Outcomes of Ductal Carcinoma *in situ* according to Detection Modality:
A Multicenter Study Comparing Recurrences between Mammography and Breast US

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Severance

INTRODUCTION

Ductal Carcinoma in situ

- A non-obligate precursor lesion for invasive breast cancer

- Heterogeneous clinical course,
  - Progression into life-threatening breast cancers
  - **47-86%** of DCIS will not progress into invasive cancers

- Diagnostic rate increased in the screening era, consists of **20-30%** of screen-detected breast cancers

Narod SA, JAMA Oncol 2015;1:888-896
Virnig BA, J Natl Cancer Inst 2010:102:170-178

INTRODUCTION

- Adding *supplementary imaging modalities to screening mammography* to improve early detection of breast cancer
  - Digital breast tomosynthesis, ultrasonography (US), breast MRI
  - Additional **3.2-5.3** breast cancers per 1,000 women
  - **20-33.3%** of the newly diagnosed breast cancer being DCIS

- Paradigm shift regarding DCIS treatment,
  - Survival benefits of aggressive treatment for low-risk DCIS being questioned

- Ways to sort out patients with *low-risk DCIS* needed
  - Little investigated on patient outcomes according to the imaging modality used for detection of DCIS

Hooley RJ, Radiology 2012:265;59-69

PURPOSE

- To determine whether disease recurrence is associated with the

    imaging modality used for DCIS detection and

    intrinsic characteristics of DCIS

    in asymptomatic women diagnosed with pure DCIS
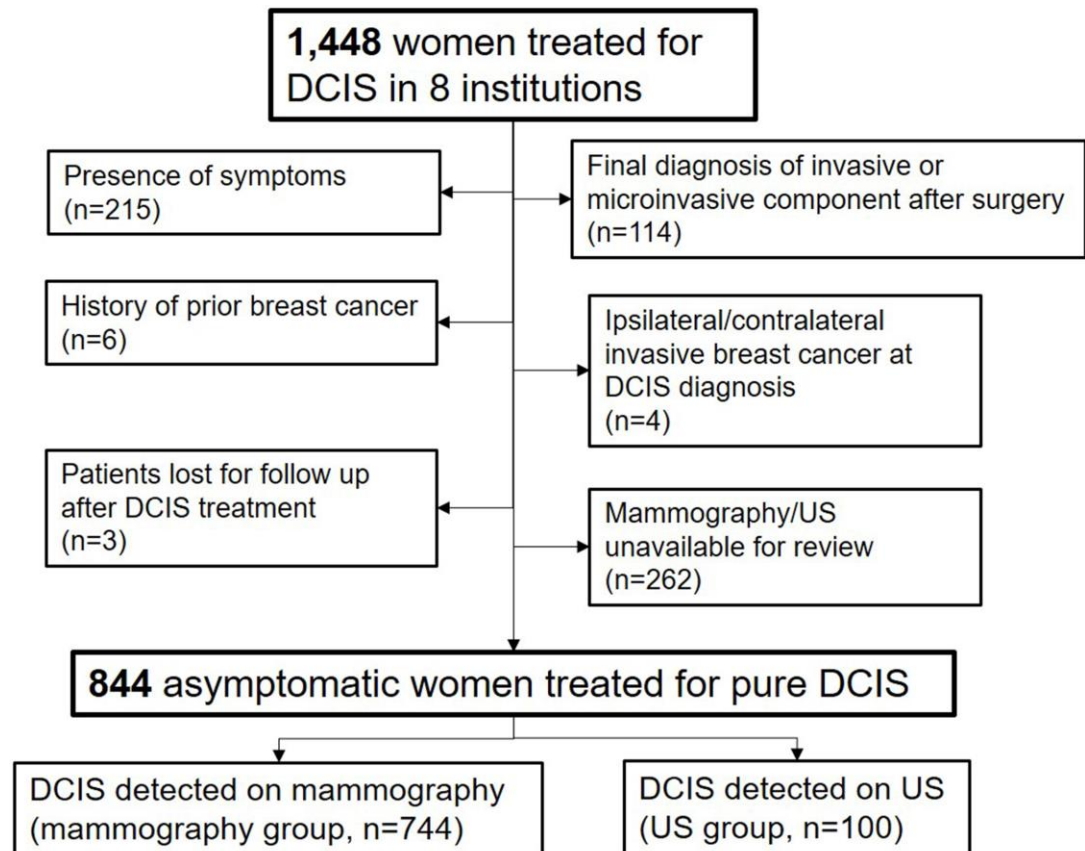
MATERIALS & METHODS

- Multicenter, retrospective study design

- Approved by the IRB of **8** institutions in Korea

- Feb. 2003-Feb. 2011

Mean age: **49.8** years (25-89 yrs)

325 (38.5%) Mastectomy

519 (61.5%) Conservation surgery

Mean follow-up interval: **91.2**

months (6.4-180.9 mths)

1,448 women treated for DCIS in 8 institutions

Presence of symptoms (n=215)

Final diagnosis of invasive or microinvasive component after surgery (n=114)

History of prior breast cancer (n=6)

Ipsilateral/contralateral invasive breast cancer at DCIS diagnosis (n=4)

Patients lost for follow up after DCIS treatment (n=3)

Mammography/US unavailable for review (n=262)

844 asymptomatic women treated for pure DCIS

DCIS detected on mammography (mammography group, n=744)

DCIS detected on US (US group, n=100)

MATERIALS & METHODS

- **1 of 8 radiologists** (3-15 years of experience) dedicated to breast imaging retrospectively reviewed the preoperative mammography, US images

DATA & STATISTICAL ANALYSIS

- **Recurrence:** newly detected breast cancer during post-treatment surveillance requiring surgical or oncological treatment
  - ipsilateral/contralateral breast
  - metastatic axillary, cervical LNs
  - distant metastasis

- **Image detectability**
  - **Mammography group:** DCIS detected on mammography regardless of US findings
  - **US group:** DCIS detected on US only

DATA & STATISTICAL ANALYSIS

- Chi-square or Fisher's exact test

- Independent two-sample t-test

- Kaplan-Meier method with log-rank test

- Univariable/multivariable Cox proportional analysis

- R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria)

RESULTS

- Of the 844 asymptomatic women treated for DCIS,
    - **744 (88.2%):** DCIS detected on mammography
    - **100 (11.8%):** DCIS detected on US

- **25 (3.0%)** developed recurrences during follow-up period
    - **21 (8 DCIS, 13, invasive cancer)** at the ipsilateral/contralateral breast
    - **3** axilla LN metastasis
    - **1** distant metastasis (bony metastasis, sacrum)
    - Mean follow-up interval: 111.1 months (20.5-170.2 months)

Demographic features of the 844 women treated for DCIS

Characteristics	Mammography (n=744)	US (n=100)	Total	P
Mean age	50.1±9.3	47.5±8.4	49.8±9.2	0.134
<50 years	381 (51.2)	66 (66.0)	447 (53.0)	**0.007**
≥50 years	363 (48.8)	34 (34.0)	397 (47.0)	
Mean size	19.5±15.3	15.3±15.4	19.1±15.7	0.556
<20 mm	408 (61.5)	62 (75.6)	470 (63.1)	**0.018**
≥20 mm	255 (38.5)	20 (24.4)	275 (36.9)	
Mammographic density				0.027
Fatty breast	135 (18.1)	28 (28.0)	163 (19.3)	
Dense breast	609 (81.9)	72 (72.0)	681 (80.7)	
Type of surgery				**<0.001**
Conservation	440 (59.1)	79 (79.0)	519 (61.5)	
Mastectomy	304 (40.9)	21 (21.0)	325 (38.5)	

Demographic features of the 844 women treated for DCIS

| Characteristics		MMG (n=744)	US (n=100)	Total	P
Nuclear grade	Non-high	424 (60.7)	72 (80.9)	496 (62.9)	**<0.001**
	High	275 (39.3)	17 (19.1)	292 (37.1)	
Comedonecrosis	Absent	254 (39.0)	48 (69.6)	302 (41.9)	**<0.001**
	Present	398 (61.0)	21 (30.4)	419 (58.1)	
ER	Negative	154 (22.1)	6 (6.7)	160 (20.4)	0.001
	Positive	542 (77.9)	84 (93.3)	625 (79.6)	
PR	Negative	198 (28.6)	6 (6.7)	204 (26.1)	<0.001
	Positive	495 (71.4)	83 (93.3)	578 (73.9)	
HER2	Negative	328 (47.9)	59 (67.1)	387 (50.1)	**0.001**
	Positive	235 (34.3)	15 (17.0)	250 (32.3)	
	Indeterminate	122 (17.8)	14 (15.9)	136 (17.6)	

Factors associated with recurrences in patients treated for DCIS

Overall (n=844)	Univariable HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
Age >50	0.774 (0.347, 1.723)	0.530		
Size	1.007 (0.983, 1.033)	0.563		
Detection				
MMG	-	-	-	-
US	**2.776** (1.101, 7.001)	**0.031**	**4.451** (1.530, 12.950)	**0.006**
Surgery				
Partial	-	-		
Total	0.599 (0.256, 1.400)	0.236		

Factors associated with recurrences in patients treated for DCIS

Overall (n=844)	Univariable HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
Nuclear grade				
Non-high	-	-		
High	1.454 (0.617, 3.430)	0.392		
IHC staining				
ER-negative	-	-		
ER-positive	0.822 (0.298, 2.267)	0.705		
PR-negative	-	-		
PR-positive	0.653 (0.260, 1.637)	0.363		
HER2-negative	-	-		
HER2-indeterminate	1.001 (0.202, 4.965)	0.999	1.154 (0.231, 5.760)	0.862
HER2-positive	**3.124** (1.154, 8.457)	**0.025**	**4.036** (1.438, 11.330)	**0.008**

Kaplan-Meier survival curve according to detection modality
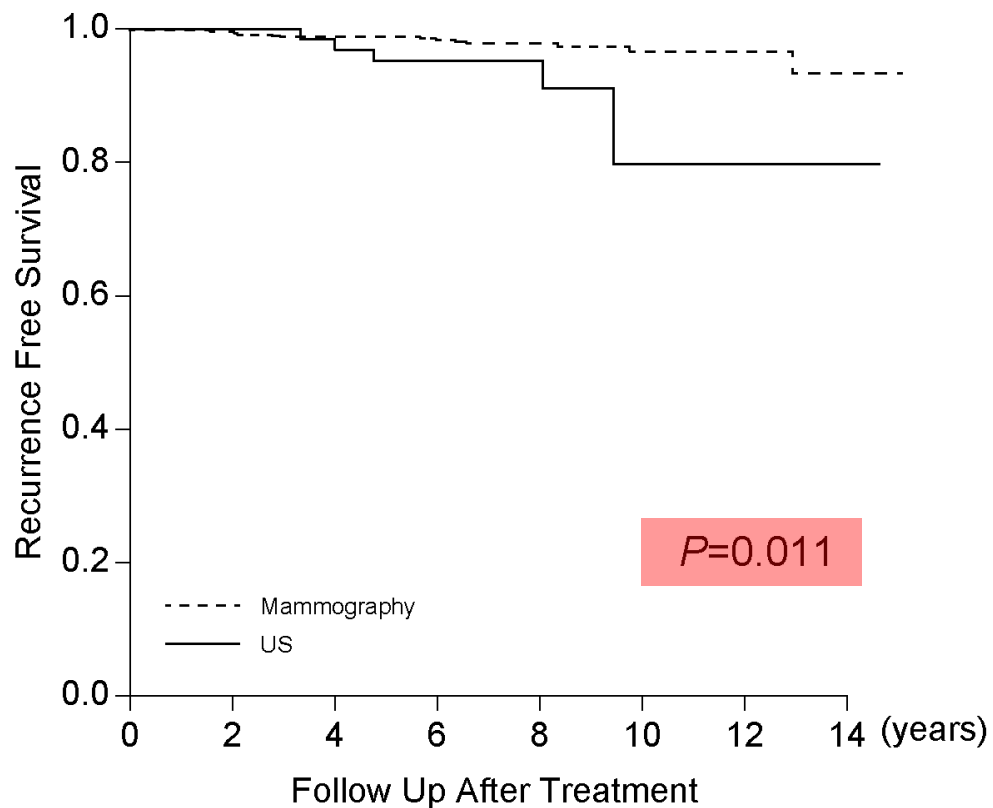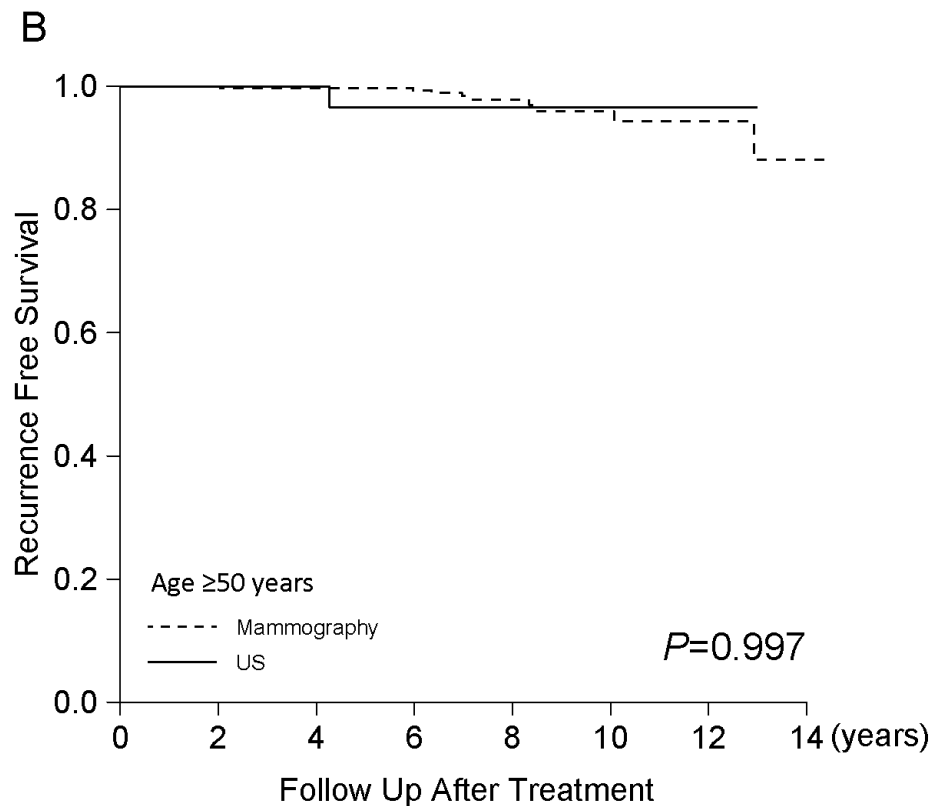

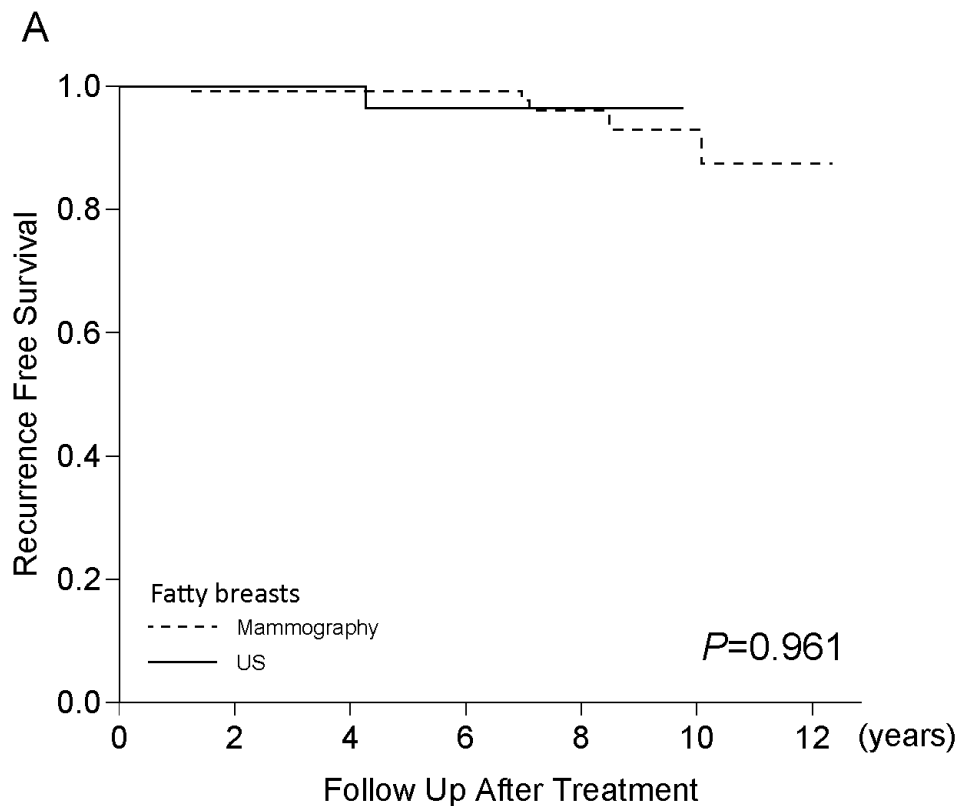|	5-year RFS	10-year RFS
Mammography	98.9 (98.1, 99.7)	96.1 (94.0, 98.3)
US	95.6 (91.5, 99.9)	84.0 (68.6, 100.0)

Kaplan-Meier survival curves for subgroups for age

A

Age <50 years
- - - Mammography
— US

P=0.002
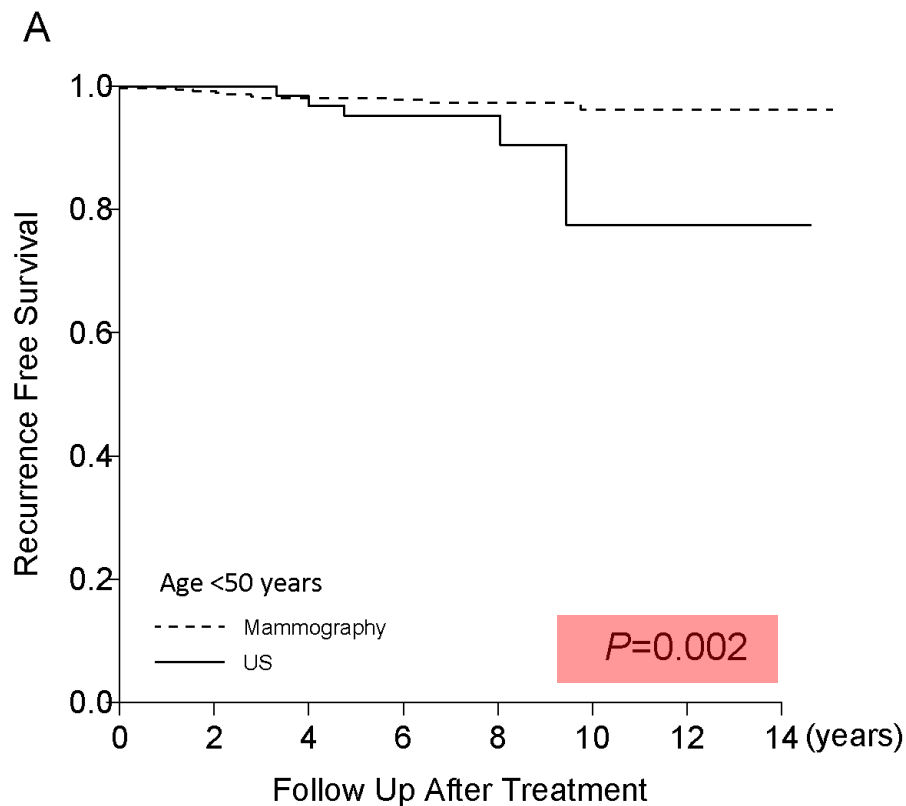
	5-year RFS	10-year RFS
Mammography	98.1 (96.7, 99.5)	96.2 (93.5, 99.1)
US	95.2 (90.1, 100.0)	77.5 (56.1, 100.0)

B

Age ≥50 years
- - - Mammography
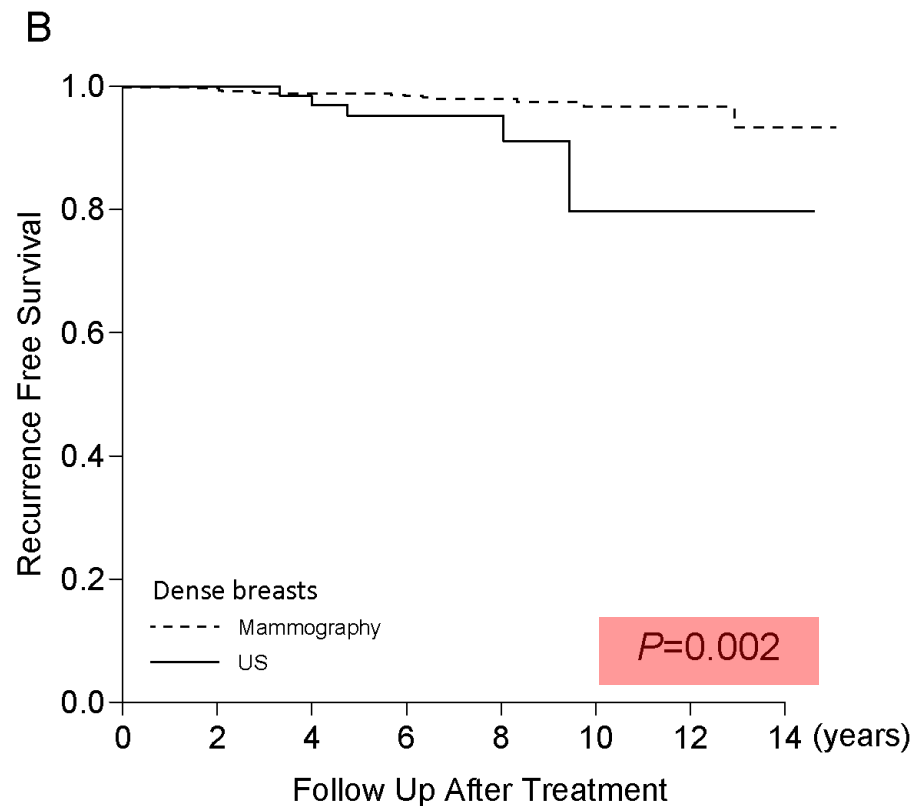— US

P=0.997

	5-year RFS	10-year RFS
Mammography	99.7 (99.2, 100.0)	95.9 (92.7, 99.2)
US	96.6 (90.1, 100.0)	96.6 (90.1,100.0)

# Kaplan-Meier survival curves for subgroups for parenchymal density

A

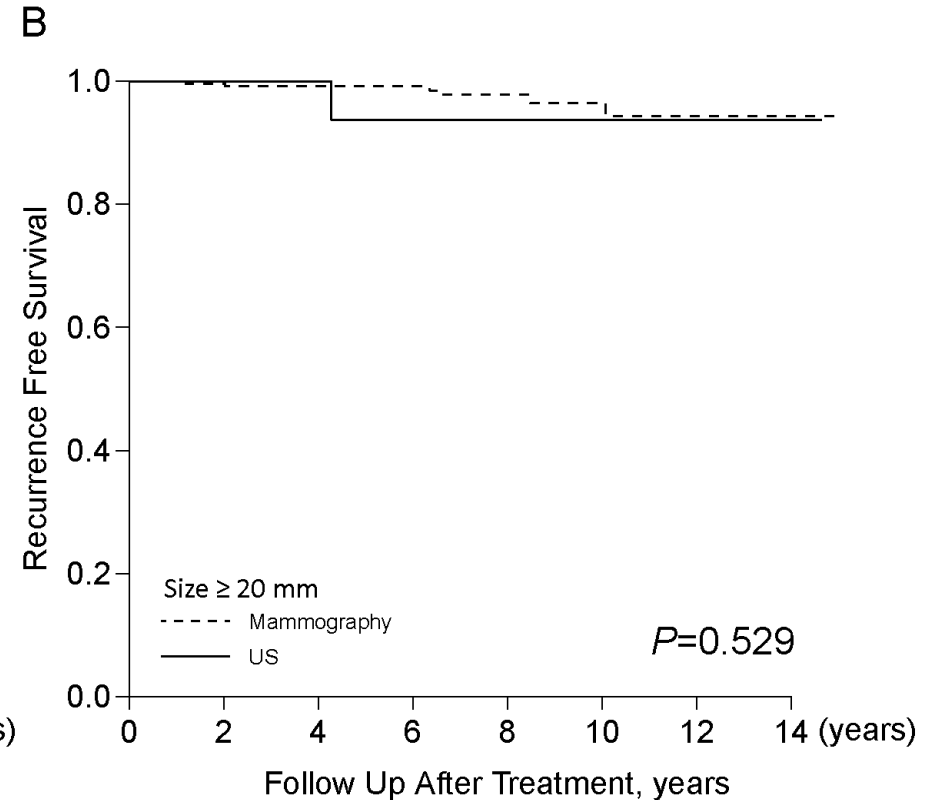|	5-year RFS	10-year RFS
Mammography	99.3 (97.8, 100.0)	92.9 (85.8, 100.0)
US	96.4 (89.8, 100.0)	NA

B

	5-year RFS	10-year RFS
Mammography	98.8 (97.9, 99.7)	96.7 (94.6, 98.8)
US	95.3 (90.2, 100.0)	79.7 (60.2, 100.0)

Kaplan-Meier survival curves for subgroups for pathologic size

A

Recurrence Free Survival

Size < 20 mm
----- Mammography
—— US

P=0.051

Follow Up After Treatment
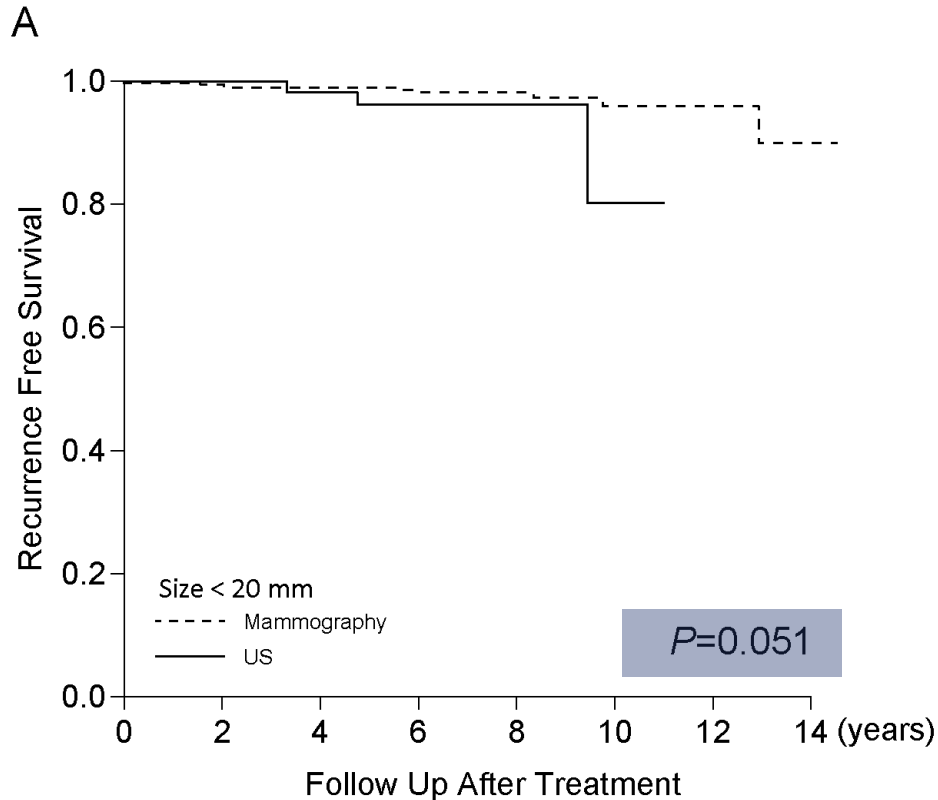
	5-year RFS	10-year RFS
Mammography	98.9 (97.8, 100.0)	96.0 (92.7, 99.4)
US	96.3 (96.3, 100.0)	80.2 (55.9, 100.0)

B

Recurrence Free Survival

Size ≥ 20 mm
----- Mammography
—— US

P=0.529

Follow Up After Treatment, years

	5-year RFS	10-year RFS
Mammography	99.2 (98.0, 100.0)	96.4 (93.0, 99.9)
US	93.8 (82.6, 100.0)	93.8 (82.6, 100.0)

LIMITATIONS

- Retrospective study design

- Both film and digital mammography had been used during the study period

- Interobserver variability among pathologists in DCIS diagnosis among the 8 institutions

CONCLUSION

- **US as the detection modality** and **HER2 positivity** were factors significantly associated with recurrence in patients treated for DCIS.

- Supplementary screening US may enable detection of clinically-important DCIS, especially in **younger women** or **women with mammographically-dense breasts**

Thank You

With the Love of God, Free Humankind from Disease and Suffering

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