

Automated Breast US as Supplemental Screening Modality in Women with Dense Breasts

DENSE BREASTS



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Photo by Ky Toh



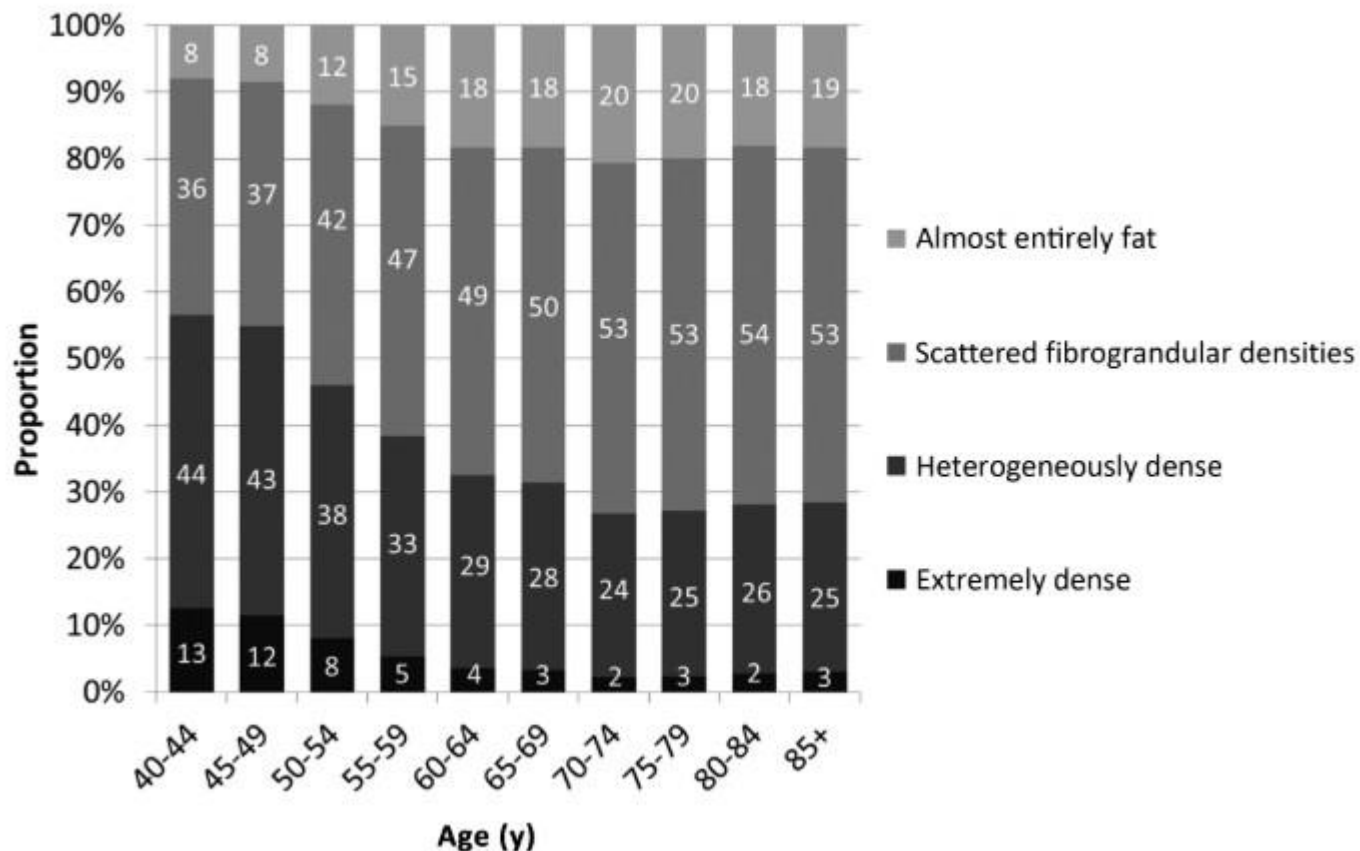
Changgyeonggung Palace, Spring
: Courtesy of JH Lee (breast radiologist)

Dense Breast

Dense Breast

- Decreased mammographic sensitivity
- Independent risk factor for breast cancer
 - Women with highest density with breasts of 75% or greater percent density have 4–6 times greater risk for developing breast cancer compared to the lowest density with breasts of 10% or less percent density

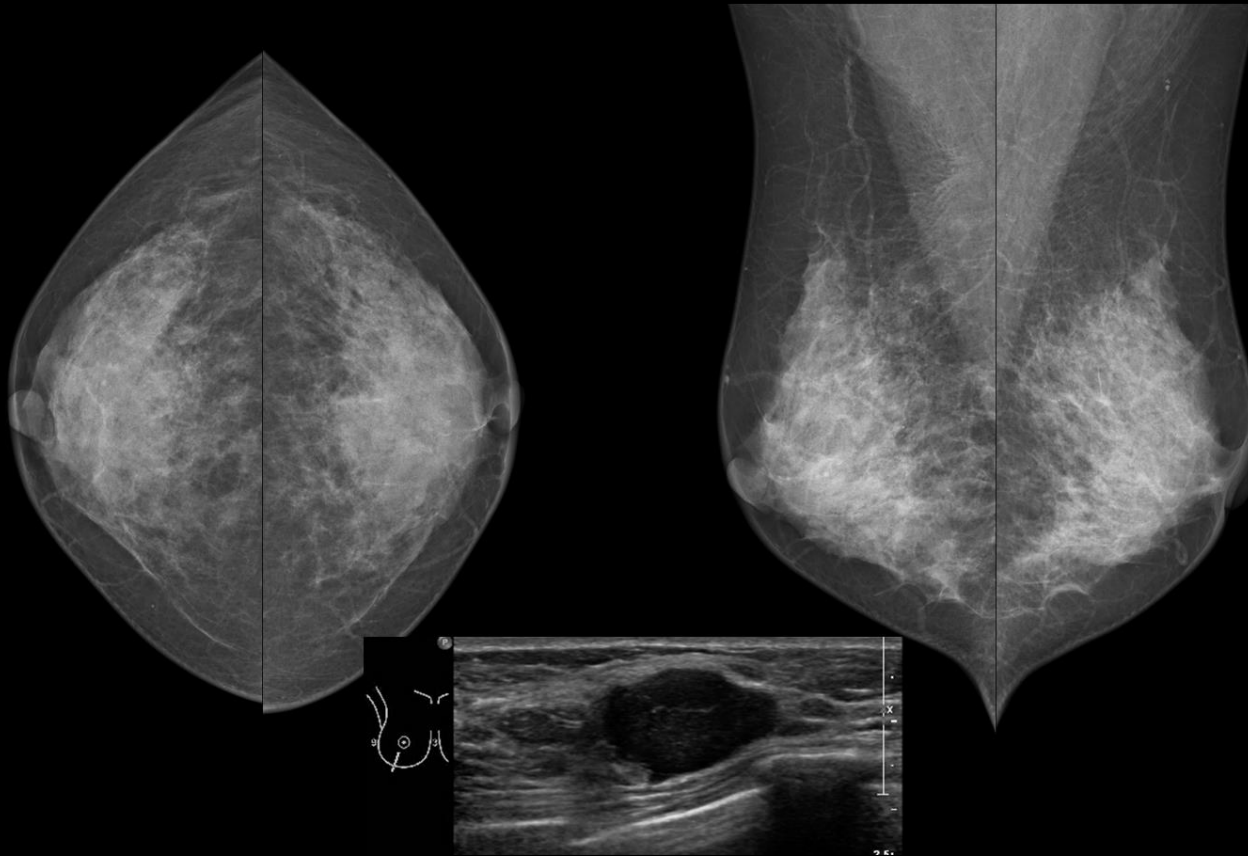
Prevalence of dense breast



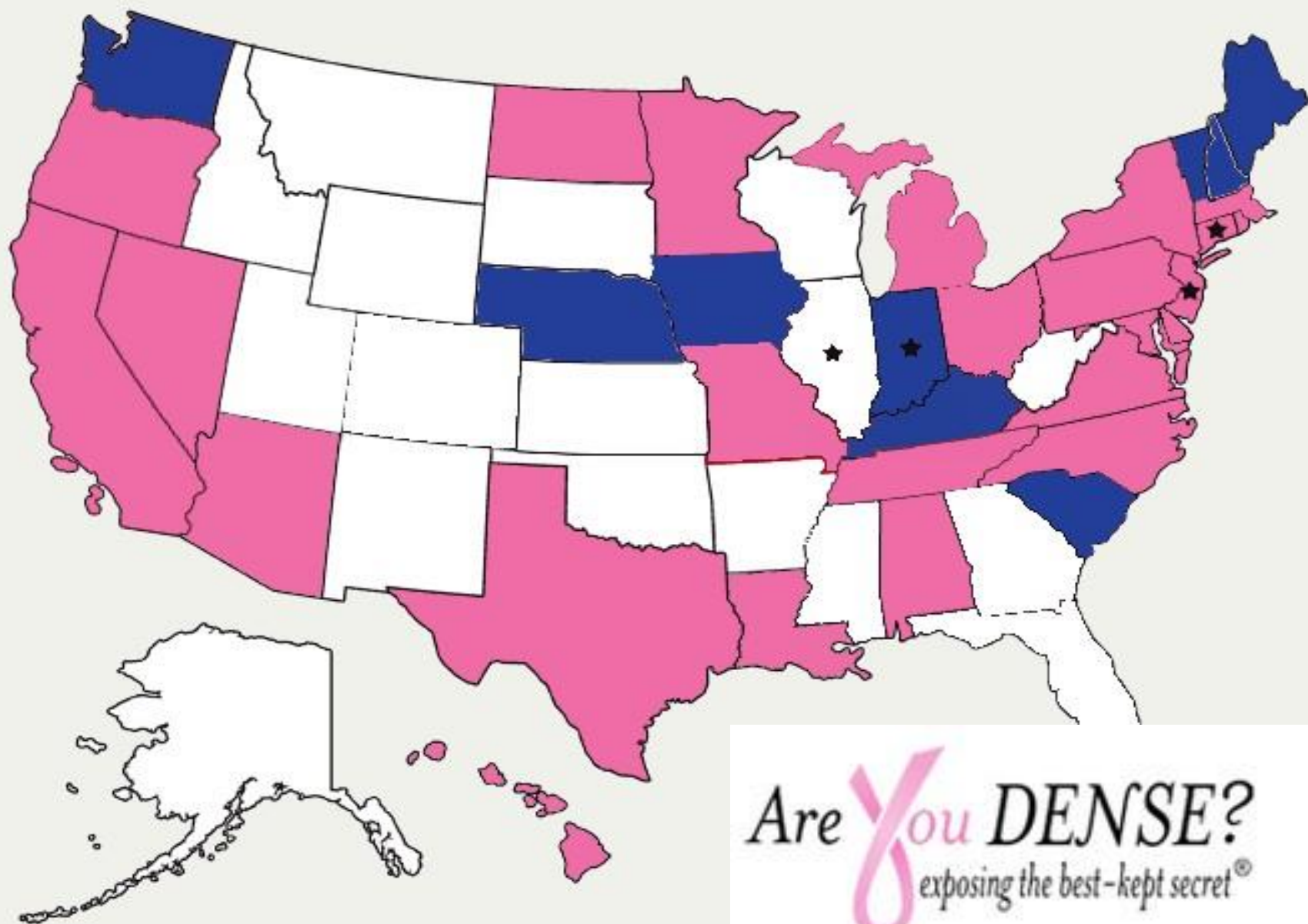
BCSC data – 43.3% of US women 40-74 years

- c. The breast is heterogeneously dense, which could obscure detection of small masses.
- d. The breast is extremely dense. This may lower the sensitivity of mammography

44/F



Click on your state to find information about "mandatory breast density notification" legislative efforts.



PINK: Enacted Law — RED: Introduced Bill — BLUE: Working on Bill — WHITE: No Action — BLACK ★ : Insurance Coverage Law

ACRIN 6666 (2004-2006)

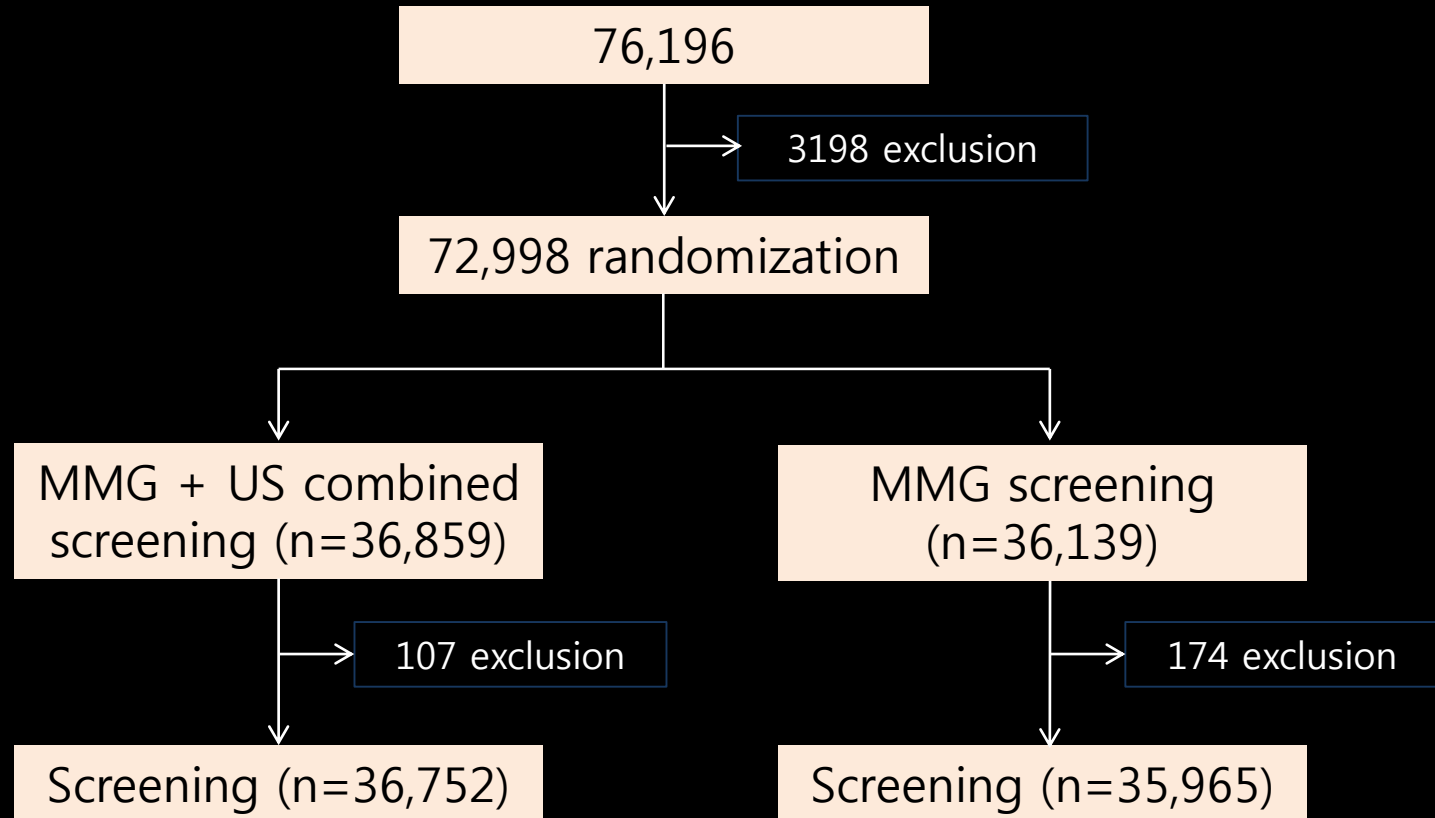
- High risk women (n= 2809)

Table 2. Summary of Performance Characteristics of Screening With Combined Mammography Plus Ultrasound Compared With Mammography Alone at the Participant Level^a

	Mammography Plus Ultrasound ^b	Mammography Alone	Comparison of Mammography Plus Ultrasound vs Mammography Alone		Ultrasound Alone ^d
			Difference	P Value ^c	
Yield per 1000					
No./total	31/2637	20/2637			20/2636
% (95% CI)	11.8 (8 to 16.6)	7.6 (4.6 to 11.7)	4.2 (1.1 to 7.2)	.003	7.6 (4.6 to 11.7)
Sensitivity					
No./total	31/40	20/40			20/40
% (95% CI)	77.5 (61.6 to 89.2)	50 (33.8 to 66.2)	27.5 (9.5 to 45.5)	.003	50.0 (33.8 to 66.2)
Specificity					
No./total	2322/2597	2481/2597			2383/2596
% (95% CI)	89.41 (88.16 to 90.57)	95.53 (94.67 to 96.30)	-6.12 (-7.24 to -5)	<.001	91.80 (90.67 to 92.82)
Area under ROC curve					
BI-RADS	0.91 (0.84 to 0.96)	0.78 (0.67 to 0.87)	0.13 (0.04 to 0.22)	.003	0.80 (0.70 to 0.88)
% Probability of malignancy	0.90 (0.83 to 0.95)	0.68 (0.53 to 0.80)	0.23 (0.10 to 0.35)	<.001	0.75 (0.62 to 0.85)
			Odds Ratio ^e		
Positive predictive value					
No./total	31/306	20/136			20/233
% (95% CI)	10.1 (7.0 to 14.1)	14.7 (9.2 to 21.8)	0.65	.03	8.6 (5.3 to 13.0)
Negative predictive value					
No./total	2322/2331	2481/2501			2383/2403
% (95% CI)	99.61 (99.27 to 99.82)	99.20 (98.77 to 99.51)	2.08	.004	99.17 (98.72 to 99.49)

J-START (2007-2011) : 40-49 yrs

RCT on effectiveness of US for breast cancer screening



1.84 / 1000 additional detection of breast cancer

J-START

		Combined screening (n=36752)	MMG screening (n=35965)
Sensitivity		91.1% (87.2-95.0)	77.0% (70.3-83.7)
Specificity		87.7% (87.3-88.0)	91.4% (91.1-91.7)
Pathology	DCIS	53/184 (29%)	31/117 (27%)
	Invasive Ca	128 /184 (70%)	86 /117 (74%)
Interval Ca		18	35
Stage	0-I	144/184 (71.3%)	79/117 (52.0%)
	II ~	37/184 (18.3%)	38/117 (25.0%)
Recall Rate		4647 (12.6%)	3153 (8.8%)

Photo by KY Toh

Changgyeonggung Palace, Spring
: Courtesy of JH Lee (breast radiologist)

Screening ABUS

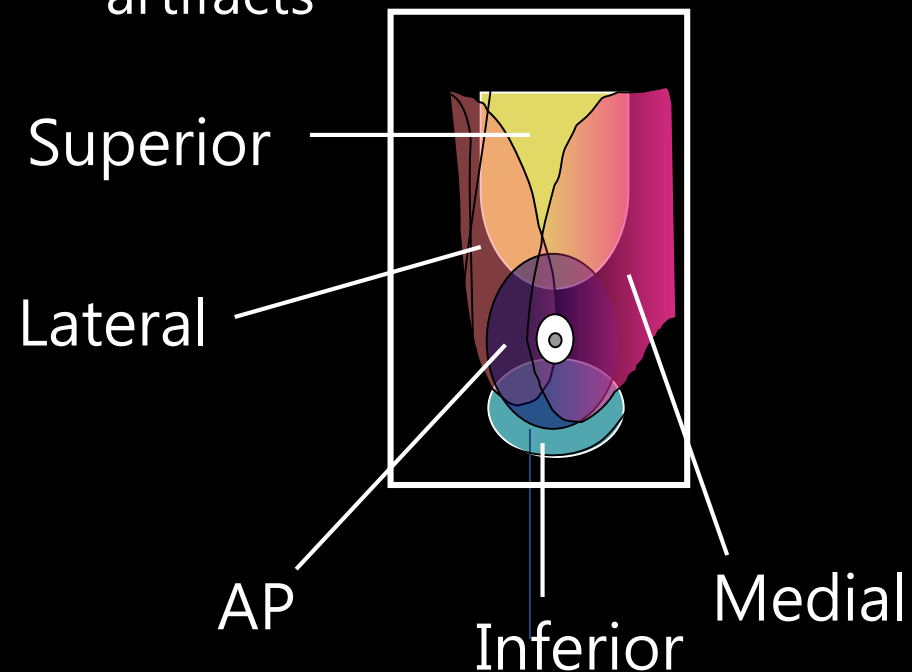
ABUS in Screening Setting

- the U-Systems' Pivotal Clinical Retrospective Reader Study
 - ❖ improved ability of ABUS to detect breast cancer
 - ❖ a clinically insignificant decrease in specificity compared to screening mammography alone (76.2% vs 78.1%, $P = 0.480$)
- U-Systems' somo•v[®] Automated Breast Ultrasound system for breast cancer screening as an adjunct to mammography for asymptomatic women with dense breast tissue



ACUSON S2000™ Automated Breast Volume Scanner

- 3 views - AP, medial, lateral
- Including tissue harmonic imaging, spatial compounding and tissue contrast enhancement technology
- New processing algorithms for nipple shadow and reverberation artifacts



Hand-held US vs. Automated breast US

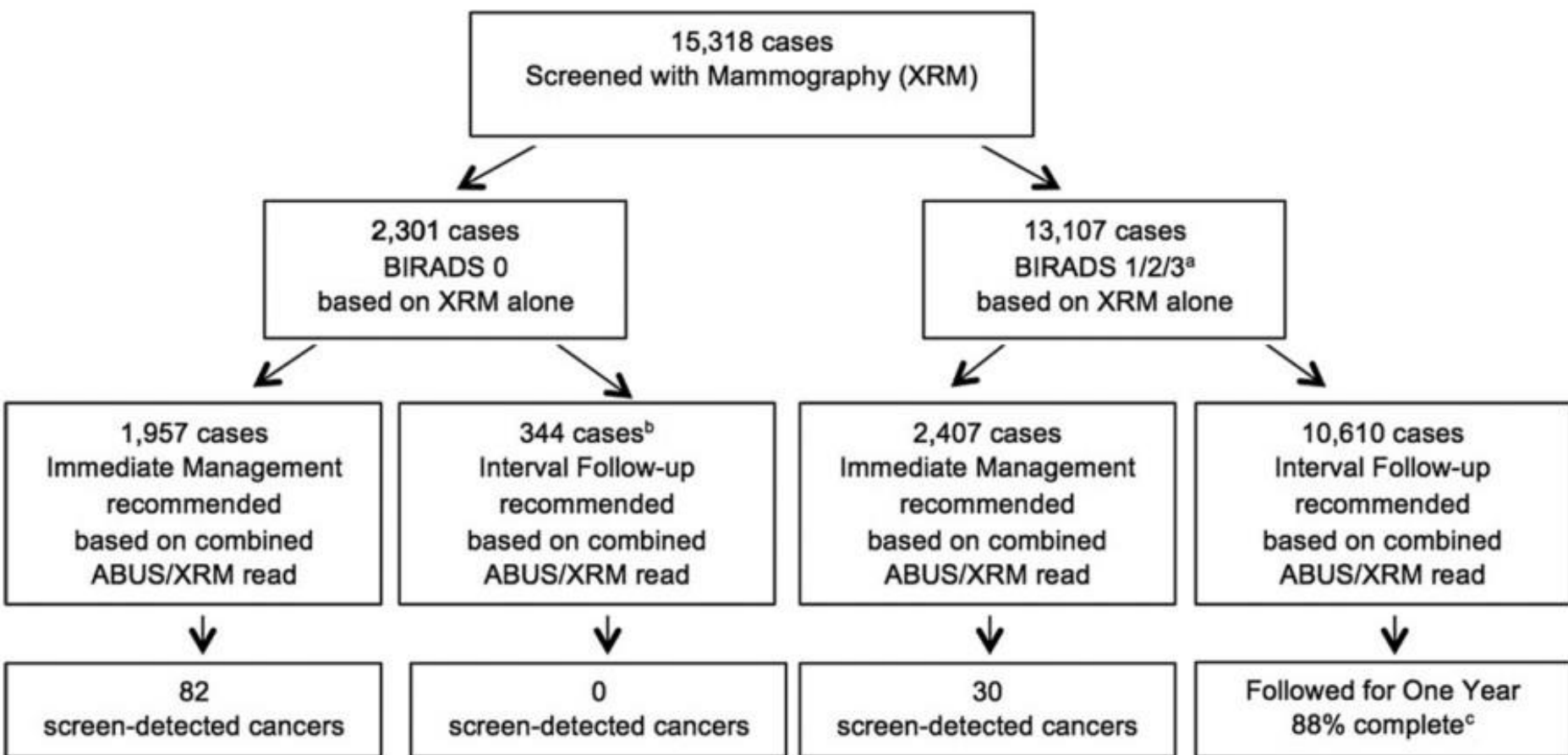
- HHUS
 - ❖ very useful for physically palpable lump
 - ❖ disadvantage
 - lack of reproducibility
 - operator dependency
- Automated breast US (ABUS)
 - ❖ Proper orientation and documentation of lesions
 - better reproducibility
 - good for follow-up studies
 - ❖ Ease of use without a long period of training
 - good for technologists
 - ❖ Time-efficient for radiologists
 - reduce interpretation time

HHUS vs ABUS

	HHUS	ABUS
3D view	-	3D reconstruction
FOV	4~6 X 4~6 cm	15X17 cm
Scan direction	Transverse, Longitudinal, Radial, Antiradial	Transverse
Probe	5-17,18 MHz	14 MHz
Elastography, Color Doppler	available	-
Focal Zone	manual setting	wide and fixed
Coupling Agent	Gel	Lotion

The SomoInsight Study

- Cancer detection
ABUS with MMG vs. MMG alone
- the largest, prospective multicenter study
(2009-2011)
- 15318 women
- SN (combined read) -26.7 % increase
(95% CI: 18.3%,35.1%)
- Recall rate -284.9 (95% CI: 278.0, 292.2; P < .001)



All women with dense breast underwent ABUS.
 In group with abnormal MMG, 82 BC were diagnosed
 with negative MMG, 30 breast cancers were detected with
 ABUS

The SomoInsight Study

- 112 breast cancer
 - 82 (using SM) - 17 (SM only), 62(SM,ABUS)
 - 30 (ABUS only)
- ABUS and MMG
 - additional 1.9 detected cancers /1000
 - (95% CI : 1.2, 2.7; P < .001)
- Invasive cancer percentage (P < .001)
 - 62.2 %(51/82, screening MMG) vs. 93.3%(28/30, +ABUS)

ABUS vs HHUS Screening

	ABUS, SomoInsight	HHUS, ACRIN 6666
Study population	Intermediate risk 15318 participants	High risk 2725 participants
Period	2009-2011	2004-2006
Additional cancer detection	1.9 cancers / 1000	5.3 cancers / 1000

Berg et al. 2008 JAMA

- Screening US
 - solution to detect MMG occult cancers in women with dense breast
 - detect small, clinically significant, invasive, and predominantly node-negative cancers.

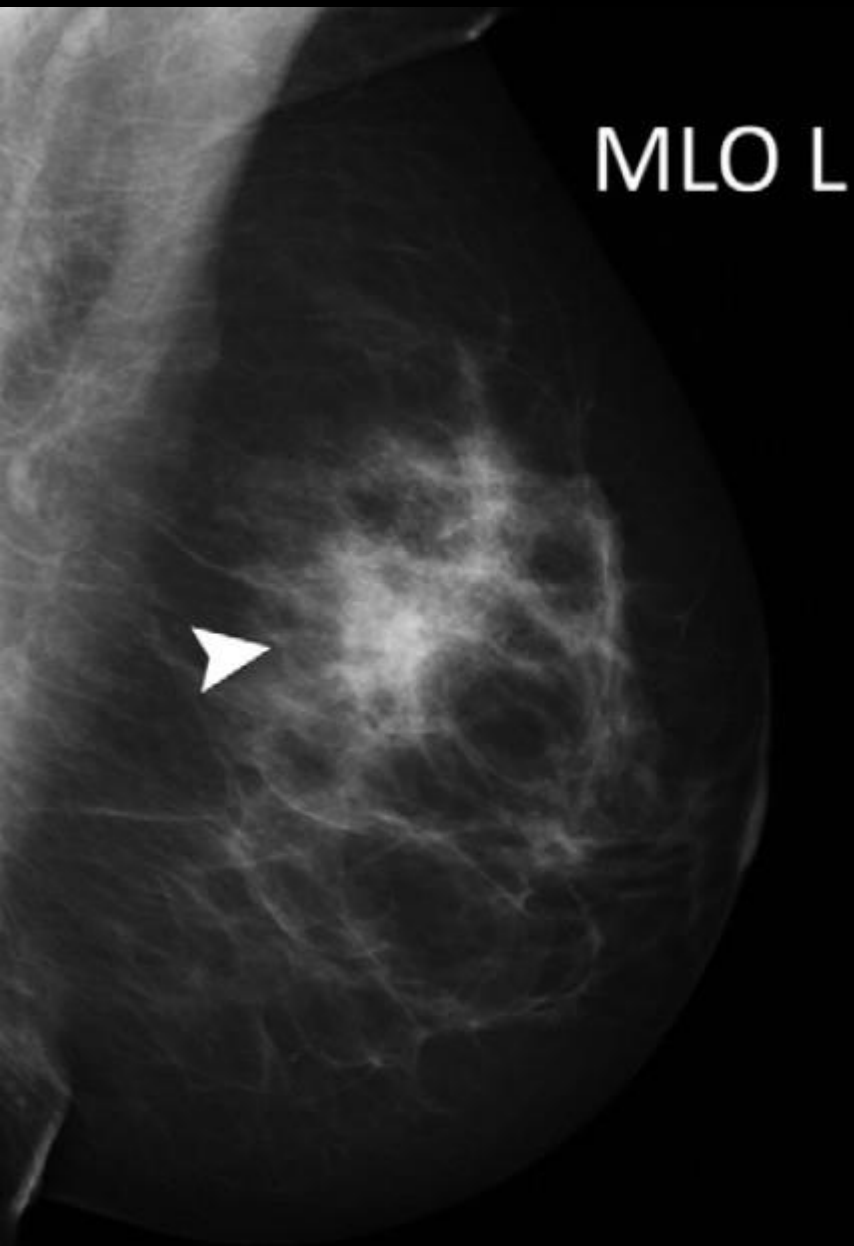
Multimodal surveillance : ABUS vs. MRI screening

- Prospective multicenter trial (2010-2012)
- Annual FFDM, DCE MRI, biannual ABUS
- 296 carriers of BRCA mutations
- Screen detected cancer -16
interval cancer -3 (by self exam)

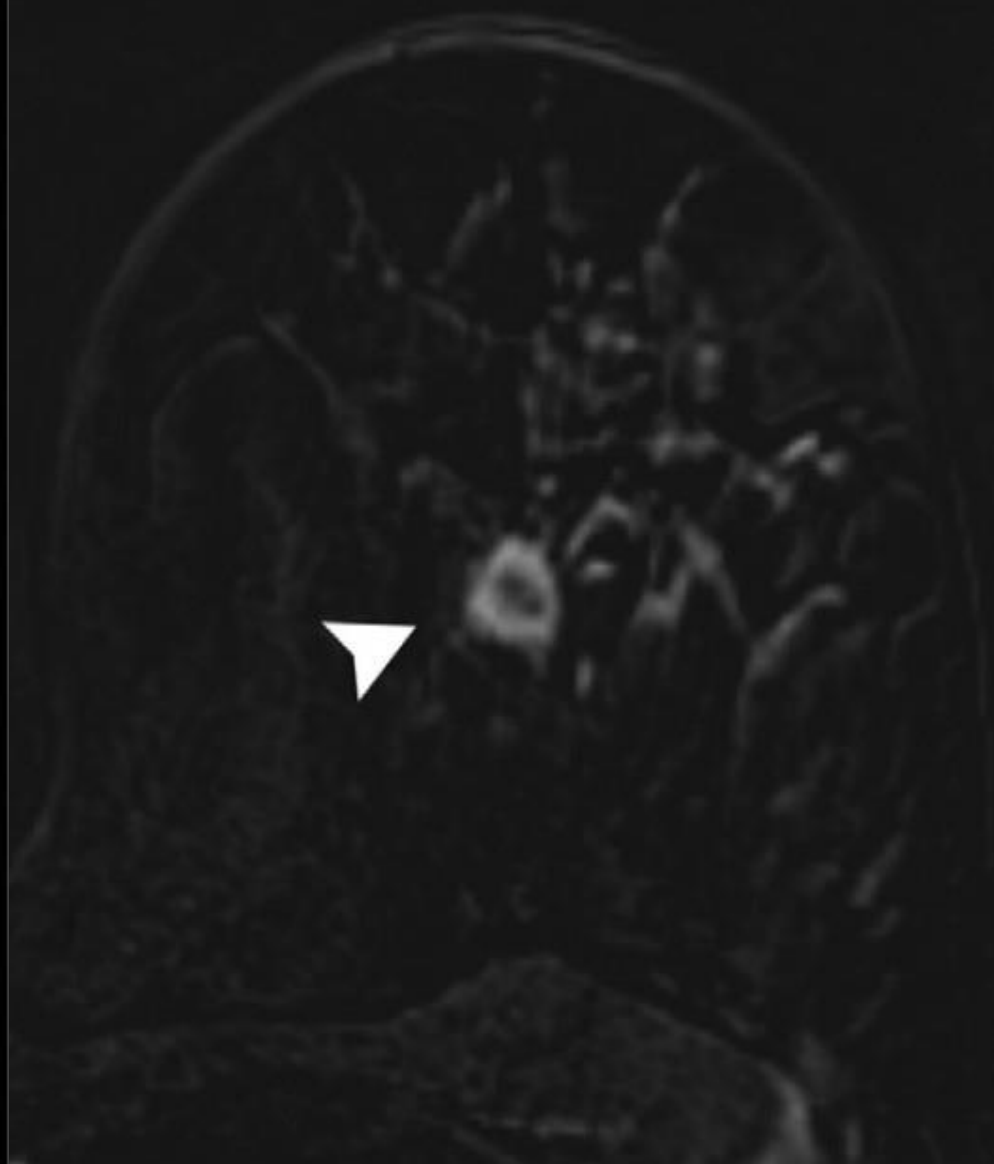
Results

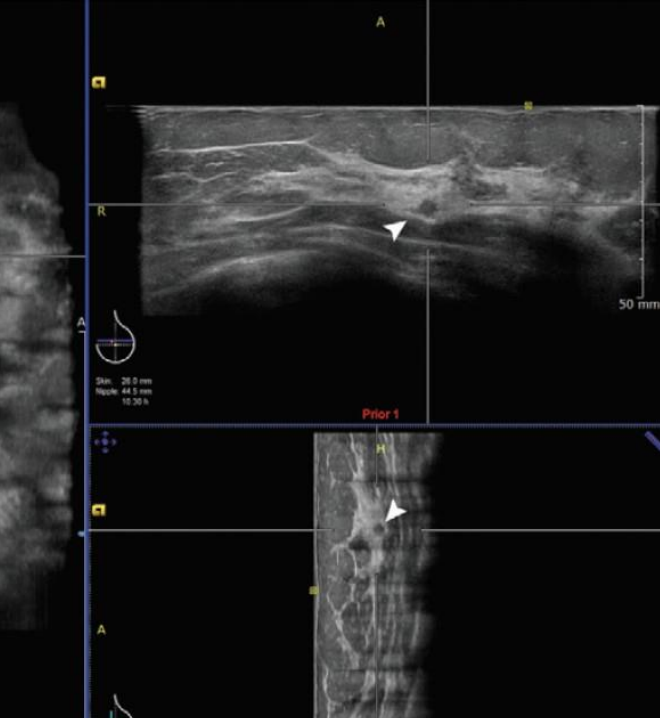
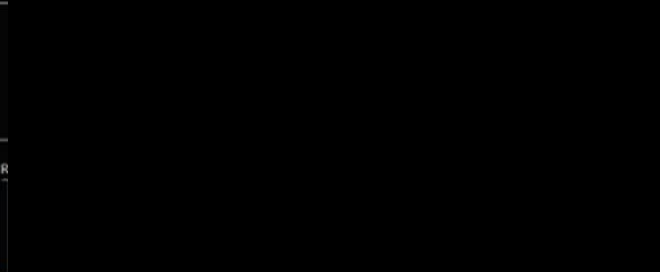
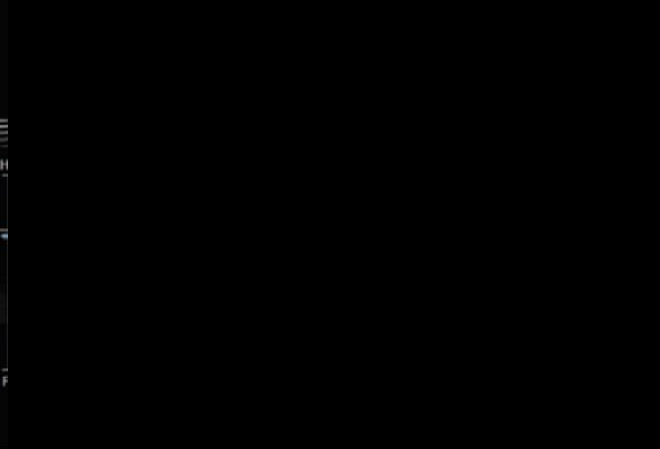
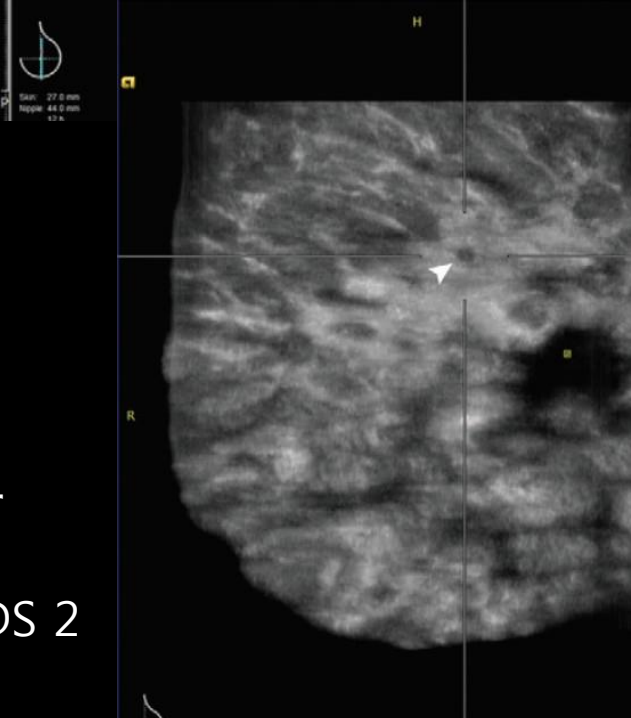
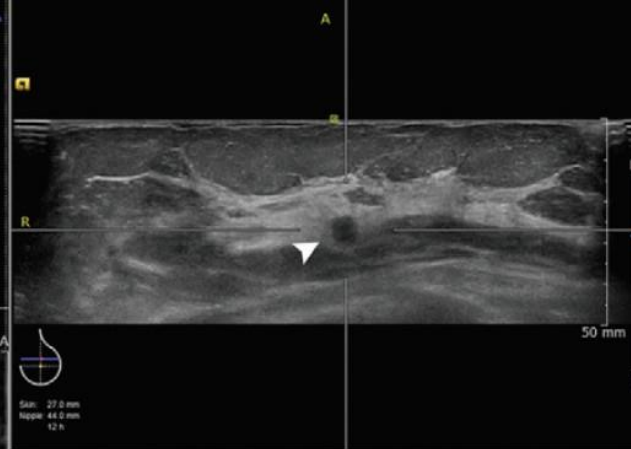
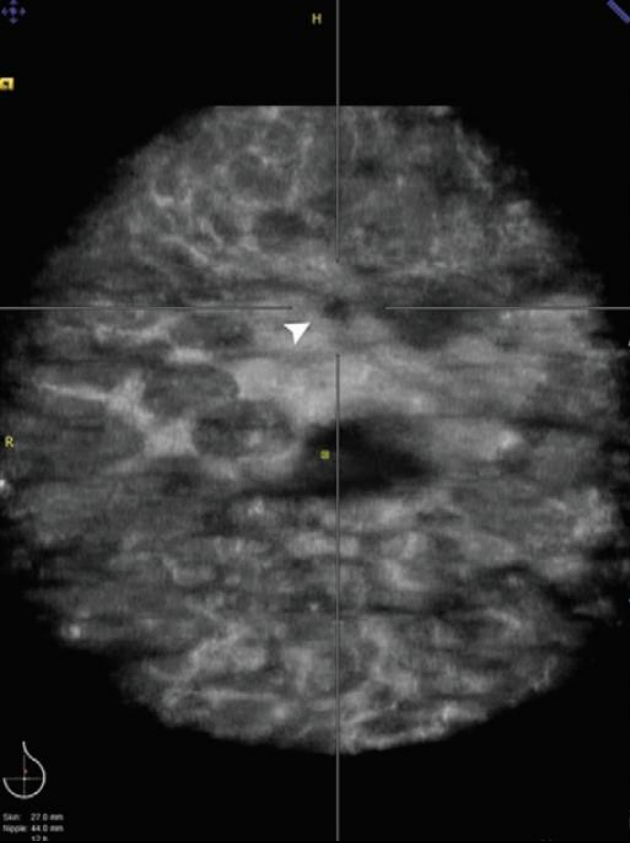
	SN(%)	SP(%)	PPV1(%)	PPV3(%)	NPV(%)	CDR(%)
MRI						
BRCA1	50.2	93.8	16.3	23.5	98.9	1.3
BRCA2	84.5	96.3	37.7	48.3	99.7	2.6
FFDM						
BRCA1	50.2	97.6	31.5	44.0	99.2	1.4
BRCA2	24.8	98.6	27.6	41.4	98.0	0.9
ABUS						
BRCA1	39.4	95.0	10.5	22.6	99.7	1.0
BRCA2	24.8	95.2	7.7	20.4	98.5	0.9

ABUS, FFDM yielded no additional cancers



11-mm invasive hormone-receptor negative HER2-positive ductal carcinoma in 56-year-old *BRCA2* mutation carrier





6 months earlier this cancer was already detected, but classified as a 4 mm BI-RADS 2 lesion.

Photo by Ky Toh



Changgyeonggung Palace, Spring
: Courtesy of JH Lee (breast radiologist)

HARMS/BALANCE

Supplemental US Screening

Supplemental US screening after a negative MMG for women aged 50 to 74 years with dense breasts

Results

- averted 0.36 additional breast cancer deaths (0.14-0.75) per 1000
- gained 1.7 QALYs (0.9 -4.7) per 1000
- resulted in 354 biopsy recommendations after a false-positive ultrasonography result (345 to 421) per 1000 women with dense breasts compared with biennial MMG screening
- The cost-effectiveness ratio was \$325 000 per QALY gained (\$112 000 - \$766 000).

Conclusion

- Supplemental ultrasonography screening for women with dense breasts would substantially increase costs while producing relatively small benefits

QALY: quality adjusted life years

BL Sprague, et al. Annals of Internal Medicine 2015

Contradictation by Radiologist

- Lenient definition of sensitivity for MMG (too high SN)
 - ❖ MMG sensitivity less than 40 % in the supplemental MR study
- Too high false positive results of US (6%)
 - ❖ FP results of any screening methods decrease with subsequent rounds
 - ❖ 4.5% in year 2 and 3 (ACRIN study)
- Modeling
 - ❖ substantially underestimates the benefit and overestimates the harms and costs

Adjunct Screening with Tomosynthesis or US

- prospective multicenter study (ASTOUND trial)
 - ❖ 3231 women with MMG negative dense breasts
 - ❖ 13 tomosynthesis detected breast cancers
 - ❖ 23 US detected cancers
 - ❖ FP recall (testing) – 3.33 % from adjunct screening and not differ between two
- Ultrasound has better incremental BC detection than tomosynthesis in mammography-negative dense breasts at a similar FP-recall rate.

The Connecticut Experiment

- Additional screening US in women with dense breast

Year	MMG	US	C1, 2	C3	C4,5	Cancer, high risk lesion per 1000	PPV (cancer only)(%)
1	30679	2706	2377	174	151	4.0	7.3
2	32500	3351	3000	168	180	3.3	6.1 (5.0)
3	32230	4128	3819	168	148	3.1	8.8 (7.4)
4	27937	3331	2889	358	53	3.3	20.1 (18.9)

- PPV for the first 3 years was under 10%, quite low. However, by year 4, PPV increased statistically significantly to 20%
- Learning curve to decide which lesions really needed biopsy and which could safely be followed
- Potentially powerful role for breast US screening

Screening US Guideline

- Dense Breast:
 - Adjunctive screening
 - No RCTs showing a survival benefit of screening women with dense breasts with US as an adjunct to mammography.
 - Limited data
 - ACR
 - ultrasound can be considered in addition to mammography
 - USPSTF, ACS
 - insufficient evidence

Asian Studies

- Additional cancer detection between 3 and 4.6 per 1000 women
- Asian Population

TABLE 3. Supplemental Ultrasound Screening in Asian Populations

Study	Population Geography	Number of Patients Enrolled	Sensitivity (Ultrasound) (%)	Sensitivity (Mammography) (%)	P Value for Sensitivity	Additional Cancer Detection per 1000 Examinations
Shen et al.	China	13,339	100	57.10	0.04	1.3
Leong et al.	Singapore	141	100	N/A	N/A	14
Chae et al.	Korea	20,864	100	54.50	0.002	2.5

N/A, not available.

In multiple studies in Asian women, ultrasound detects additional cancer when utilized in addition to screening mammography and has significantly increased sensitivity compared to mammography (38–40).

- ❖ performance of US in comparison with MMG
 - significantly greater SN / no difference in SP
 - cost (China) \$7879 for US vs \$45,253 for MMG vs. \$21,599 for both
 - a greater portion of invasive, node-negative cancers—cancer detected at an earlier stage with potential for early intervention and improved breast cancer-associated mortality outcome

Balance

- Population
 - MMG dense breast
 - 40-59 years old
- Learning period for technologists and radiologists
 - to obtain desirable PPV
- Reducing BI-RADS categories 3 and 4 cases
 - by applying supplemental techniques, such as elastography and/or Doppler US
 - by applying strict criteria
 - new criteria of category 3, 4 for screening

Photo by KY Toh



Changgyeonggung Palace, Spring
: Courtesy of JH Lee (breast radiologist)

Korean ABUS Screening Trial

Inclusion
 • Asymptomatic

Exclusion
 • Symptomatic
 • Breast surgery or mammotome history
 • Current pregnancy/lactation

Women aged 40-49

Informed consents

Year 0: ABUS (n=1200)

No Recall

Recall: C0

C 1,2

C 0

C 3

C 4,5

HHUS or MMG

6m FU

Biopsy

C1-2

C3

C 4,5

C3

C 4,5

Benign

Malignant

Year 1: FU
MG + ABUS

No detected ca

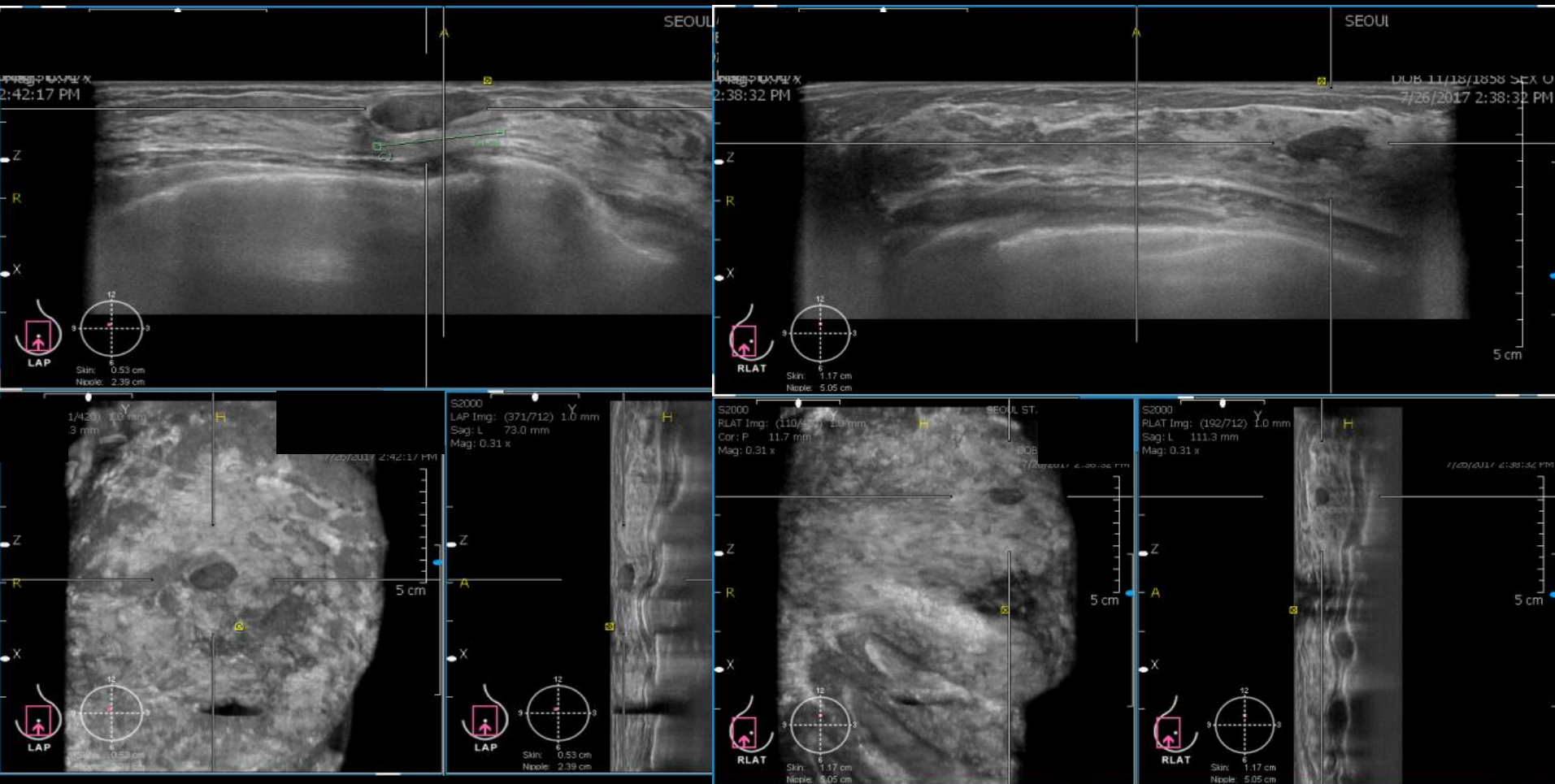
Interval ca
Subsequent screening detected ca

Primary endpoint
 : recall rate
 : cancer detection rate
 : Sensitivity, Specificity
 : PPV1 (Recall), PPV2(C4,5),
 PPV3 (Bx)

ABUS criteria in screening setting

Category	Finding	Size
2	Simple cyst/IMN/Calcified FA/fat-containing lesion	
	Multiple, oval, circumscribed complicated cysts or masses	
	Round, circumscribed, solid mass	< 5mm
	Oval circumscribed, parallel solid mass	<10mm
3	Isolated complicated cyst	
	Round circumscribed solid mass	>5mm
	Oval circumscribed parallel mass	>10mm
	Clustered microcysts	
	Intraductal well defined lesion	
4	Others	
5	Irregular, spiculated mass	

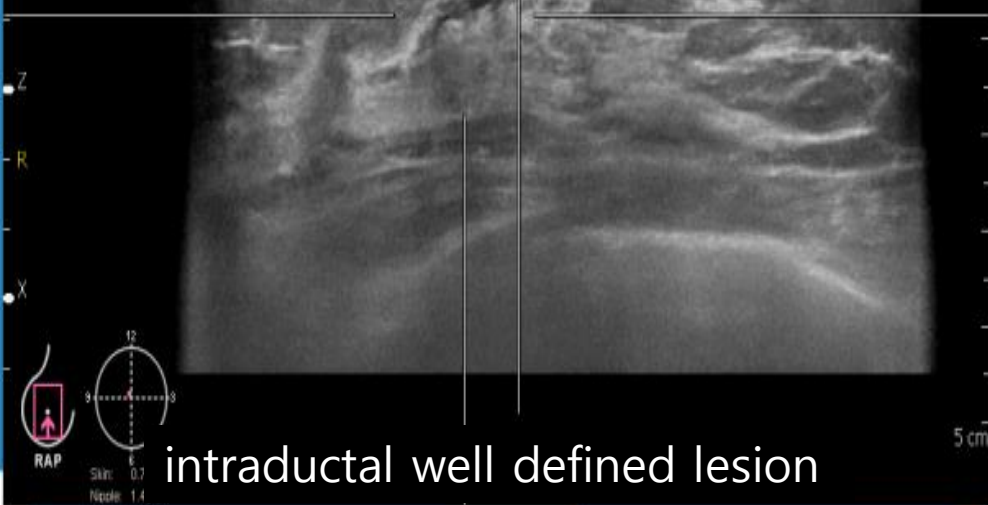
Category 2



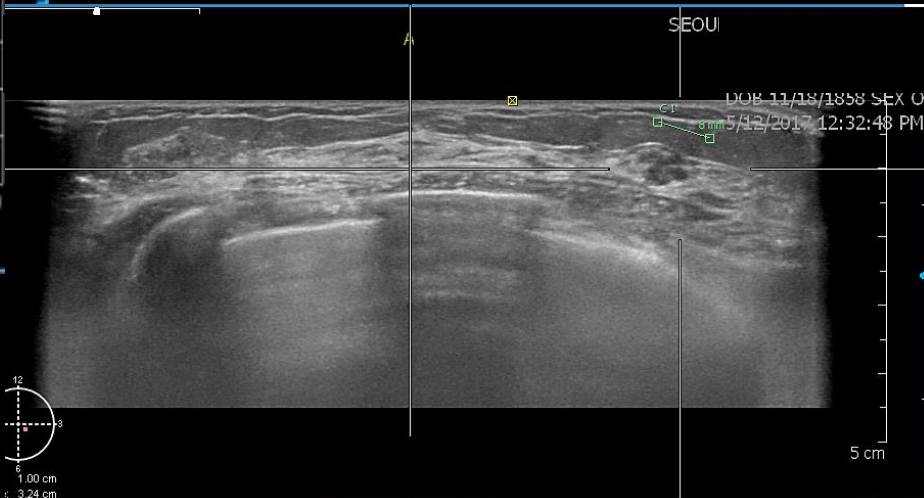
Multiple bilateral circumscribed oval hypoechoic masses

Category 3

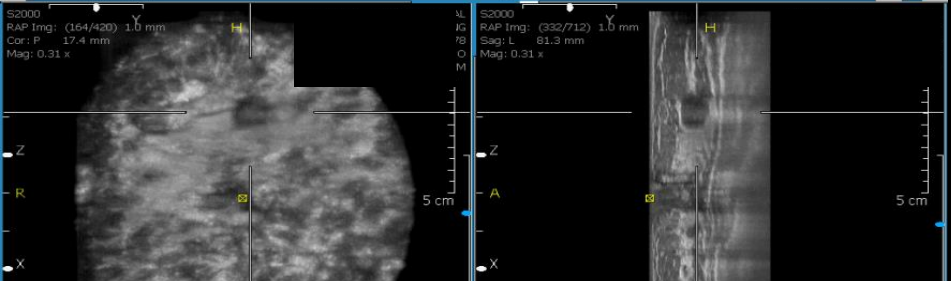
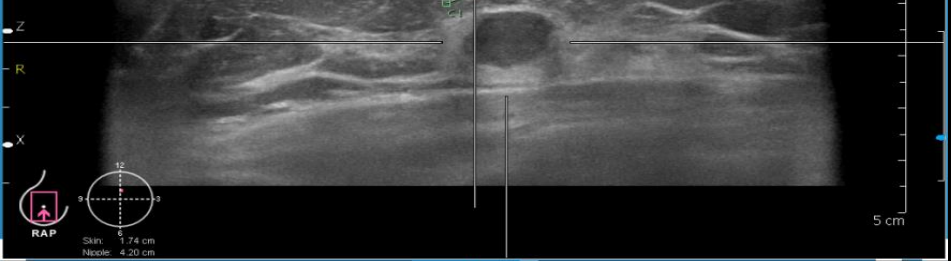
2:15:23 PM



intraductal well defined lesion



2:30:07 PM

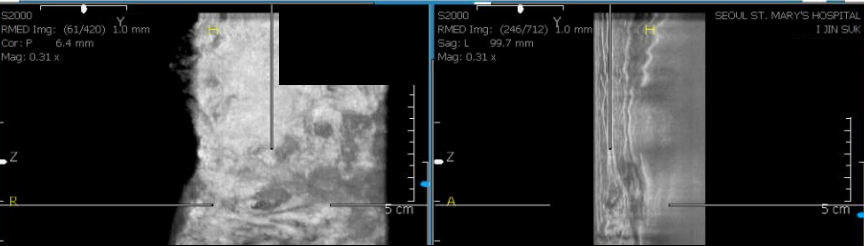
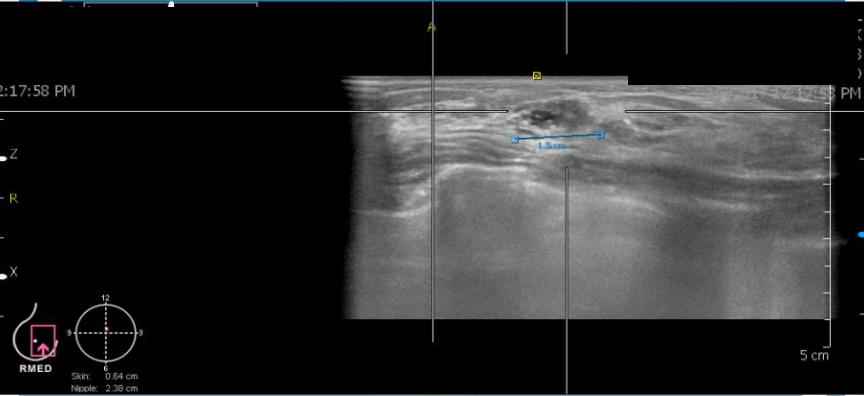


circumscribed oval solid mass >1 cm

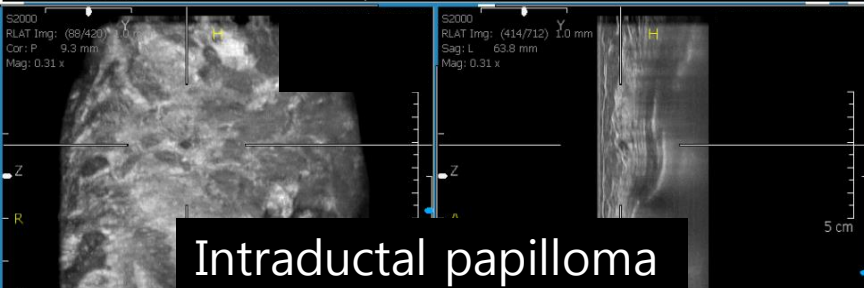
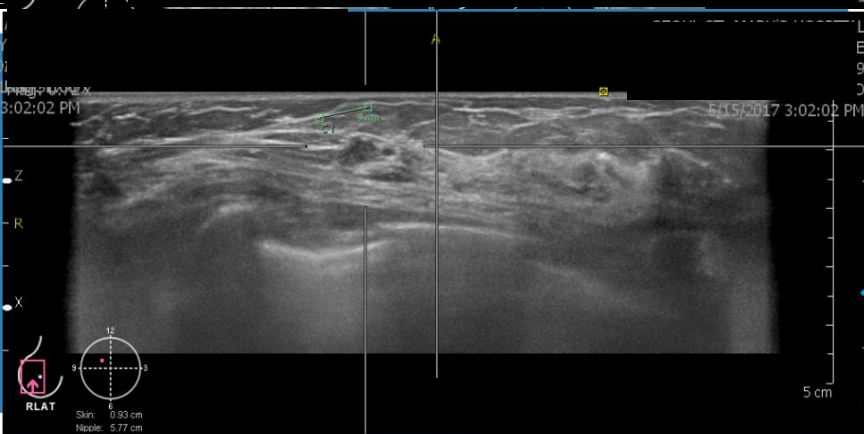


clustered microcysts

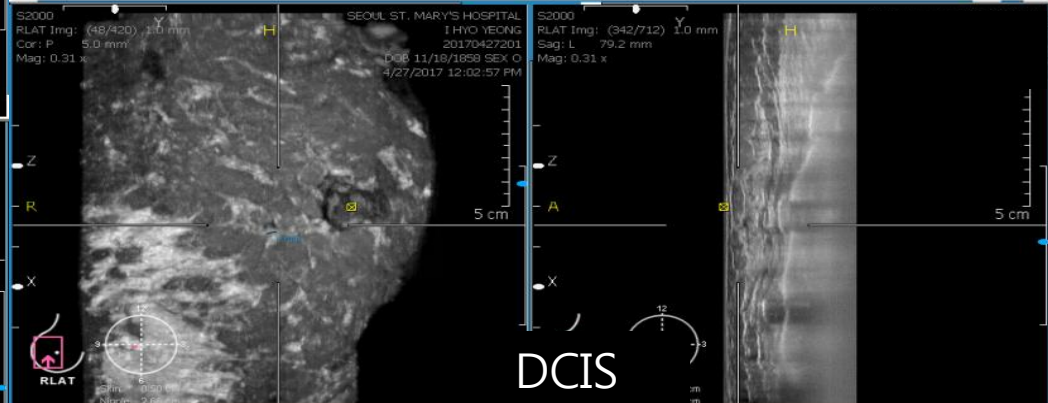
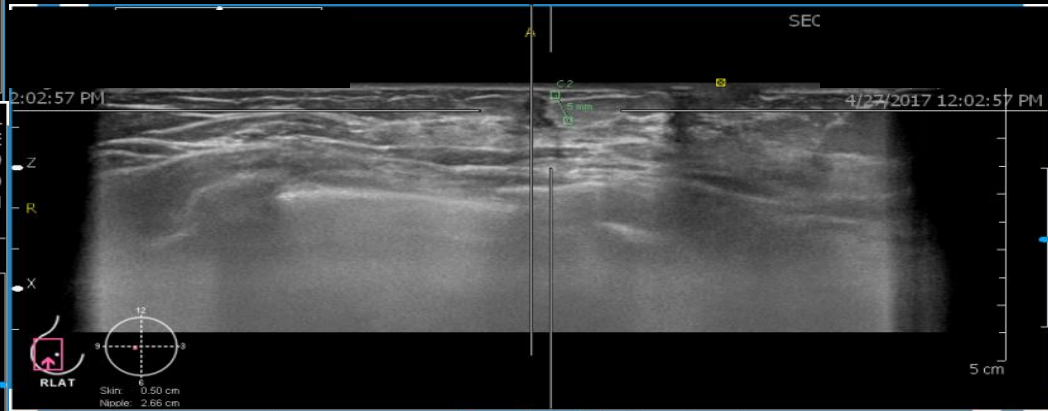
Category 4



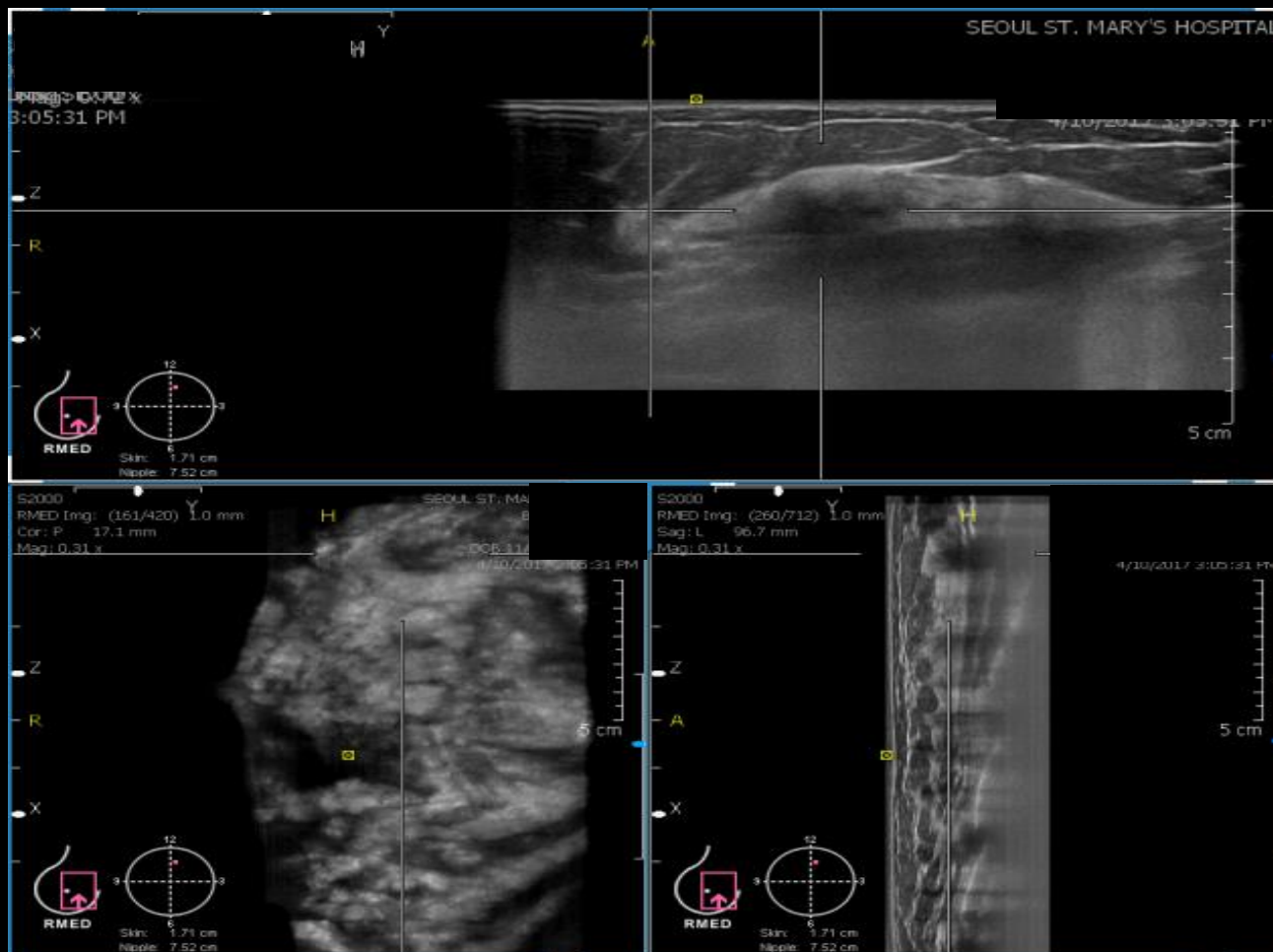
atypical ductal hyperplasia



Intraductal papilloma



Category 5



IDC

KABUS interim results

- 2017.3.1 ~ : 846 cases

	Recall rate (%)	SN (%)	SP (%)	PPV 3 (%)	CDR (per 1000)
	7.32 (62/846)	100 (5/5)	83.2 (784/841)	27.7 (5/18)	5.91
	C0 (n=3) C3 (n=41) C4,5 (n=18)			IDC (n=4) DCIS (n=1)	

False positive rate – 1.5 % (13/846), Biopsy

PPV 1 - 8.06 % (5/62) PPV2,PPV3,- 27.7 % (5/18)

IDC stage – Stage I (n=2) Stage II(n=1,T3N0) Stage III (n=1, T1N3)

Take Home Message

Benefits

Availability
Early (invasive) cancer detection
No radiation hazard

Harms

High false positive
Increased recall

Asian women

High incidence in their forties
High rate of dense breasts

Uncertain

Mortality reduction
Cost-effectiveness

Thank you
for your attention

