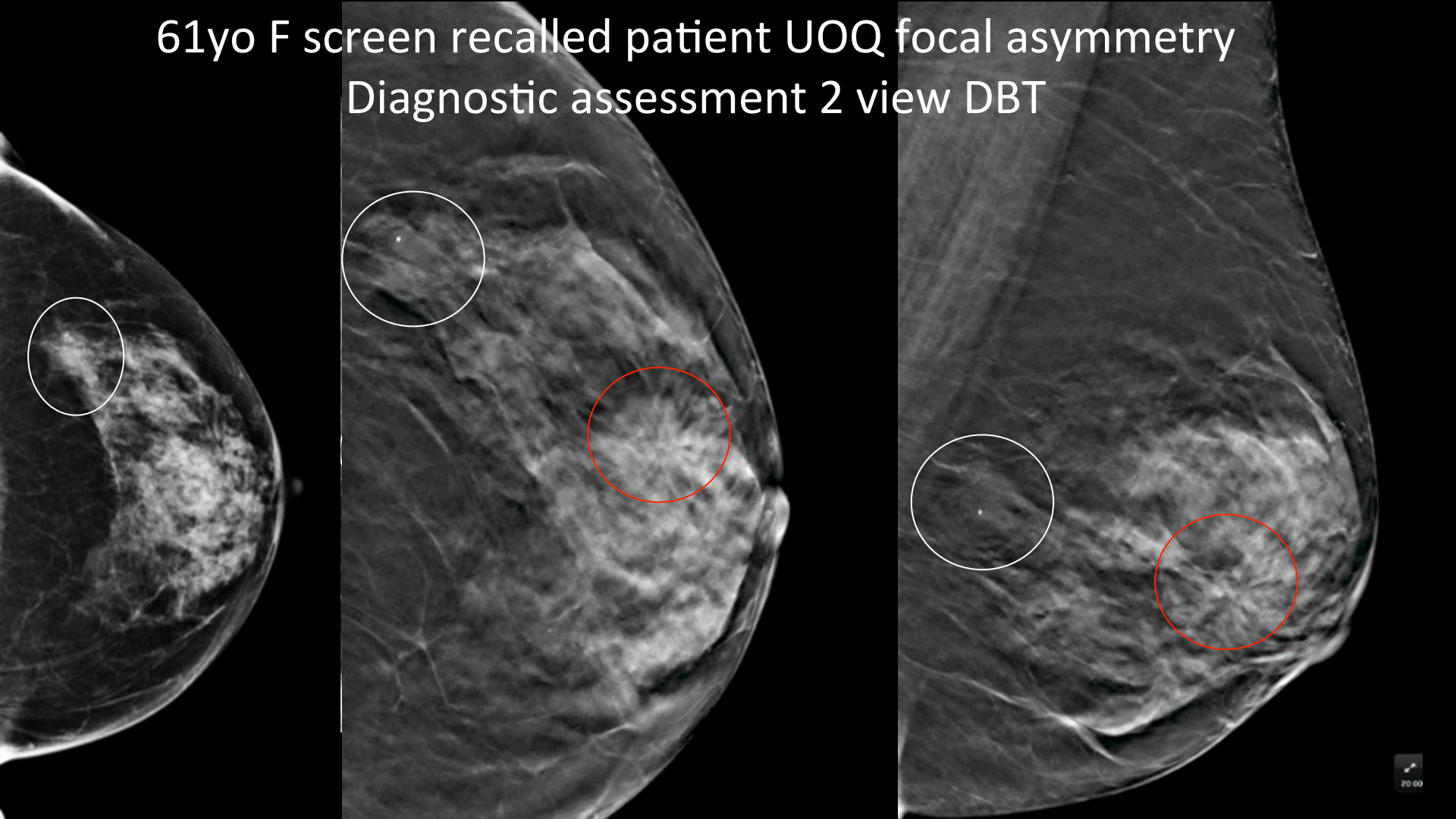
- DBT showed significant higher specificity (538/694) 77.5% than DM (265/694) 38.2%
  - DBT PPV 47.6% (142/298) vs DM 24.9% (142/571)
- 278 biopsies could have been avoided if DBT was used

Sharma N etl al. Radiology 2019:00

Abbreviated diagnostic work-up

- Additional spot-compression views are less often necessary
- One-view findings remain an uncommon form of malignancy; when seen on DBT have a higher PPV 4% on DBT+DM vs 1.8% on DM
- Shift in distribution of screening recalls to more masses and architectural distortion

Cohen EO, et al. AJR 2018; 211:445-451.


61yo F screen recalled patient UOQ focal asymmetry
Diagnostic assessment 2 view DBT

US

Fibroadenoma

Invasive ductal carcinoma

Architectural Distortion (AD)

- Two studies demonstrate change in PPV for AD
  - 43.4% with DM to 10.2% with DBT+DM ($p<0.001$)*
  - 73.6% with DM to 50.7% ($p<0.001$)**
- US correlate more frequent for AD with DM vs DBT+DM (84% vs 56%)
- PPV > 2% - biopsy is required

*Alshafeiy TI et al .Radiology 2018: 288
**Bahl M et al. AJR 2017: 209

Recall Calcifications

- **Magnification views** remain the preferred method to characterize fully their morphology and distribution
- Some reported lower sensitivity for calcs, others equivalent conspicuity but higher sensitivity and more accurate prediction of malignancy

Shift in BI-RADS assessment categories and increase positive predictive values

- Superior lesion assessment has led to higher PPV for biopsies (PPV3)
  - 29.6% with DM to 50% with DBT+DM*
- Decreased number of biopsies 69% to 36% for same cancer detection in NHS**
- 70% increase in performance with no loss of sensitivity
- Results in fewer false positive biopsies, reducing anxiety, patient discomfort and costs
- Decrease in BI-RADS 3 rates*

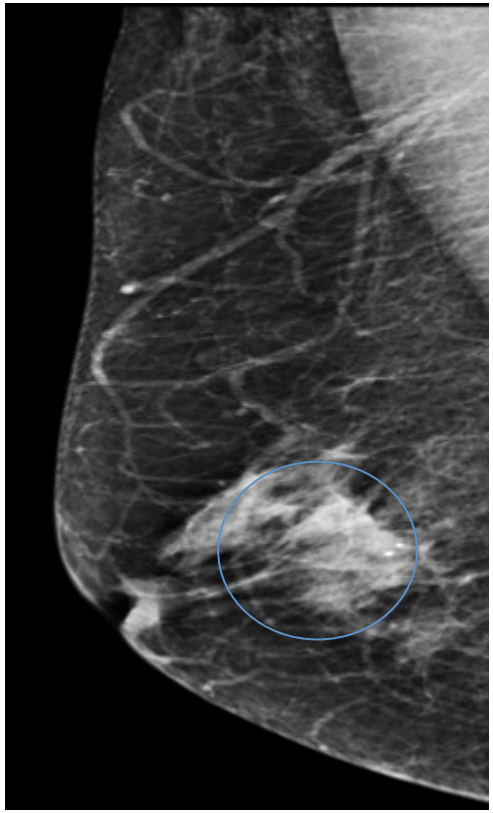
*Raghu M et al. Radiology 2016; 281
**Sharma N etl al. Radiology 2019:00

Workflow

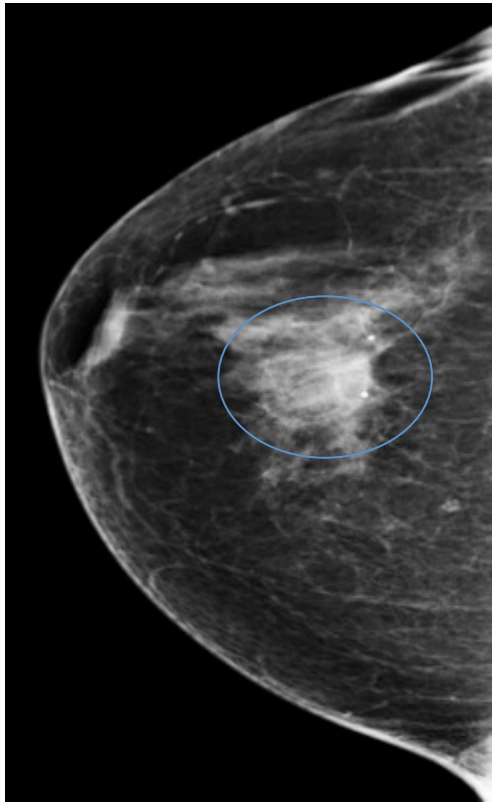
- Improved patient throughput
- Improved efficiency of breast centre

Diagnostic DBT in Canada

- Most centers start using DBT for diagnostic assessment
- Improves workflow
- Increases confidence and accuracy of radiologist



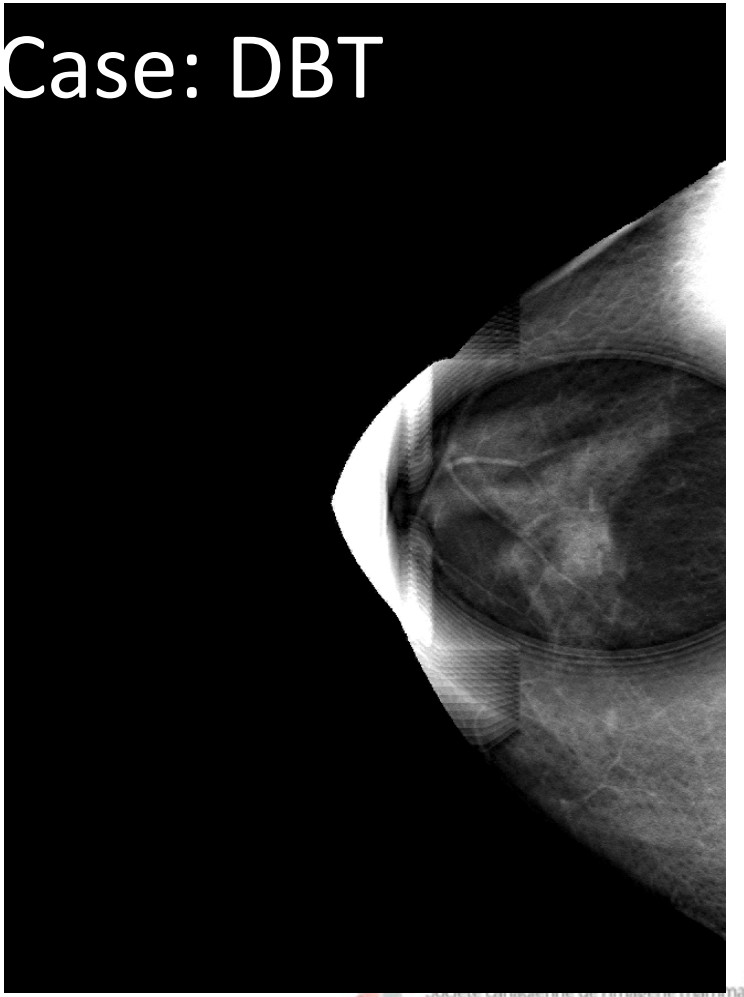
Medio-lateral oblique (MLO)

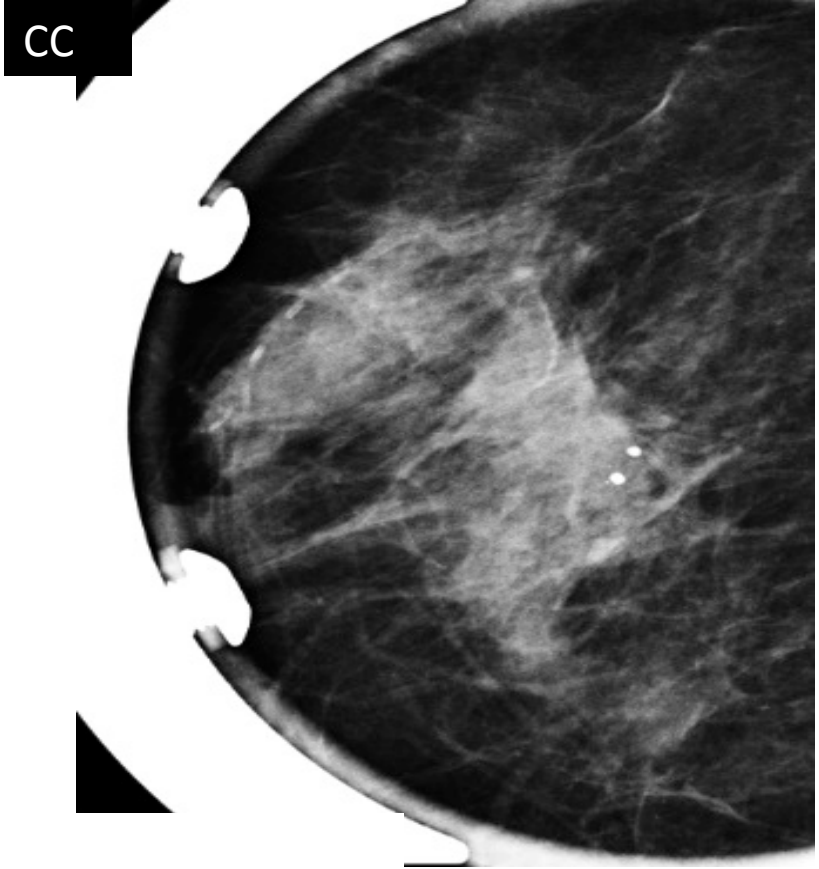


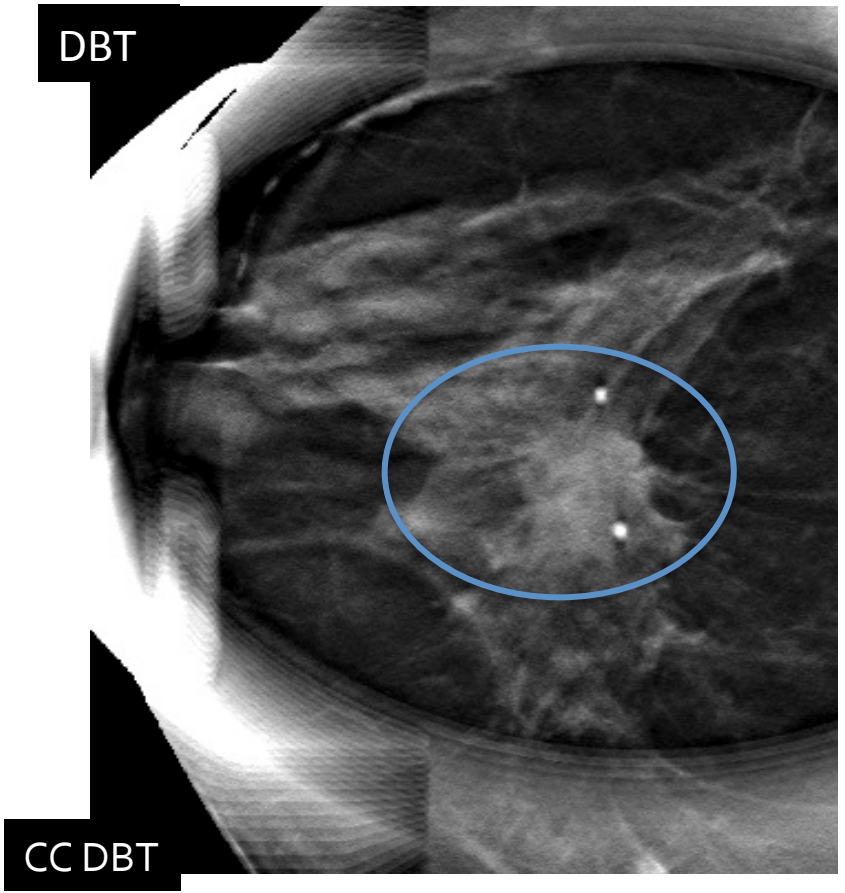
Cranio-caudal (CC)

Focal asymmetry right

Case: DBT



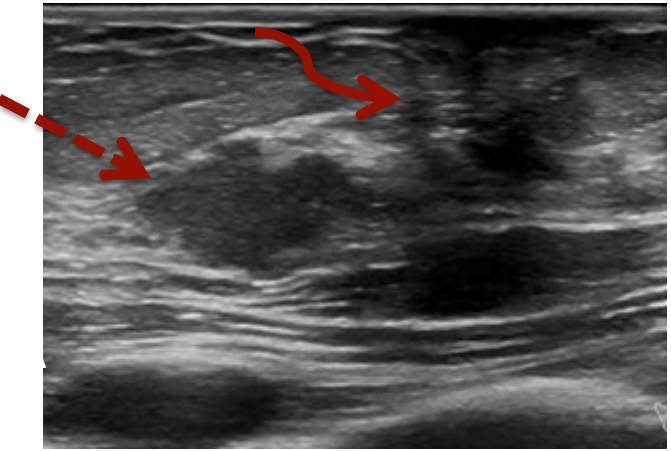


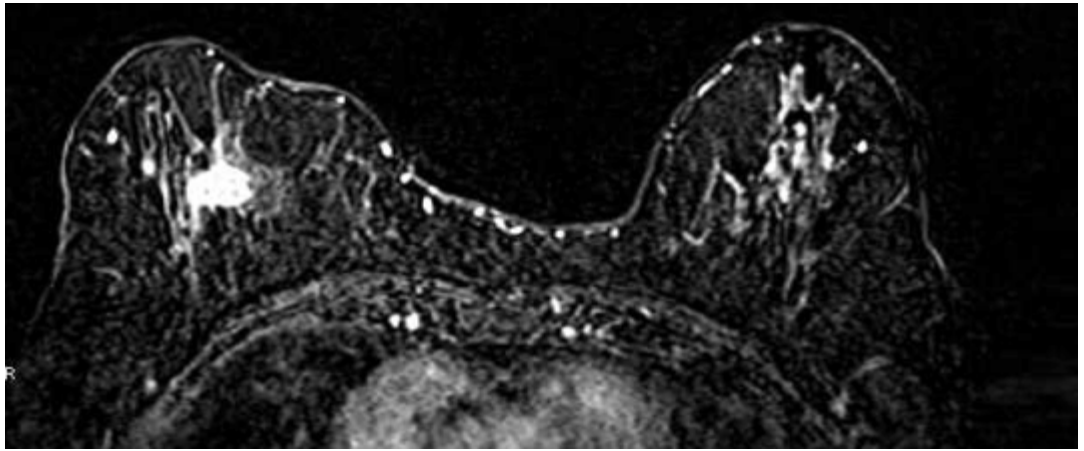


Comparison of MG with DBT:

The asymmetry persists on the MLO and CC coned down views

The spiculated mass is much better seen on DBT



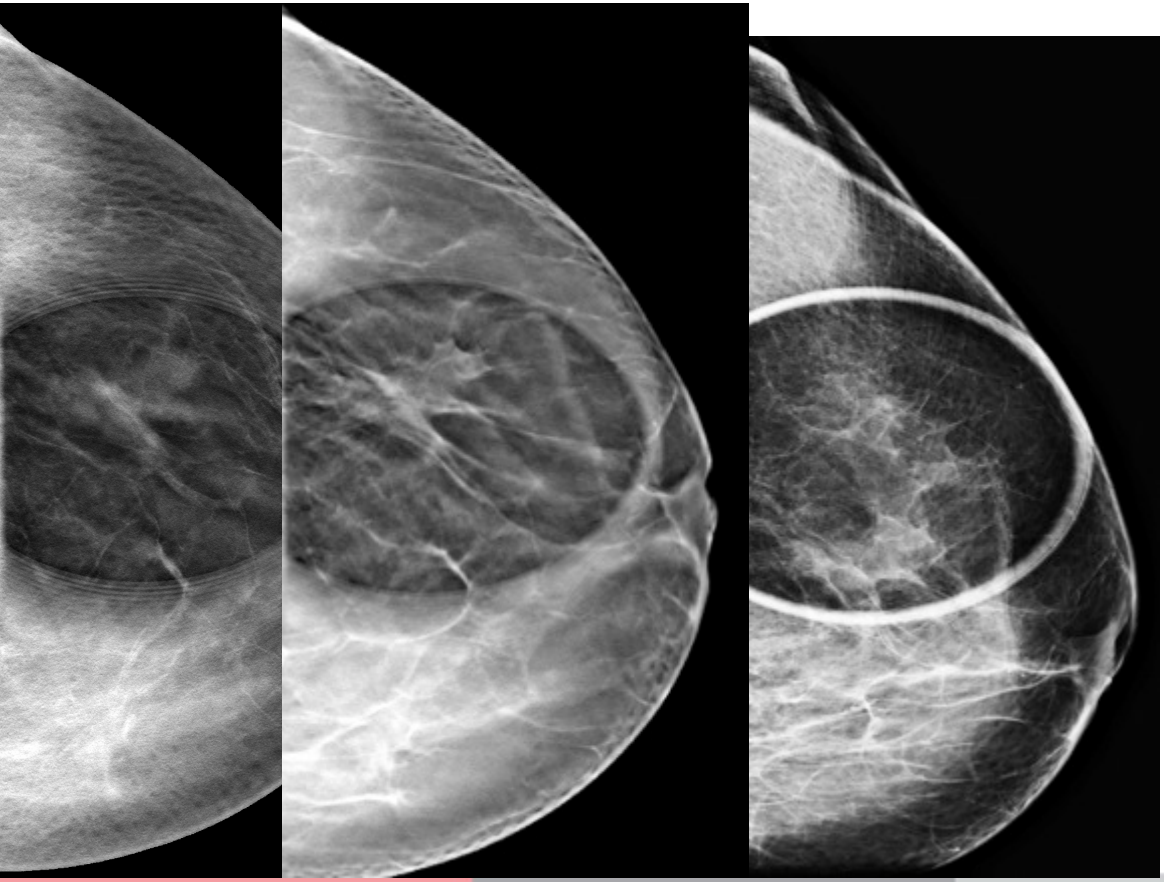


Suspicious, irregular mass on US adjacent to nipple

Pre-op enhanced MRI at 2 minutes confirms the irregular spiculated enhancing mass. Biopsy confirmed invasive ductal carcinoma.

Biopsies

DBT Biopsy



- Abnormality only seen on DBT - ? target?
- No ability to biopsy a lesion only seen on DBT
- Options: MRI, Second look US, DBT biopsy

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Advantages of DBT guided biopsy

- More comfortable for patients
  - Sitting or lateral decubitus position
  - Easier positioning
- Better at sampling far posterior lesions
    - challenging on standard 2D prone stereotactic tables
- Faster biopsies*
    - Faster targeting

*Schrading S, et al. Radiology. 2015;274:654–62
*Waldherr C, et al. Eur Radiol. 2016;26:1582–9

Prone 2D vs Upright 3D

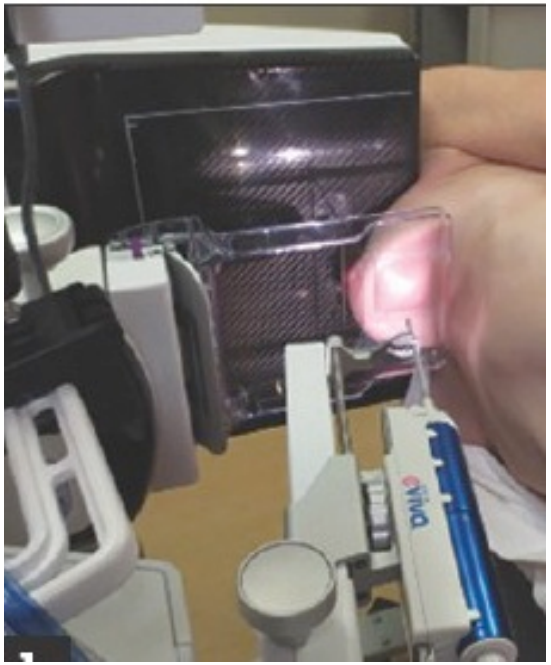
2D Prone

- Small biopsy window
- Positioning difficulties
- Unable to biopsy 1 view findings
- Cannot biopsy DBT only findings (classic – distortion)
- Longer procedure time

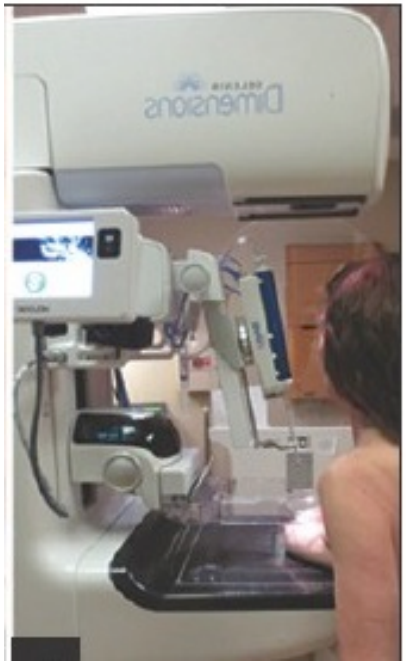
Upright DBT

- Large biopsy window - full detector size
- Easier positioning
- Can typically biopsy 1 view findings
- Can biopsy DBT only findings
- Can access far posterior lesions
- Can revert to 2D
- Shorter procedure time

Decubitus medial approach

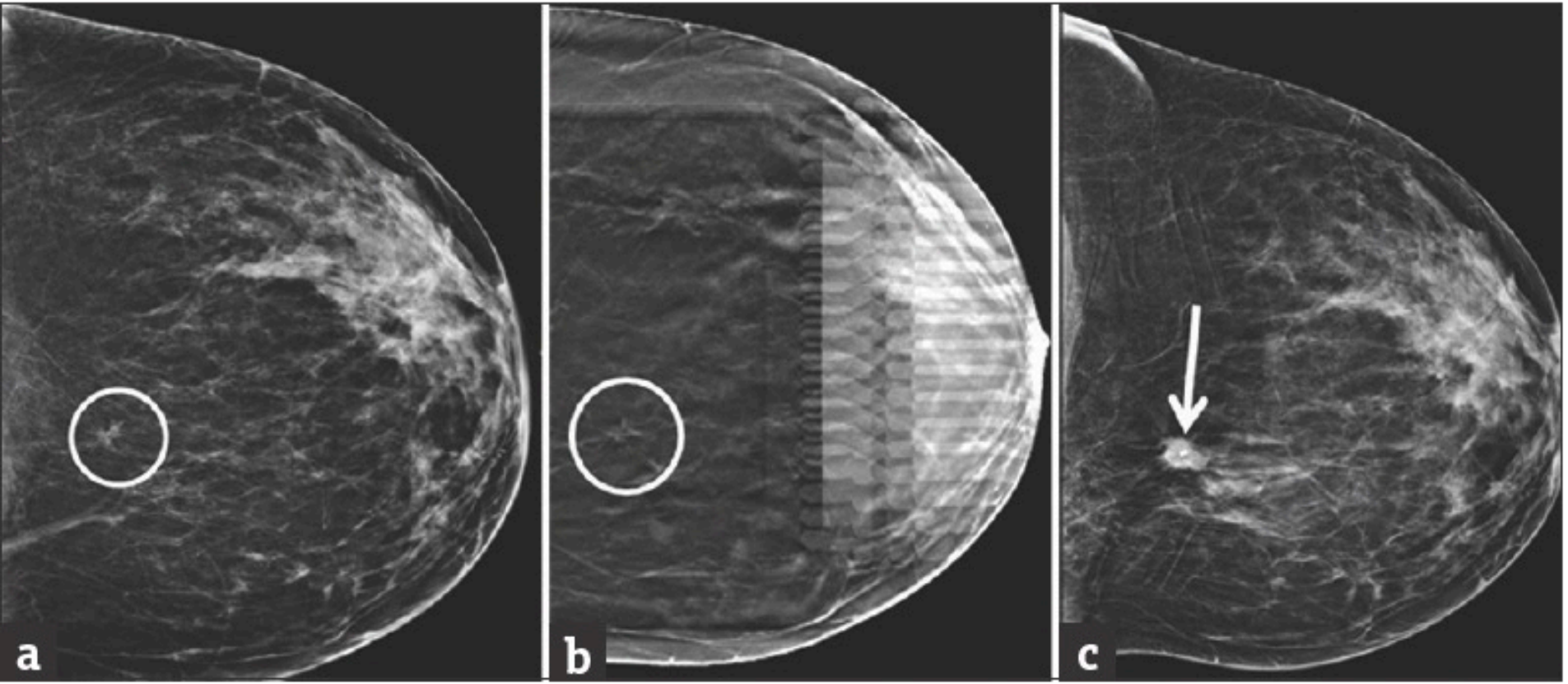


Decubitus inferior approach



Upright superior approach

Shin K et al. J Clin Imaging Sci. 2018; 8: 28


a
b
c

Upright DBT VAB: Comparison with Prone Stereotactic VAB - Schrading et al[1]

- 205 pts with 216 suspicious mammographic findings
  - Upright DBT VAB on 46 pts w/ 51 lesions
  - Prone Stereotactic VAB on 159 pts w/ 165 lesions
- 9 gauge needle / standard number tissue samples

	DBT VAB	PS VAB
Technical success	51/51 (100%)	154/165 (93%)
Mean procedure time	13 min	29 min
Rad-path discordance	0	0
Tissue sampling time	=	=
Exposures	5	8

[1]*Radiology: Volume 274: Number 3—March 2015*

DBT-guided biopsy

- Necessary with DBT
- Increased speed of biopsy
- Greater ease for patients
  - Risk of vasovagal
- Improved workflow
- Learning curve for technologists
  - Positioning training essential

Current state in Canada

- 90-110 Hologic DBT units in Canada
- ?? GE units in Canada
- Primarily being used for diagnostic assessment of recalled cases: asymmetries, masses
- Screening in some centres in Alberta, Quebec, and for baseline screens in Ontario

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

TOMOSYNTHESIS MAMMOGRAPHIC IMAGING SCREENING TRIAL (TMIST) EA1151

Sponsor:
Canadian Clinical Trials Group MAC22
Collaborator:
National Cancer Institute (NCI)
Information provided by (Responsible Party):
Eastern Cooperative Oncology Group (ECOG-ACRIN Cancer Research Group)

ClinicalTrials.gov Identifier: NCT03233191

This study is to be conducted according to International Conference of Harmonization [ICH] guidelines, U.S. federal regulations, standards of Good Clinical Practice, and ACRIN research policies and procedures

Ottawa Site-PI: Dr. Jean Seely

Physics Lead

- Martin Yaffe, PhD
- PI: TMIST Lead-in Study
- EA1151: Central Physics

TMIST Scientific Rationale

Should Tomosynthesis replace Digital Mammography for breast cancer screening?

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TMIST Scientific Rationale

1. We have not had a breast cancer screening trial since the 1980s

2. More recent screening technologies (tomosynthesis (TM), US, MRI) find more cancers than the current standard of care, digital mammography (DM), but also have more false positives

3.TM is generally done with greater radiation to patient (up to 2X), costs more and takes more time to interpret than digital mammography

TMIST Scientific Rationale

- Study Question: Does TM find *life-threatening* cancers?

1. Randomized clinical trials with mortality endpoints are very expensive and impractically long (10-30 years)

2. TMIST primary endpoint measures the difference in potentially *life-threatening cancers* in women screened with DM versus TM.

3. If there are fewer *life-threatening cancers* in women screened with TM over 4.5 years of screening, TM should replace DM for breast cancer screening

TMIST Primary aim

- Compare the number of advanced cancers detected using TM vs. DM
  - With advanced cancers defined as-

    1) Those with metastases.

    2) Those with positive nodes.

    3) All invasive cancers $\geq$ 2.0 cm. in size.

    4) All invasive cancers that are > 1 cm. in size and which have prognostic markers that suggest aggressive behavior, (i.e. triple negative or her2+).

TMIST Secondary aim

1.Patient-Centered Aim

To compare health care utilization (including cancer care received) and cost of an episode of breast cancer screening by TM versus DM

2. Imaging Aims

- ✓ To compare the recall and biopsy rates due to abnormal screening examinations for TM versus DM
- ✓ To compare diagnostic accuracy of TM versus DM
- ✓ To compare interval cancer rates.

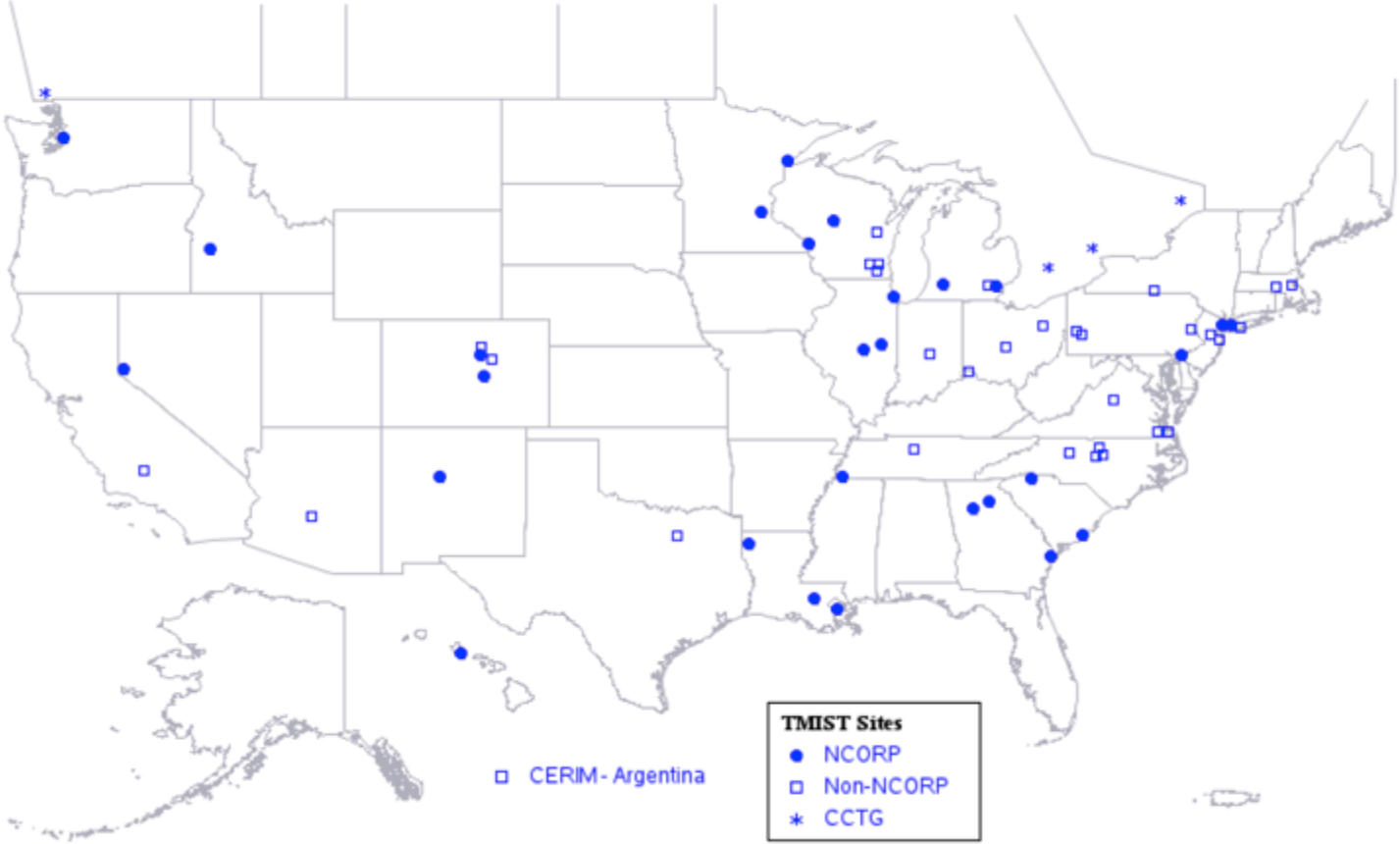
3. Biological Aims

- ✓ To determine correlates of TM/DM findings, pathology and genetic analysis, and other patient characteristics with long-term patient outcomes, including interval cancer rate.
- ✓ To assess and compare the characteristics (e.g. stage, grade, cell subtype) of cancers detected from screening by TM and DM.

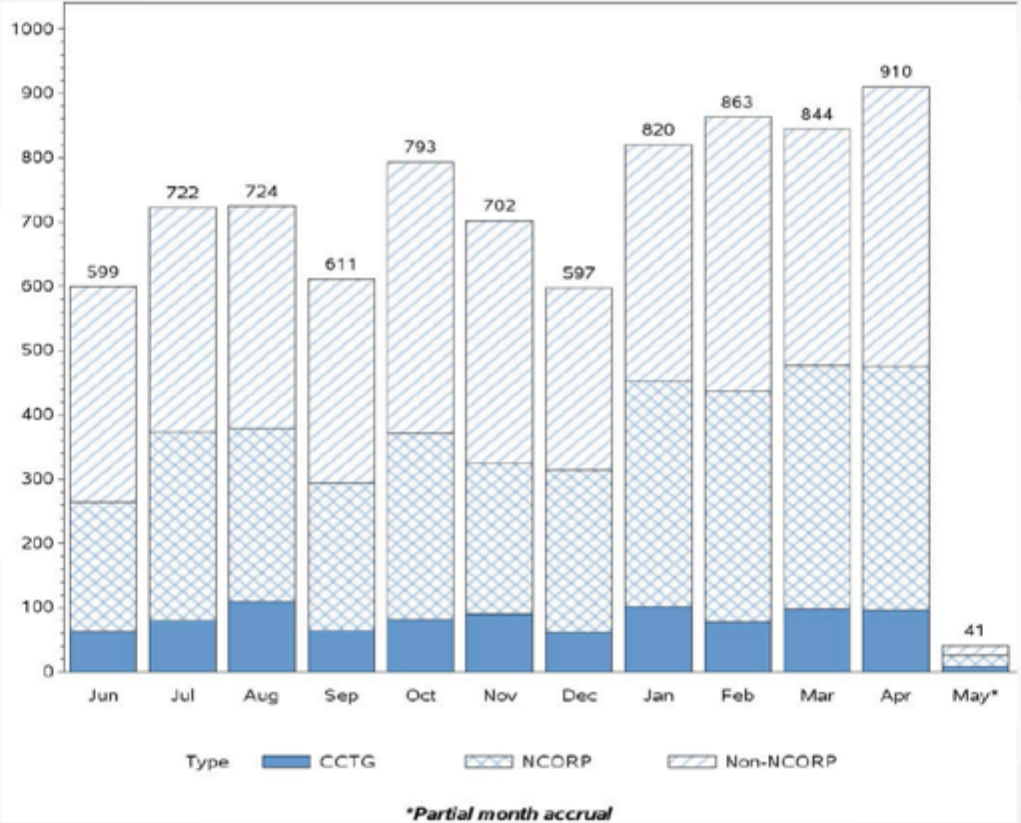
- 1. Study Type: Randomized Clinical Trial.
- 2.Patient Population: Asymptomatic women presenting for screening mammography, ages 45-74. No prior breast cancer, implants. Can’t be pregnant or lactating.
- 3.Number of Women: 164,946 women (82,473 per arm)
- 4.Randomization Assignments: Breast Tomosynthesis (TM) or Digital Mammography (DM).

- 1. Annual screening will take place at entry and 1, 2,3 and 4 years after entry. (5 screens)
- 2.Biennial screening will take place at entry and 2 and 4 years after entry (3 screens).
- 3.Truth on breast cancer status will be determined by biopsies and follow-up information.
- 4.Total numbers of advanced cancers will be compared 4.5 years after randomization in both study populations (TM vsDM).

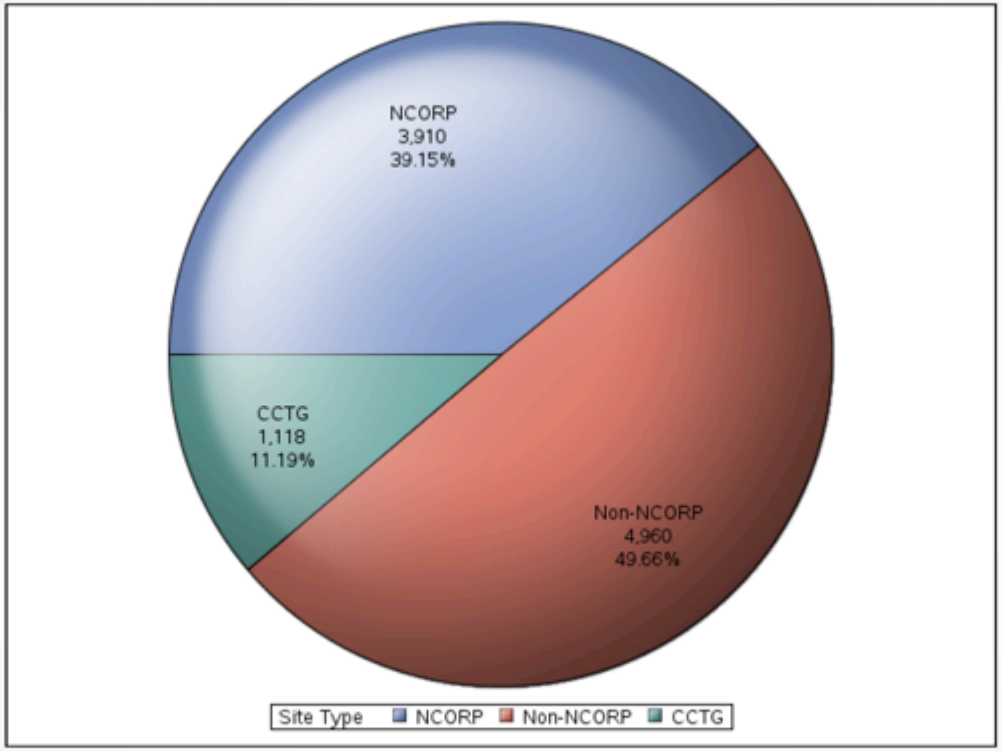
64 Sites are Open and Accruing (05/02/2019)
9988 Participants Enrolled



TMIST Monthly Enrollment – Last 12 Months



TMIST Enrollment by Type of Site



TMIST RESEARCH TEAM

The Ottawa Hospital | L'Hôpital d'Ottawa

Affiliated with • Affilié à uOttawa

Thank you

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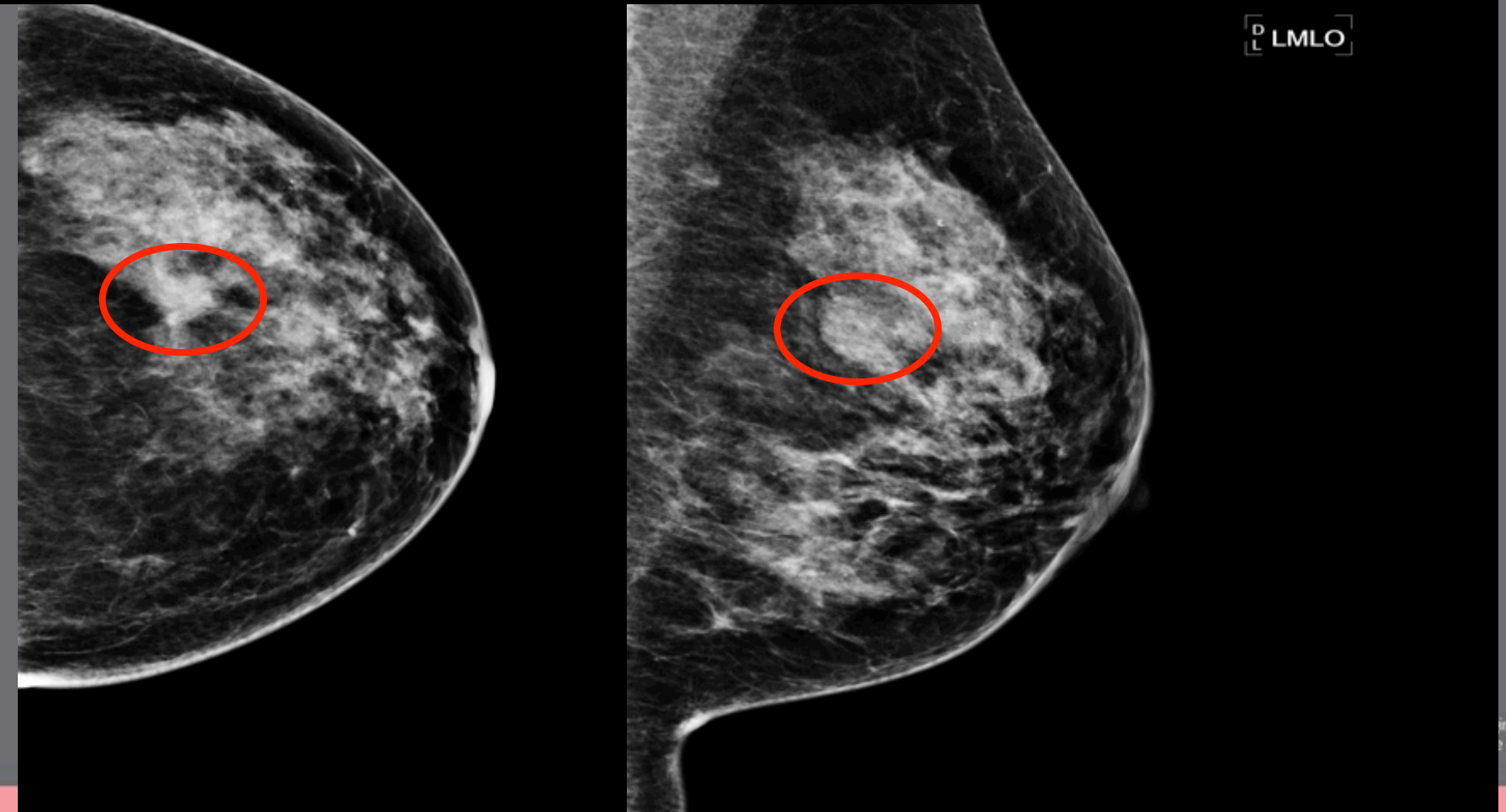
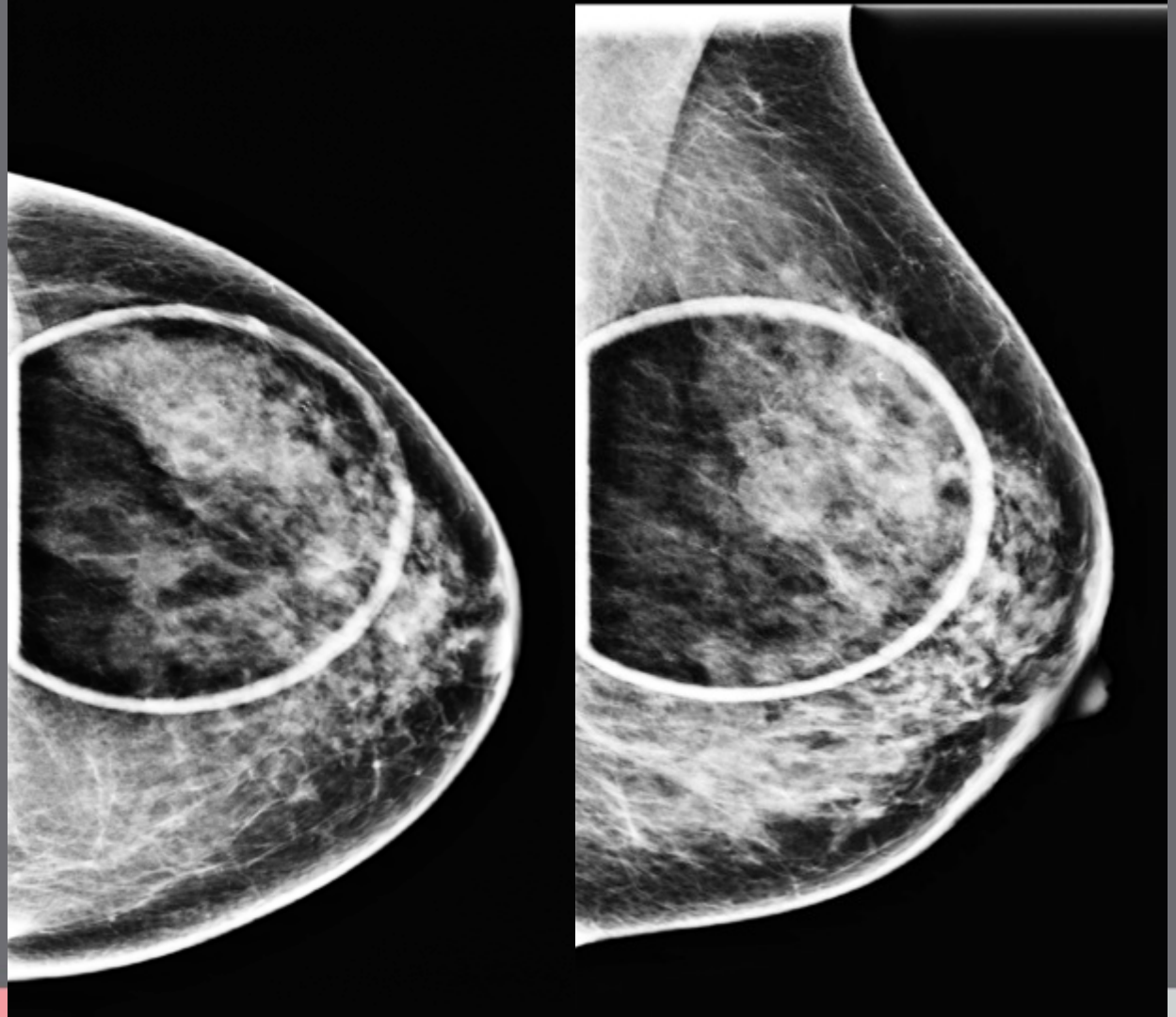
Screen-detected mass



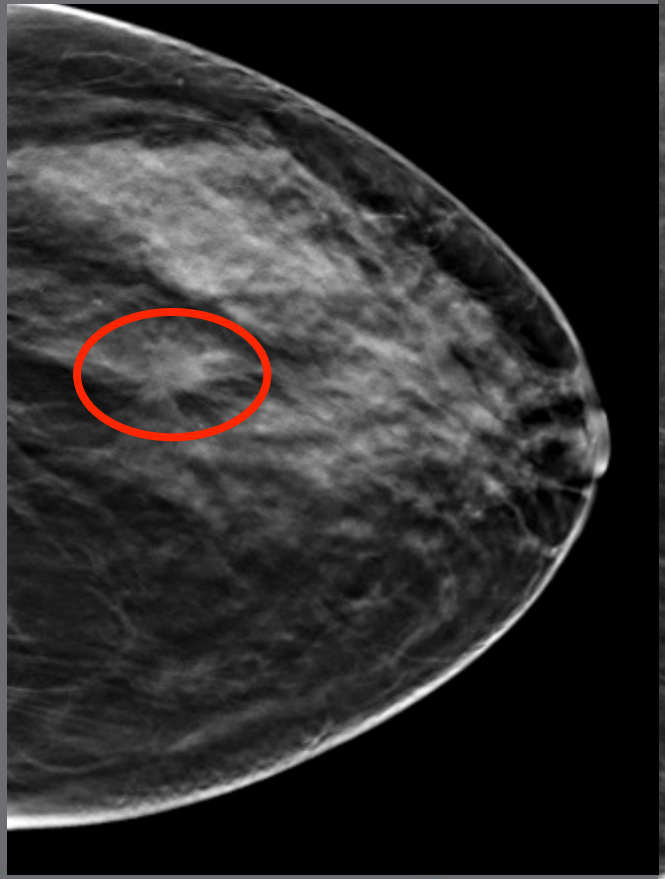


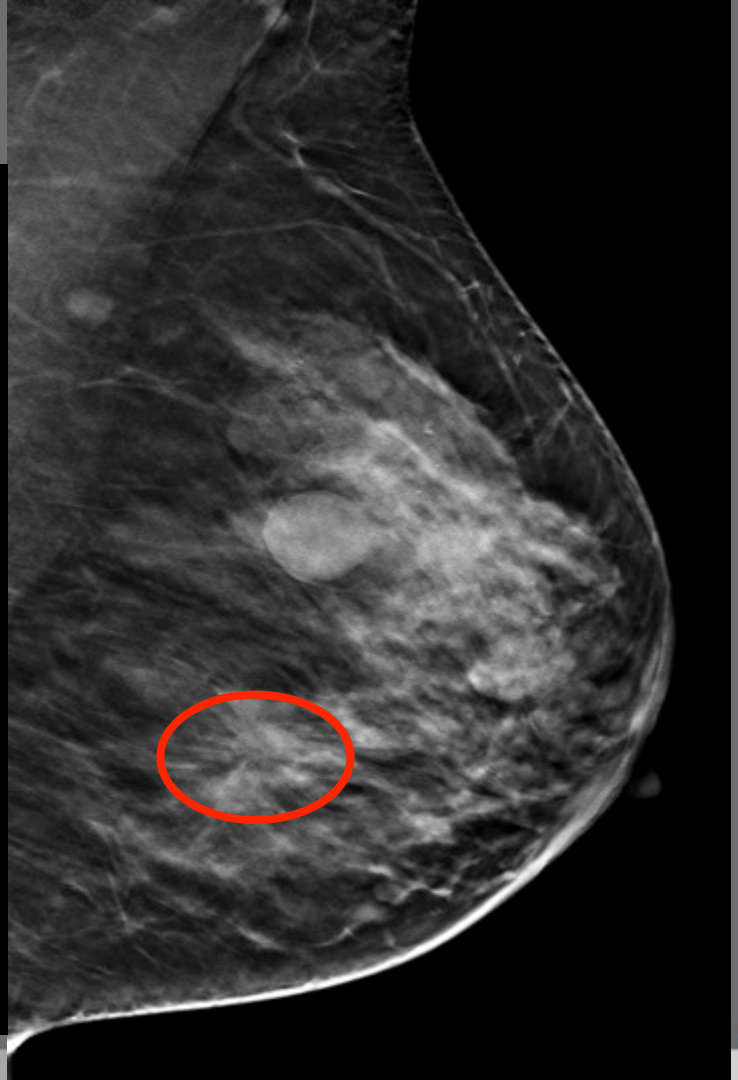
Coned compression views showed partly well circumscribed mass

Ultrasound confirmed a simple cyst

DBT showed well circumscribed mass – likely benign
And…

A suspicious spiculated mass not seen on the FFDM





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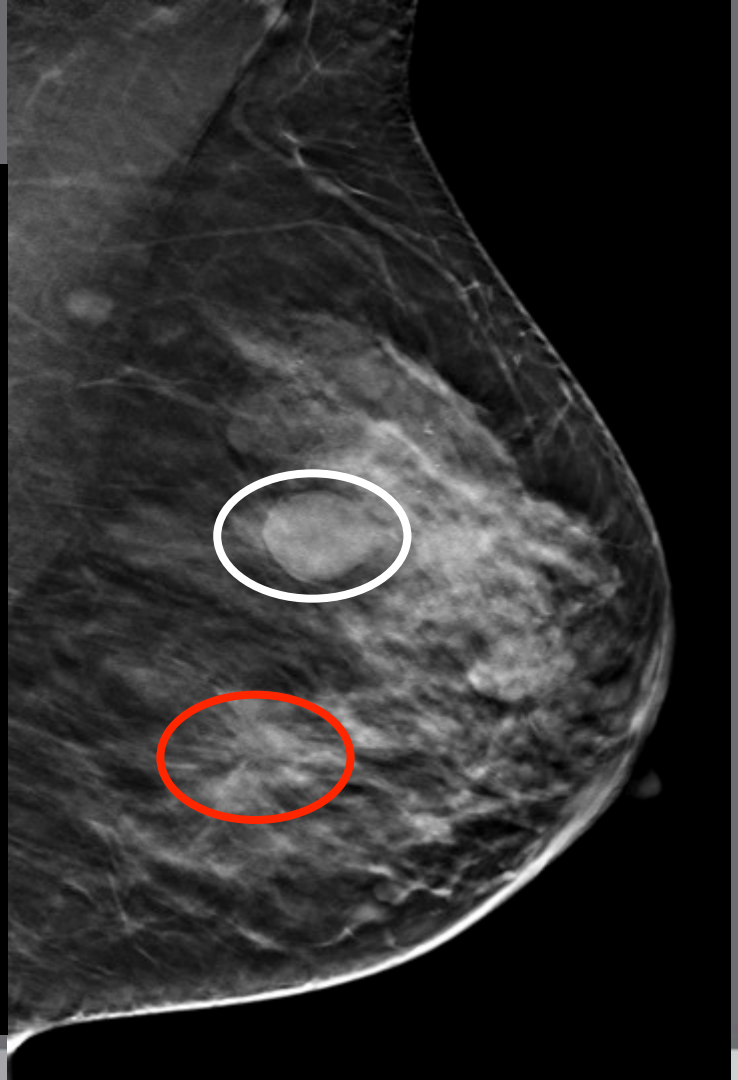

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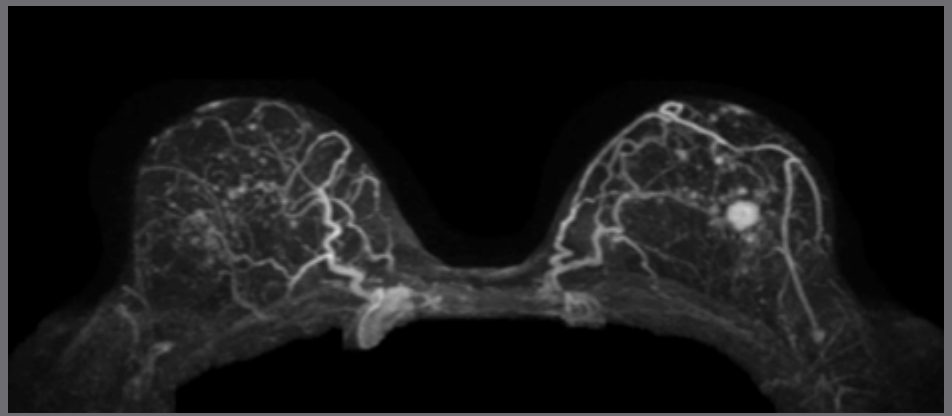

2 cm invasive ductal carcinoma
4 mm multifocal IDC
Treated by mastectomy

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