Non-contrast MRI for Screening and Surveillance of Breast Cancer

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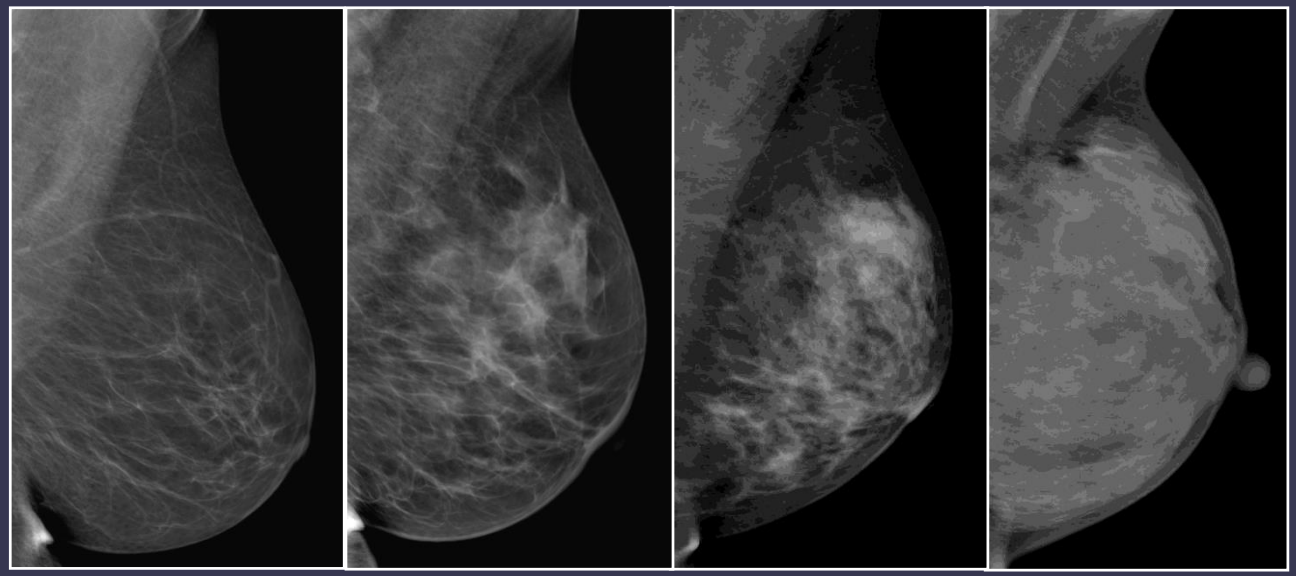
Cotents

- Gadolinium Deposition and Need for Non-contrast MRI Screening
- Challenges of DWI as a Stand-alone Screening Modality
- Concepts and Protocols of Noncontrast DWI Screening Trial in Korea

Limitation of Conventional Imaging

- Mammography
  - Ca^{++} detection

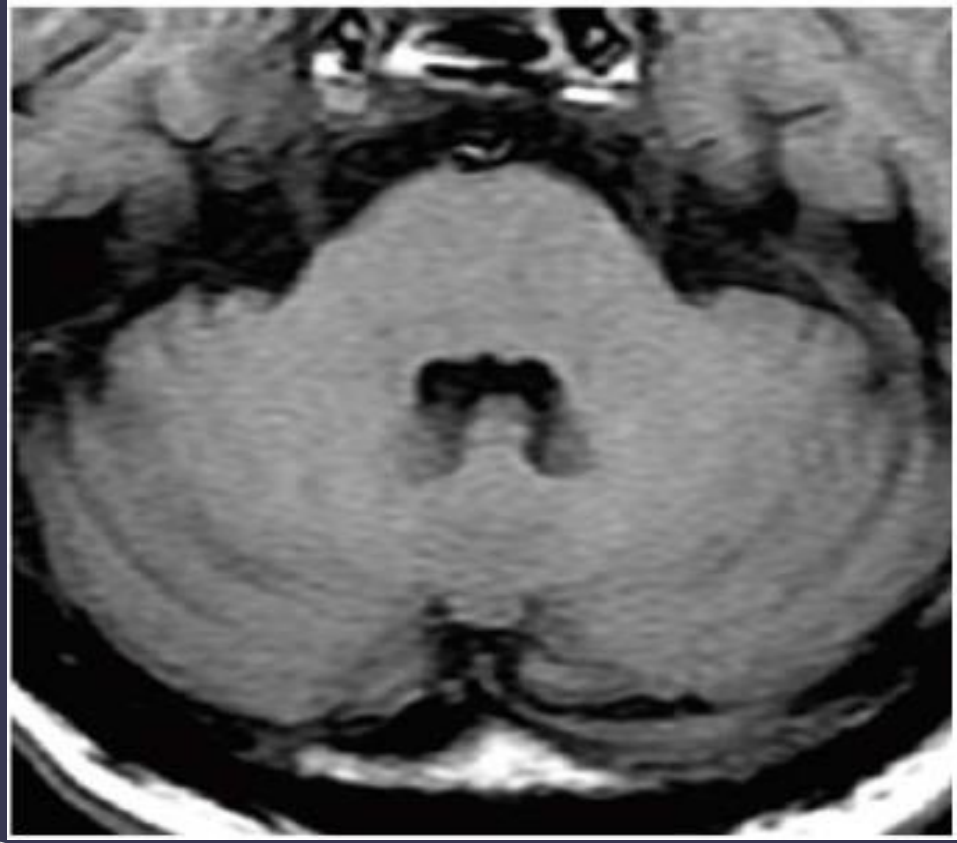


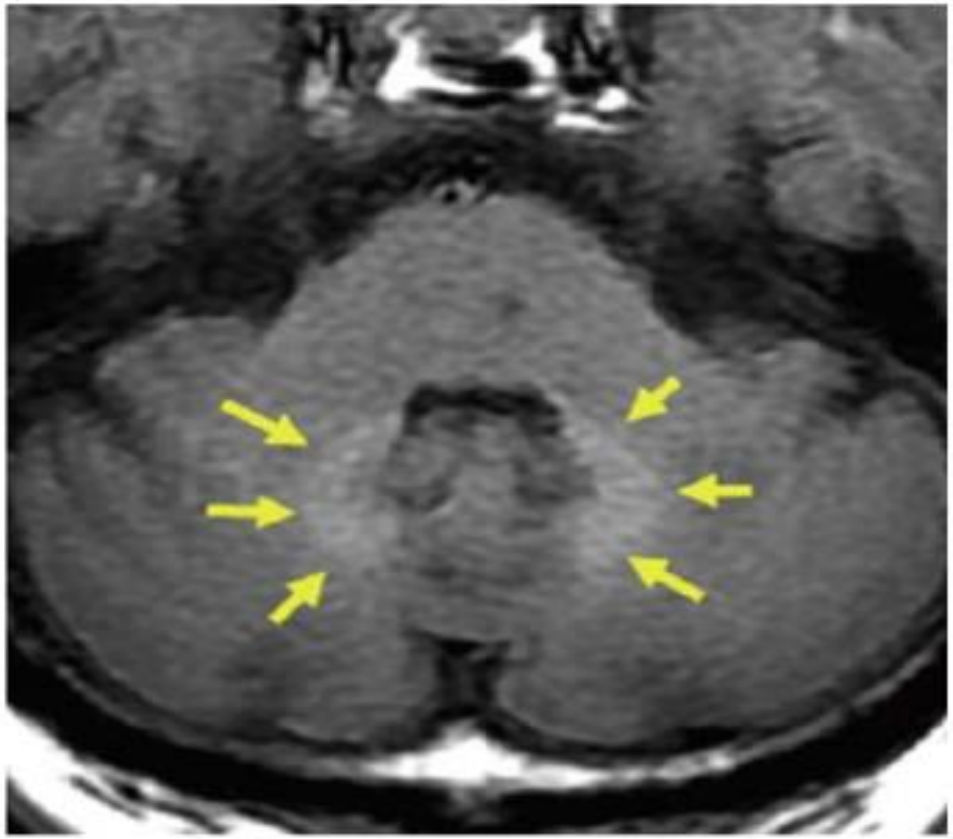
- US – sensitive but high false-positive rate
- Conventional DCE-MRI – highest sensitivity for detection of invasive cancer, but modest specificity
  - DCE-MRI needs gadolinium contrast

Gadolinium Deposition

Tomonori Kanda, MD, PhD
Kazunari Ishii, MD, PhD
Hiroki Kawaguchi, MD
Kazuhiro Kitajima, MD, PhD
Daisuke Takenaka, MD, PhD

High Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-weighted MR Images: Relationship with Increasing Cumulative Dose of a Gadolinium-based Contrast Material





Gadolinium Deposition

- Autopsy of 13 cases (≥4) & 10 controls

  McDonald RJ, et al. Radiology 2015

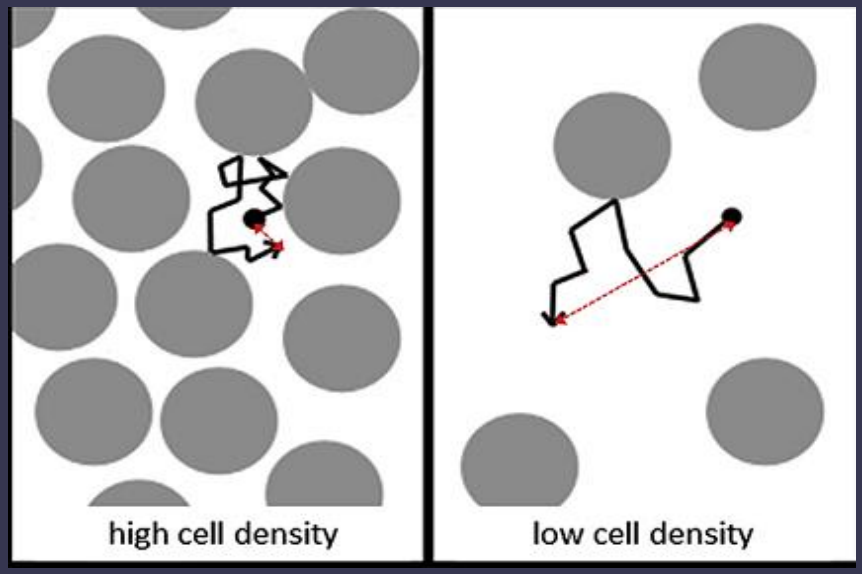
  - Repeated IV exposure to GBCAs → neuronal tissues deposition → Dose-dependent relationship
    - Independent of patient age, sex, baseline renal function, or interval between Gd exposure & death
- FDA regulatory statements

  September 20, 2018

  - Minimize repetitive & closely spaced administration
- *Growing health concerns – Repetitive and long-term use of GBCA used in conventional breast MRI*

Diffusion-weighted Imaging

- Fast unenhanced MR sequence
  - Motion-sensitizing gradients to measure Brownian motion of water
- Degree of water diffusion within tissue
  - Inversely correlated to tissue cellularity & integrity of cell membrane



Breast malignancies exhibit restricted diffusion on DWI compared to normal breast tissue

Partridge et al. MRI Cin N Am 2013

Breast DWI

- Noncontrast MR imaging technique

→ Qualitative and quantitative evaluation of breast lesions with a short scan time

  - As an alternative to Gd-enhanced MR evaluation in patients at risk for nephrogenic systemic sclerosis
  - Can assist in differentiating benign & malignant lesions
  - Identifying early response in tumors undergoing NAC
  - Noncontrast screening modality

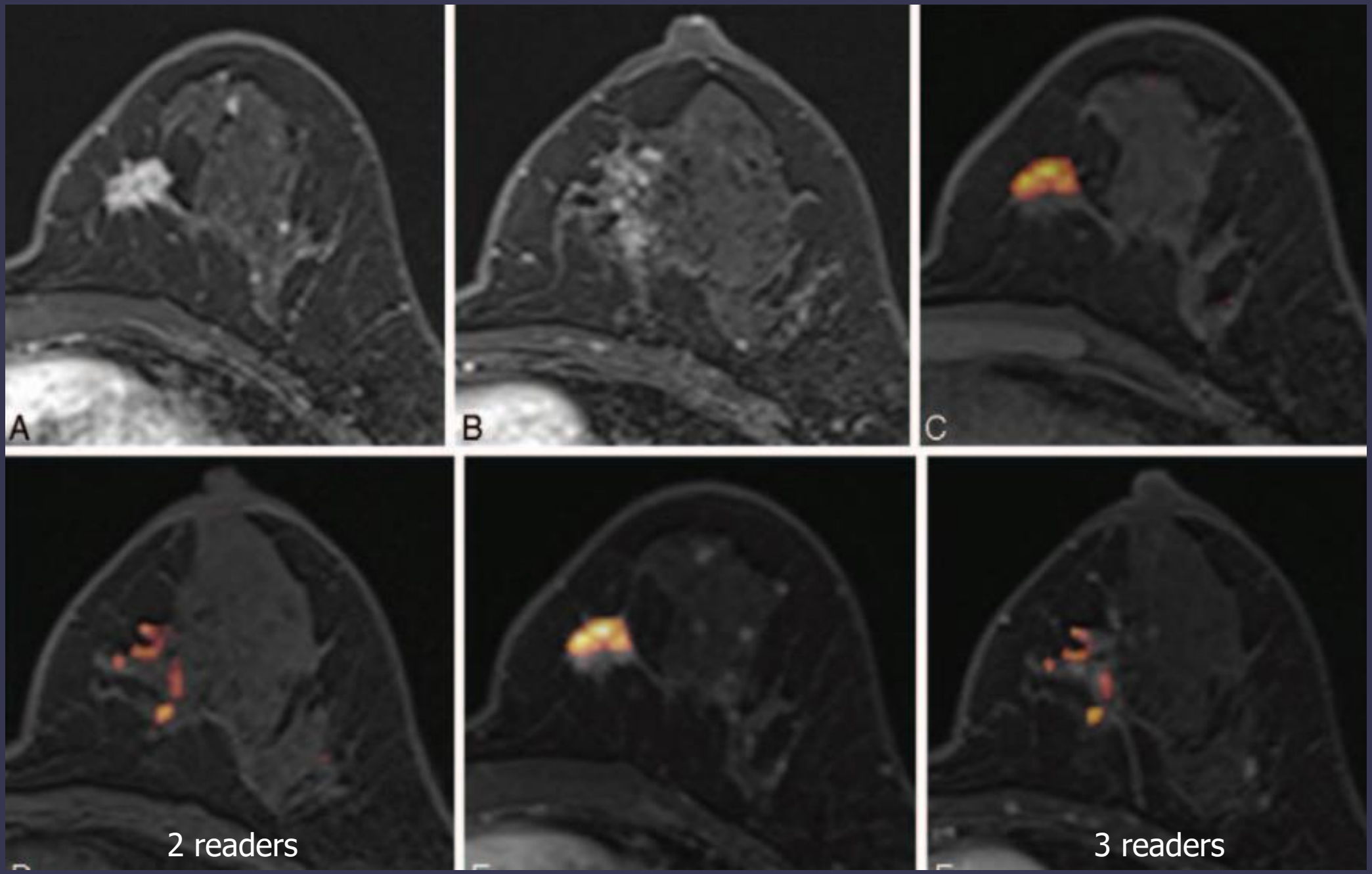
Diagnostic Performance of Fused Diffusion-Weighted Imaging Using Unenhanced or Postcontrast T1-Weighted MR Imaging in Patients With Breast Cancer

Hee Jung Shin, MD, Eun Young Chae, MD, Woo Jung Choi, MD, Su Min Ha, MD, Jin Young Park, MD, Ki Chang Shin, BA, Joo Hee Cha, MD, and Hak Hee Kim, MD

- Fused DWI: Non-contrast vs. early post-contrast
  - 87 pts with 129 lesions – preoperative staging
- Compare the diagnostic performance of UFMR & PCFMR
  - UFMR – fused DWI using unenhanced T1WI + high b-value DWI
  - PCFMR – fused DWI using early post-C T1WI + high b-value DWI
  - Five readers – lesion detection, size, BIRADS final assessment, probability of malignancy, lesion conspicuity, ADCs
  - Detection rates of index malignant lesions – similar
  - Lesion conspicuity – significantly higher on PCFMR than UFMR

Shin HJ et al. Medicine 2016; 95:e3502

44-year-old patient with an IDC of the left breast



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LCIS and Flat Epithelial Atypia

Meta-analysis of DWI

Studies	N	Sensitivity	Specificity
All studies	14	0.92 (0.87–0.95)	0.86 (0.80–0.90)
DCE-MRI alone	10	0.93 (0.85–0.97)	[illegible]
DWI alone	10	0.86 [illegible]	[illegible]
1.5 T	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	(0.64–0.83)
[illegible]	[illegible]	[illegible] 0.89)	0.88 (0.84–0.92)
[illegible]	[illegible]	0.86 (0.75–0.94)	0.70 (0.51–0.85)
[illegible]000	8	0.94 (0.91–0.96)	0.85 (0.79–0.89)
b<1000	5	0.86 (0.82–0.89)	0.84 (0.79–0.88)
High quality	6	0.95 (0.89–0.98)	0.86 (0.75–0.92)
Suboptimal quality	8	0.87 (0.80–0.92)	0.86 (0.79–0.91)

Benign vs. Malignant lesions

Sensitivity and specificity of DWI: 86% & 76%

Sensitivity and specificity of DCE-MRI: 93% & 71%

Zhang Li et al. Acta Radiol 2016

Diagnostic NC-DWI

Author	Total (Cancer%)	Field Strength	NC-MRI technique	Study population	Sen.	Sp.
Baltzer, 2010	67%	1.5T	ssEPI, T2-TSE	BIRADS 4/5 masses	94%	[illegible]%
Yabuuchi, 2011	67%	1.5T	ssEPI, b=1000 T2-STIR	Mixed: asympto[illegible] cance[illegible]	[illegible]	[illegible]%
Wu, 2013	45%	3T	ssEPI, T[illegible]	[illegible]	[illegible]	[illegible]
Trimboli, 2014	32%	1.5[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Telegra[illegible]	[illegible]	[illegible]	[illegible]	[illegible]4/5; [illegible]tive family Hx, dense	94%	58%
[illegible]	[illegible]	[illegible]	[illegible] MIP, b=1500	Screening detected BIRADS 4/5	92%	96%
[illegible]	[illegible]%	1.5T	ssEPI, STIR	Mixed; cancer or equivocal	79%	97%
Shin, 2016	83%	3T	rsEPI, b=1000 MIP, T1-VIBE	Biopsy-proven malignancy	92%	86%
Baltzer, 2018	59%	3T	rsEPI, b=850	BIRADS 4/5	91%	73%
Pinker, 2018	63%	3T	ssEPI, b=850	BIRADS 0/4/5	82%	87%

Wide Variations of Sensitivity & Specificity
d/t Heterogeneity of DWI technique
Lack of standardization of interpretation criteria

Balzer et al. Inves Radiol 2018; 53:229-235

Potential Clinical Roles

- Reduce toxicity of GBCA for annual screening of high-risk women
- Cost-effective supplementary tool to MG in intermediate-risk women with dense breasts
- Women with contraindication to contrast:
  - Pregnancy, reduced GFR, allergies
- Benefit of screening DWI over CE-MRI
  - Lesion detection on DWI – Independent of BPE, breast density, menopausal status, or timing during menstrual cycle

Hidetake Yabuuchi
Yoshio Matsuo
Shunya Sunami
Takeshi Kamitani
Satoshi Kawanami
Taro Setoguchi
Shuji Sakai
Masamitsu Hatakenaka
Makoto Kubo
Eriko Tokunaga
Hidetaka Yamamoto
Hiroshi Honda

Detection of non-palpable breast cancer in asymptomatic women by using unenhanced diffusion-weighted and T2-weighted MR imaging: comparison with mammography and dynamic contrast-enhanced MR imaging

Diffusion-Weighted MRI as an Adjunct to Mammography in Women Under 50 Years of Age: An Initial Study

Toshiki Kazama, MD,[1*] Yoshifumi Kuroki

Rubina M. Trimboli[1]
Nicola Verardi[1]
Francesco Cartia[2]
Luca A.

Breast Cancer Dete
Double Rea
MRI

Noncontrast MRI – higher performance & sensitivity than MG alone, but lower than CE-MRI

(STIR, T2-weighted TSE, DWIBS): An accurate
strategy for detecting and differentiating
breast lesions☆

Michele Telegrafo, Leonarda Rella, Amato Antonio Stabile Ianora, Giuseppe Angelelli, Ma

Elizabeth S. McDonald[1,2]
Jill A. Hammersley[1]
Shinn-Huey S. Chou[1]
Habib Rahbar[1]
John R. Scheel[1]
Christoph I. Lee[1]
Cheng-Liang Liu[1]
Constance D. Lehman[1]
Savannah C. Partridge[1]

Performance of DWI as a Rapid Unenhanced Technique for Detecting Mammographically Occult Breast Cancer in Elevated-Risk Women With Dense Breasts

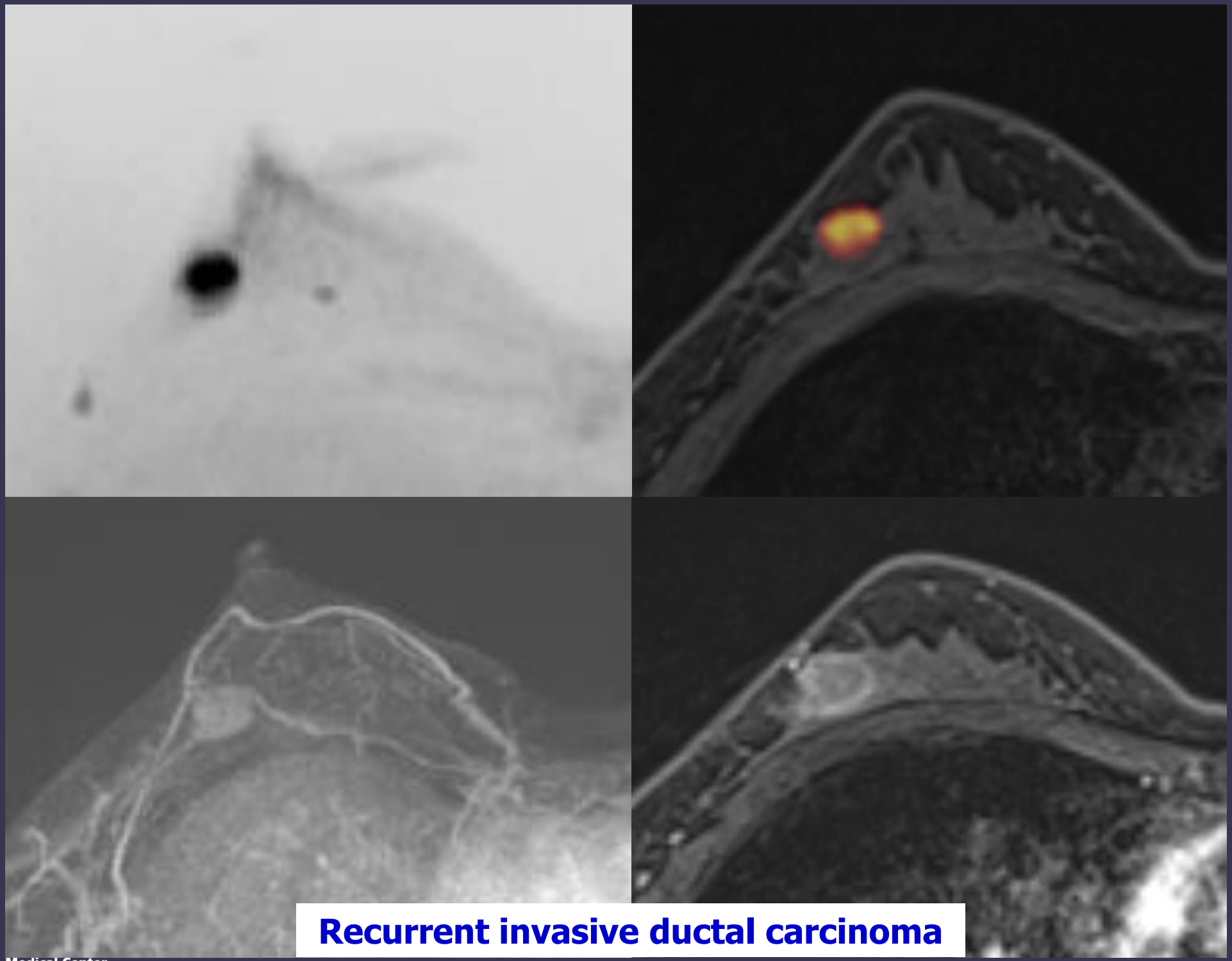
Unenhanced magnetic resonance screening using fused diffusion-weighted imaging and maximum-intensity projection in patients with a personal history of breast cancer: role of fused DWI for postoperative screening

Ji Won Kang[1] · Hee Jung Shin[1] · Ki Chang Shin[1] · Eun Young Chae[1] · Woo Jung Choi[1] · Joo Hee Cha[1] · Hak Hee Kim[1]

- Screening: Non-contrast fused DWI vs. DCE-MRI at 3T
  - 343 pts with a personal history of breast cancer
  - Three radiologists – lesion detection & final assessment
  - Non-contrast fused DWI & DWI MIPs
  - Full protocol DCE-MRI & DCE MIPs
- Acquisition time – 10 min ↓ vs. reading time – 10 sec ↓
- Sensitivity of 93% (89~100%)
- Specificity of 94% (93-95%)

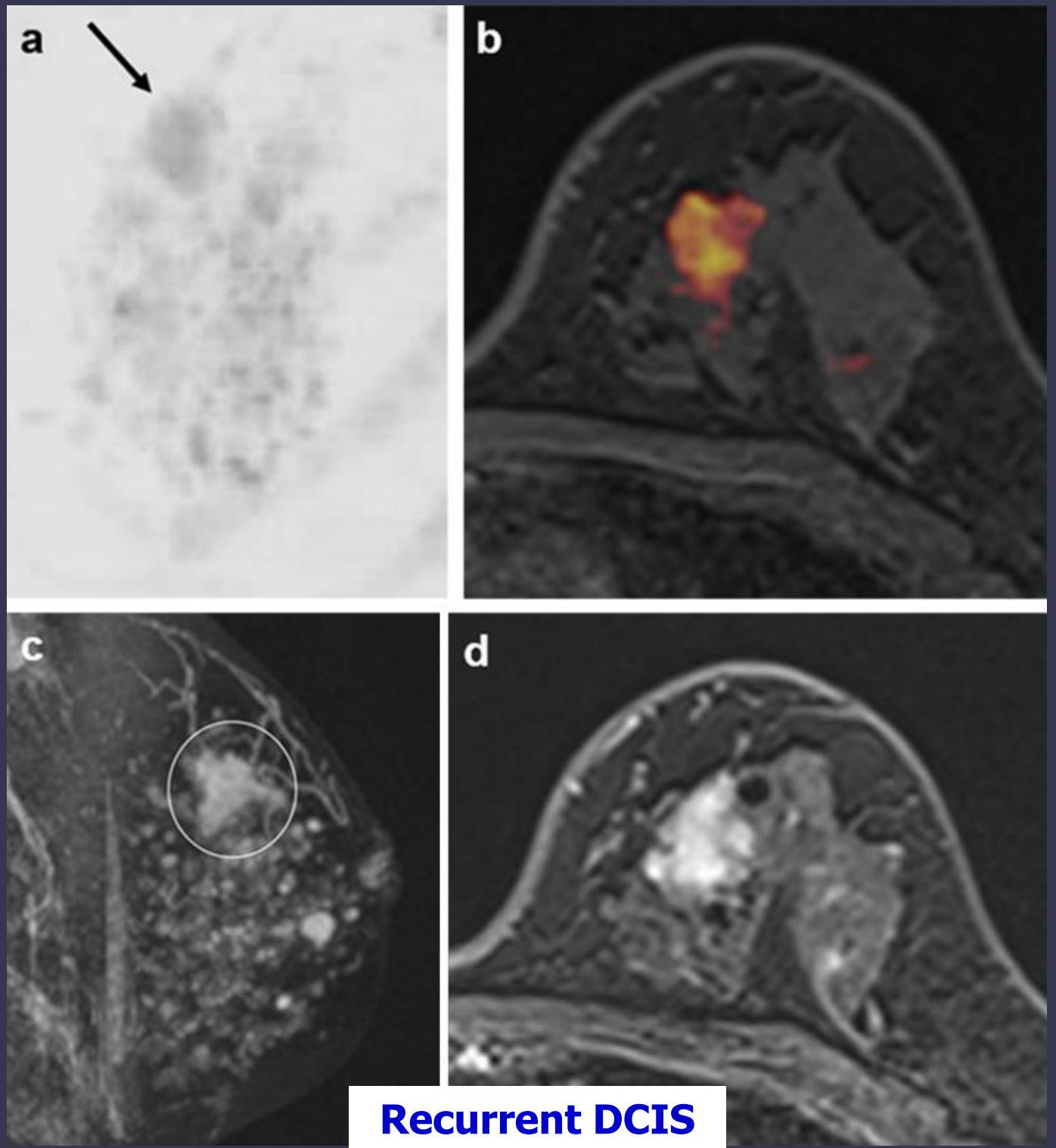
Breast Cancer Res Treat 2017; 165:119-128

A 43-year-old patient who underwent left mastectomy due to IDC 3 years ago



Recurrent invasive ductal carcinoma

A 52-year-old patient who underwent right mastectomy due to DCIS 3 years ago



Recurrent DCIS

Screening DWI

Author	Total (Cancer%)	Field Strength	NC-MRI Sequence	Voxel size	Study population	Sen	Sp	PPV	NPV
Yabuuchi 2011	63 (67%)	1.5T	ssEPI, T2WI	2.8x4 x5	Asymptomatic with BIRADS 4/5 on DCE-MR	50			49
Kazama 2012	46 (27%)	1.5T	ssEPI, T2WI, ADC	1.8x3 x5	Patient				75
Trimboli 2014	67 (32%)	1.5T	ssEPI						
T 2					suspicious of US findings & high-risk screening	94	79	79	94
Mc 201		& 3T	EPI, T2WI, T1WI, ADC	1.9x1.9x5 & 1.5x1.5x3	High-risk women with dense breast, matched case-control	45	91	63	81
Kang (AMC) 2017	343 (2.5%)	3T	rsEPI MIP, fused T1WI	1.7x1.7x3	Asymptomatic women with history of breast cancer	93	94	30	99.7

Sensitivity: 45~94% and specificity: 79~95%
d/t Advanced technique (rs-EPI or DWIBS)
MR scanner (1.5T or 3T)

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Partridge et al. Radiology Under revision

Challenges of Screening DWI

- False Negatives
  - Low spatial resolution
  - Variable image quality
  - Low lesion conspicuity

  } Addressed by
    - Protocol optimization
    - Advanced technique

- False Positives →
  - Refined interpretation strategies
  - Optimized ADC cutoffs

Partridge S. Korean Soc MRI Meeting 2018

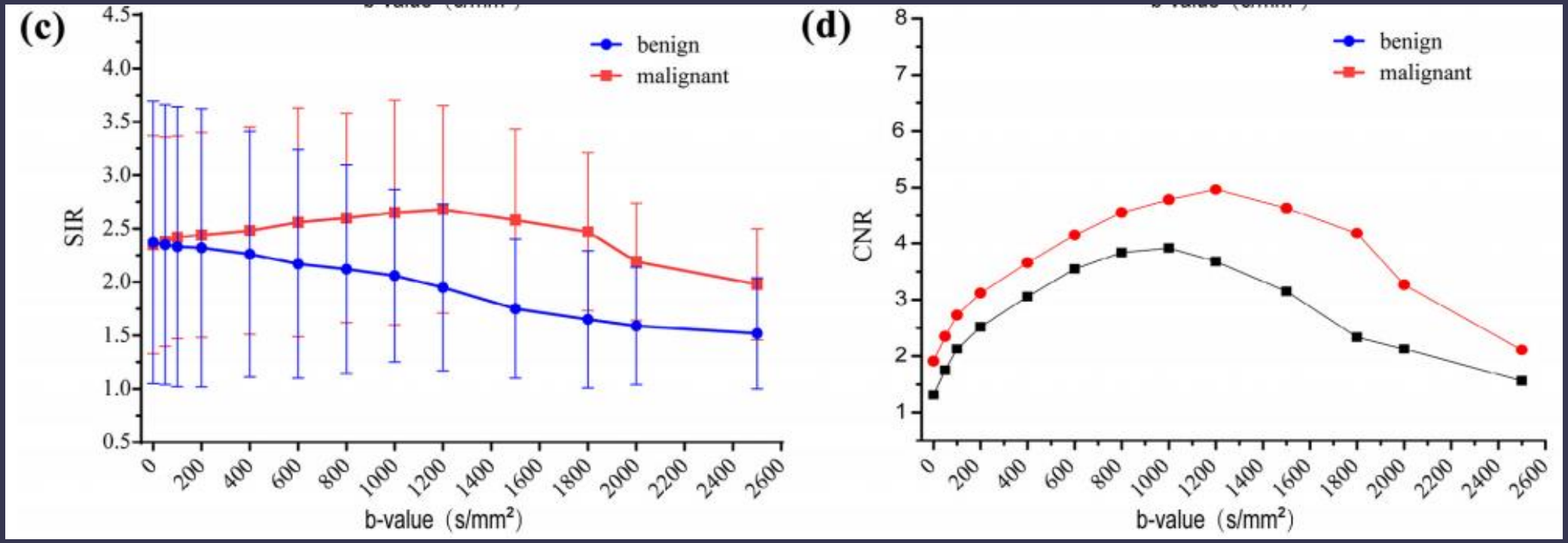
DWI Protocol Optimization

- European Society of Breast Radiology guideline
  - Field strength ≥ 1.5T
  - Max. gradient strength – a least 30 mT/m
  - Dedicated breast coil ≥ 4 channels
  - EPI-based axial acquisition of bilateral breasts
  - In-plane resolution ≤ 2x2 mm^2 & thickness ≤ 4 mm
  - TE as low as possible & TR ≥ 3000 ms
  - High quality shimming
  - Parallel imaging with acceleration factor of 2~4

Partridge S and Shin HJ et al. Radiology 2019 under revision

b-value Selection at 3T

- Effect on lesion conspicuity



Signal intensity ratio (SIR), and contrast-to-noise ratio (CNR) of lesions at different b-values

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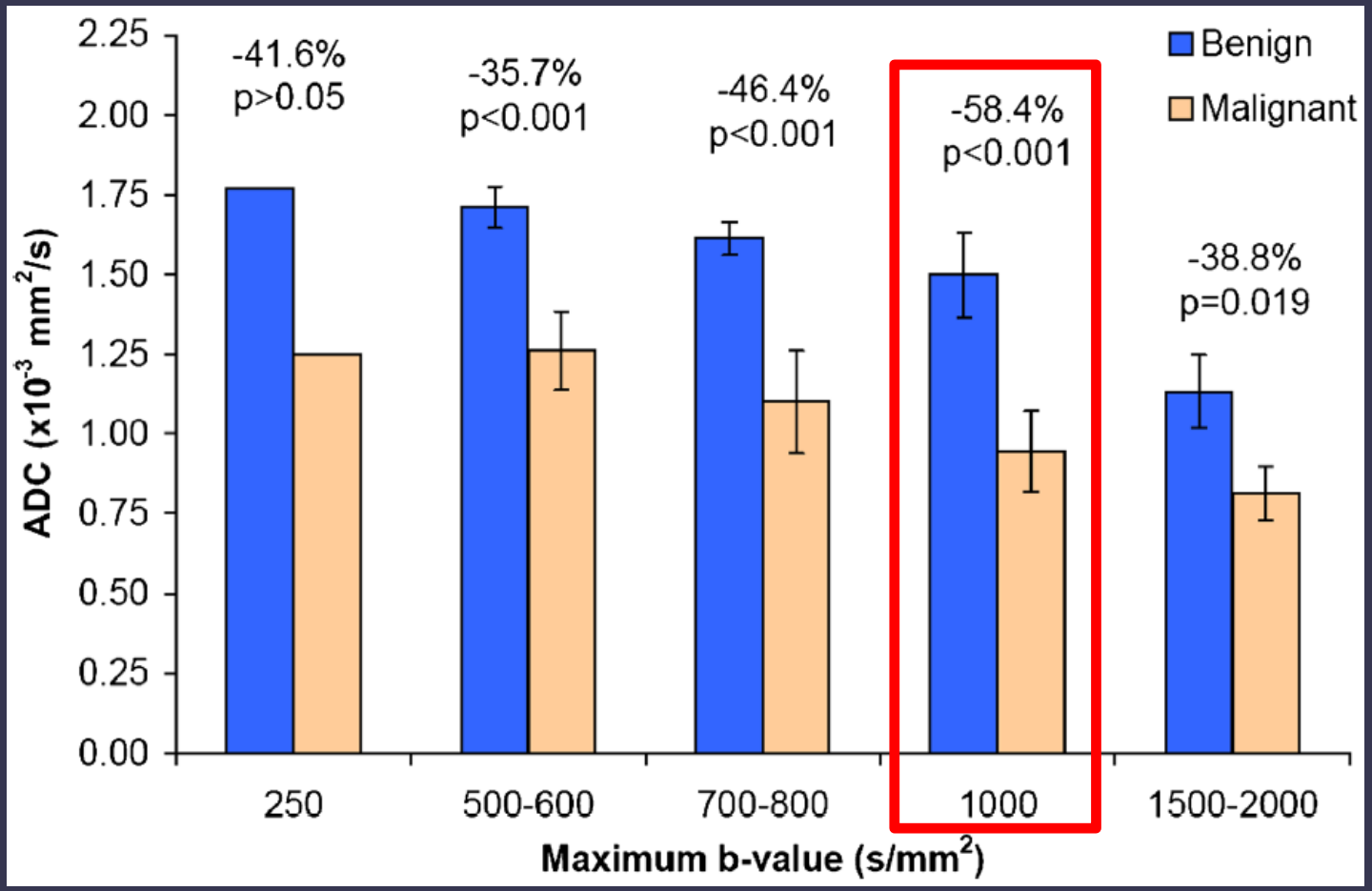
Han X et al. Acad Radiol 2016

Effect of b value & Contrast

- Meta-analysis of 26 articles at 1.5T scanner
  - Two b-values – b=0 & 10000 – best for differentiating benign from malignant lesions



Dorrius et al. Eur Radiol 2014

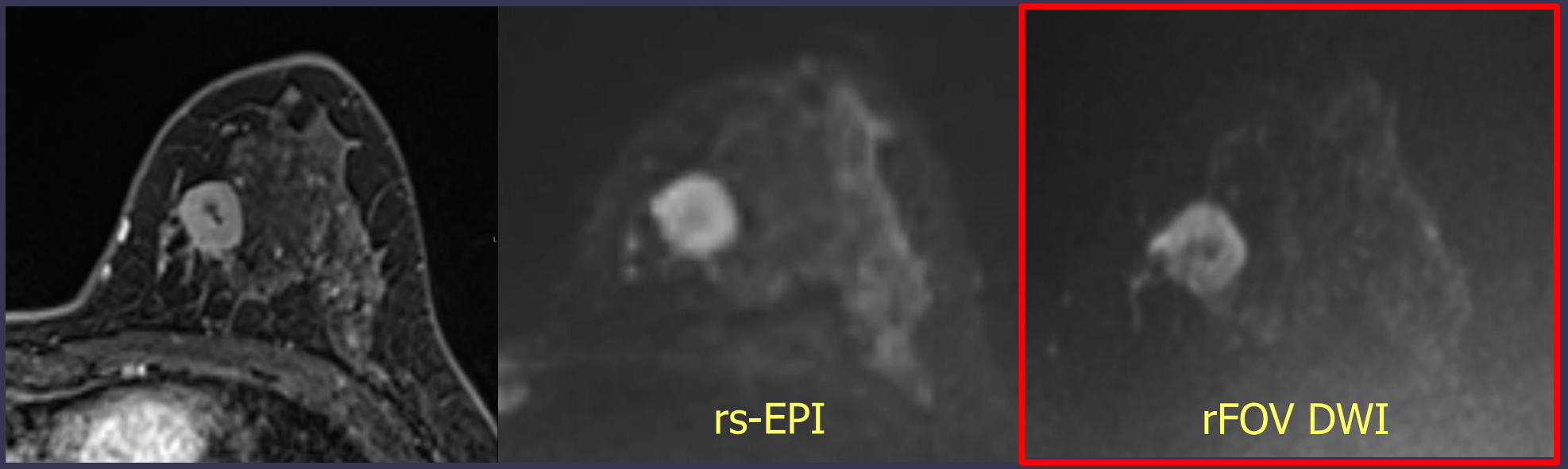
Advanced Technique

- High-resolution DWI
  - readout-segmented EPI (rs-EPI)
  - reduced field-of-view EPI (rFOV EPI)
- Image registration algorithms
  - reduce spatial inaccuracies and artifacts
- DWI MIPs and DWIBS
- Fusion of high b-value DWI to ue T1WI or T2WI
- Computed high b-value DWI

Comparison of Readout Segmented Echo Planar Imaging (EPI) and EPI With Reduced Field-of-View Diffusion-Weighted Imaging at 3T in Patients With Breast Cancer

rs-EPI (1.7 x 1.7 x 3 mm) vs. rFOV-DWI (0.6 x 0.6 x 3 mm)

rFOV DWI – higher image quality, lesion conspicuity, signal-to-noise ratio (SNR) than rs-EPI



Park JY and Shin HJ et al. JMRI 2015

DWI Registration

Pre-Registration

Post-Registration

ADC Range

0 0.8 1.25 1.51 3.0

	volume(cc)	% tumor
Orange	1.460 cc	92.69 %
Red	0.112 cc	7.10 %
Green	0.003 cc	0.22 %
Yellow	0.000 cc	0.00 %
Total Vol.	1.575 cc	

Diameter(mm)	18.28 x 16.22 x 12.14
Entropy	7.1132
Hot-spot ADC Min / Max	0.1731 / 0.8414

ADC Mean/Min/Max

0.46	0.10	1.26

ADC Range

0 0.8 1.25 1.51 3.0

	volume(cc)	% tumor
Orange	1.558 cc	98.50 %
Red	0.020 cc	1.28 %
Green	0.003 cc	0.21 %
Yellow	0.000 cc	0.00 %
Total Vol.	1.582 cc	

Diameter(mm)	18.28 x 16.22 x 12.14
Entropy	6.7929
Hot-spot ADC Min / Max	0.1762 / 0.7254

ADC Mean/Min/Max

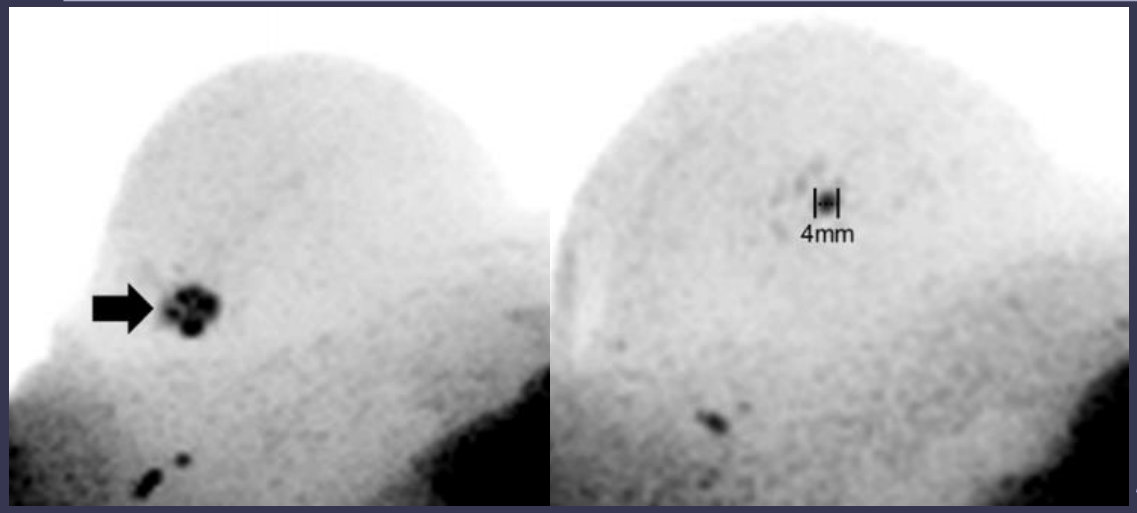
0.45	0.10	1.28

Sebastian Bickelhaupt, MD
Frederik B. Laun, PhD
Jana Tesdorff, MD
Wolfgang Lederer, MD
Heidi Daniel, MD
Anne Stieber, MD
Stefan Delorme, MD
Heinz-Peter Schlemmer, MD, PhD

Fast and Noninvasive Characterization of Suspicious Lesions Detected at Breast Cancer X-Ray Screening: Capability of Diffusion-weighted MR Imaging with MIPs[1]

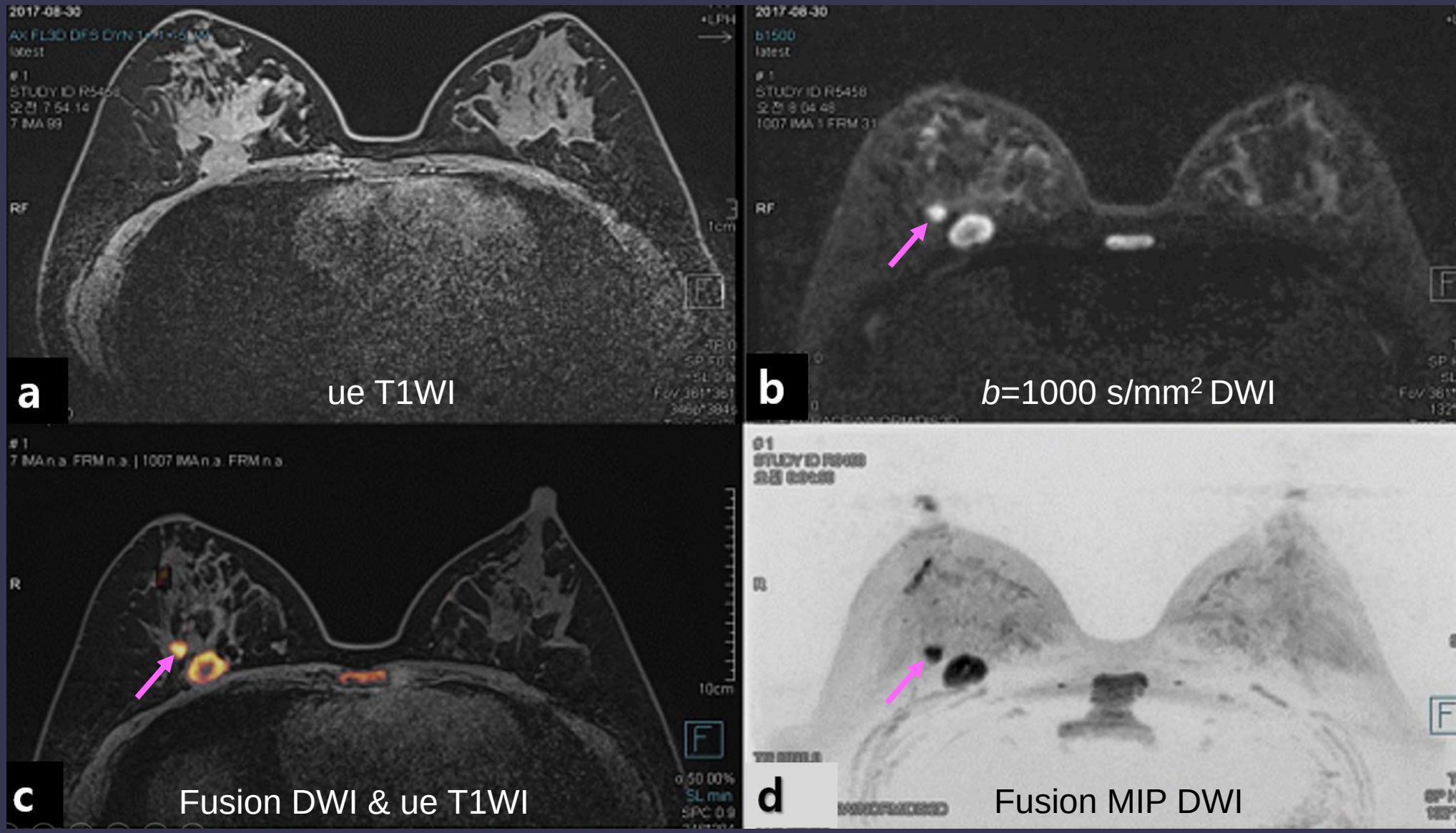
- DWI with background suppression (DWIBS)
  - 50 women with suspicious screening MG
  - DWI with DWIBS had an NPV of 92% & an acquisition time of less than 7 min

	Time	Sensitivity	Specificity	NPV	PPV
DWI & DWIBS	29.7s	92	94	92	93
1st CEMR & MIP	29.6s	85	90	87	89

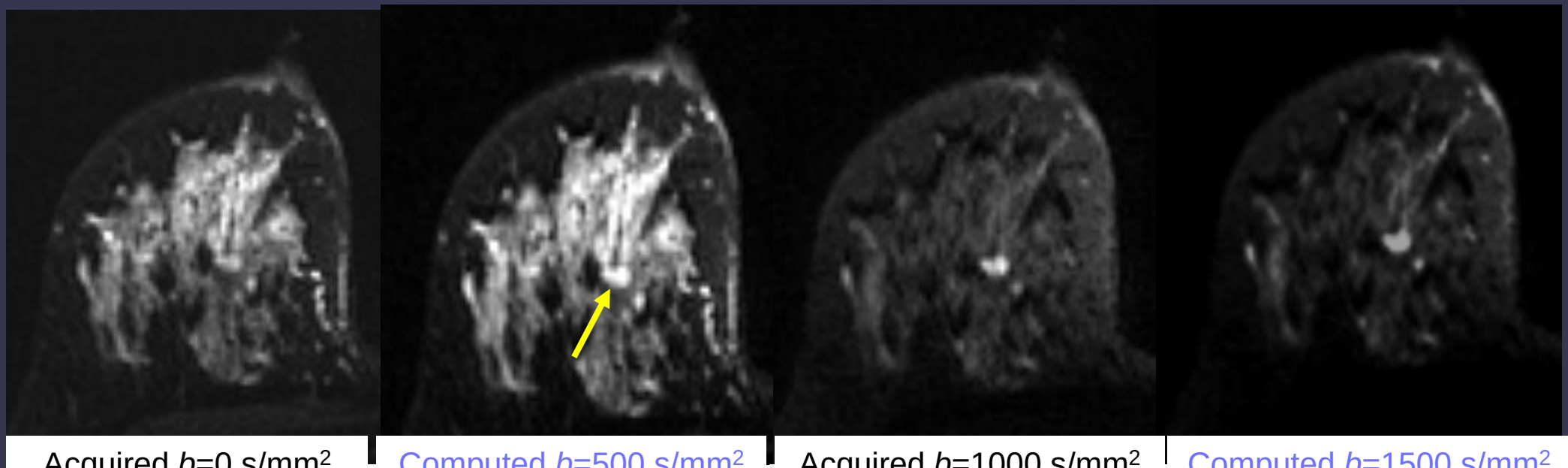


Bickelhaupt et al. Radiology 2016

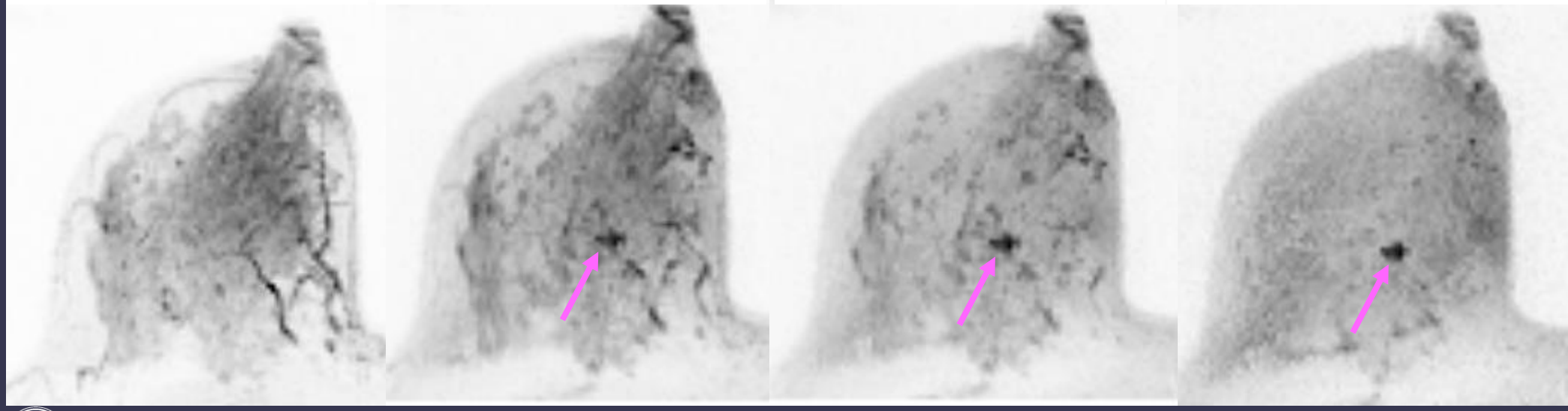
Fused DWI



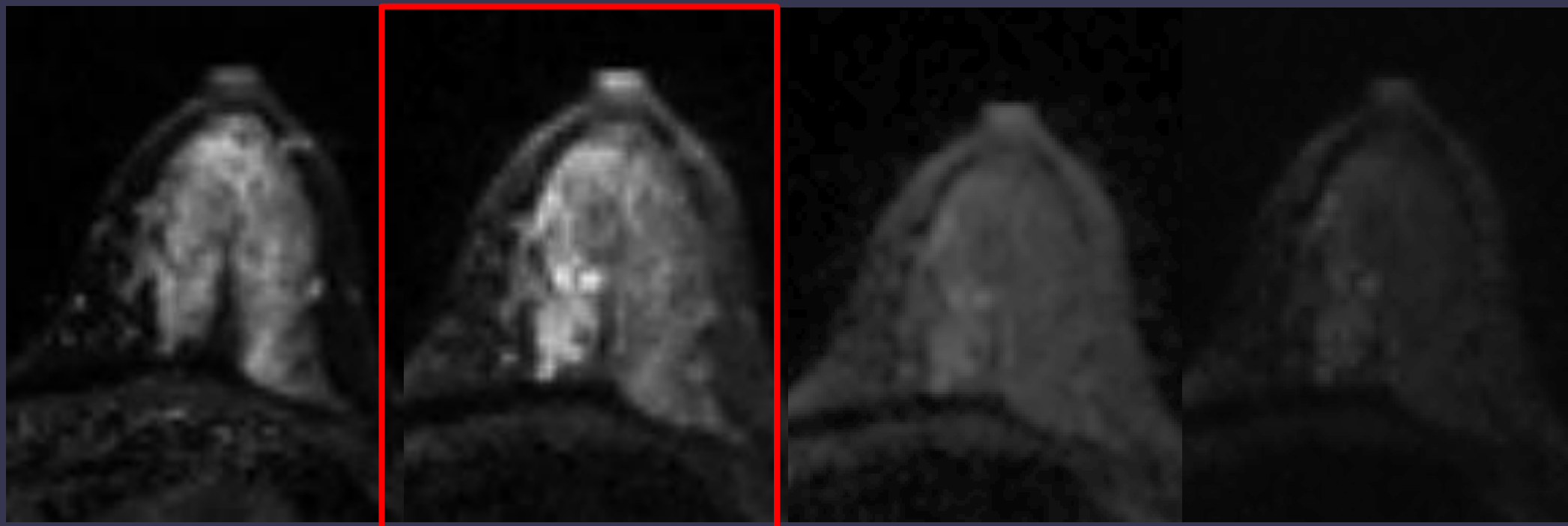
Computed DWI



Acquired b=0 s/mm^2 | Computed b=500 s/mm^2 | Acquired b=1000 s/mm^2 | Computed b=1500 s/mm^2



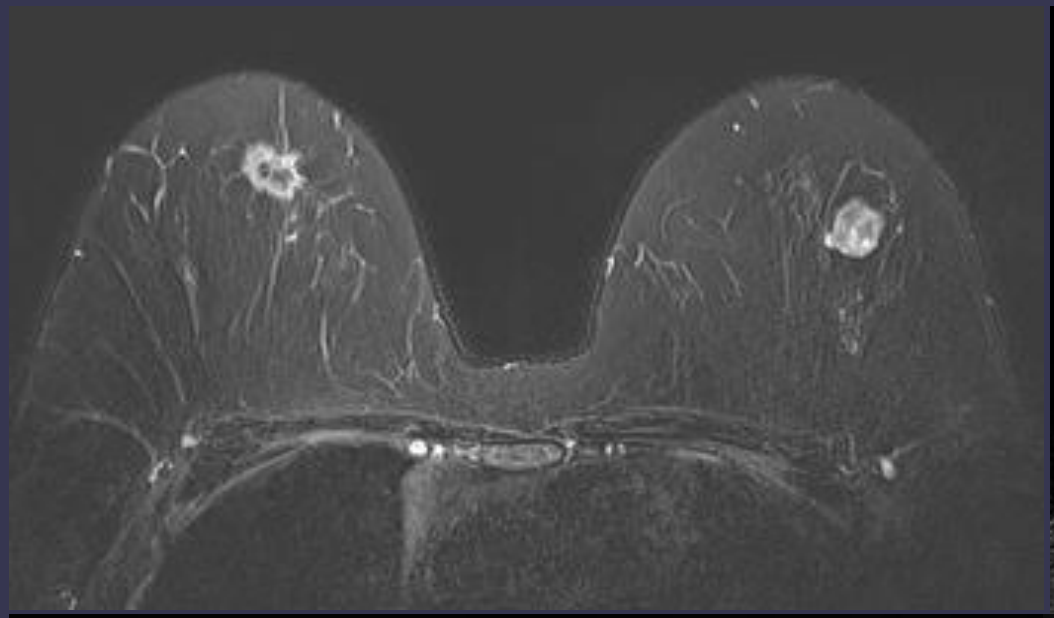
Computed DWI

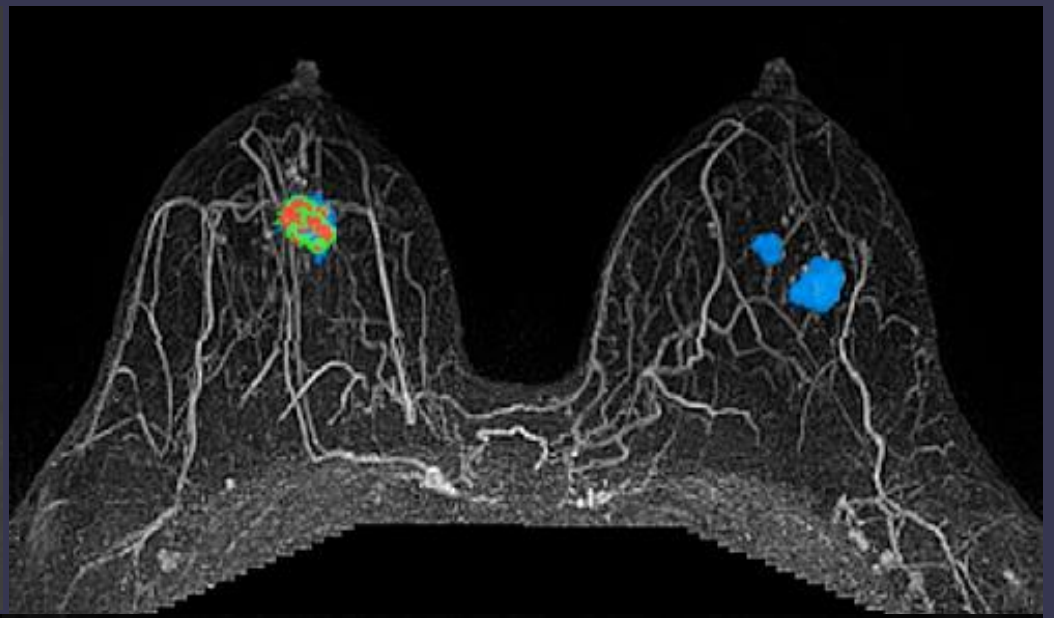


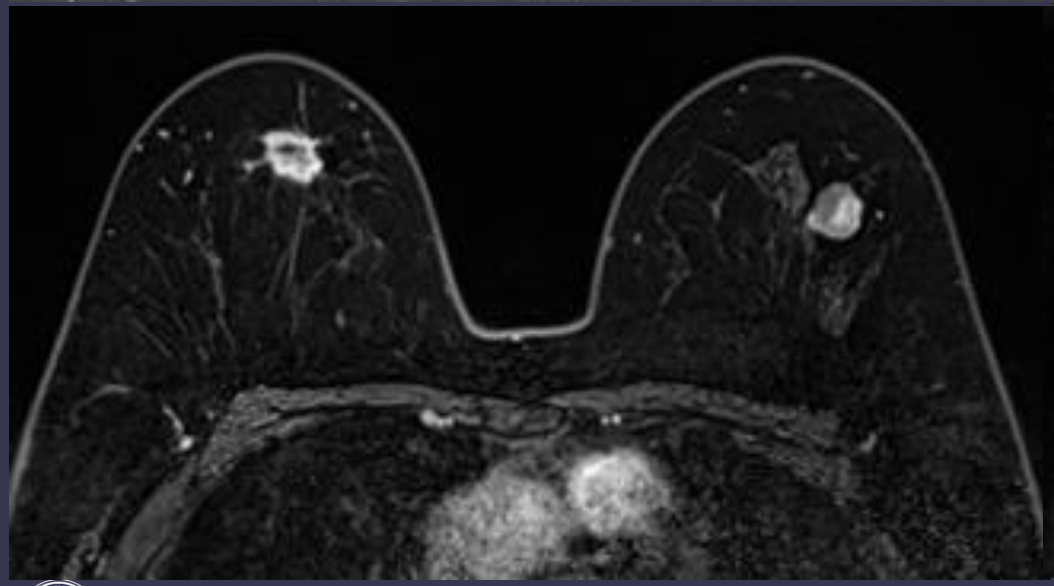
Acquired *b*=0 s/mm^2 | Computed *b*=500 s/mm^2 | Acquired *b*=1000 s/mm^2 | Computed *b*=1500 s/mm^2

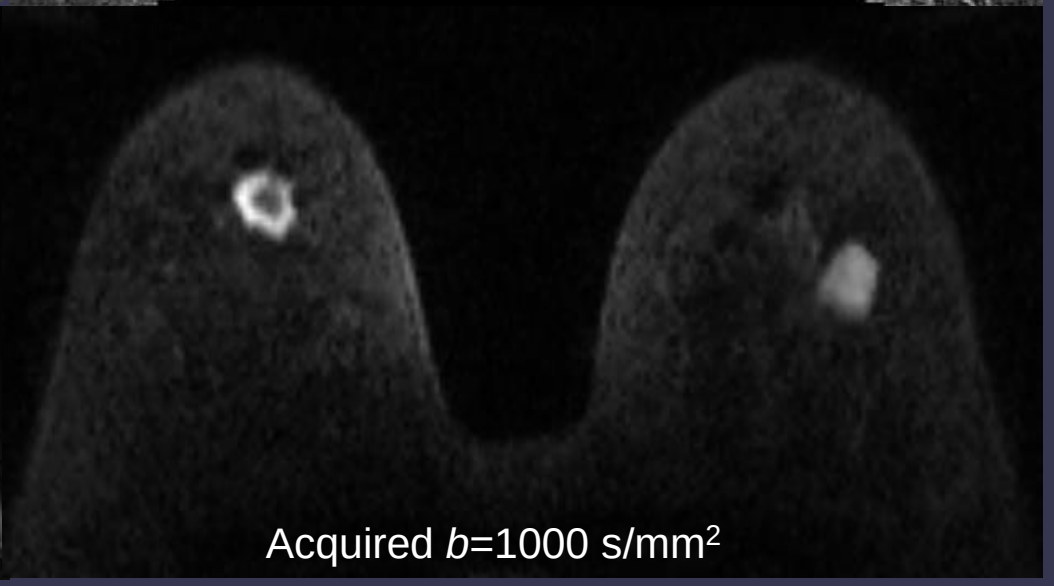
DCIS – may benefit from lower b value DWI

F/51 Rt cancer, Lt benign

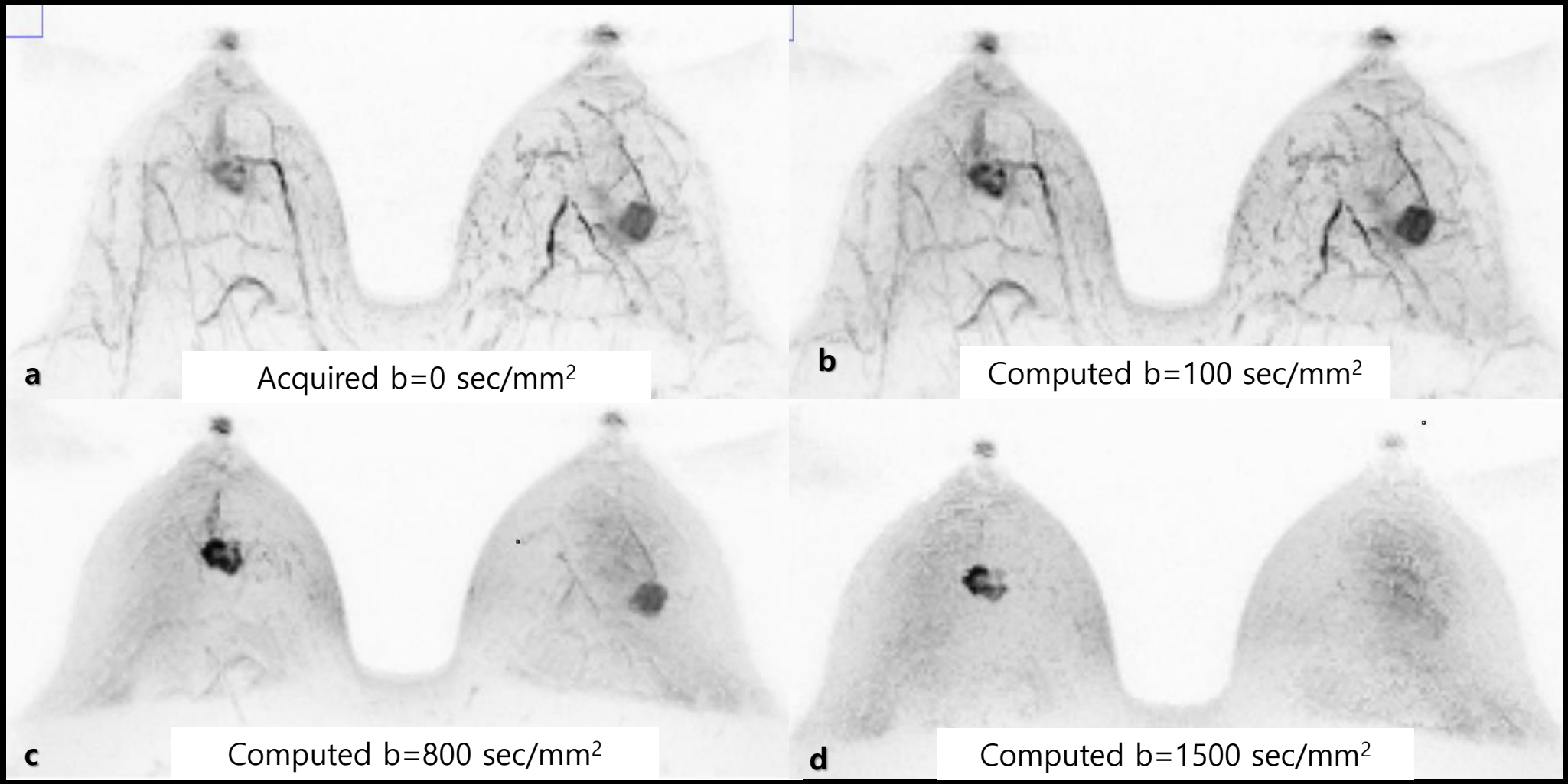






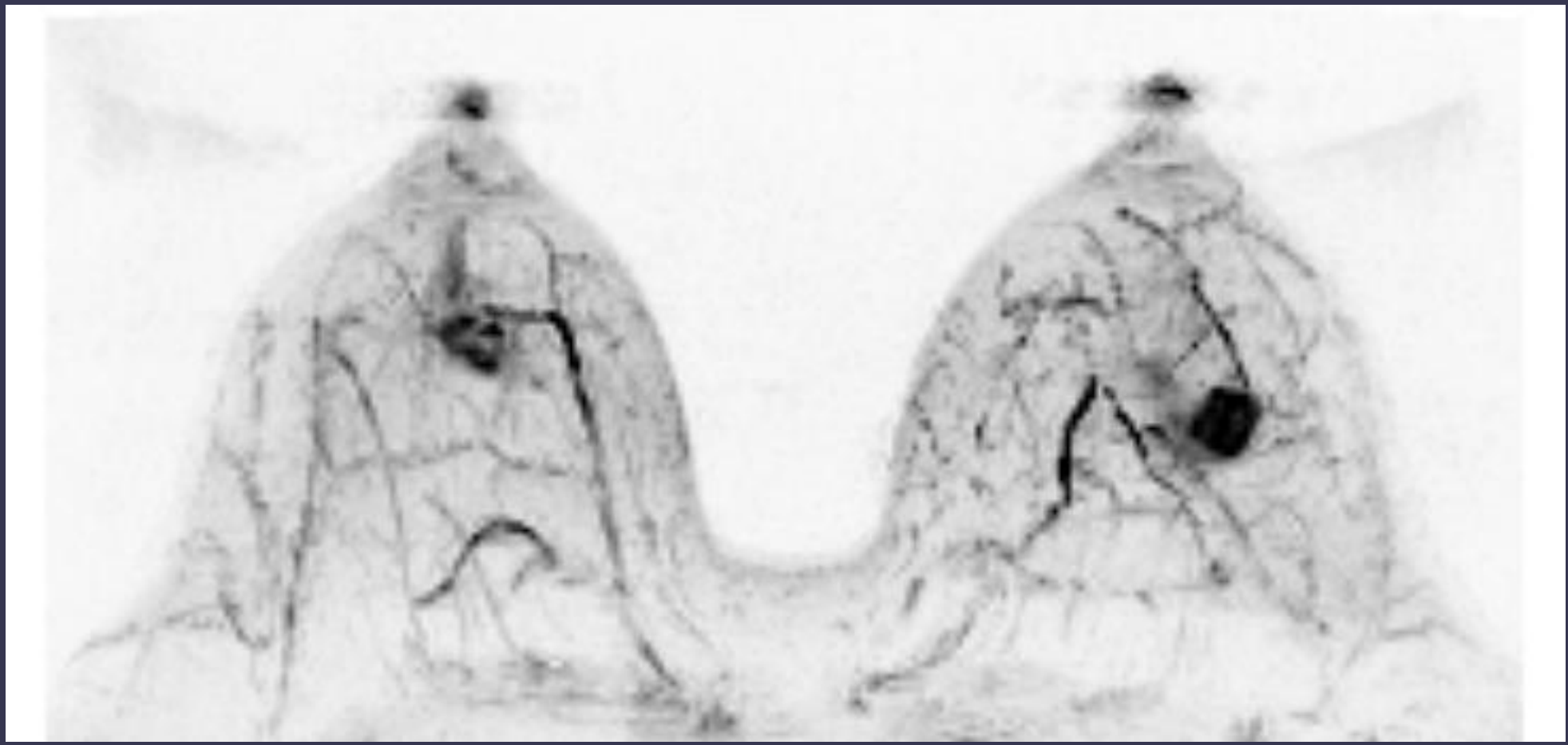


Acquired b=1000 s/mm^2

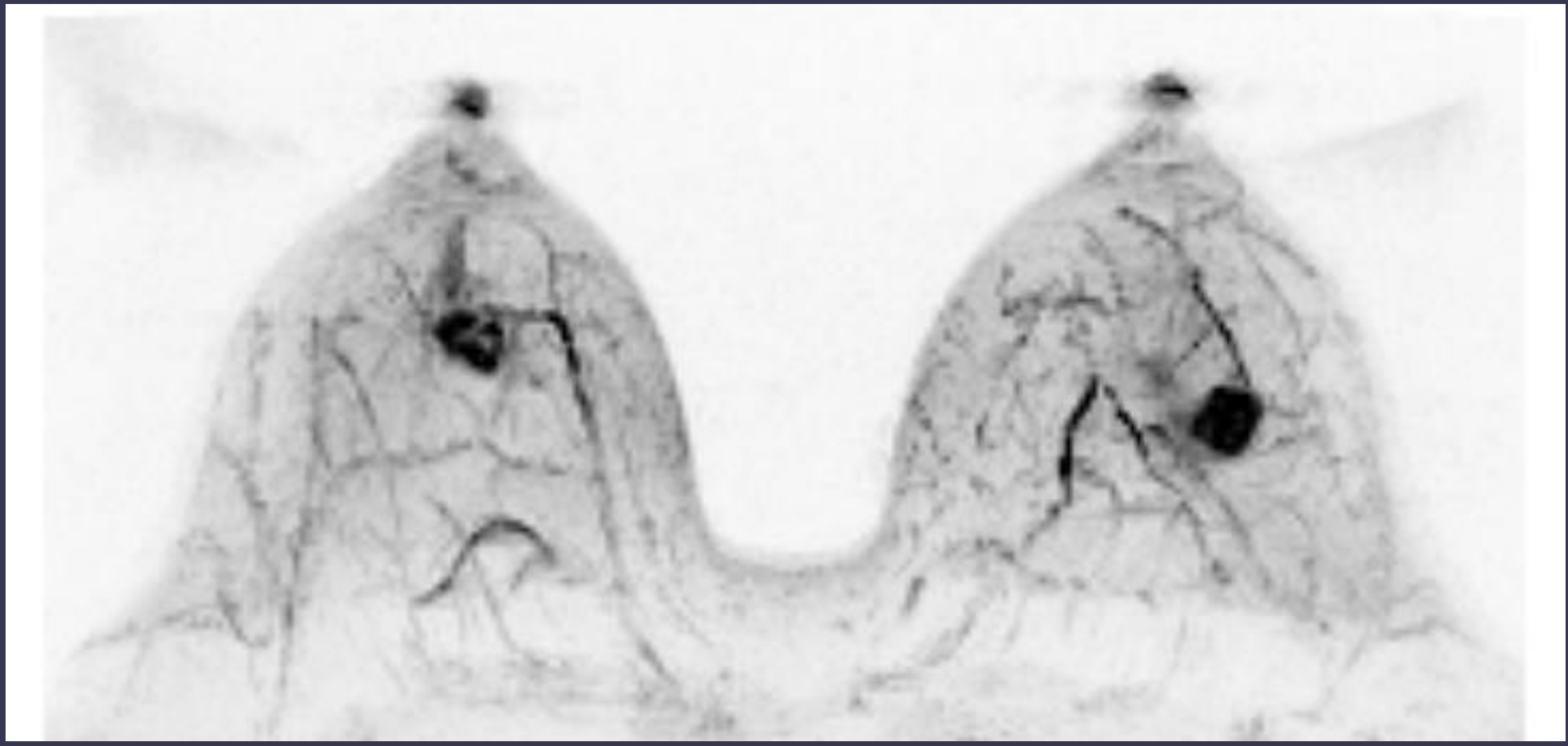


ADC 0.9 x 10^{-3} mm^2/sec (Rt) & 1.5 x 10^{-3} mm^2/sec (Lt)

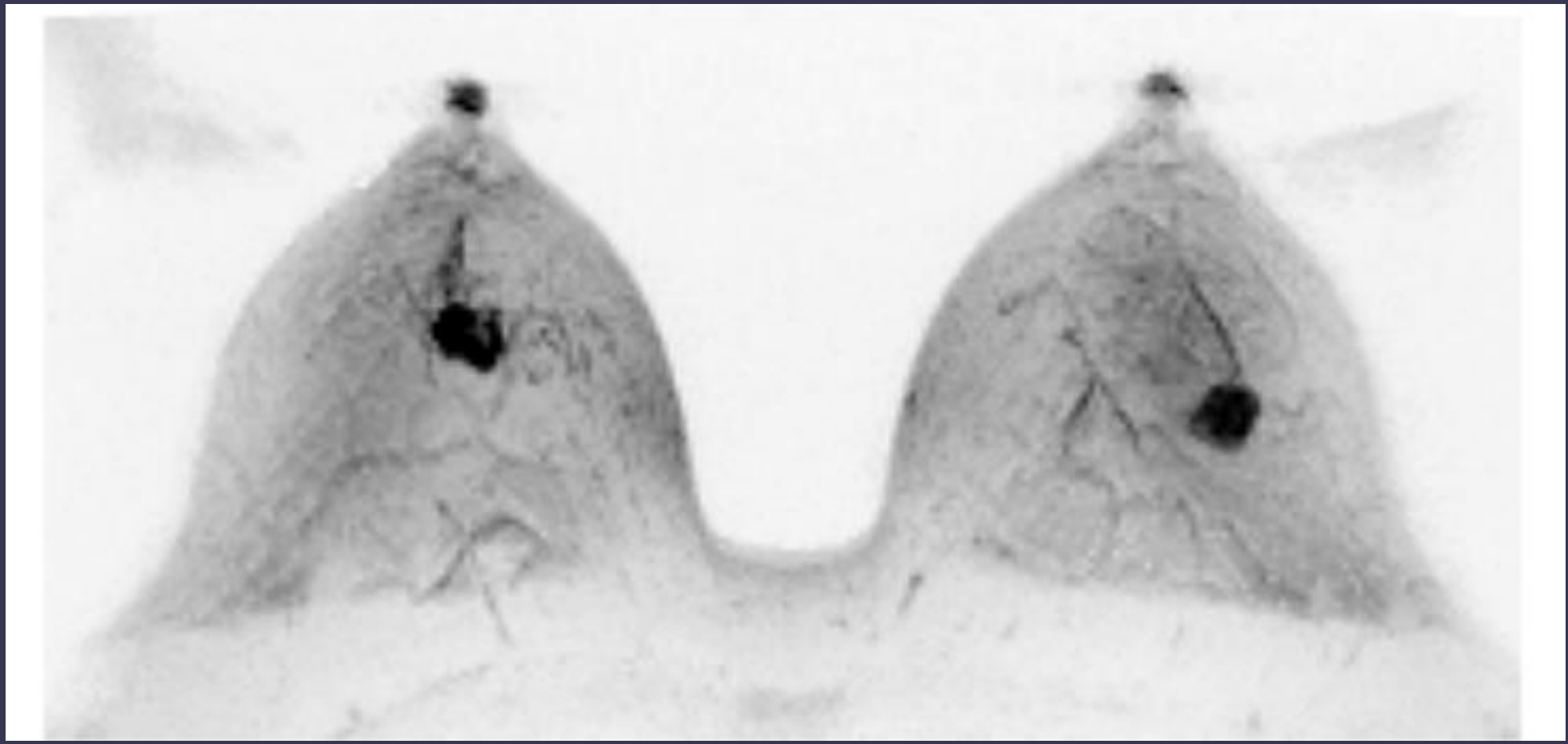
Computed MIP Series



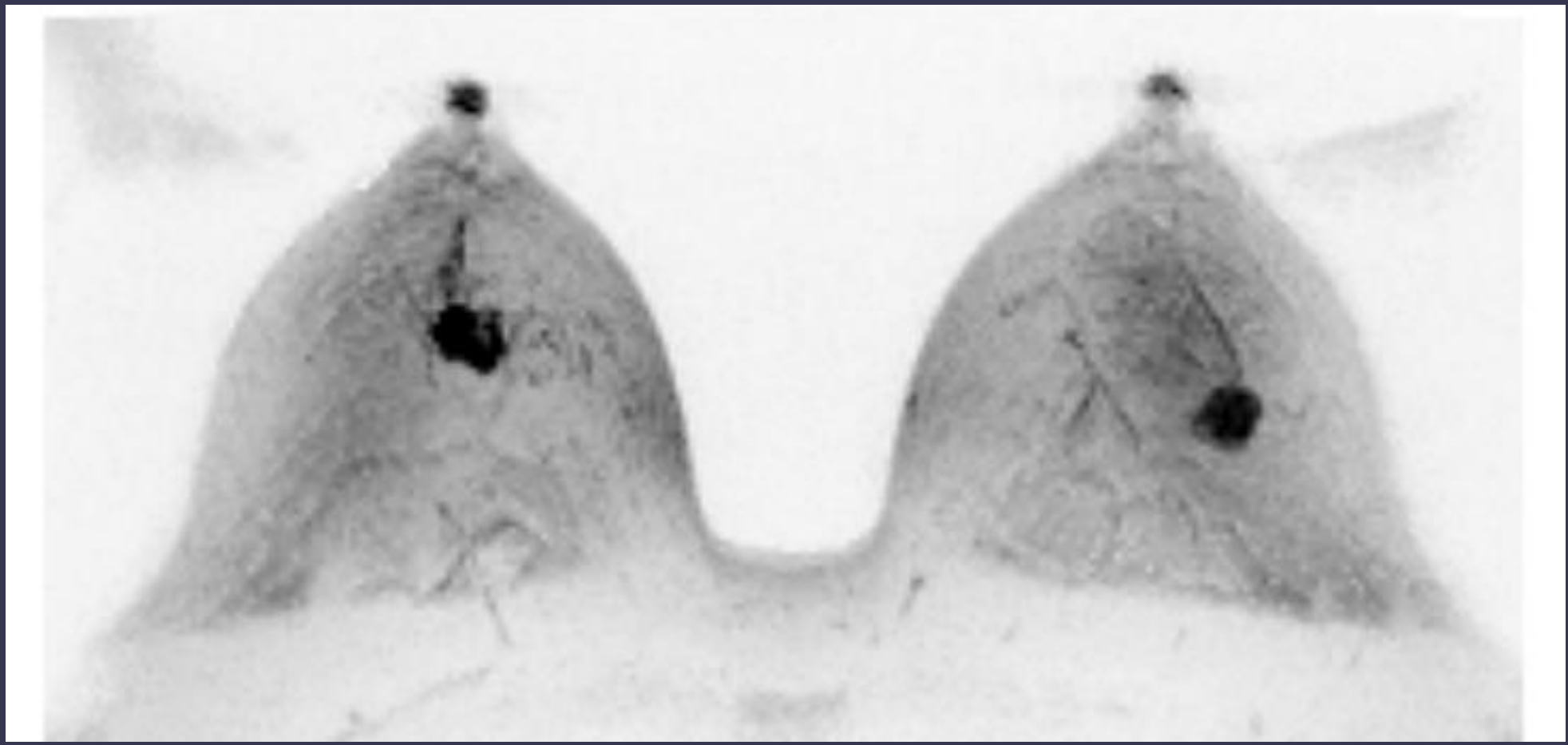
Acquired b = 0 sec/mm^2



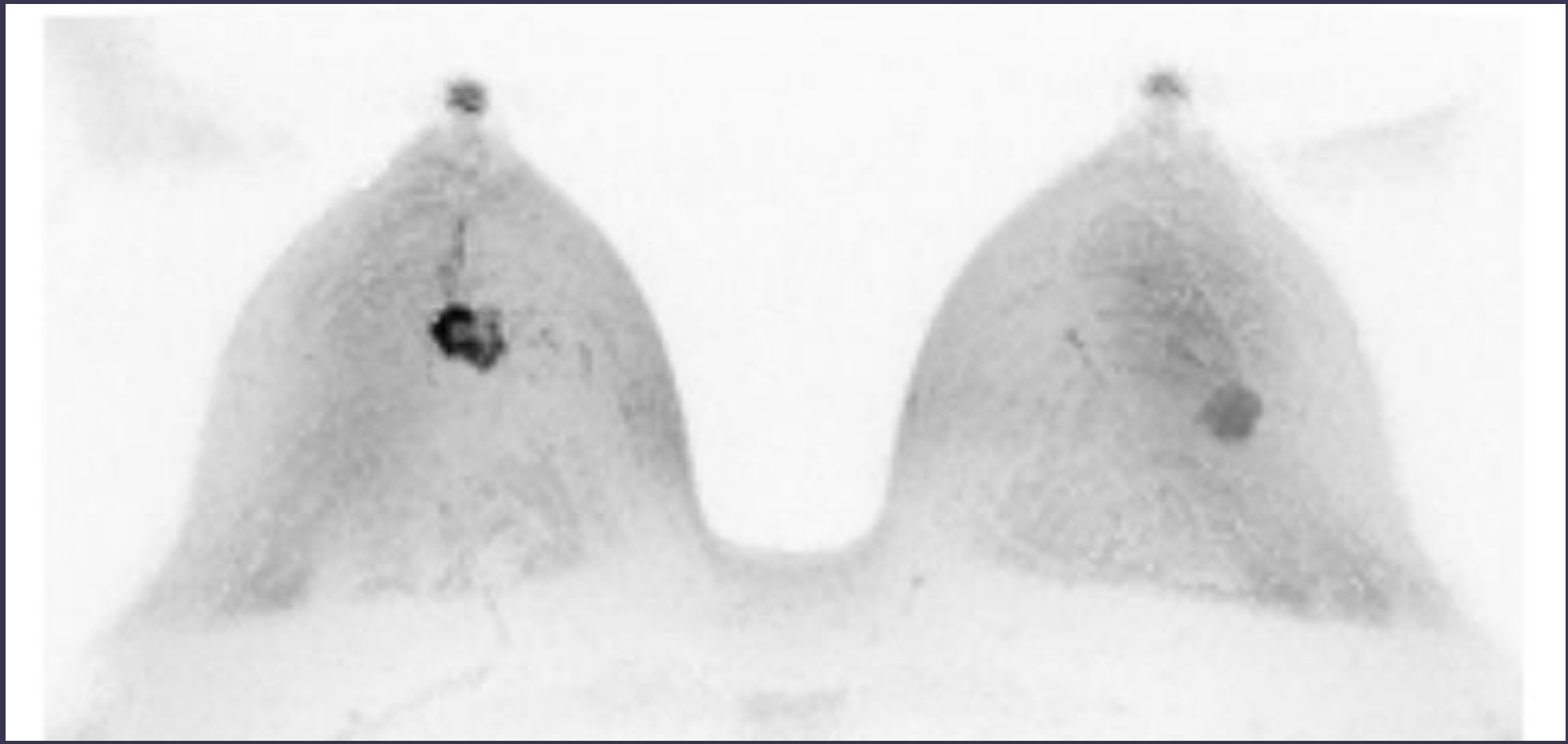
Computed b = 100 sec/mm^2



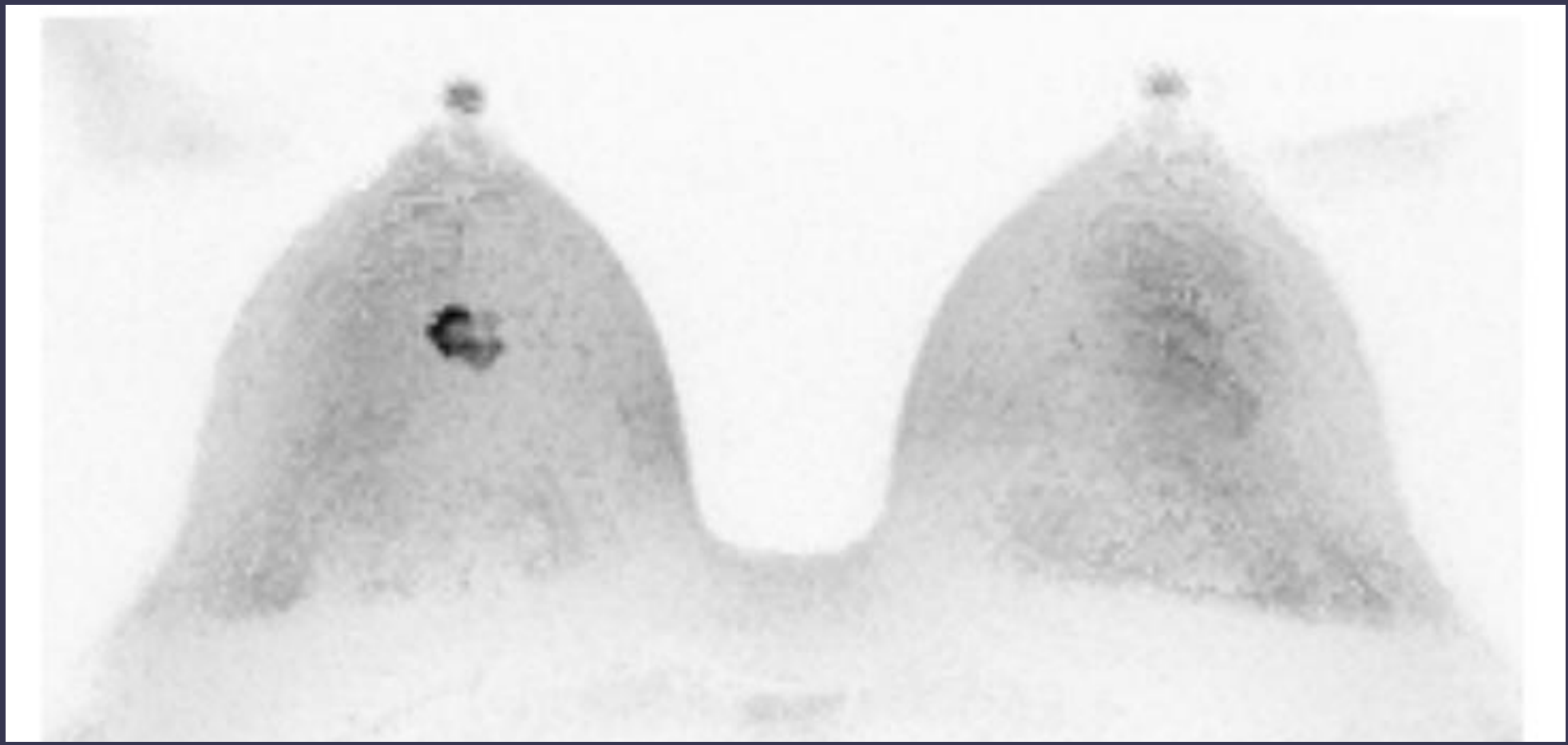
Computed b = 500 sec/mm^2



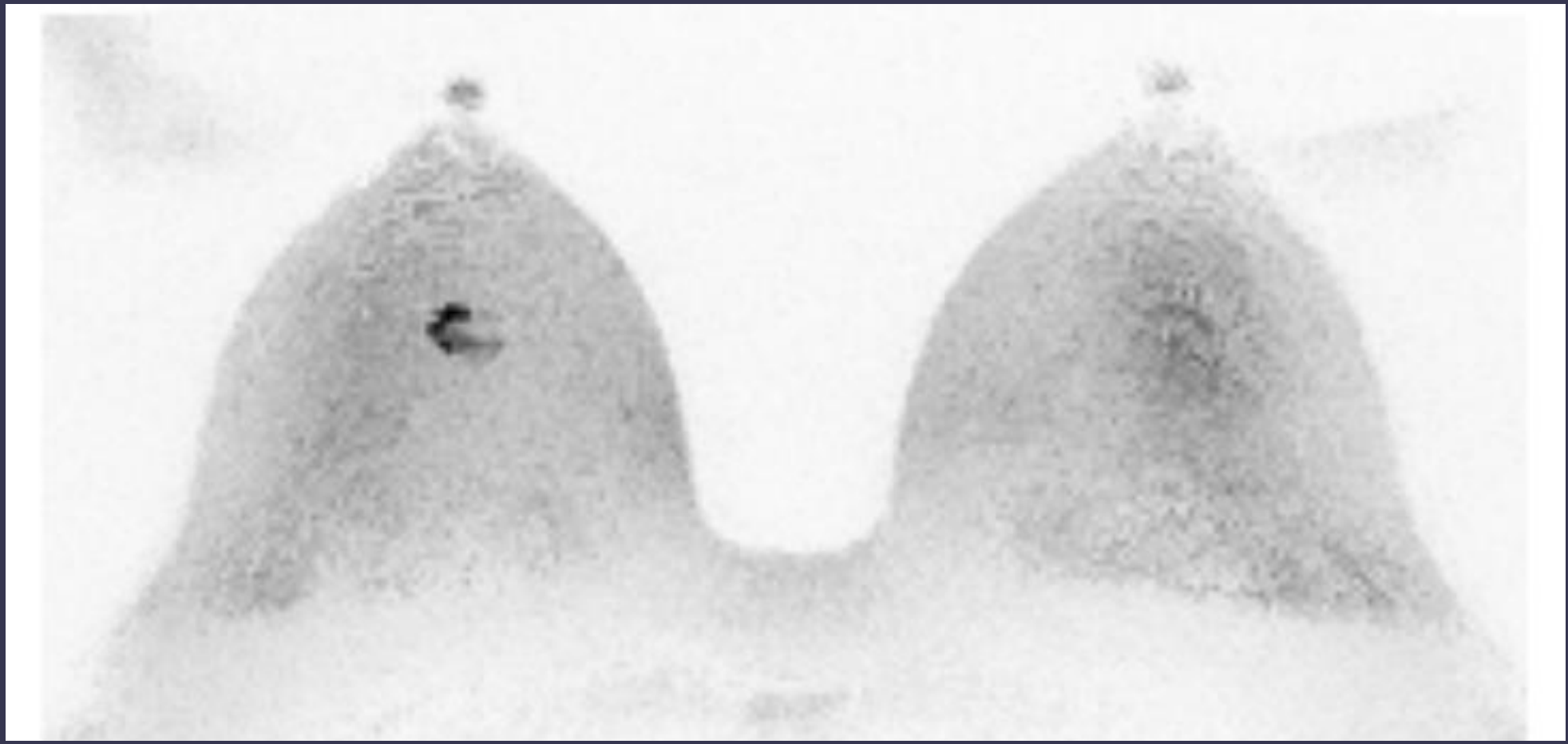
Computed b = 800 sec/mm^2



Acquired b = 1000 sec/mm^2



Computed b = 1500 sec/mm^2



Computed b = 2000 sec/mm^2

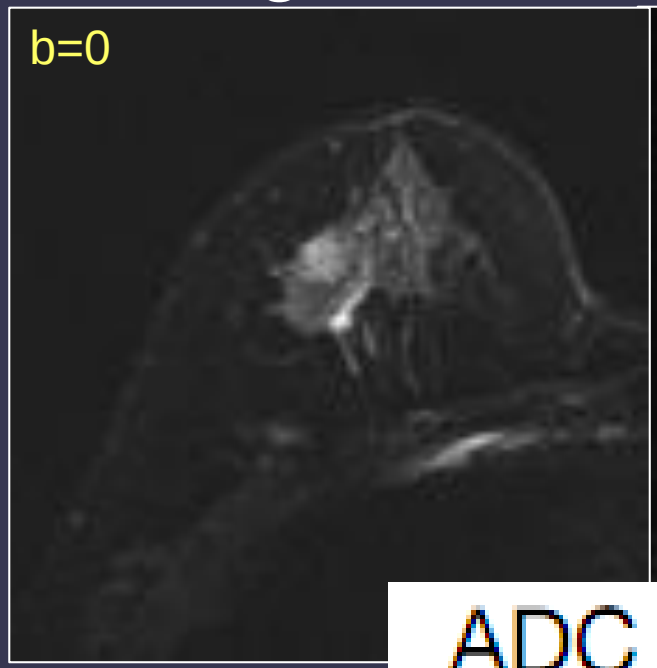
Challenges of Screening DWI

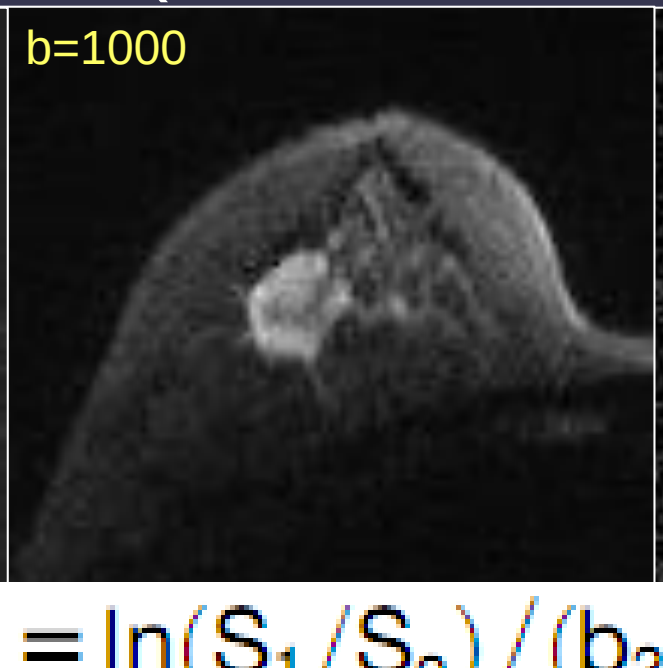
- False positives
  - Complicated/proteineous cyst
  - Fibroadenoma, artifactual signal at the ni
  - Intramammary LN, bleedi
  - gatives
  - DCIS, especially low-grade
  - Mucinous carcinoma
  - Triple-negative cancer with extensive necrosis

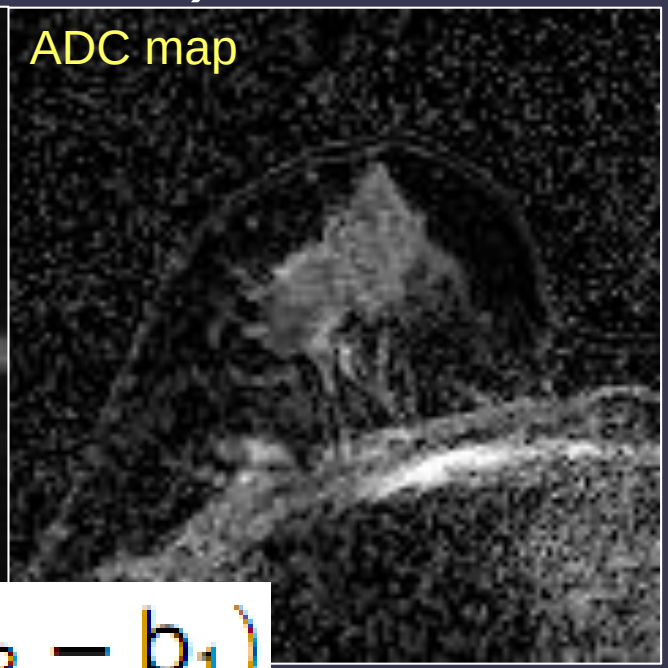
Cross-correlation of ADC map: crucial

Breast DWI Multicenter Study

- Identifying early response in tumors undergoing NAC (ACRIN 6698 Trial)
- Can assist in differentiating benign and malignant lesions (ACRIN 6702 Trial)







$$ADC = \ln(S_1/S_2)/(b_2 - b_1)$$

ASAN Medical Center

By courtesy of Woo Kyung Moon

Utility of Diffusion-weighted Imaging to Decrease Unnecessary Biopsies Prompted by Breast MRI: A Trial of the ECOG-ACRIN Cancer Research Group (A6702)

- Prospective multicenter study to determine ADC can decrease MRI false positives
  - 67 patients with 81 lesions from 9 institutions
  - ADC threshold (1.53×10^{-3} mm^2/s) → reduced the biopsy rate by 21% without affecting sensitivity
  - DWI can reclassify a substantial fraction of suspicious MR findings as benign → decrease unnecessary biopsies

Partridge et al. Clin Cancer Res 2019

Korean Screening DWI Multicenter Study

Funded by National R&D Program for Cancer Control (Nov 2017 - Oct 2022)

ASAN Medical Center

NCT03835897

Korean DWI Screening Trial

- Breast Cancer Screening with DWI in Women at High Risk for Breast Cancer
  - Prospective observational multicenter cohort study to compare the outcome of breast cancer surveillance using MG, US, DCE-MRI, and DWI
  - Primary objective – Sensitivity
  - Secondary objective
    - Specificity
    - Cancer detection rate
    - Biological characteristics of detected cancers

ASAN Medical Center

NCT03835897

Korean Screening DWI Trial

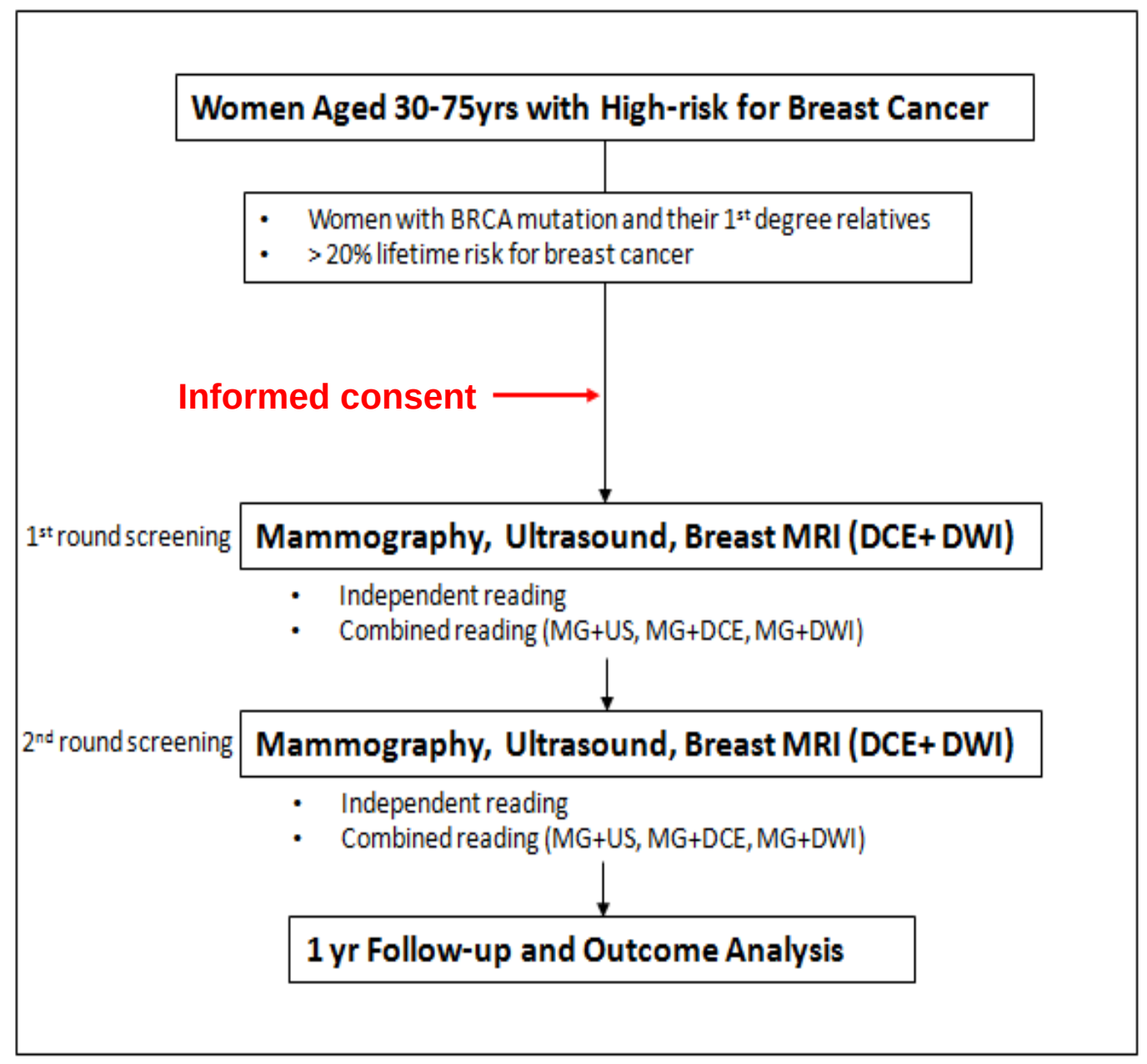
- Principal investigator: Woo Kyung Moon (SNUH)

  Sub-PI: Hee Jung Shin (AMC)
- Co-investigators (8 institutions)
  - SNUH – Su Hyun Lee, Jung Min Chang
  - AMC – Hak Hee Kim, Woo Jung Choi
  - SMC – Boo-Kyung Han, Ko Woon Park
  - Severance – Min Jung Kim
  - SNUBH – Sun Mi Kim, Bo La Yun
  - NCC – Kyung Ran Ko
  - Seoul St Mary H – Bong Joo Kang
  - Ajou UH – Tae Hee Kim

Korean Screening DWI Trial

- Inclusion Criteria
  - 890 women at high risk for breast cancer
    - BRCA1/2 mutation or 1st degree relatives
    - Cumulative lifetime risk ≥ 20% on risk assessment tool based on familial history (IBIS)
- Exclusion criteria
  - Pregnant or lactating women
  - Patients who have symptoms or signs of breast cancer or recurrence
  - Bilateral mastectomy
  - Any cases of contraindication to MRI examination

Study Scheme



Protocol Optimization

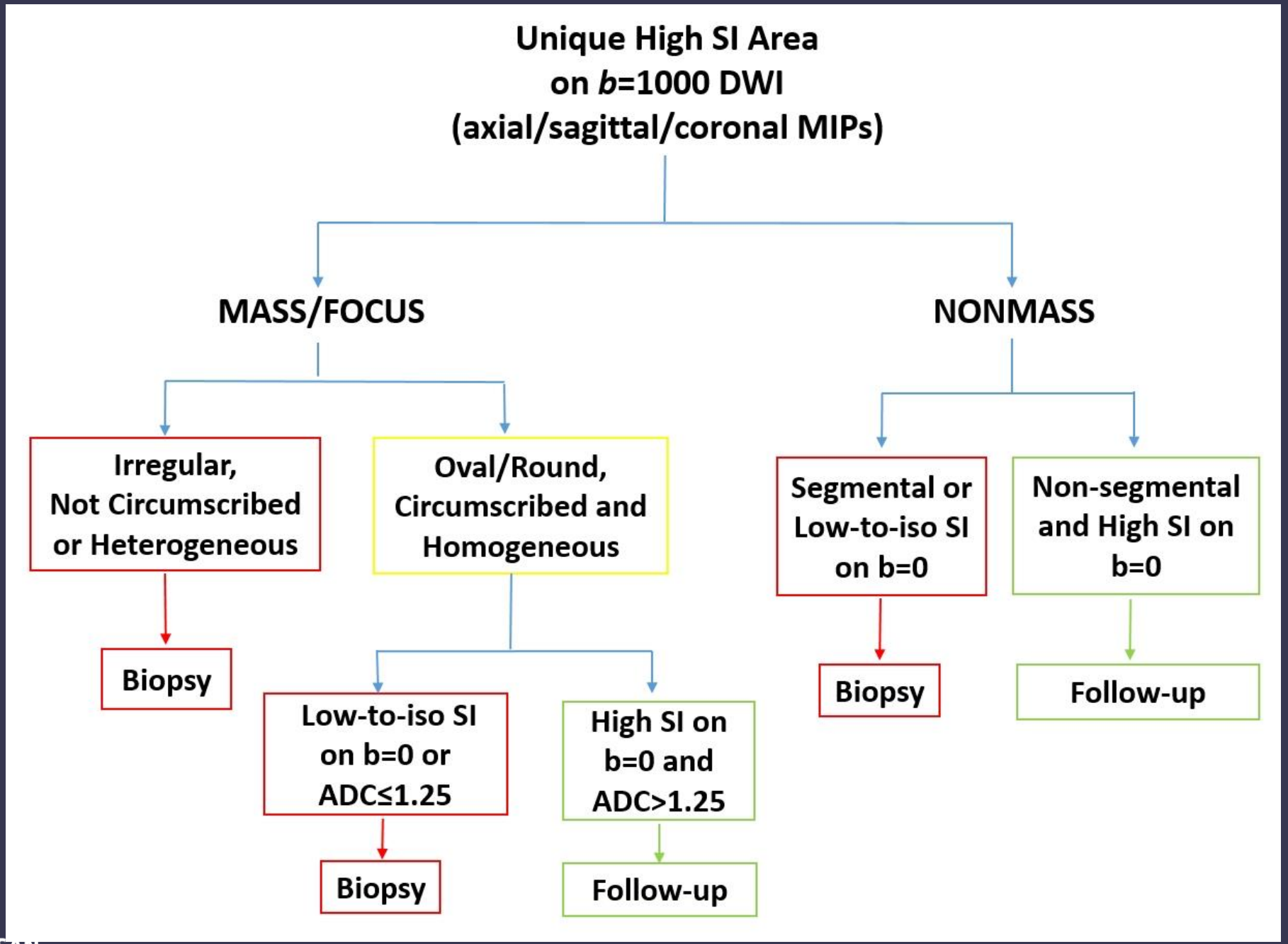
- Advanced acquisition technique
  - rs-EPI, high quality ss-EPI with DWIBS at 3T
  - Improved spatial resolution (≤ 1.3 mm)
- Lesion detection & accurate ADC quantitation
  - Selection of b values (0, 800, 1200 sec/mm^2)
- Advanced post-processing tools
  - DWI MIP series
  - Computed DWI at varying *b*-values

Partridge S and Shin HJ et al. Radiology 2019 under revision

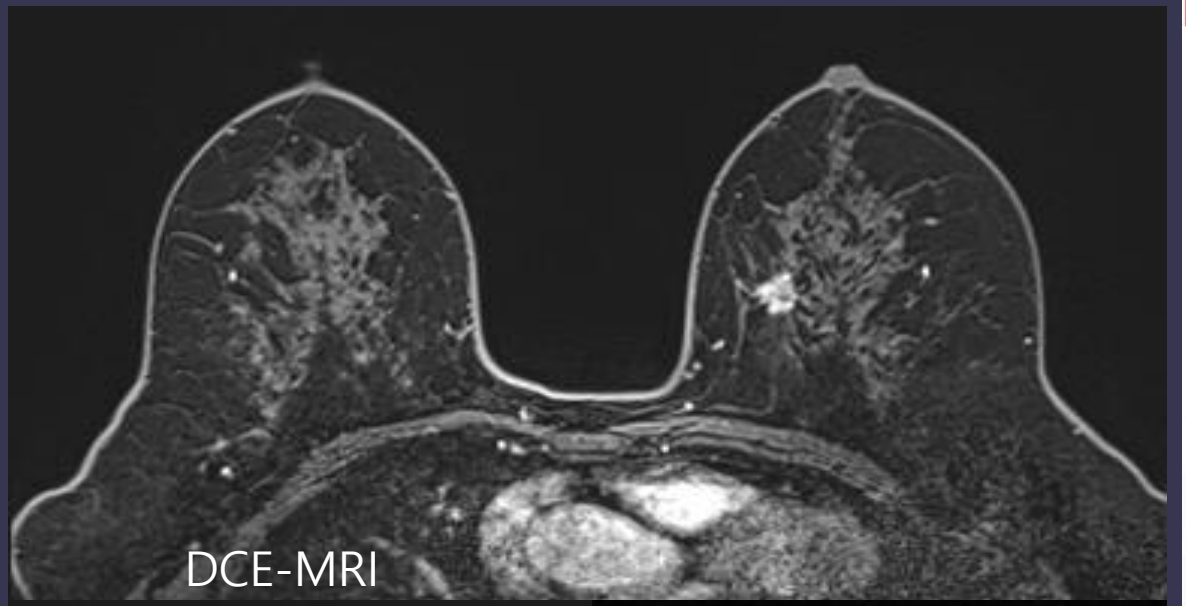
DWI Acquisition

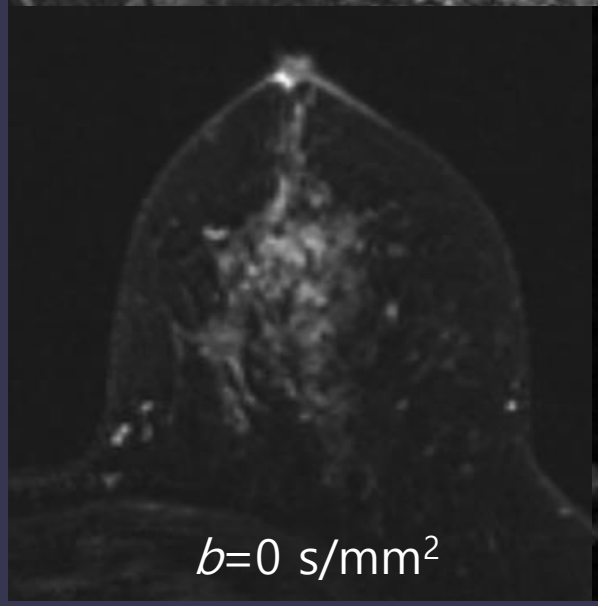
구분	Siemens	Philips	GE
Equipment	3T Skyra	3T Ingenia (CX)	3T architect
Scan dimension	Bilateral Axial	Bilateral Axial	Bilateral Axial
DWI technique	rs-EPI (RESOLVE)	ss-EPI (SENSE)	ss-EPI (ASSET)
Fat suppression	Fat Sat (SPAIR)	STIR	STIR
TR/TE (msec)	9930/69	9161/71(60) (TI=230)	7500/72.6/(TI=115)
Field of view (mm)	340 x 207	340 x 212	340 x 204
Flip angle (degree)	180	90	90
Number of averaging	1	6	3
Thickness (mm)	3	3	3
Intersection gap (%)	0	0	0
Matrix	256 x 156	Recon matrix: 320 x 320 Acq. matrix: 256 x 160	256 x 152
Voxel size (mm)	1.3 x 1.3 x 3	1.1 x 1.1 x 3 (1.3 x 1.3 x 3)	1.3 x 1.3 x 3
Slices	50	50	50
b-value (sec/mm^2)	0, 800, 1200	0, 800, 1200	0, 800, 1200
Acquisition time	7:26	6:49	8:15

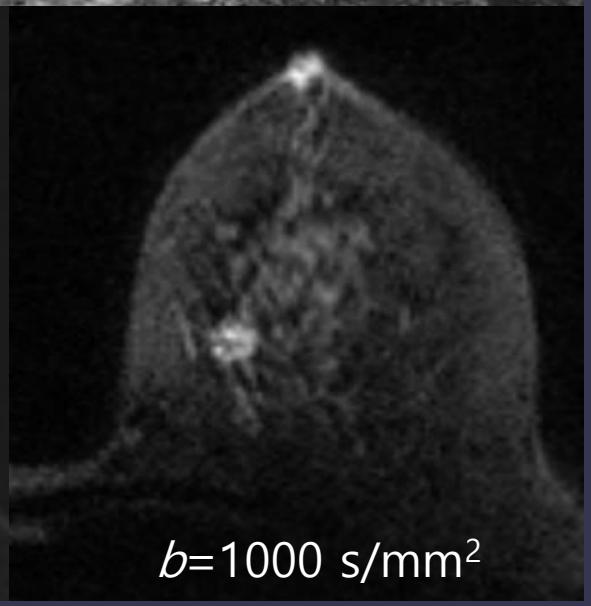
DWI Interpretation Algorithm

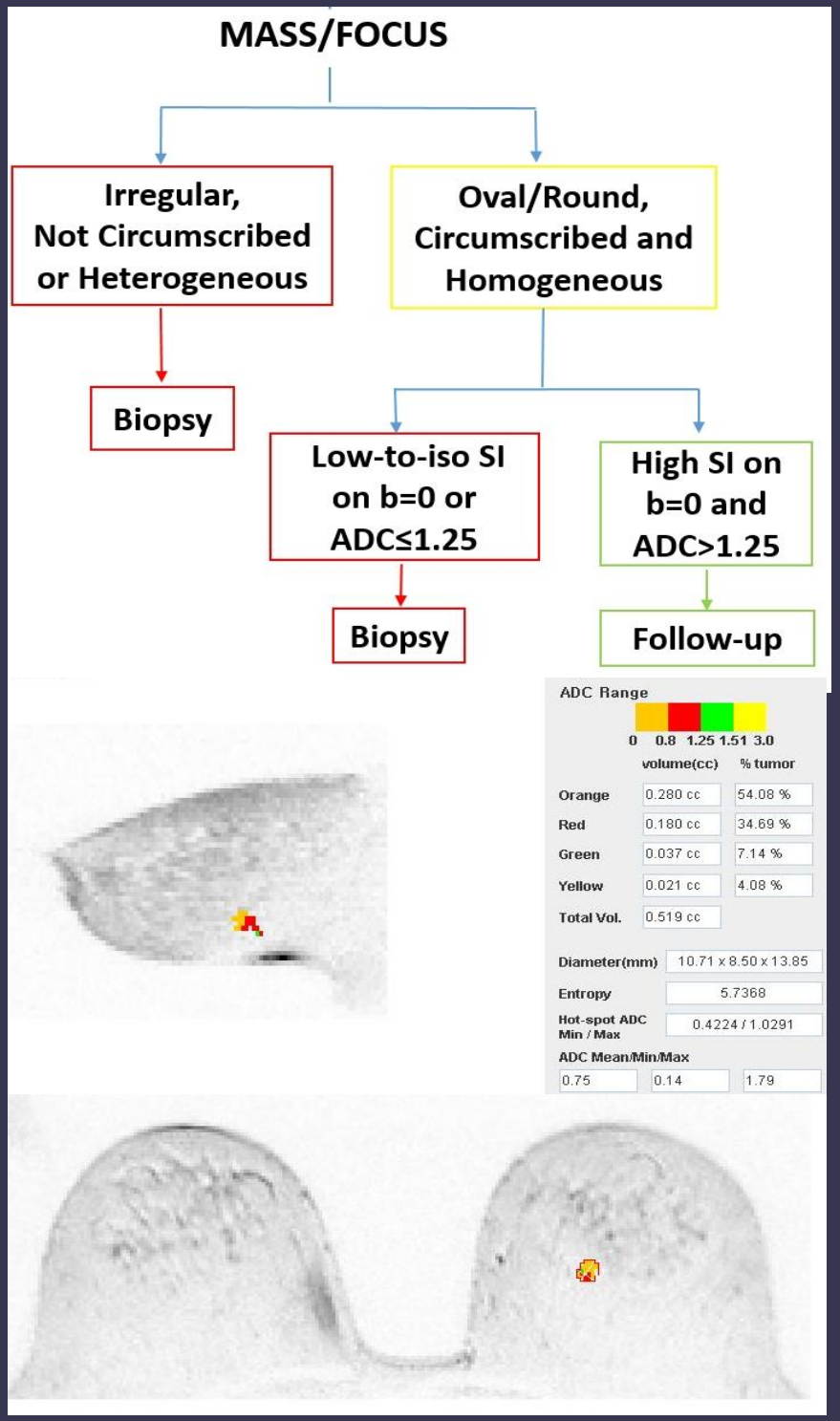


Mass



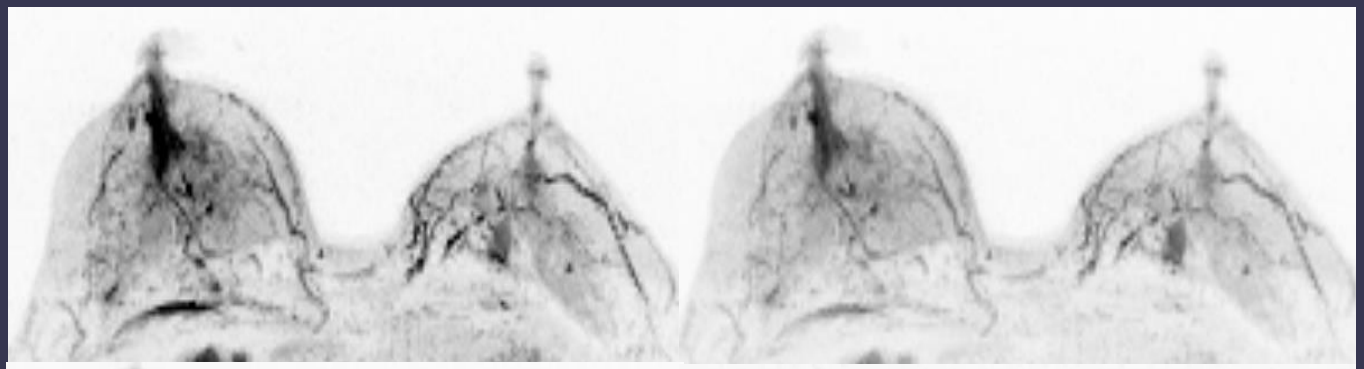


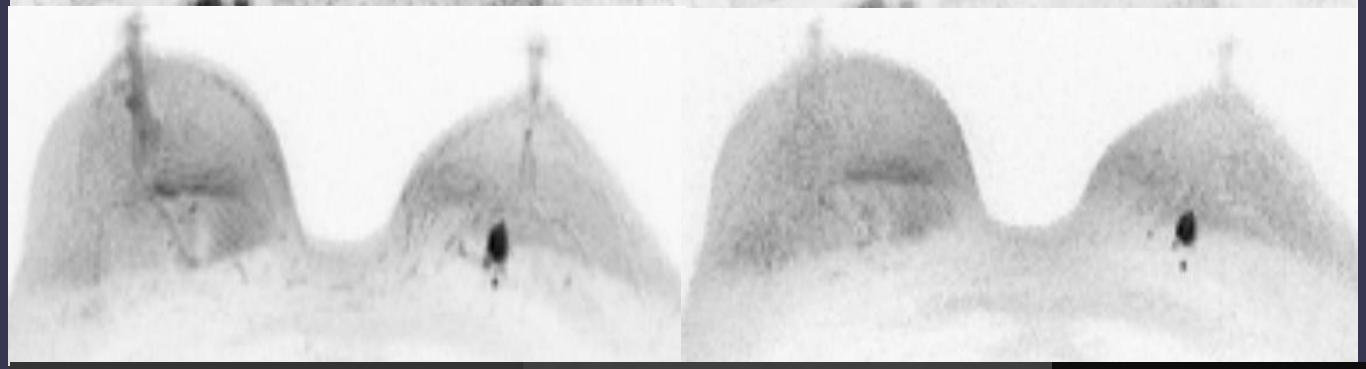


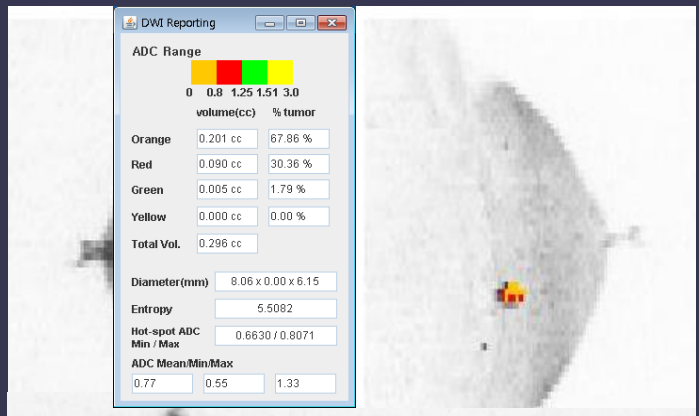


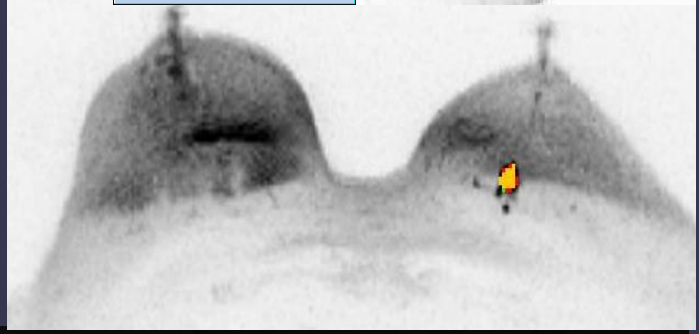
Irregular, heterogeneous & ADC=0.75 x 10^{-3} mm^2/sec → IDC

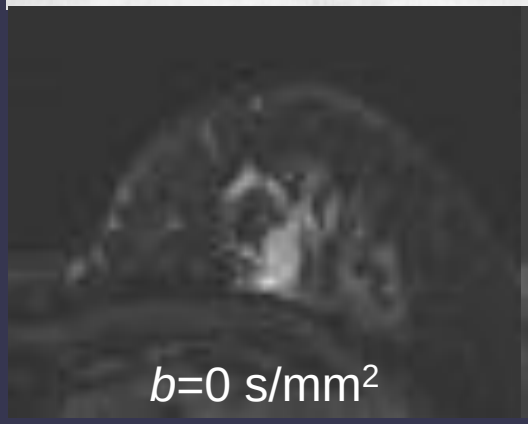
Mass

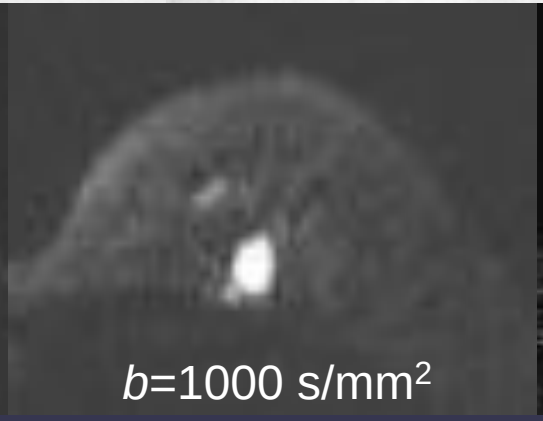


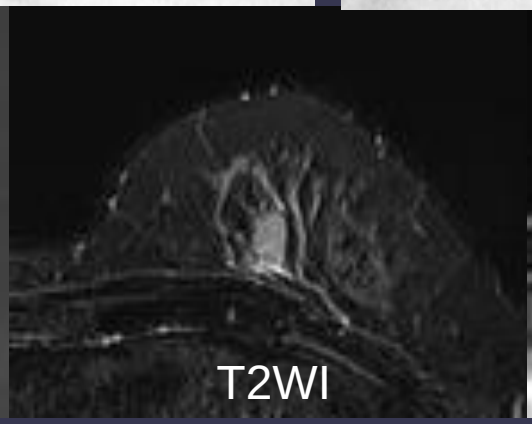


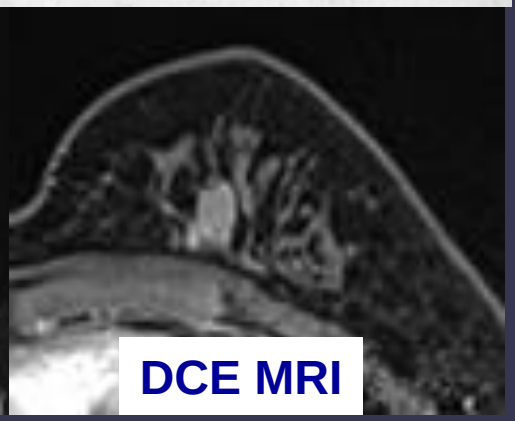






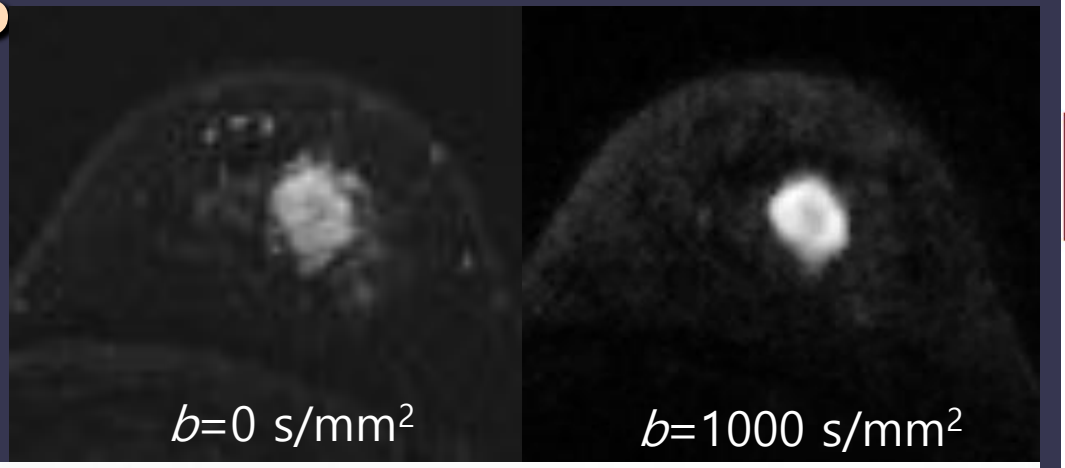


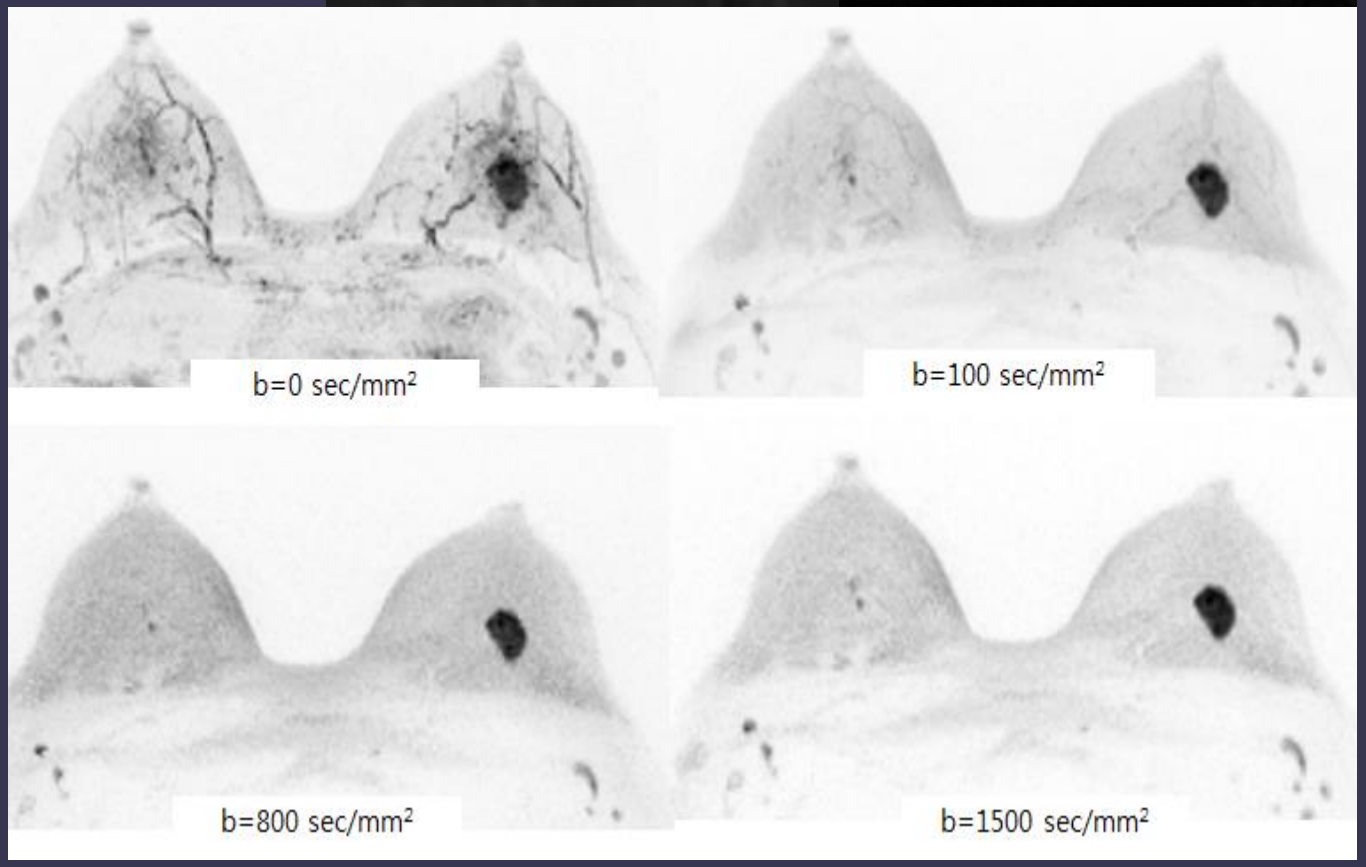


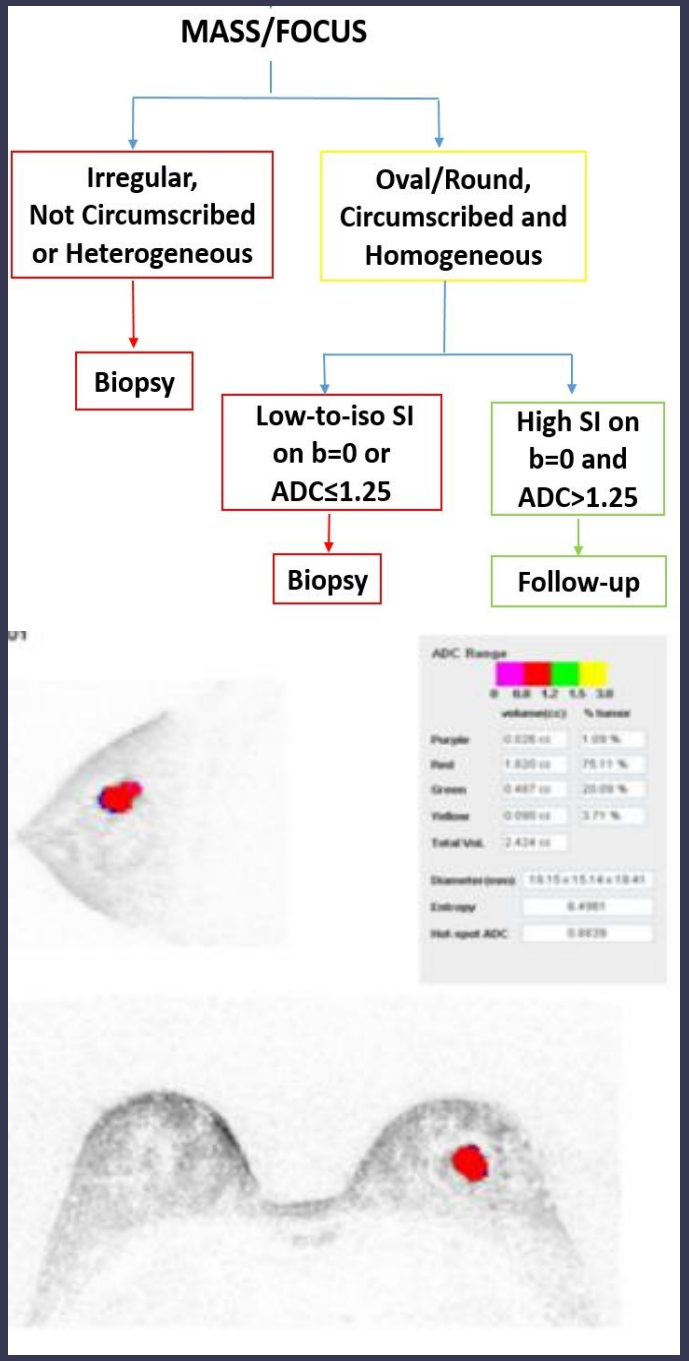


Oval, Iso SI on *b*=0 & high SI on *b*=1000 → ADC: 0.77 x 10^{-3} mm^2/sec

Mass

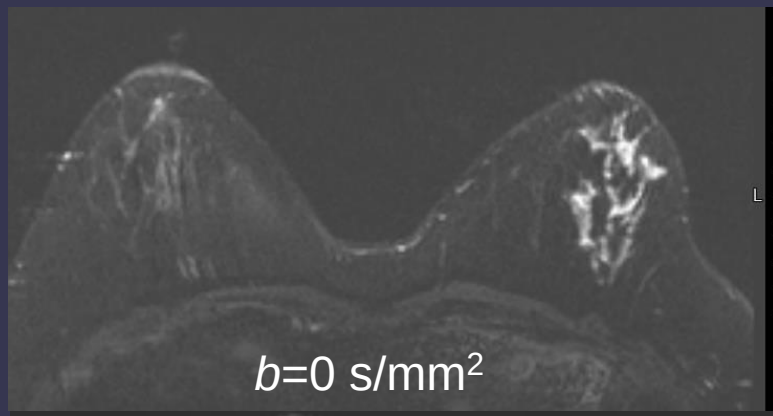




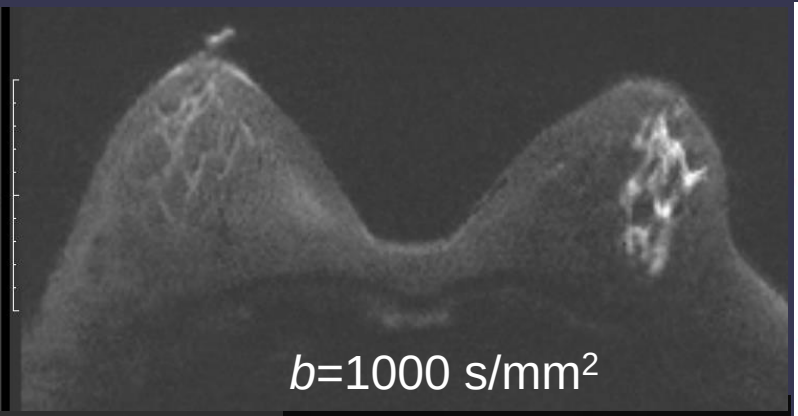


Oval/Rim, High SI on both *b*=0 & 1000 → ADC: 0.87 x 10^{-3} mm^2/sec

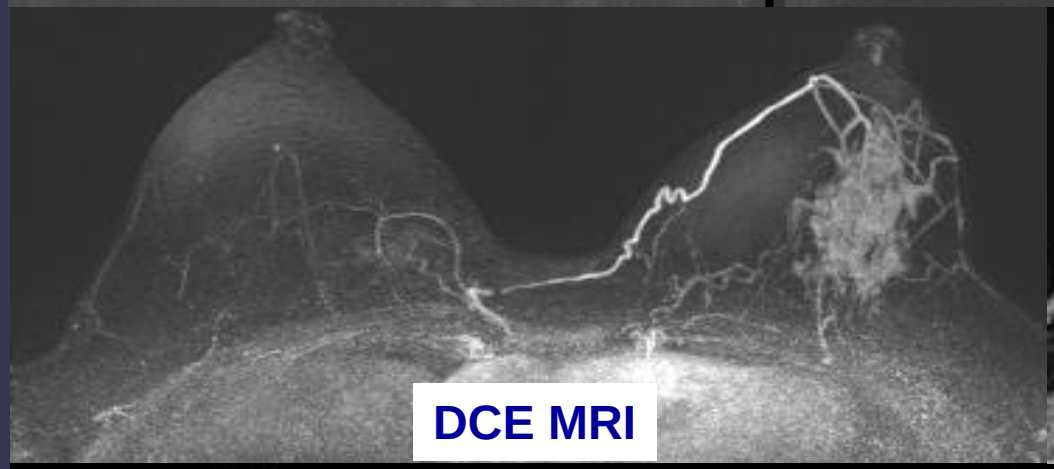
Nonmass – microIDC



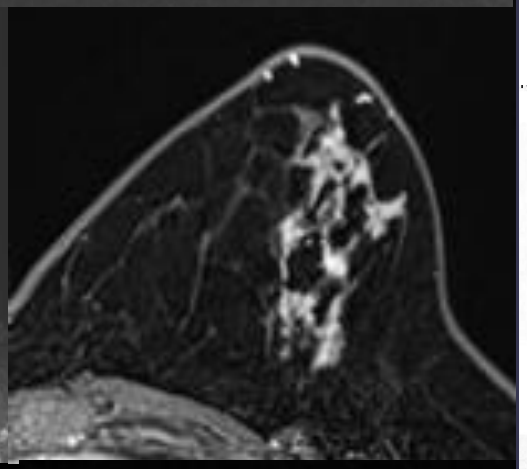
b=0 s/mm^2

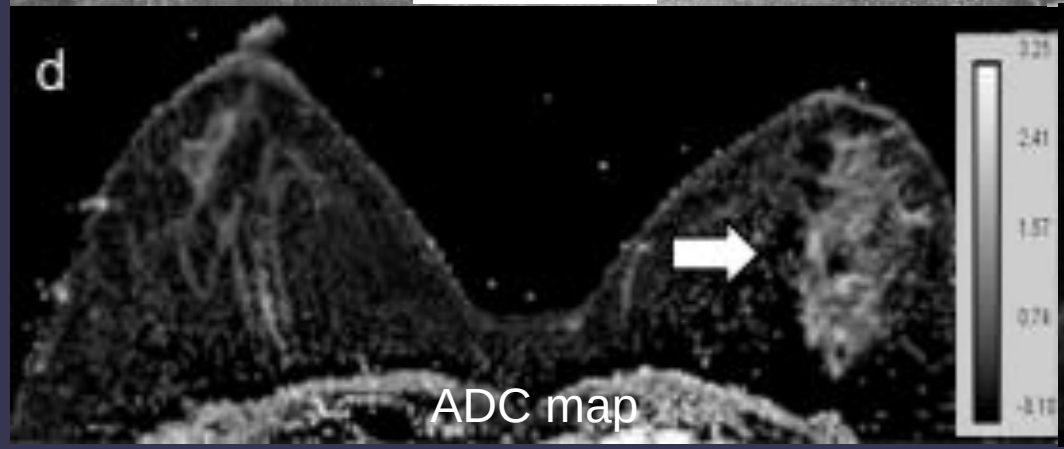


b=1000 s/mm^2

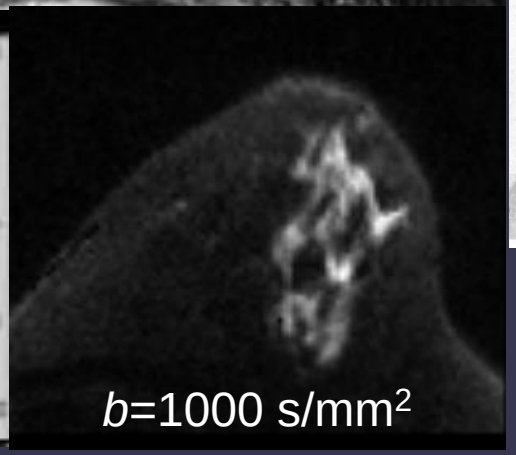


DCE MRI

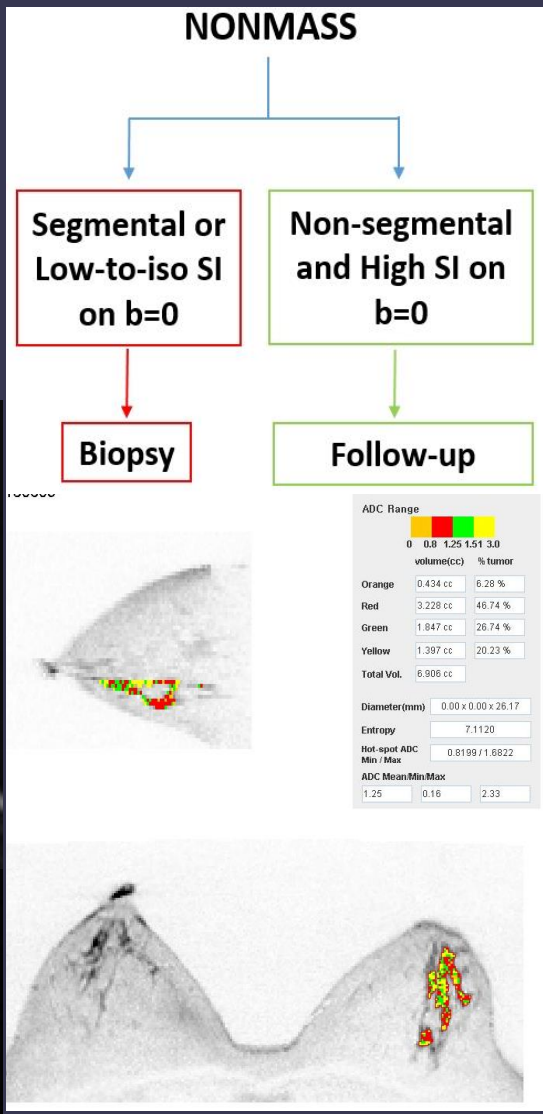




ADC map

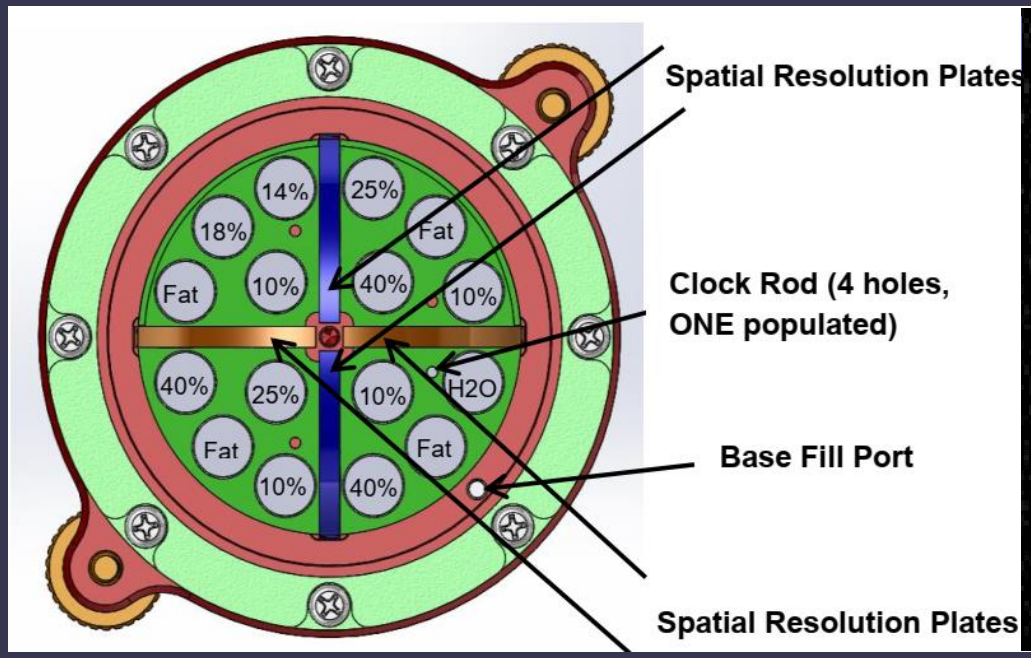


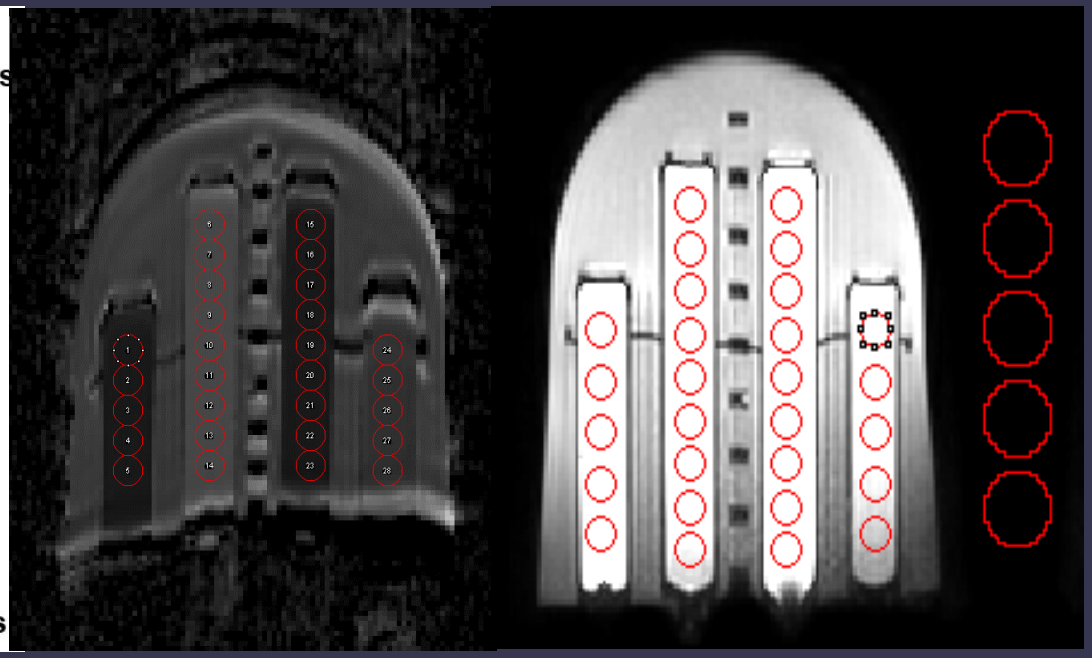
b=1000 s/mm^2

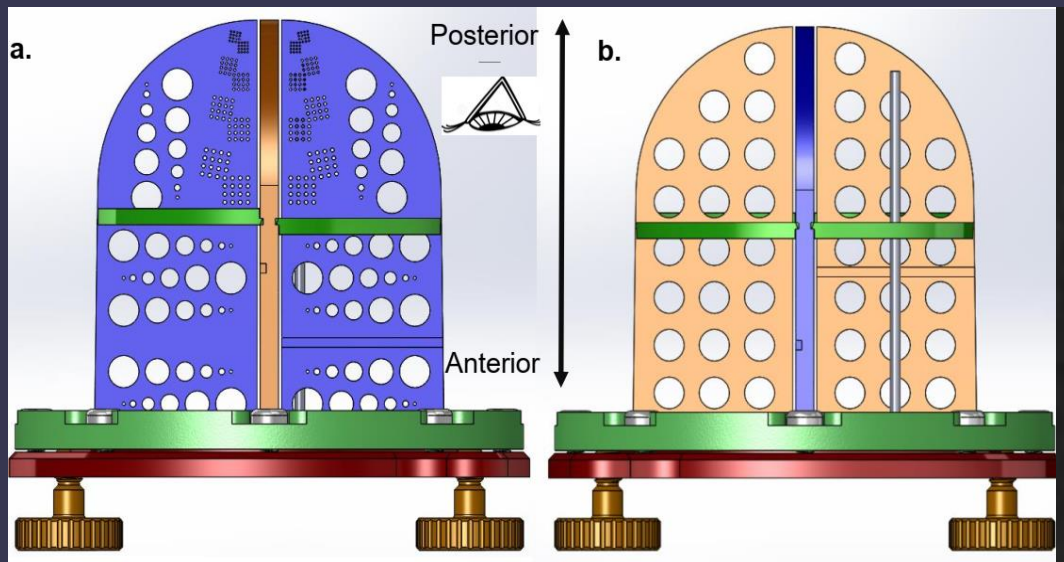


Segmental & high SI on both *b*=0 & 1000 → ADC: 1.25 x 10^{-3} mm^2/sec

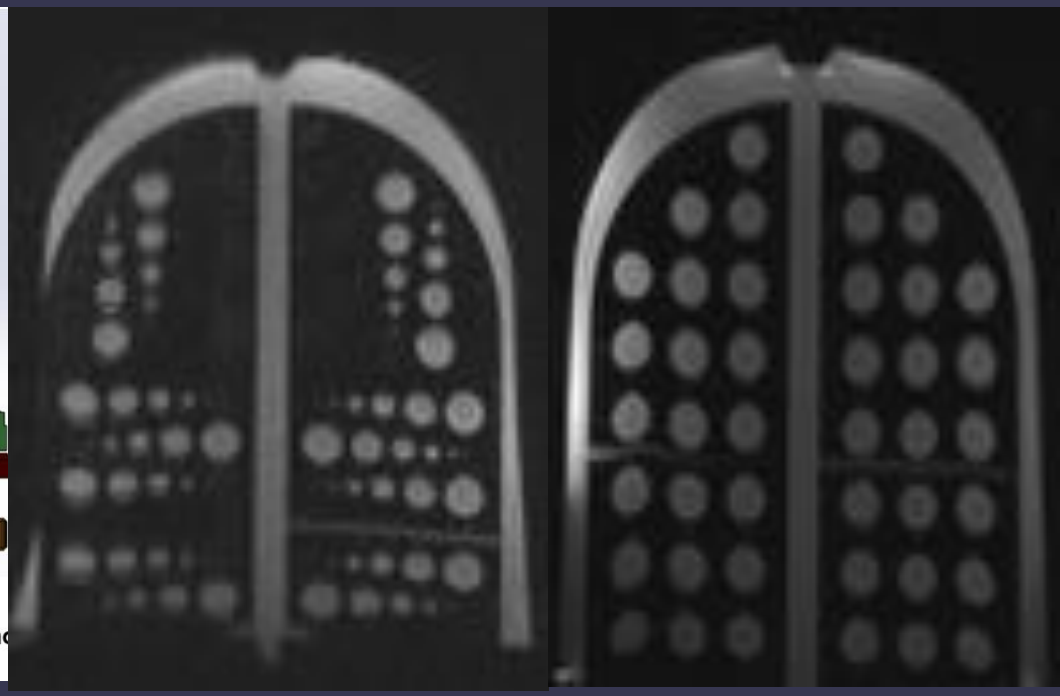
DWI QC Phantom







gure 1. a) 14 Resolution pattern holes: 10mm, 8mm, 6mm, 4mm, 2mm, 1mm with center spacing:
mm, 9mm, 7mm, 5mm, and 3mm, respectively. 2 Resolution insets: 1.25mm, 1mm, .75mm, .5mm
ameter. The sub-patterns are rotated 10 degrees from each-other. b) Spacing insets with 10 mm h
l holes are on 15mm spacing, across both halves.



Summary

- DWI – a fast, safe & cost-effective modality in identifying mammographically occult malignancy
  - DWI – sensitivity lower than DCE-MRI, but perhaps superior to that of MG and breast US
- The ability of DWI – enhanced using optimal acquisition and interpretation protocols
- Korean prospective multicenter trial can provide promising results for the noncontrast MR screening in the future


Thank you for your attention