Memorial Sloan Kettering Cancer Center

Management of High-Risk Breast Lesions

Anne Grabenstetter, MD

Assistant Attending

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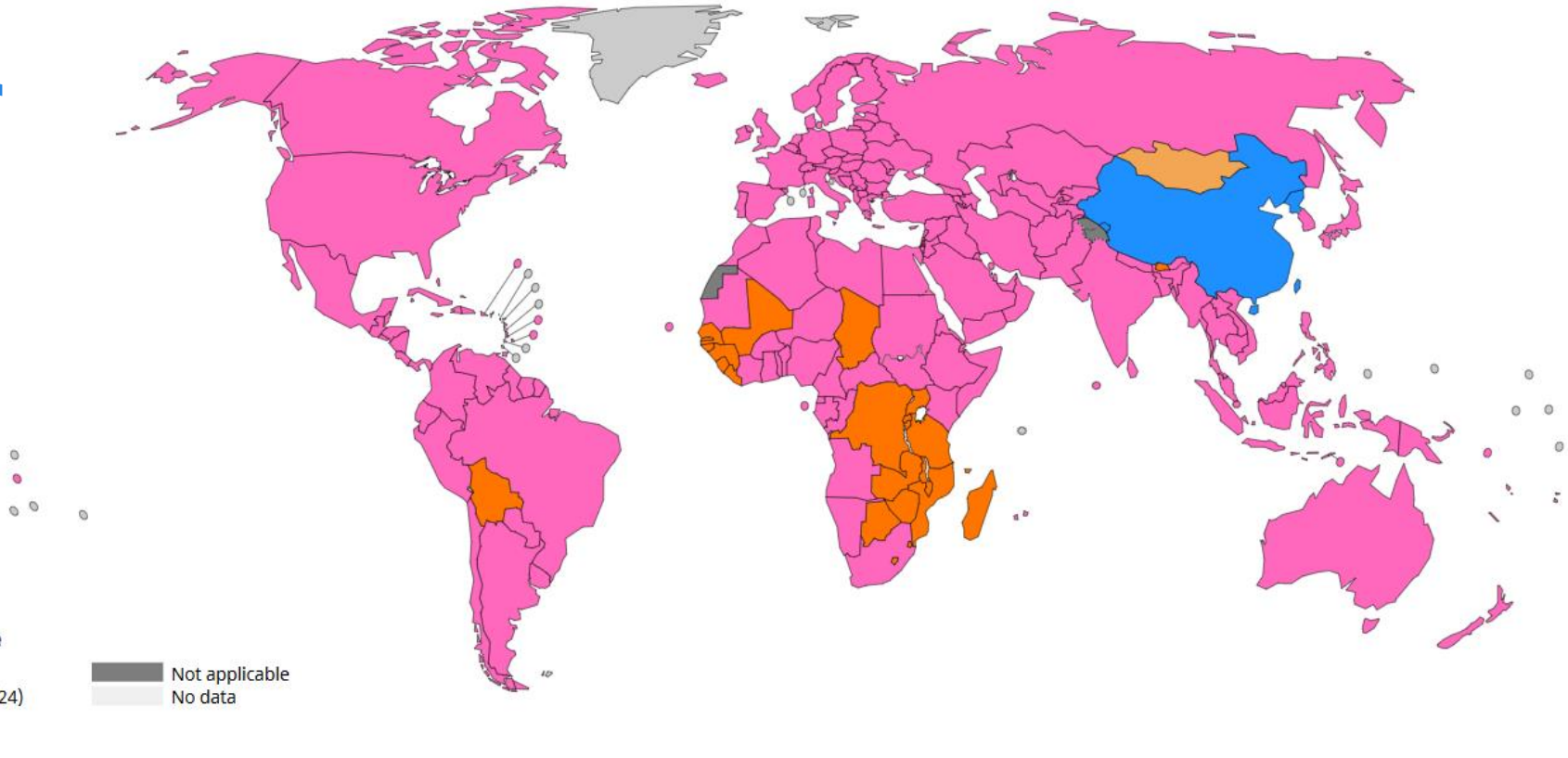
I have nothing to disclose related to the content of this presentation.

Breast Cancer



Breast cancer is the most commonly diagnosed cancer in women in 157 countries

- Accounts for 1 in 4 cancer cases

Breast cancer is the leading cause of death from cancer in women, with a disproportionate number of these deaths occurring in low-resource settings

Available at: https://gco.iarc.fr/today/en/dataviz/maps-most-common-sites?mode=cancer&key=total&sexes=2&cancers=20

Breast Cancer Screening

Malignant

Screening Exam → Suspicious → **Diagnostic Exam** → Suspicious → **Biopsy** → **High-risk Lesion**

Papillary lesions
Mucocele-like lesions
Radial scars
Lobular neoplasia
FEA
ADH

Not suspicious

Benign

Benign

Variability in the Management Recommendations Given for High-risk Breast Lesions Detected on Image-guided Core Needle Biopsy at U.S. Academic Institutions

Eniola Falomo, MD[a,*], Catherine Adejumo, MBBS[b], Kathryn A. Carson, ScM[c], Susan Harvey, MD[a], Lisa Mullen, MD[a], Kelly Myers, MD[a]

[a] The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins School of Medicine, Baltimore, MD
[b] Emory University School of Public Health, Atlanta, GA
[c] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Survey was 9 questions:

1) Name of institution (confidential)

2-8) When a core biopsy reveals ★, what is your typical management recommendation?

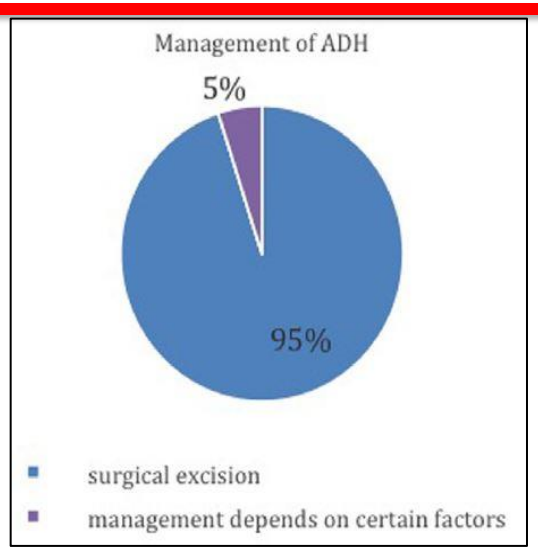
a) Surgical excision
b) Short-interval follow-up
c) Return to screening
d) It depends on certain factors

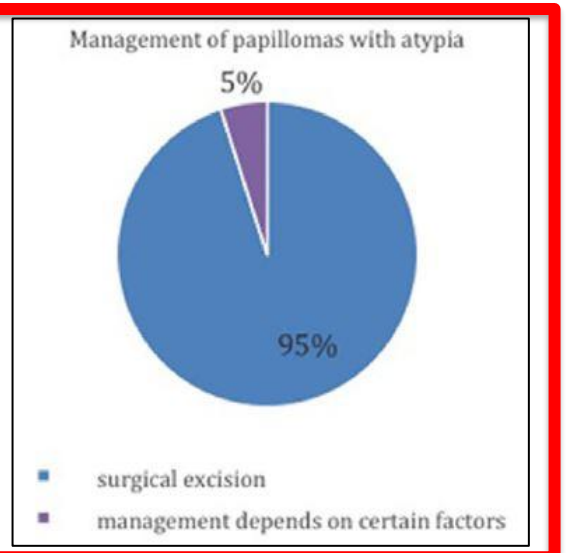
★ ADH, ALH, LCIS, Papilloma with and without atypia, FEA, Radial scar/Complex sclerosing lesion

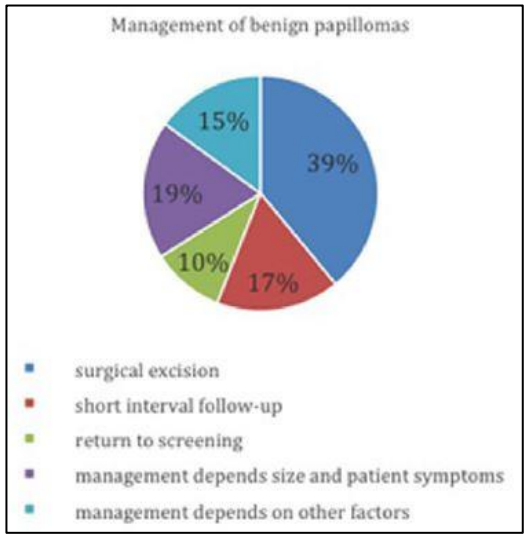
9) Do your breast imaging colleagues at your institution typically give the same recommendations?
Yes or No

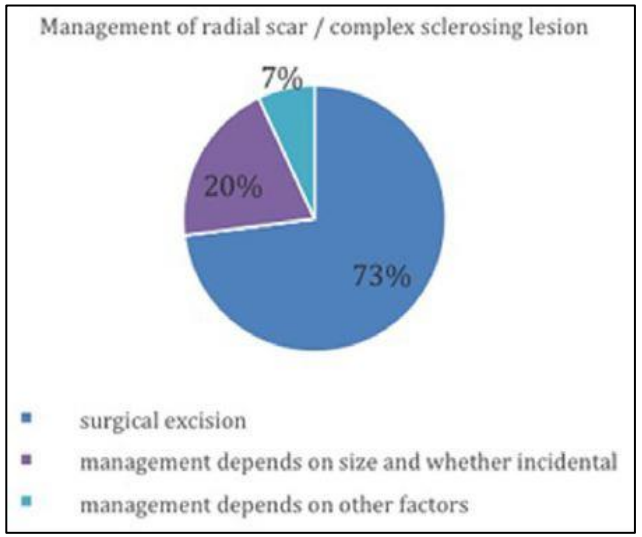
Current Problems in Diagnostic Radiology. 2019; 48: 462-466.

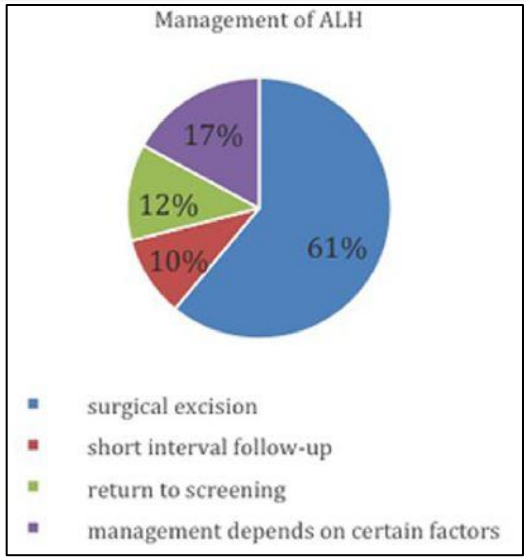
Surgical excision rates ranged between 39% to 95% between centers

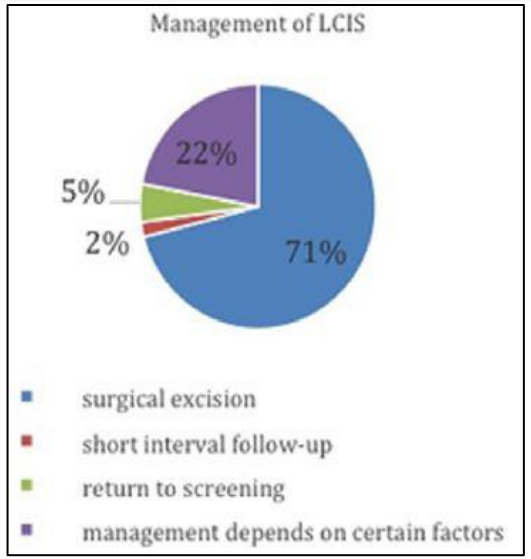


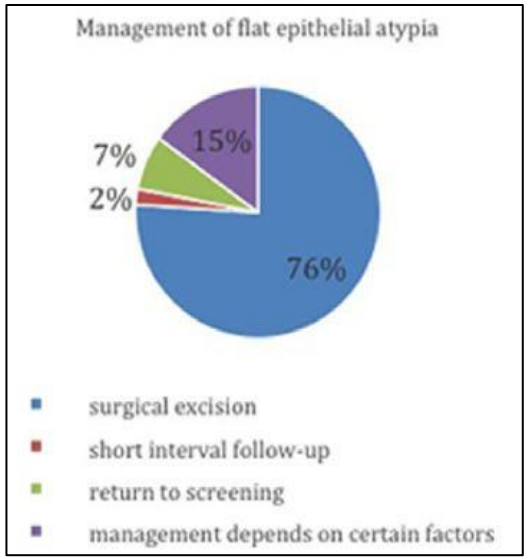












90% (37/41) reported consistent recommendations with colleagues

7 institutions with multiple responses:

- 86% (6/7) conflict on at least 1 recommendation
- 43% (3/7) conflict on 3

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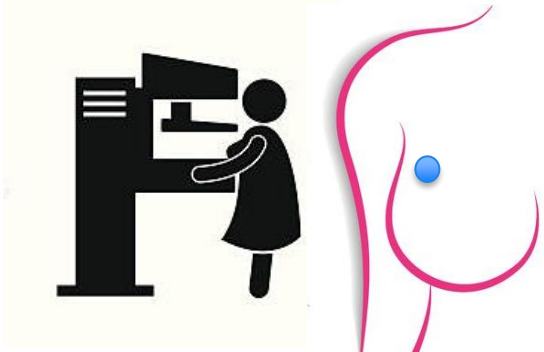
Falomo et al. *Current Problems in Diagnostic Radiology*. 2019; 48: 462-466.

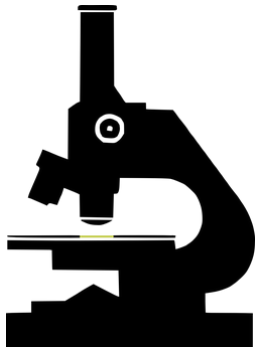
Is Excision Necessary?

- Papillomas
- Mucocele-like Lesions
- Radial Scar/Complex Sclerosing Lesion
- Lobular Neoplasia
- Flat Epithelial Atypia (FEA)
- Atypical Ductal Hyperplasia (ADH)

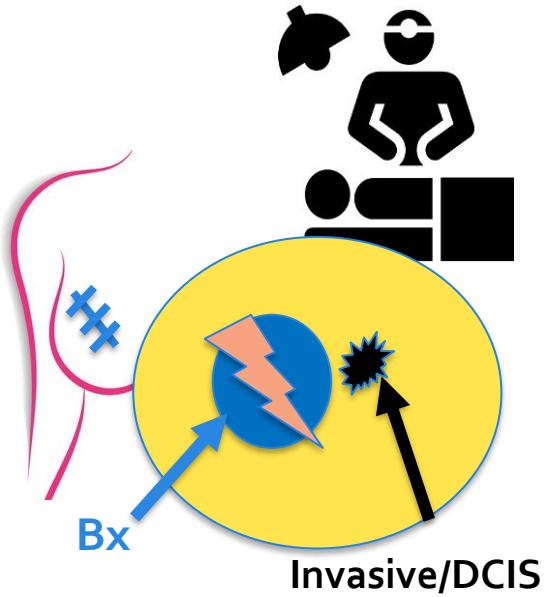
What is an Upgrade?



Imaging abnormality
CNB



CNB Diagnosis:
benign or atypical



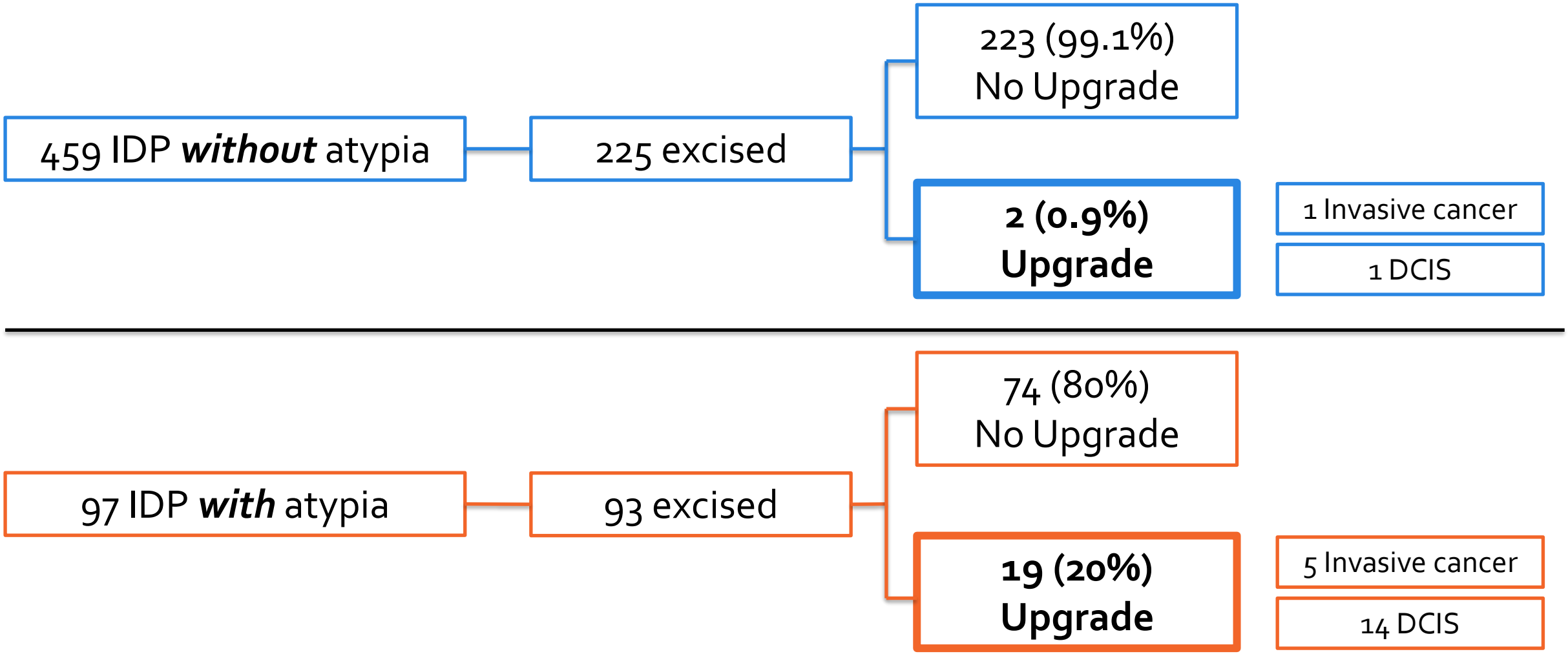
Surgical Excision

Surgical excision yields the biopsied lesion and invasive carcinoma and/or DCIS – **this is an upgrade**

Slide courtesy of Dr. M. Murray

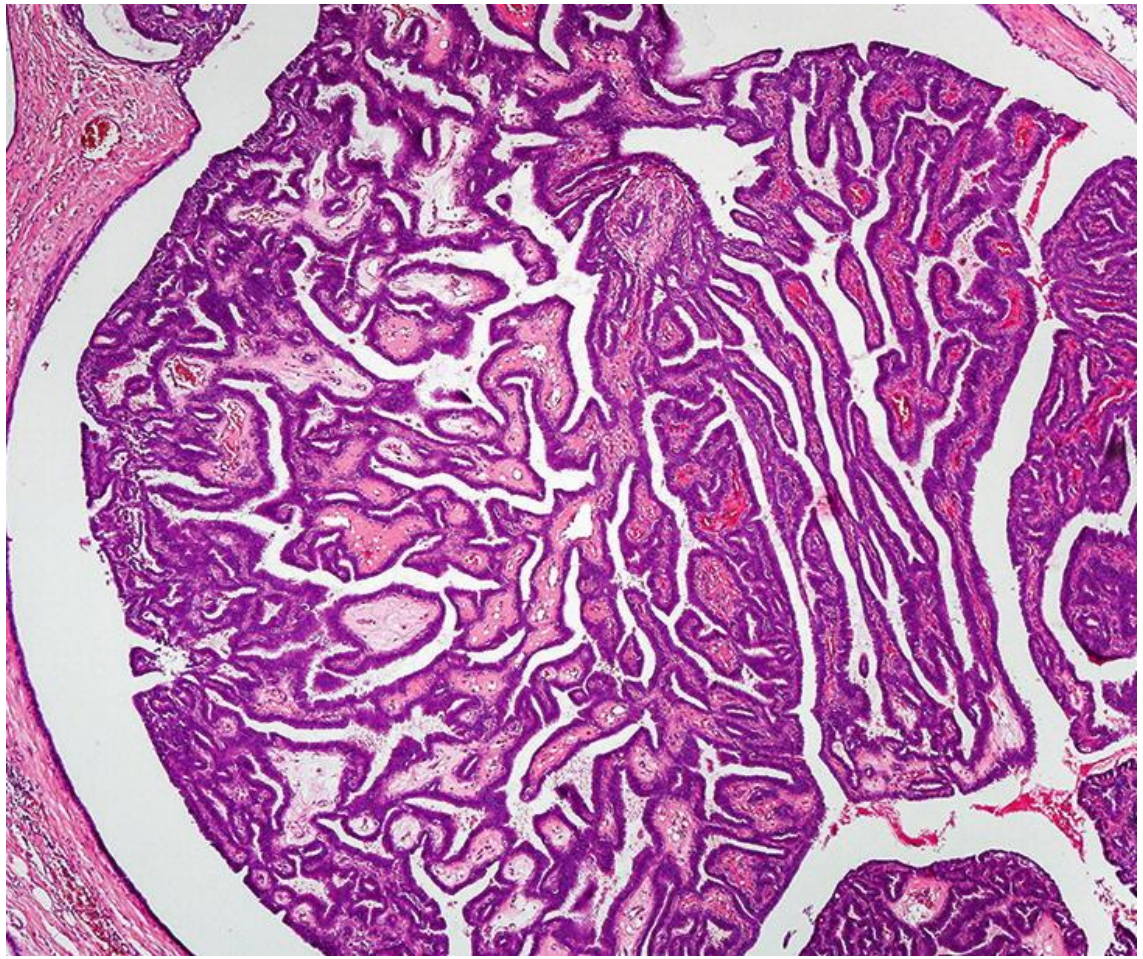
Intraductal Papilloma

Upgrade of Intraductal Papilloma *with* and *without* Atypia



Corbin et al. *Human Pathology*. 2022; 128: 90-100.

Intraductal Papilloma (IDP) without Atypia



- 1.5 – 2x relative risk
- ~5-7% lifetime risk

- Risk similar to that for moderate or florid UDH

ORIGINAL ARTICLE – BREAST ONCOLOGY

Management of Benign Intraductal Solitary Papilloma Diagnosed on Core Needle Biopsy

Ryan E. Swapp, MD[1], Katrina N. Glazebrook, MB, ChB[2], Katie N. Jones, MD[2], Hannah M. Brandts, MD[2], Carol Reynolds, MD[1], Daniel W. Visscher, MD[1], and Tina J. Hieken, MD[3]

[1]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; [2]Department of Diagnostic Radiology, Mayo Clinic, Rochester, MN; [3]Department of Surgery, Mayo Clinic, Rochester, MN

299
Solitary IDP on CNB
Radiologically Concordant

240
Benign IDP

49
Atypical Papillary Lesion

10
Malignant Papillary Lesion

16 excluded

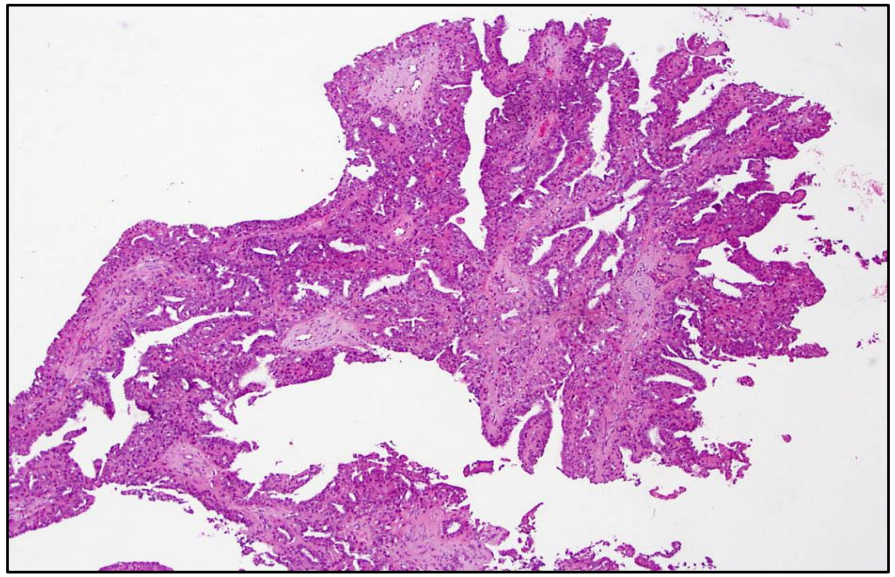
77
Excision

147
No Excision

77
Benign
(no upgrades)

100
Stable follow up
(mean 36 months)

47
Lost to
Follow-up



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Ann Surg Oncol. 2013; 20: 1900-1905.

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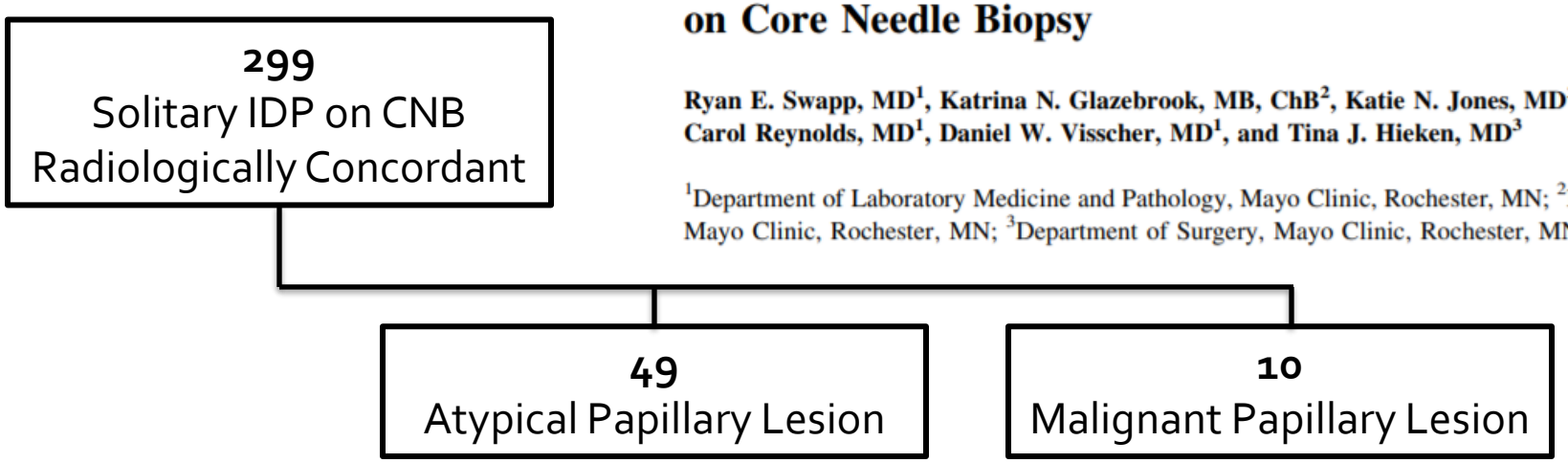

14 (24%) were originally diagnosed as benign

13 reclassified as atypical

- 7 not excised → all stable clinically/radiologically (mean 54.9 months)
- 6 excised → 2 malignant (DCIS), 2 atypical, 2 benign

1 reclassified as malignant → encapsulated papillary carcinoma on excision

Ann Surg Oncol. 2013; 20: 1900-1905.

Upgrade Rates of Papillomas Without Atypia

Study	Number Excised	# Carcinoma at excision			Predictors of upgrade
		Total	Invasive	DCIS	
Bennett (2010)	40	0	0	0	Not investigated
Chang (2011)	49	0	0	0	None
Swapp (2013)	77	0	0	0	Not investigated
Nakhlis (2015)	42	0	0	0	Clinical sx
Pareja (2016)	171	4 (2.3%)	2 (1.1%)	2 (1.1%)	Concurrent ipsilateral carcinoma
Hong (2016)	234	14 (6%)	NS	NS	Age >54 y, size >10 mm
Kim (2016)	137	4 (2.9%)	1 (0.7%)	3 (2.1%)	None
Han (2018)	383	3 (0.8%)	0	3 (0.8%)	Clinical sx, concurrent contralateral carcinoma, multifocal, BIRADS ≥ 4B
Ahn (2018)	250	17 (6.8%)	6 (2.4%)	11 (4.4%)	Clinical sx, size >15 mm, peripheral location, BIRADS ≥ 4B
Grimm (2018)	136	1 (0.7%)*	0	1 (0.7%)*	Not investigated
Zaleski (2018)	206	8 (3.8%)	0	8 (3.8%)	Not investigated
Genco (2020)	126	2 (1.6%)	0	2 (1.6%)	Size >10 mm
Moseley (2021)	96	3 (3.1%)	1 (1%)	2 (2%)	Personal hx of breast cancer, clinical symptoms, size >10 mm
Limberg (2021)	99	3 (3.3%)	0	3 (3.3%)	None
Nakhlis (2021)	85	0	0	0	Not investigated
Lee (2021)	465	13 (2.7%)	NS	NS	Age >60 y, clinical sx, size <10 mm

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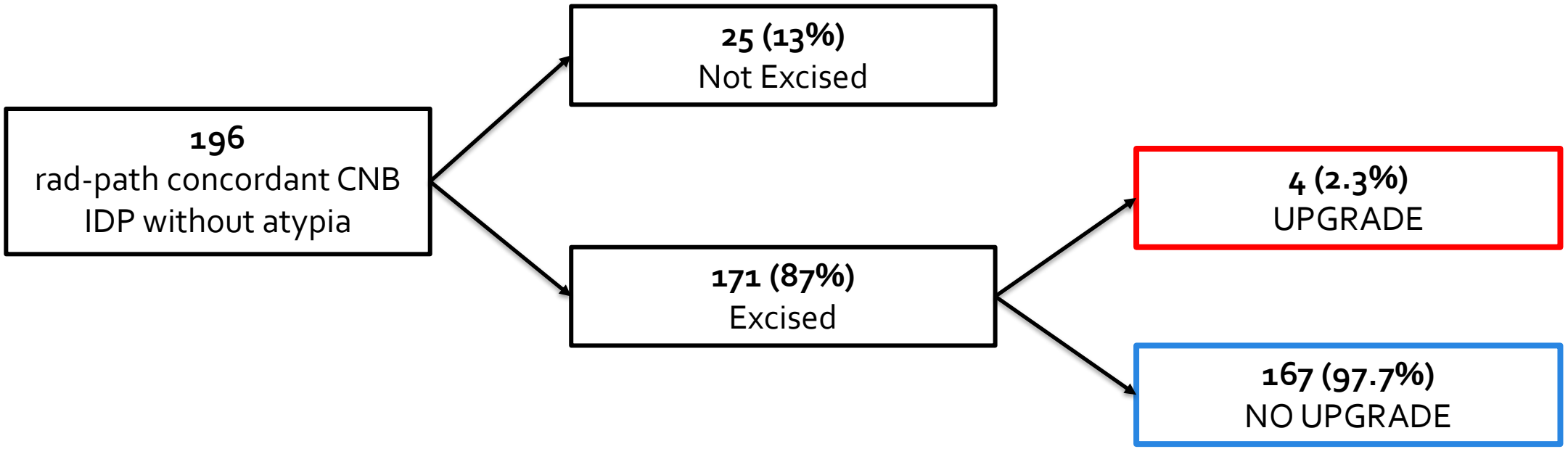
MSK Study: Breast Intraductal Papillomas without Atypia in Radiologic-Pathologic Concordant Core Needle Biopsies: Predictors of Upgrade to Carcinoma at Excision



Pareja et al. *Cancer*. 2016; 122 (18): 2819-2827.

MSK Study:
2.3% upgrade rate to DCIS and/or Invasive Carcinoma

	Case 1	Case 2	Case 3	Case 4
Excision Findings	DCIS	DCIS	ILC, DCIS	ILC
Size of carcinoma	2 mm	2 mm	ILC: 1 mm DCIS: 1.5 mm	2 mm
Nuclear Grade	1	2-3	1	2
Residual IDP size	7 mm	0.7 mm	8 mm	4 mm
Distance of carcinoma from IDP	DCIS involves IDP	11 mm	ILC: 8 mm DCIS: >10 mm	15 mm

Pareja et al. *Cancer*. 2016; 122 (18): 2819-2827.

Slide courtesy of Dr. M. Murray

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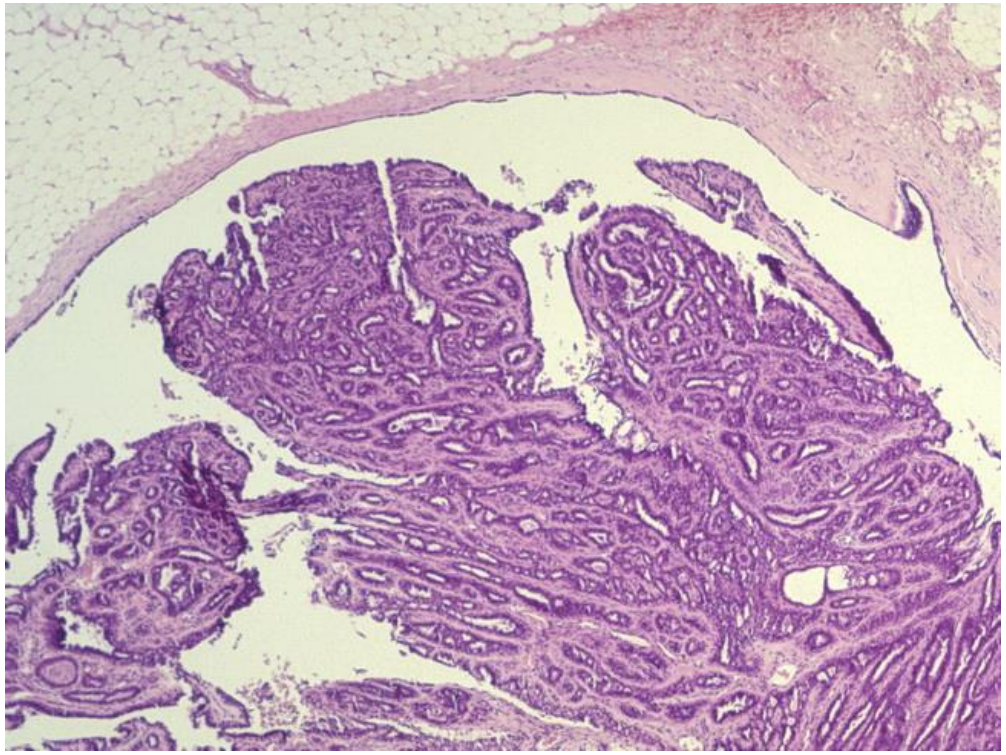
Distance of carcinoma from IDP	DCIS involves IDP	11 mm	ILC: 8 mm DCIS: >10 mm	15 mm
Type of Upgrade	True	Incidental	Incidental	Incidental

Pareja et al. *Cancer.* 2016; 122 (18): 2819-2827.

The Incidence of Adjacent Synchronous Invasive Carcinoma and/or Ductal Carcinoma In Situ in Patients with Intraductal Papilloma without Atypia on Core Biopsy: Results from a Prospective Multi-Institutional Registry (TBCRC 034)

Faina Nakhlis, MD[1,2], Gabrielle M. Baker, MD[3], Melissa Pilewskie, MD[4], Rebecca Gelman, PhD[5], Katherina Z. Calvillo, MD[1,2], Kandice Ludwig, MD[6], Priscilla F. McAuliffe, MD, PhD[7], Shawna Willey, MD[8], Laura H. Rosenberger, MD[9], Catherine Parker, MD[10], Kristalyn Gallagher, DO[11], Lisa Jacobs, MD[12], Sheldon Feldman, MD[13], Paulina Lange, BS[2], Stephen D. DeSantis, BS[2], Stuart J. Schnitt, MD[2], and Tari A. King, MD[1,2]

[1]Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, MA; [2]Breast Oncology Program, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA; [3]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [4]Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; [5]Department of Data Sciences, Dana-Farber Cancer Institute, Boston, MA; [6]Indiana University Cancer Center, Indianapolis, IN; [7]UPMC Hillman Cancer Center, Pittsburgh, PA; [8]Georgetown University Cancer Center, Washington, DC; [9]Duke University Medical Center, Durham, NC; [10]University of Alabama, Birmingham, AL; [11]University of North Carolina, Chapel Hill, NC; [12]Johns Hopkins University, Baltimore, MD; [13]Montefiore Medical Center, New York, NY



116 cases were included

Upgrades: 2 (1.7%)

Low grade DCIS, 0.3 cm

ADH bordering on low grade DCIS

Central Review: confirmed 85 cases

DCIS not confirmed

Upgrades: 0 (0%)*

*One excision did not have all slides for review

Ann Surg Oncol. 2021; 28: 2573-2578

MSK Study: Cancer History in Patients with Upgrade at Excision

Personal History of Breast Cancer	Total	No Upgrade	Upgrade	p-value
Yes	58 (34.9%)	55 (34%)	3 (75%)	0.123
No	108 (65.1%)	107 (66%)	1 (25%)	
Concurrent				
Yes	28 (16.9%)	26 (16%)	2 (50%)	0.133
No	138 (83.1%)	136 (84%)	2 (50%)	
Concurrent and ipsilateral				
Yes	12 (7.2%)	10 (6.2%)	2 (50%)	**0.027**
No	154 (92.8%)	152 (93.8%)	2 (50%)	
Prior				
Yes	30 (18.1%)	29 (17.9%)	1 (25%)	0.553
No	136 (81.9%)	133 (82.1%)	3 (75%)	

Adapted from Pareja et al. *Cancer*. 2016; 122 (18): 2819-2827.

Cancer History in Patients with Upgrade at Excision

Personal History of Breast Cancer	Total	No upgrade	Upgrade	p-value
No	86	85 (98.8%)	1 (1.2%)	**0.03**
Yes	6	4 (66.7%)	2 (33.3%)	
Unknown	10	10 (100%)	0	

Adapted from Moseley et al. *Ann Surg Oncol* 2021; 28(3):1347-55.

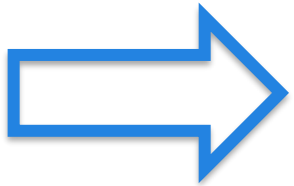
It is reasonable to consider a patient's history of breast carcinoma in the presence of other worrisome symptoms or larger lesion size when evaluating the absolute need for surgical excision

Upgrade Rate of Papilloma without Atypia after Observation

Study	Number Observed (follow up)	Upgrade after observation		
		Total	Invasive	DCIS
Bennett (2010)	75 (≥ 24 mo)	0	0	0
Swapp (2013)	100 (4.8-93.8 mo)	0	0	0
Ahn (2018)	177 (9-112 mo)	2 (1.1%)	0	2 (1.1%)
Grimm (2018)	200 (≥ 24 mo)	0	0	0
Limberg (2021)	76 (5-111 mo)	1 (1.3%)	0	1 (1.3%)
Lee (2021)	146 (≥ 24 mo)	0	0	0
Corbin (2022)	234 (24-140 mo)	0	0	0
Jatana (2022)	112 (≥ 23 mo)	2 (1.7%)	1 (0.8%)	1 (0.8%)

Management for Intraductal Papilloma on CNB

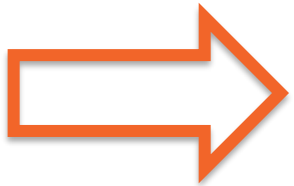
Papilloma without atypia
AND
Rad-path concordance



No Excision
Routine imaging

Papilloma with atypia

Papilloma without atypia
AND
Rad-path discordance

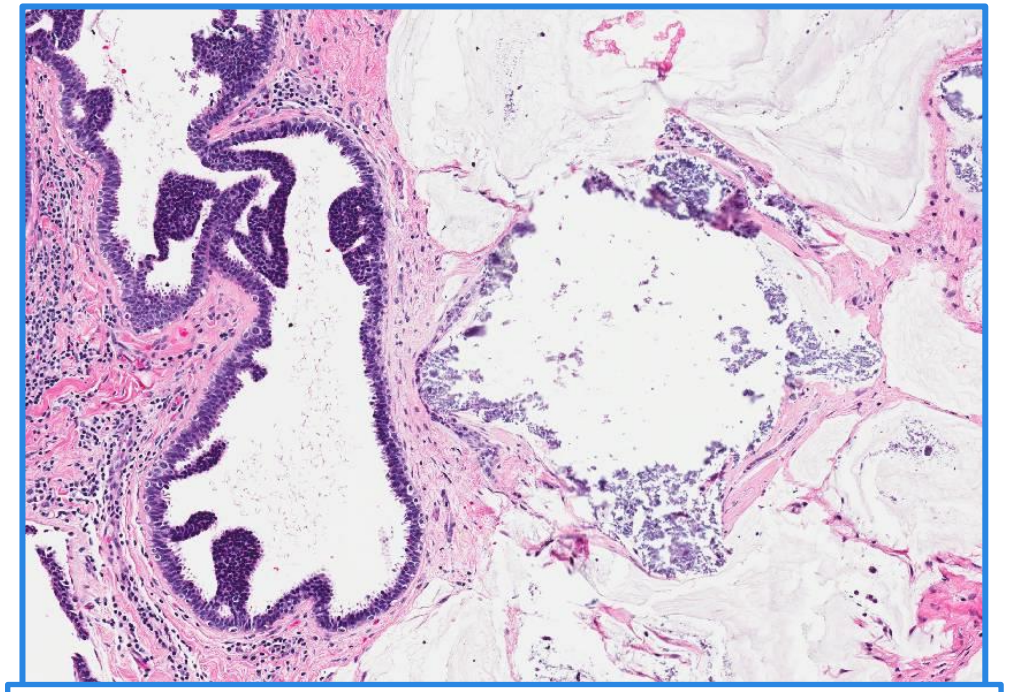


Surgical Excision

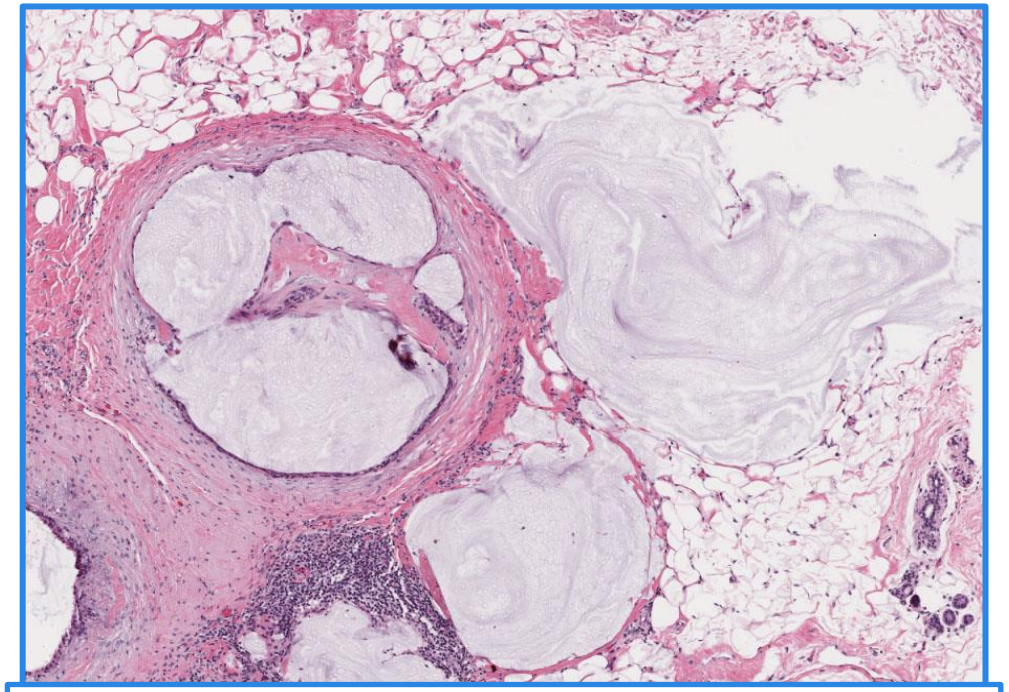
Mucocele-like Lesions

Mucocele-like Lesion (MLL)

- Rare: <1% of diagnoses by core needle biopsy
- Most commonly presents as mammographic lesion
  - Calcifications ± smoothly circumscribed mass
- ~1/3 associated with atypia



MLL with atypia



MLL without atypia

Upgrade Rates of Rad-Path Concordant CNB with MLL

Study	CNB with EXC	Upgrade rate
Sutton (2012)	38	13% (5/38)
Rakha (2013)	54	4% (2/54)
Edelweiss (2013) **MSK STUDY**	28	14% (4/28)
Ha (2015)	24	4% (1/24)
Gibreel (2016)	26	3.8% (1/26)*
Zhang (2017)	28	14% (4/28)
Moseley (2019)	28	3.5% (1/28)
Towne (2022)	39	15% (6/39)

* Case was rad-path discordant

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Study	CNB with EXC	Upgrade rate
Sutton (2012)	38	13% (5/38)
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Towne (2022)	39	15% (6/39)
TOTAL	**265**	**9% (24/265)**

Study	CNB with EXC	Atypia		No Atypia		Upgrade rate
		Number of cases	Upgrade rate	Number of cases	Upgrade rate	
Sutton (2012)	38	16	31% (5/16)	22	0% (0/22)	13% (5/38)
Rakha (2013)	54	0	-	54	4% (2/54)	4% (2/54)
Edelweiss (2013) **MSK STUDY**	28	18	22% (4/18)	10	0% (0/10)	14% (4/28)
Ha (2015)	24	12	8% (1/12)	12	0% (0/12)	4% (1/24)
Gibreel (2016)	26	14	0% (0/14)	12	8% (1/12)*	3.8% (1/26)*
Zhang (2017)	28	9	33% (3/9)	19	5% (1/19)	14% (4/28)
Moseley (2019)	28	16	6% (1/16)	12	0% (0/12)	3.5% (1/28)
Towne (2022)	39	20	20% (4/20)	19	11% (2/19)	15% (6/39)

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		Number of cases	Upgrade rate	Number of cases	Upgrade rate	
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* Case was rad-path discordant

17% (18/105)

3% (5/159)

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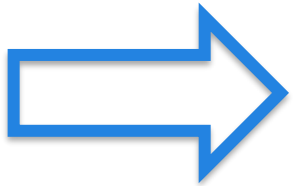
		17% (18/105)		**3% (5/159)**		

* Case was rad-path discordant

Management for Mucocele-like lesion on CNB

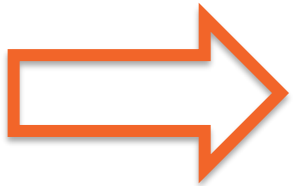
MLL without atypia
AND
Rad-path concordance



No Excision
Routine imaging

MLL with atypia

MLL without atypia
AND
Rad-path discordance

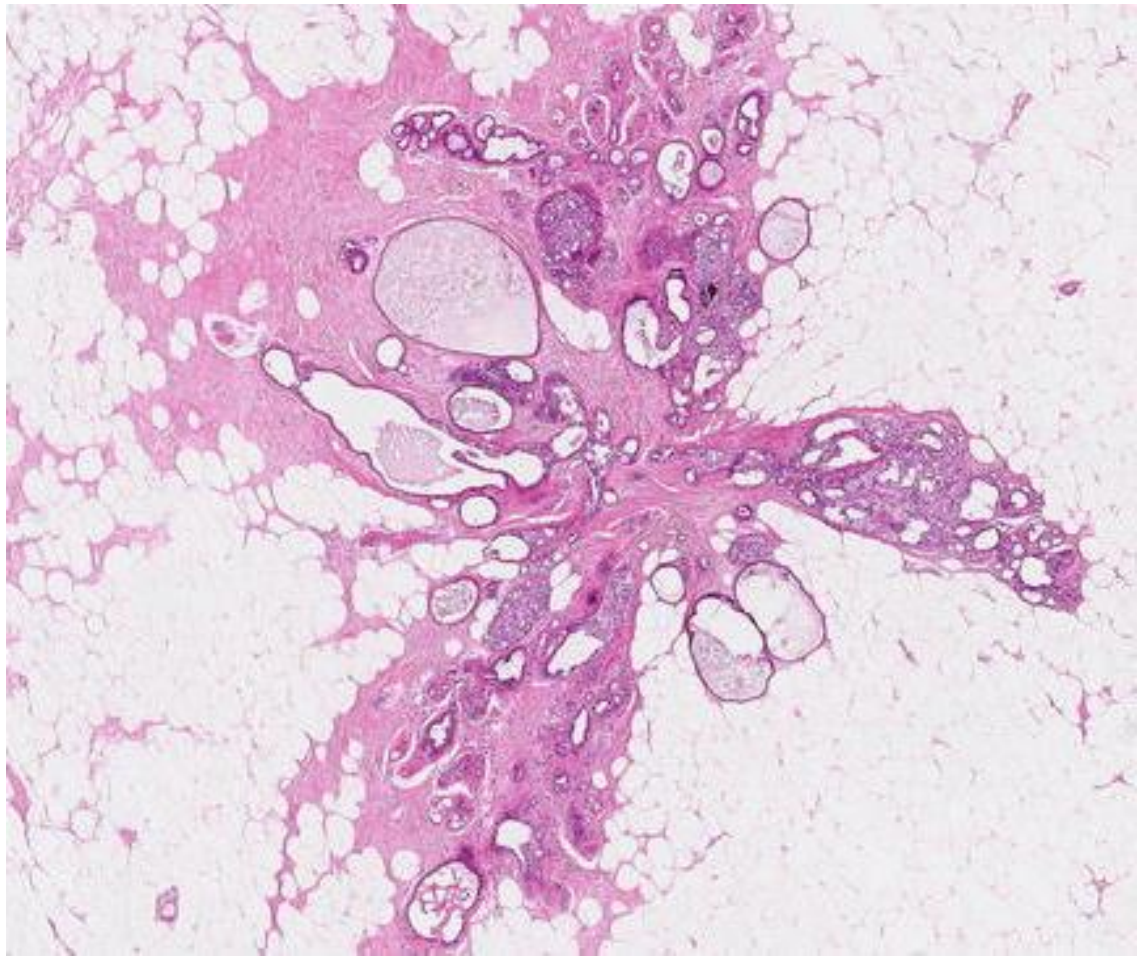


Surgical Excision

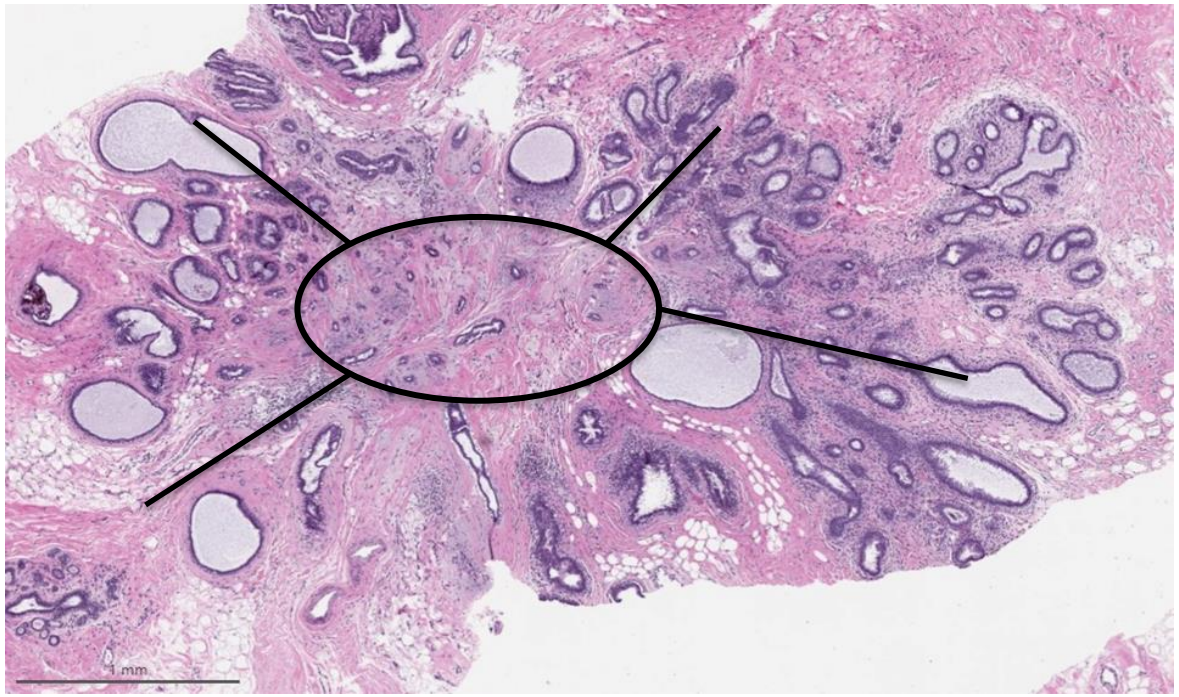
Radial Sclerosing Lesions (RSLs):
Radial Scar (RS)
Complex Sclerosing Lesion (CSL)

Definitions

- RS and CSL – spectrum of breast sclerosing lesions
  - ~2-3 fold relative risk
  - Lifetime risk of carcinoma ~6%

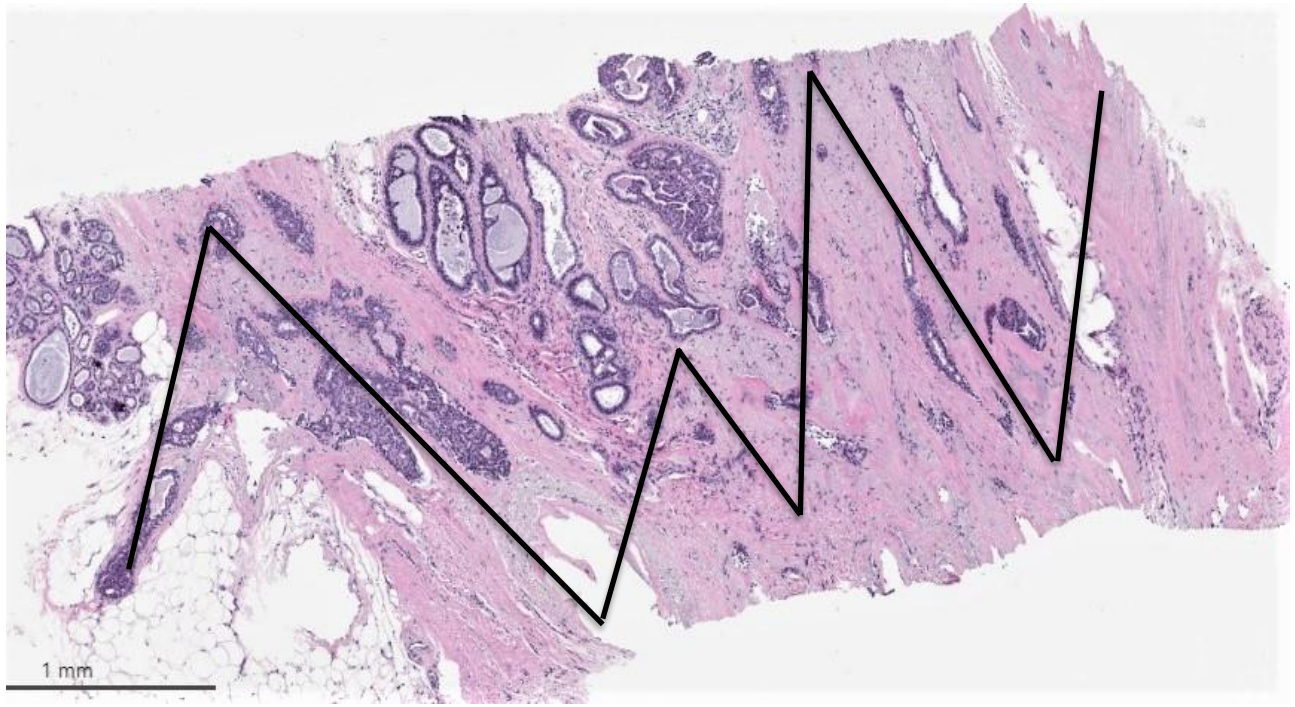


Radial Scar (RS)



Central hyalinized nidus and radiating arms, forms irregular mass or architectural distortion on imaging

Complex Sclerosing Lesion (CSL)



Ill-defined/non-concentric lesions
Sometimes defined as RS >1 cm

Digital Breast Tomosynthesis

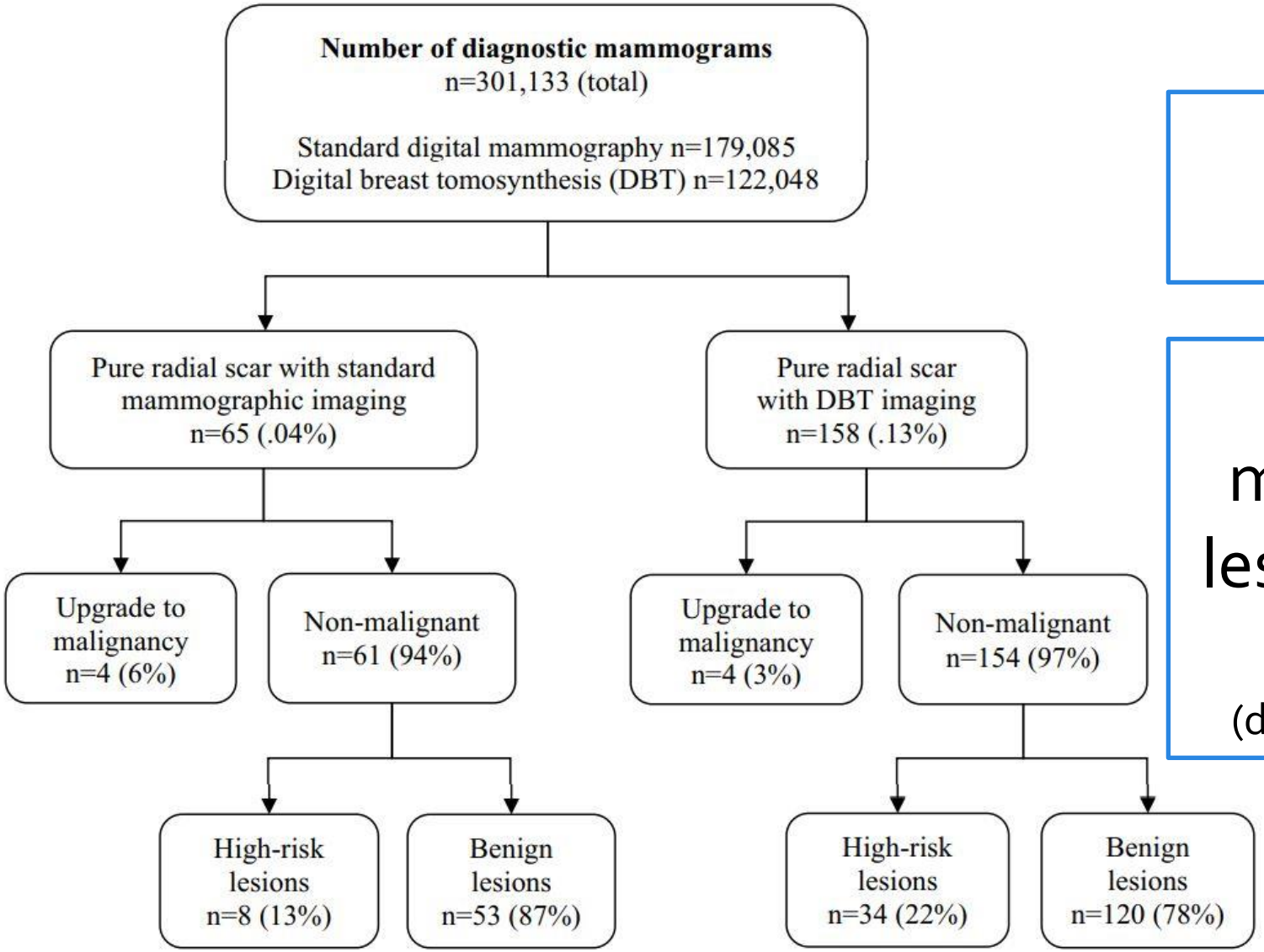
TABLE 1: Comparison of 2D Digital Mammography (DM) and Digital Breast Tomosynthesis (DBT) Cases

Finding	2D DM Cases	DBT Cases	*p*
Patient or clinical characteristic			
Age (y), mean (range)	58 (30–95)	59 (26–86)	0.62
Race (white)	111/121 (91.7)	249/274 (90.9)	0.78
Breast density (heterogeneously dense or extremely dense)	63/121 (52.1)	147/274 (53.6)	0.77
Imaging feature			
Proportion of mammographic examinations with architectural distortion	121/166,661 (0.07)	274/202,438 (0.14)	< 0.001
Architectural distortion detected on screening examination	54/121 (44.6)	180/274 (65.7)	< 0.001
Architectural distortion evaluated by ultrasound	115/121 (95.0)	264/274 (96.4)	0.54
Proportion of examinations with architectural distortion given BI-RADS final assessment category of 4	100/121 (82.6)	265/274 (96.7)	< 0.001
Proportion of examinations with architectural distortion given BI-RADS final assessment category of 5	21/121 (17.4)	9/274 (3.3)	< 0.001

Note—Except where otherwise indicated, data are number of examinations/total examinations (%).

Bahl et al. *AJR*. 2017; 209: 1162-1167.

Rate of radial scars by core biopsy and upgrading to malignancy or high-risk lesions before and after introduction of digital breast tomosynthesis



Increase in rate of RS diagnosed

Rates of upgrade to malignancy and high risk lesions were similar before and after DBT

(differences not statistically significant)

Phantana-angkool et al. *Breast Cancer Research and Treatment*. 2019; 173: 23-29.

Pathologic Upgrade Rates of High-Risk Breast Lesions on Digital Two-Dimensional vs Tomosynthesis Mammography

	DM (n = 475)		DBT (n = 425)		Total (n = 900)		
High-risk breast lesion	**n**	**%**	**n**	**%**	**n**	**%**	**p Value**
Atypical ductal hyperplasia	197	41.5	140	32.9	337	37.4	<0.01
Flat epithelial atypia	81	17.1	62	14.6	143	15.9	0.31
Radial scar	46	9.7	65	15.3	111	12.3	0.01
Papilloma	22	4.6	54	12.7	76	8.4	<0.001
Papilloma with atypia	5	1.1	10	2.4	15	1.7	0.19*
Papilloma without atypia	17	3.6	44	10.4	61	6.8	<0.001
Atypical lobular hyperplasia	30	6.3	43	10.1	73	8.1	0.04
Biphasic neoplasm	39	8.2	22	5.2	61	6.8	0.07
Lobular carcinoma in situ	34	7.2	23	5.4	57	6.3	0.28
LCIS with pleomorphism	4	0.8	2	0.5	6	0.7	0.69*
LCIS without pleomorphism	30	6.3	21	4.9	51	5.7	0.37
Nonspecific atypia	26	5.5	16	3.8	42	4.7	0.22

*Calculated with Fisher exact test.
DBT, digital breast tomosynthesis; DM, digital two-dimensional mammography; LCIS, lobular carcinoma in situ.

No statistically significant differences in overall upgrade rates of high risk lesions on DM (11.4%, 54/475) vs DBT (11.3%, 48/425)

Upgrade Rates of Radial Sclerosing Lesions without Atypia

Study	Number Excised	Upgrades at Excision		
		Total	Invasive	DCIS
Resetkova (2011)	10	0	0	0
Donaldson (2016)	37	0	0	0
Leong (2016)	161	1 (0.6%)	0	1 (0.6%)
Nakhlis (2018)	10	0	0	0
Ferreira (2017)	89	12 (14%)	5 (6%)	7 (8%)
Ha (2018)	64	2 (3.1%)	0	1 (1.3%)
Quinn (2020)	77	7 (9%)	0	7 (9%)
Kraft (2021)	98	1 (1%)	0	1 (1%)
Yan (2021)	93	1 (1%)	1 (1%)	0
Grabenstetter (2024)	130	2 (1%)	2 (1%)	0

Meta-analysis of upgrade rates in 3163 radial scars excised after needle core biopsy diagnosis

- Systematic review of Pubmed, Cochrane and Embase databases
  - Full papers, published after 1998
  - Included at least 5 RS
  - Provided information on biopsy gauge and upgrade rates
    - No information on rad-path concordance

- Findings were grouped into categories based on biopsy type, needle gauge and presence of atypia

- 51 studies met criteria with data on 3163 RS excised
  - Overall upgrade rate (for RS with and without atypia) was 6.9% (217/3163)
    - 71 Invasive, 144 DCIS

Farshid & Buckley. *Breast Cancer Research and Treatment*. 2019; 174: 165-177

Meta-analysis of upgrade rates in 2213 RS without atypia

	No. of studies	Excised RS	Upgrade to invasive cancer	Upgrade to DCIS	Upgrade rate*
RS diagnosed on 14G NCB	14	828	18	30	5%
RS diagnosed on a mix of 8-16G NCB	19	1263	10	29	2%
RS diagnosed on VAB 8-11G biopsies	5	122	0	2	1%

*Pooled estimates of upgrade (95% confidence interval)

Farshid & Buckley. *Breast Cancer Research and Treatment*. 2019; 174: 165-177

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Farshid & Buckley. *Breast Cancer Research and Treatment*. 2019; 174: 165-177

Meta-analysis of upgrade rates in 296 RS with atypia

	No. of studies	Excised RS	Upgrade to invasive cancer	Upgrade to DCIS	Upgrade rate*
RS diagnosed on 14G NCB	7	114	5	22	28%
RS diagnosed on a mix of 8-16G NCB	7	171	7	18	11%
RS diagnosed on VAB 8-11G biopsies	1	11	Not specified	Not specified	18% (2/11)

*Pooled estimates of upgrade (95% confidence interval)

Farshid & Buckley. *Breast Cancer Research and Treatment*. 2019; 174: 165-177

Upgrade Rates of Radial Sclerosing Lesions without Atypia

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		Total	Invasive	DCIS
Resetkova (2011)	10	0	0	0
Donaldson (2016)	37	0	0	0
Leong (2016)	161	1 (0.6%)	0	1 (0.6%)
Nakhlis (2018)	10	0	0	0
Ferreira (2017)	89	12 (14%)	5 (6%)	7 (8%)
Ha (2018)	64	2 (3.1%)	0	1 (1.3%)
Quinn (2020)	77	7 (9%)	0	7 (9%)
Kraft (2021)	98	1 (1%)	0	1 (1%)
Yan (2021)	93	1 (1%)	1 (1%)	0
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MSK study: Benign RSL and Upgrade

	Age	Clinical history	Imaging modality	Imaging finding (lesion diameter)	Needle gauge	Pathology on core biopsy	RSL: Incidental or Target	Imaging target removed by biopsy	Pathology on excision
Case 1	43	Concurrent contralateral ILC	MRI	NME (28 mm)	9G VAB	RSL, florid UDH, papillomatosis	Target	No	Microinvasive ILC
Case 2	69	BRCA2, family hx breast cancer	MRI	Mass (6 mm)	9G VAB	RSL, fibrocystic changes	Incidental	Yes	IMC, 2 mm; DCIS, 2 mm*

*Patient had subsequent mastectomy showing benign pathology only

Both upgrades are small invasive carcinomas not associated with the biopsy site and deemed incidental.

Grabenstetter et al. *Histopathology* 2024; 85 (3): 397-404.

Upgrade Rates of RSLs without Atypia after Observation

Study	Number Observed (median follow up)	Upgrades after Observation		
		Total	Invasive	DCIS
Resetkova (2011)	46 (30 months)	0	0	0
Nakhlis (2018)	62 (2.2 years)	3 (4.8%)*	1 (1.6%)	2 (3.2%)
Ferreira (2017)	26 (not specified)	0	0	0
Ha (2018)	16 (5 years)	0	0	0
Kraft (2021)	50 (16 months)	0	0	0
Yan (2021)	30 (3 years)	0	0	0
Grabenstetter (2024)	25 (31 months)	0	0	0

*All upgrades occurred at least 3 years and ≥3 cm away from initial biopsy

Radial scar with atypia

Study	Excised RS	Upgrade to Invasive Cancer	Upgrade to DCIS	Upgrade rate
Donaldson (2016)	22	2	5	33% (7/22)
Rakha (2019)	157	12	27	24.84% (39/157)
Quinn (2020)	9	1	2	33% (3/9)

Donaldson et al. *The Breast*. 2016; 201-207.
Rakha et al. *J Clin Pathol*. 2019; 72: 800-804.
Quinn et al. *Breast Cancer Research and Treatment*. 2020; 183: 677-682.

Radial scar with atypia

Study	Excised RS	Upgrade to Invasive Cancer	Upgrade to DCIS	Upgrade rate	RS without atypia
Donaldson (2016)	22	2	5	33% (7/22)	0% (3/27)
Rakha (2019)	157	12	27	24.84% (39/157)	N/A
Quinn (2020)	9	1	2	33% (3/9)	9% (7/77)

Upgrade rate significantly higher in atypical group

Donaldson et al. *The Breast*. 2016; 201-207.
Rakha et al. *J Clin Pathol*. 2019; 72: 800-804.
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Management for Radial Sclerosing Lesions on CNB

RS/CSL without atypia
AND rad-path concordant

→ No Excision
Routine imaging

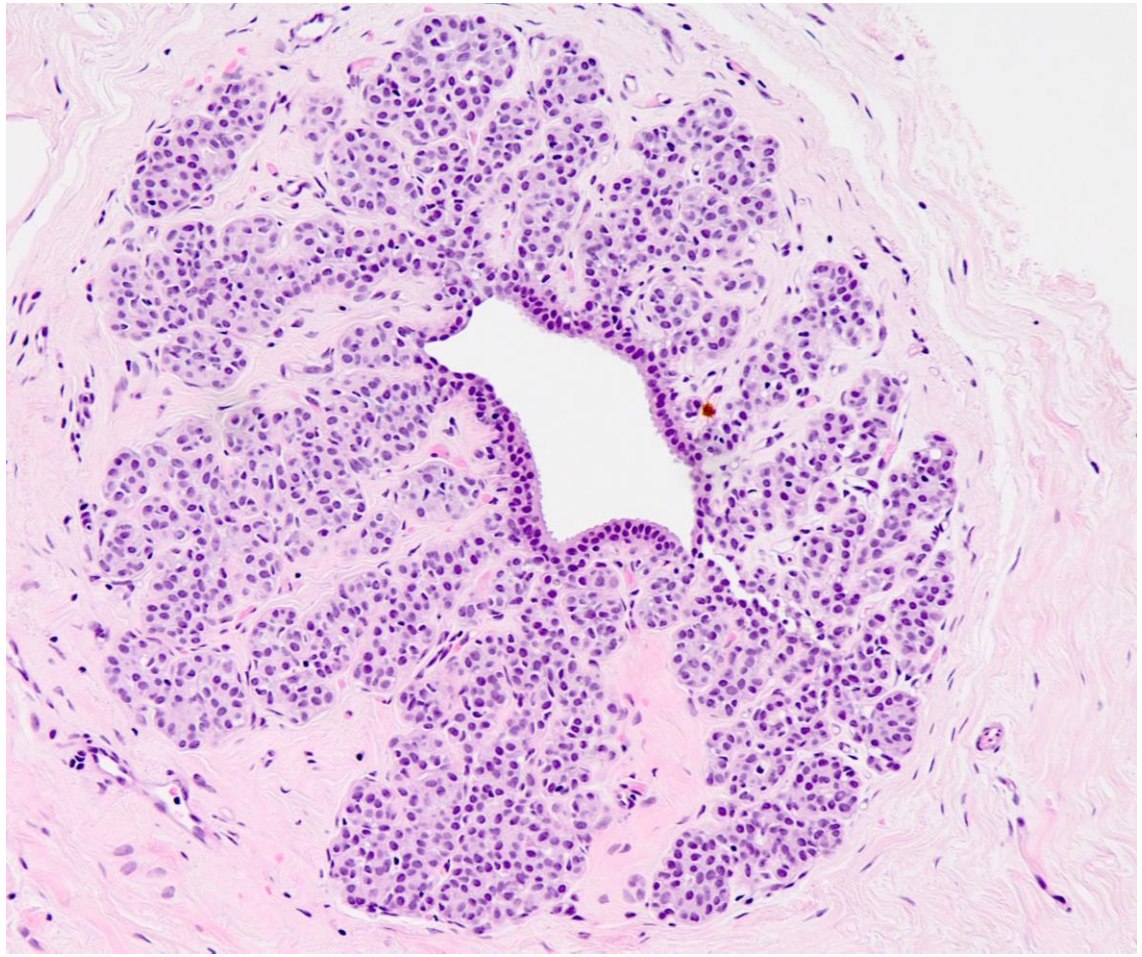
RS/CSL with atypia

RS/CSL without atypia
AND rad-path discordant

→ Surgical Excision

Classic Lobular Neoplasia

Atypical lobular hyperplasia (ALH)
Lobular carcinoma in situ (LCIS), classic type



- Lobular neoplasia (LN)
  - Bilateral cancer risk
    - 2/3 ipsilateral, 1/3 contralateral
  - Cancers develop >10 years after diagnosis of LN
- ALH
  - Relative risk: 4-5x
  - 13-17% lifetime risk
- LCIS
  - Relative risk: 8-10x
  - 30% lifetime risk

Classic lobular neoplasia on CNB: Upgrade rates

Study	Excised cases	Invasive Carcinoma	DCIS	Upgrade rate	Rad-path correlation
Shah-Khan (2012)	91	1	0	1%	Yes
Murray (2013) **MSK STUDY**	72	1	1	3%	Yes
Atkins (2013)	38	0	0	0%	Yes
Chaudhary (2013)	87	2	1	3.4%	Yes
Nakhlis (TBCRC 020) (2016)	74	0	1	1%	Yes
Genco (2020)	287	6	5	3.8%	Yes
Ibrahim (2012)	84	15	13	33%	No
Destounis (2012)	63	6	14	33%	No
Zhao (2012)*	237	4	7	4.6%	No

*Excluded all cases with imaging findings of a mass or any lesion other than calcifications

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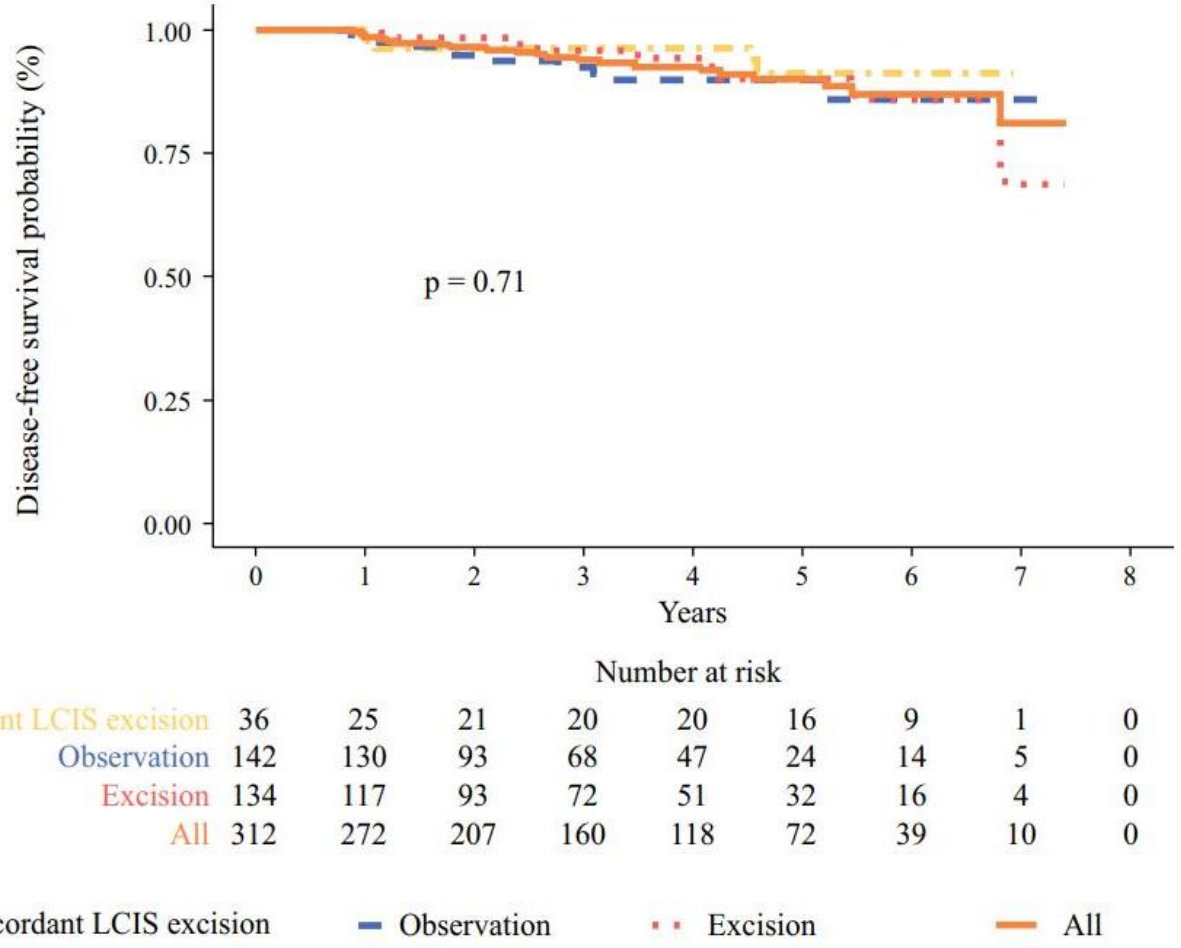
Classic lobular neoplasia on CNB: Upgrade rates

Study	Excised cases	Invasive Carcinoma	DCIS	Upgrade rate	Rad-path correlation	Discordant upgrades
Shah-Khan (2012)	91	1	0	1%	Yes	10% (1/10)
Murray (2013) **MSK STUDY**	72	1	1	3%	Yes	38% (3/8)
Atkins (2013)	38	0	0	0%	Yes	29% (2/7)
Chaudhary (2013)	87	2	1	3.4%	Yes	100% (1/1)
Nakhlis (TBCRC 020) (2016)	74	0	1	1%	Yes	-
Genco (2020)	287	6	5	3.8%	Yes	-
Ibrahim (2012)	84	15	13	33%	No	
Destounis (2012)	63	6	14	33%	No	
Zhao (2012)*	237	4	7	4.6%	No	

Routine excision of ALH/classic LCIS is not required if radiologically-pathologically concordant

Comparison of outcomes for classic-type LCIS managed with surgical excision after core biopsy versus observation



312 women with CNB dx classic LCIS (1/2013 – 4/2020)

- 170 Excision → 11 (6.5%) [4 ipsilateral/same quadrant]
- 142 Observation → 11 (7.7%) [5 ipsilateral/same quadrant]

Developed carcinoma

Estimated 5-year rates of cancer development:

- Excision group: 9.9%
- Observation group: 10.3%

Median follow up of 3.1 years, DFS did not significantly differ by management strategy

Matar et al. *Ann Surg Oncol*. 2022; 29: 1670-1679.

Management for Classic Lobular Neoplasia on CNB

Classic LCIS & ALH
AND
Rad-path concordance

→

No Excision
Routine imaging
+/- Chemoprevention

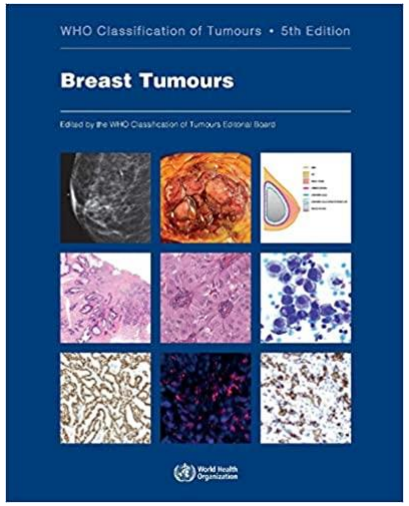
Classic LCIS & ALH
AND
Rad-path discordance

→

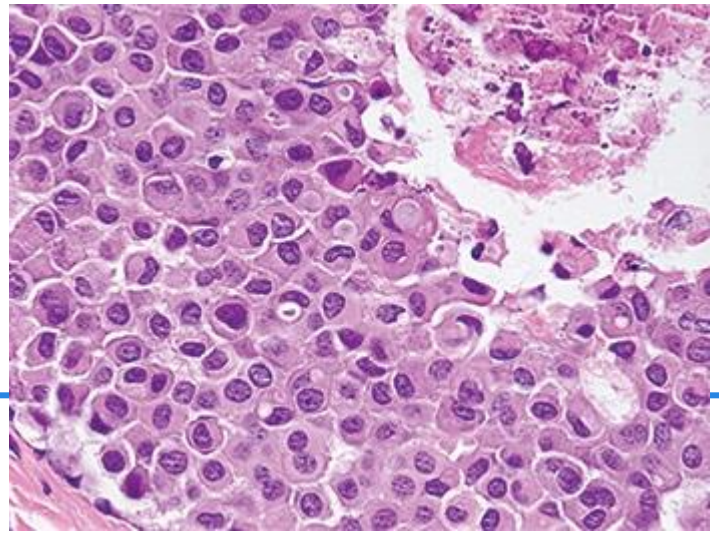
Surgical Excision

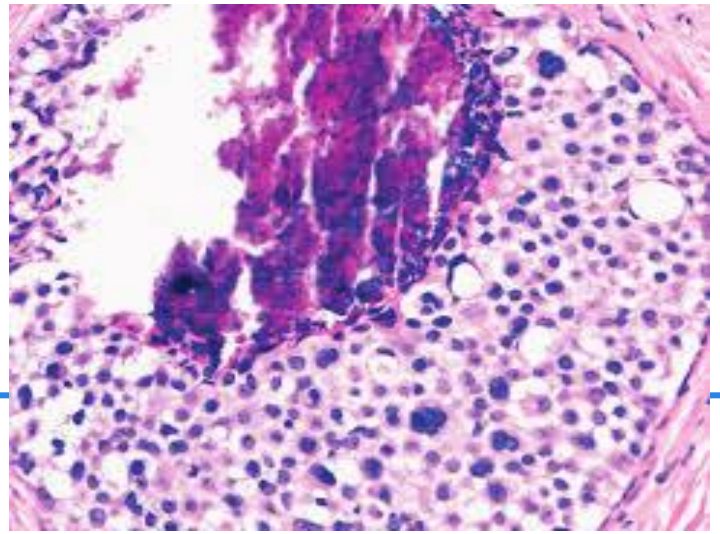
Non-classic LCIS: Pleomorphic and Florid

Pleomorphic LCIS (PLCIS)
Florid LCIS (FLCIS)



- Variant forms of LCIS recently defined by the WHO
  - Pleomorphic
  - Florid
- Have morphologic and molecular features not present in classic LCIS
- Natural history is unknown
  - Likelihood of association with (micro)invasion higher than classic type





Upgrade Rate of Non-classic LCIS

Study	Excised Cases	Upgrades at Excision		
		Total	Invasive	DCIS
Carder (2010)	10	3 (30%)	3 (30%)	0
Flanagan (2015)	23	11 (47.8%)	7 (30.4%)	4 (17.4%)
Guo (2018)	25	16 (64%)	16 (64%)	0
Fasola (2018)	20	6 (30%)	4 (20%)	2 (10%)
Desai (2018)	15	2 (20%)	3 (20%)	0
Nakhlis (2019)	76	27 (35%)	17 (22%)	10 (13%)
Shamir (2019)	14	5 (36%)	4 (29%)	1 (7%)
Foschini (2019)	70	31 (44.3%)	28 (40%)	3 (4.3%)
Singh (2020)	19	6 (31.5%)	5 (26.3%)	1 (5.2%)
Kuba (2021)	32	6 (19%)	6 (19%)	0

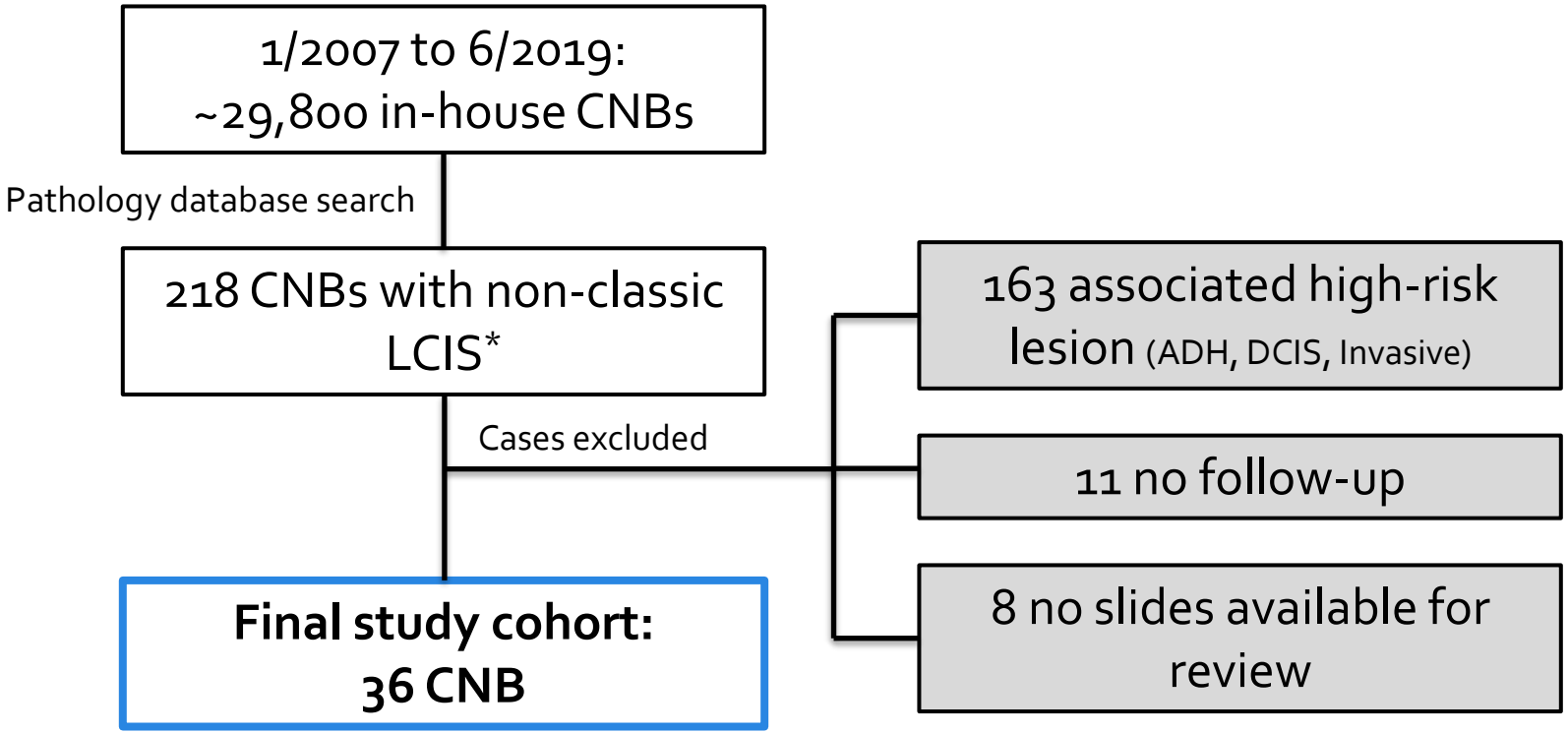
MSK Study: Morphologic subtypes of LCIS diagnosed on CNB: Clinicopathologic features and findings at follow-up excision

Biopsy modality

- Stereotactic – 70% (25/36)
- MRI-guided – 22% (8/36)
- US-guided – 8% (3/36)

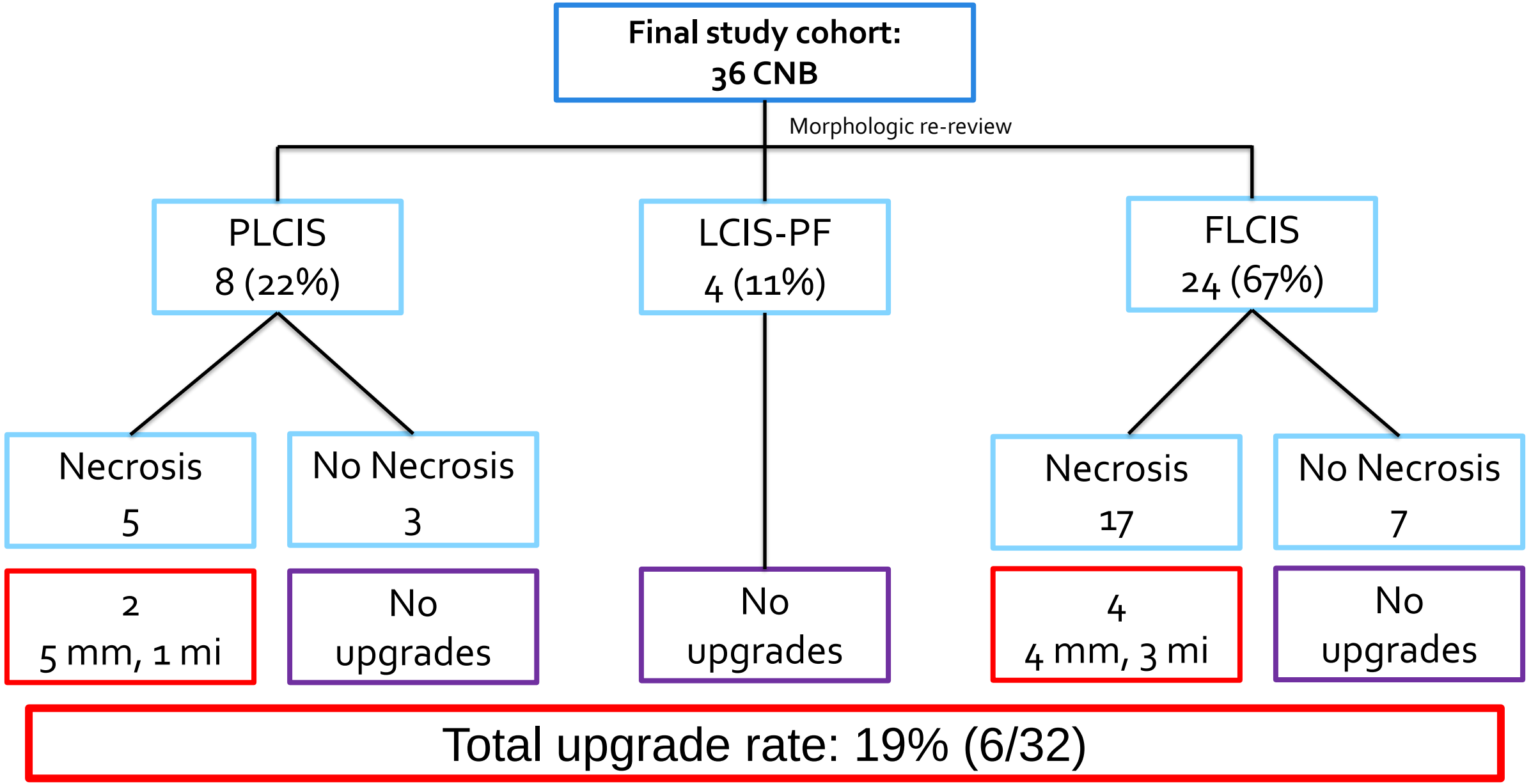
Imaging target

- Calcifications – 67% (24/36)
- NME – 22% (8/36)
- Mass – 8% (3/36)
- Distortion – 3% (1/36)



*From 2009-2019, 322 CNBs had diagnosis of only classic LCIS

Kuba at al. *Modern Pathology.* 2021; 34(8): 1495-1506



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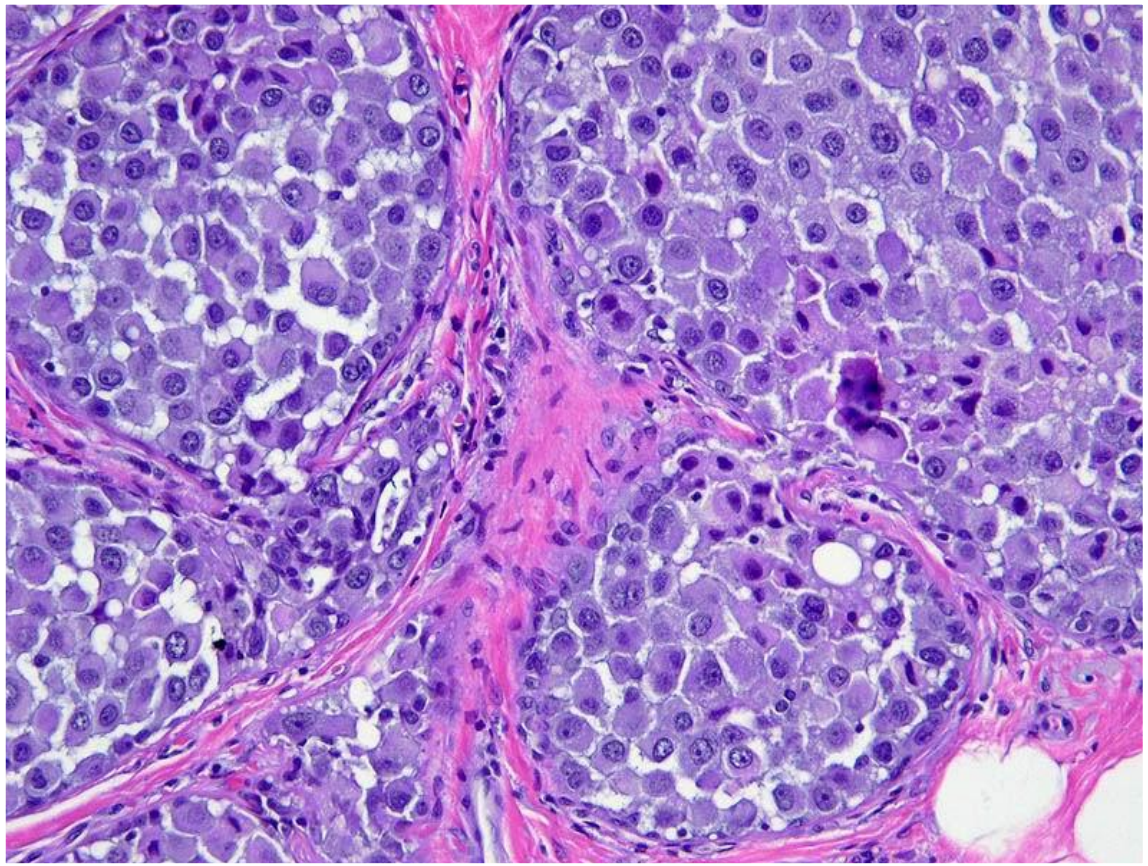
Kuba at al. *Modern Pathology.* 2021; 34(8): 1495-1506

MSK Study: Features of upgraded cases



Radiologic target in all cases was calcifications

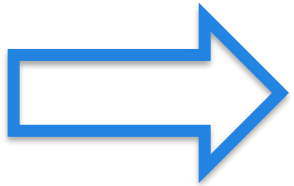
Presence of necrosis showed positive trend (p=0.062)

Extensive PLCIS or FLCIS on excision (mean size 3.2 cm v 0.9 cm) (p=0.001)

Kuba at al. *Modern Pathology.* 2021; 34(8): 1495-1506

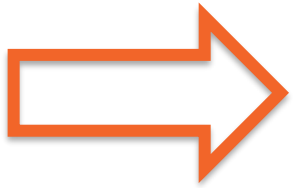
Management for Lobular Neoplasia on CNB

Classic LCIS & ALH
AND
Rad-path concordance



No Excision
Routine imaging
+/- Chemoprevention

Non-classic LCIS



Surgical Excision

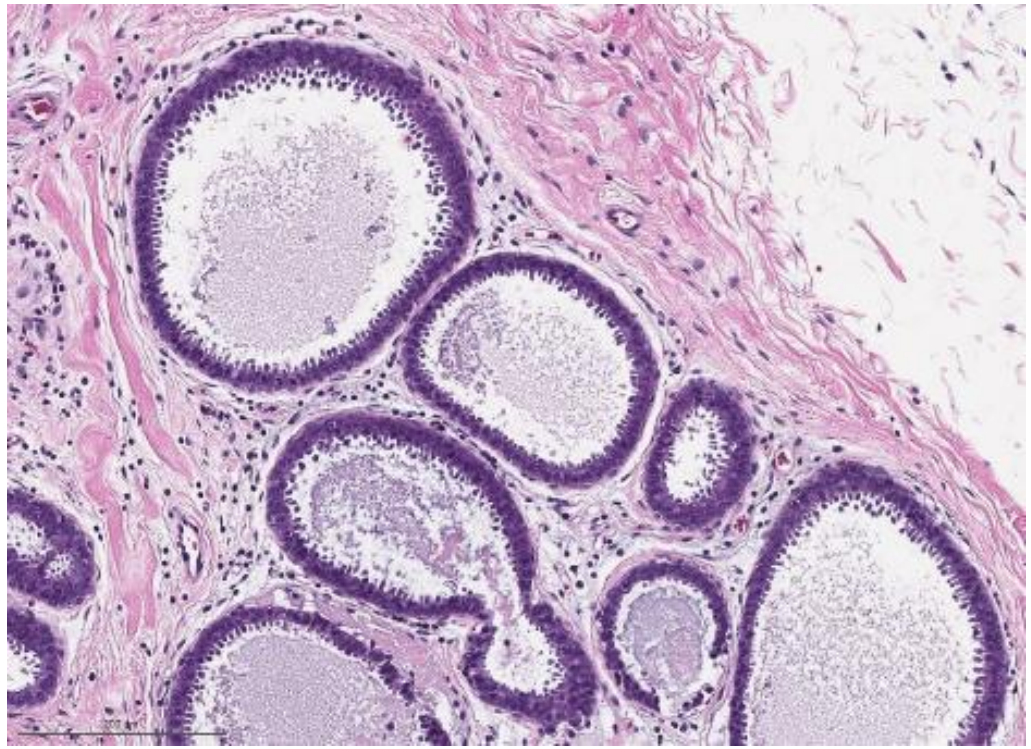
Flat Epithelial Atypia (FEA)

Flat Epithelial Atypia (FEA)

- Increase breast cancer risk by ~1.5x
- 5-7% lifetime risk of developing invasive cancer
  - Risk similar to UDH

- Need for routine excision remains uncertain
  - Limitations of study design
  - Wide variation in reported upgrade rate

- Radiologic pathologic correlation is recommended for determining further management



Boulos et al. *Cancer.* 2012; 118: 2372-2377.

Upgrade Rate of FEA in Selected Series

Study	Number excised	Rad-path correlation	Upgrades at excision			Recommend excision
			Total	Invasive	DCIS	
Kunju & Kleer (2007)	12	No	3 (25%)	1 (8.3%)	1 (8.3%)	Yes
Martel (2007)	19	No	7 (36%)	7 (36%)	0	No
Piubello (2009)	20	Yes	0	0	0	No
Lavoue (2011)	60	No	8 (13%)	2 (3.3%)	6 (10%)	Yes
Uzoaru (2012)	95	No	3 (3%)	2 (2%)	1 (1%)	No
Dialani (2014)	29	Yes	1 (3.4%)	0	1 (3.4%)	No
Calhoun (2015)	73	Yes	5 (7%)	2 (3%)	3 (4%)	No
Lamb (2017)	208	Yes	5 (2.4%)	0	5 (2.4%)	No
McCroskey (2018)	43	Yes	1 (2%)	1 (2%)	0	No
Ouldamer (2018)	20	Yes	3 (15%)	1 (5%)	2 (10%)	No
Hugar (2019)	111	Yes	1 (0.9%)	1 (0.9%)	0	No
Grabenstetter (2020)	40	Yes	2 (5%)	2 (5%)	0	No
Miller-Ocuin (2020)	33	Yes	2 (6%)	1 (3%)	1 (3%)	No
Liu (2020)	116	Yes	1 (0.8%)	0	1 (0.8%)	No

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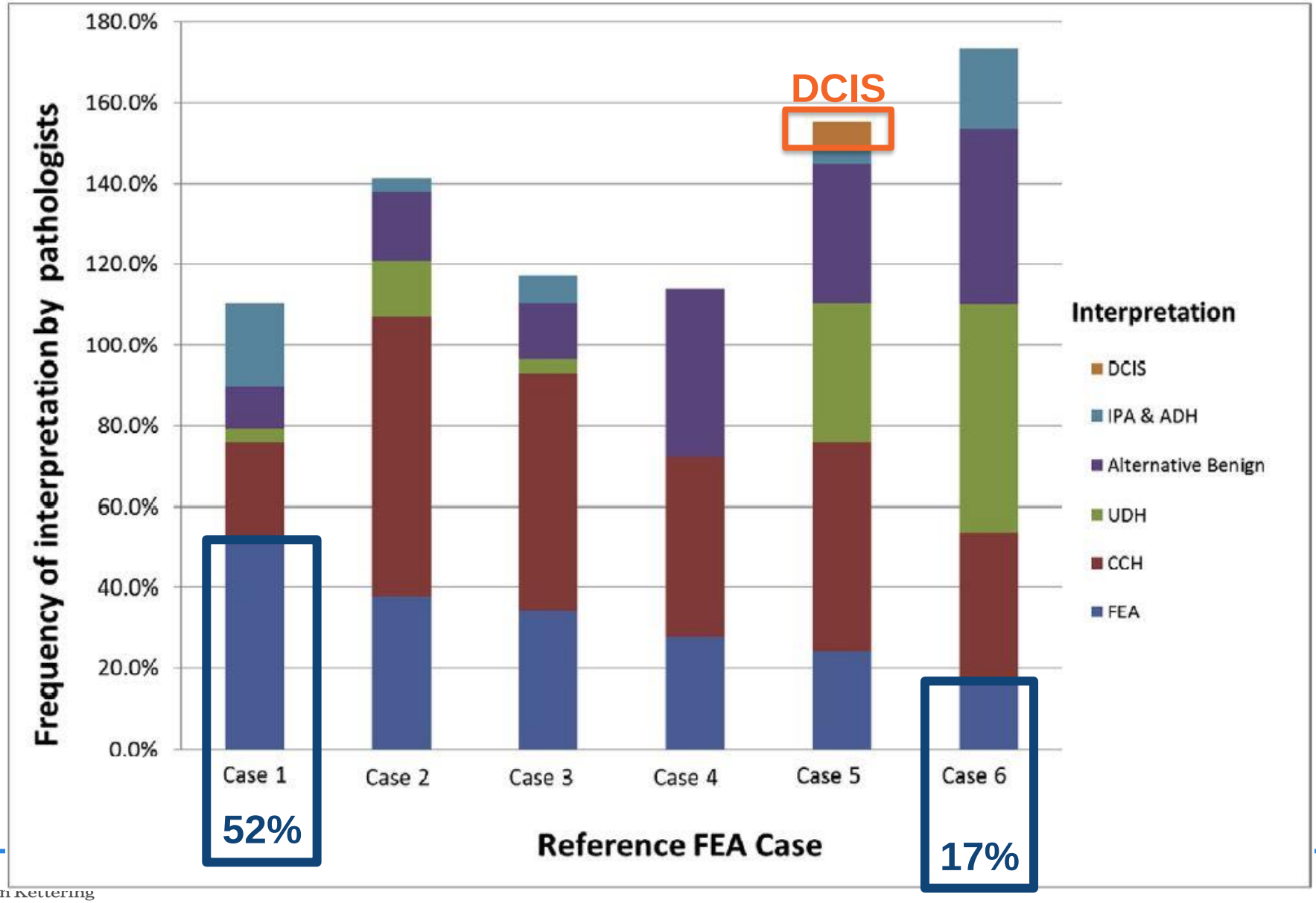
Variability in Diagnosis of FEA



Samples LS et al. *Breast.* 2017;34:34-43.

MSK Study

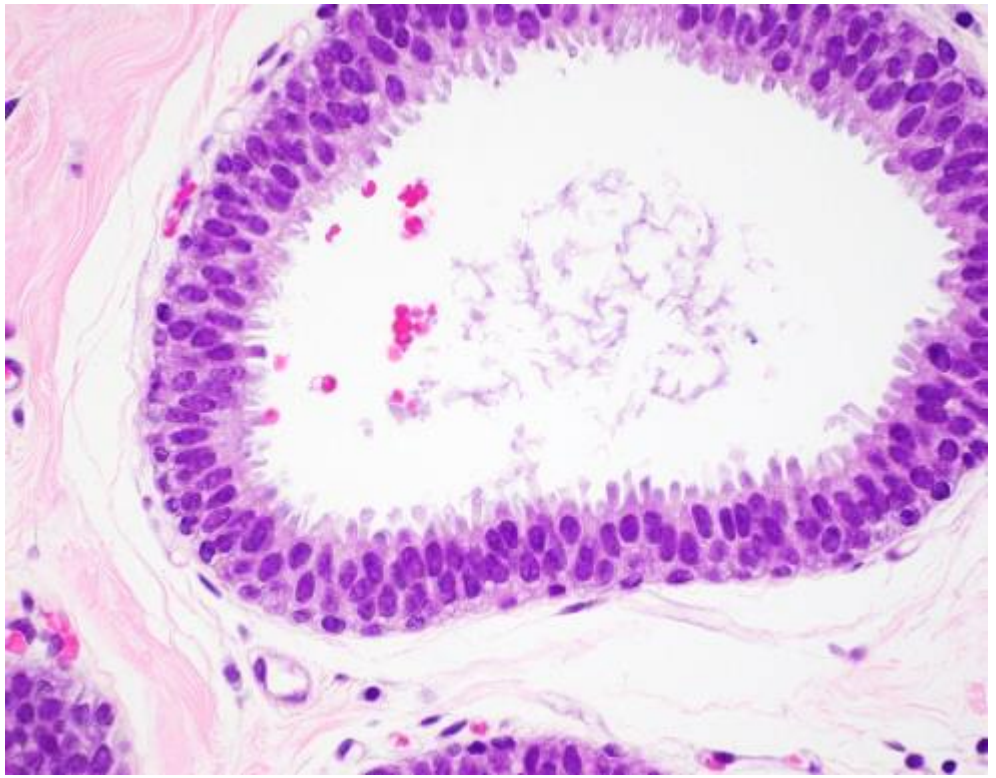
~15,700 CNBs between 1/2012 – 7/2018

106 CNBs with FEA (0.7%)

52 CNBs Excluded

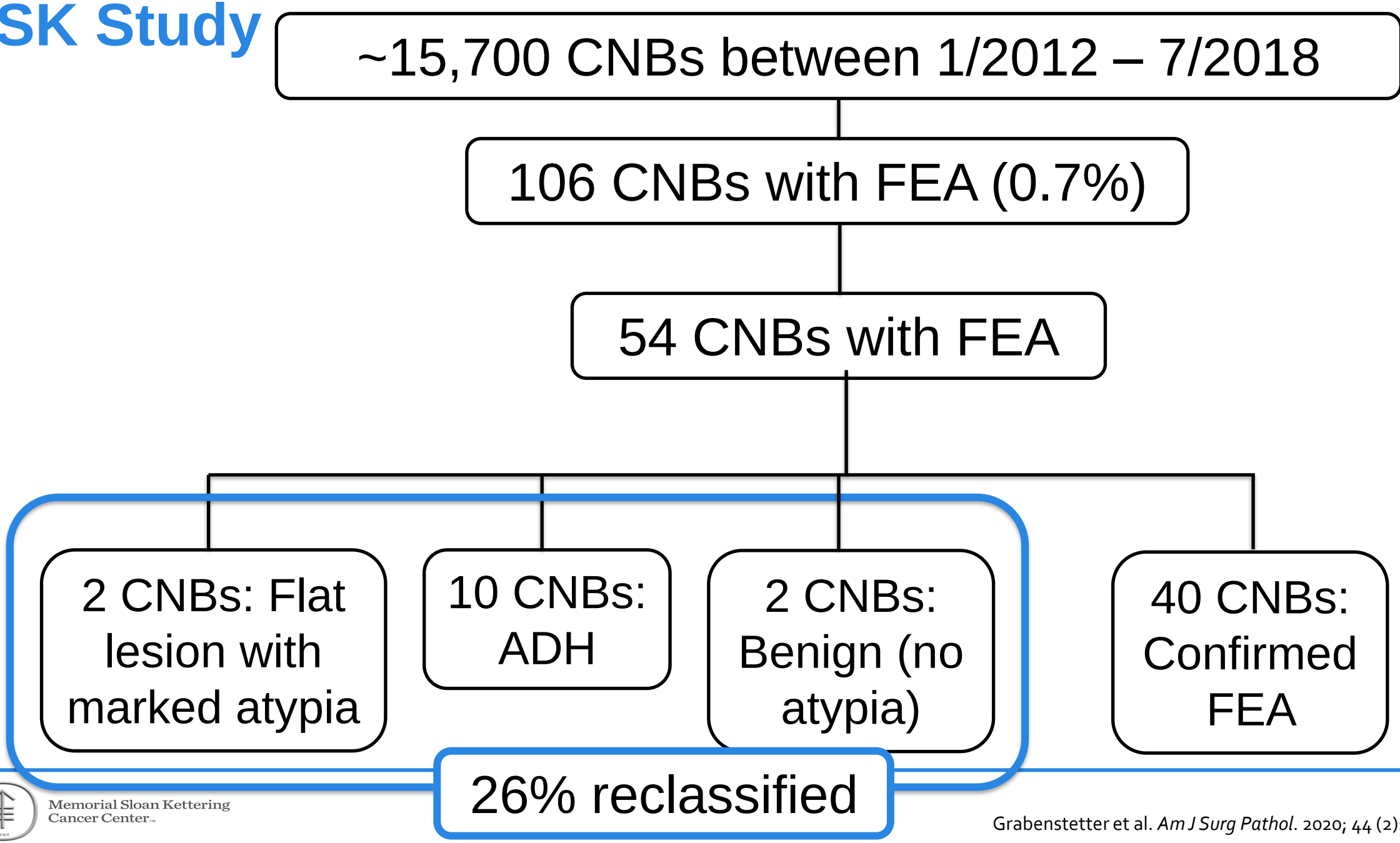
40 prior/concurrent Invasive/DCIS

12 no F/U excision



Grabenstetter et al. *Am J Surg Pathol*. 2020; 44 (2): 182-190.

MSK Study



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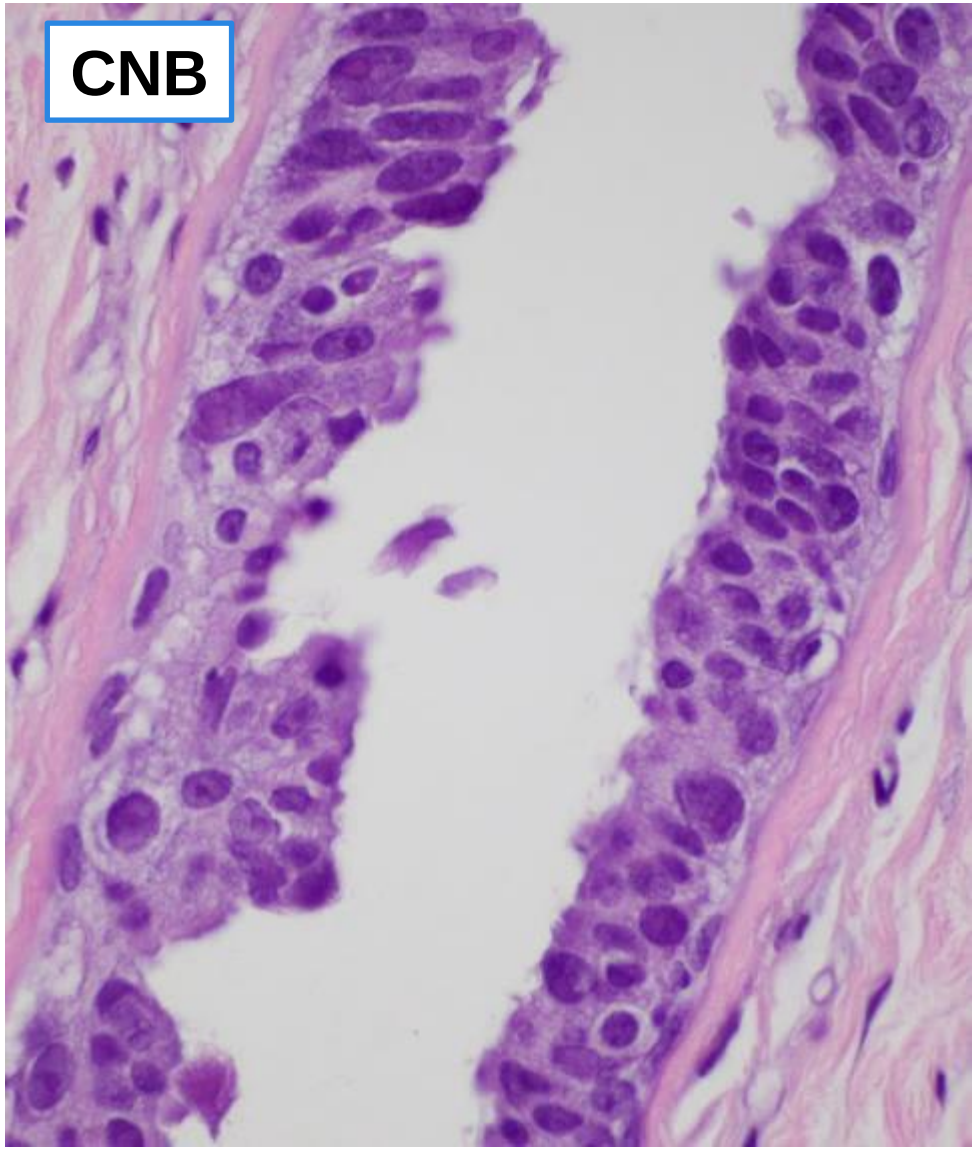
Grabenstetter et al. *Am J Surg Pathol*. 2020; 44 (2): 182-190.

Two CNBs reclassified as "flat lesion with marked nuclear atypia"

Excision

DCIS
3 mm focus

Focal DCIS arising in background of ADH

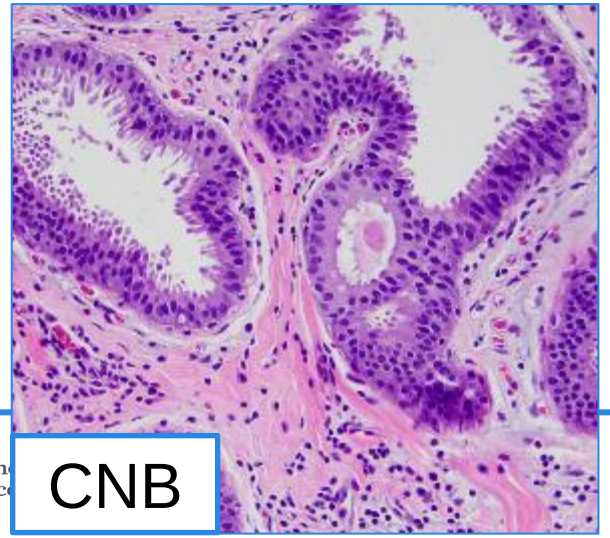


Grabenstetter et al. *Am J Surg Pathol*. 2020; 44 (2): 182-190.

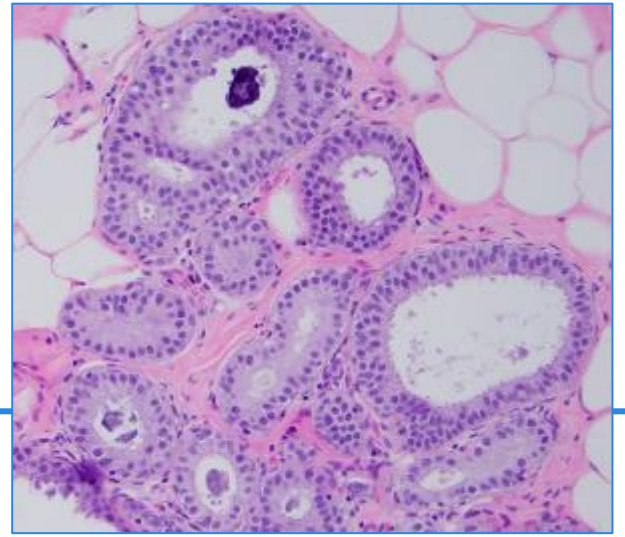
10 CNBs reclassified as ADH

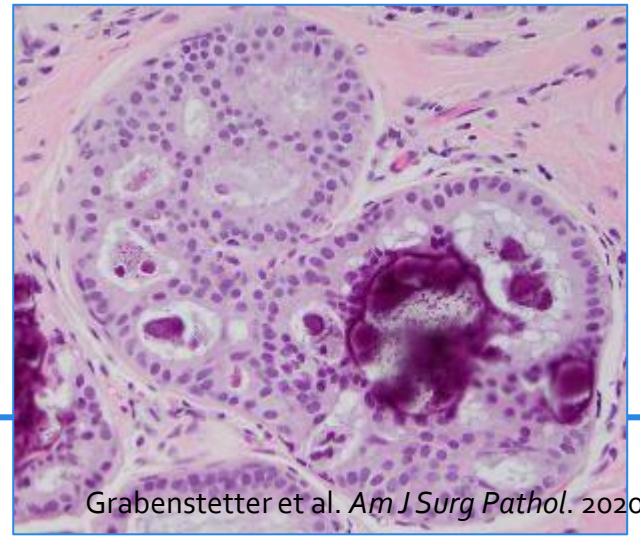
Excision

- IDC, grade II/III 12 mm
- Tubular carcinoma 6 mm
- DCIS 2 mm focus
- 6 ADH
- Benign breast



CNB





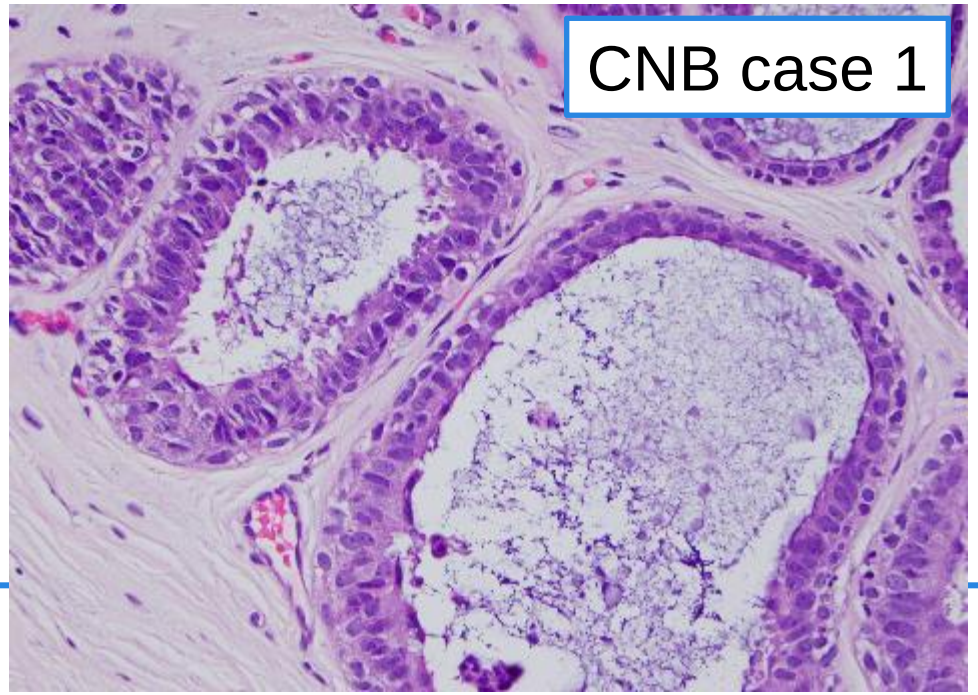
Grabenstetter et al. *Am J Surg Pathol*. 2020; 44 (2): 182-190.

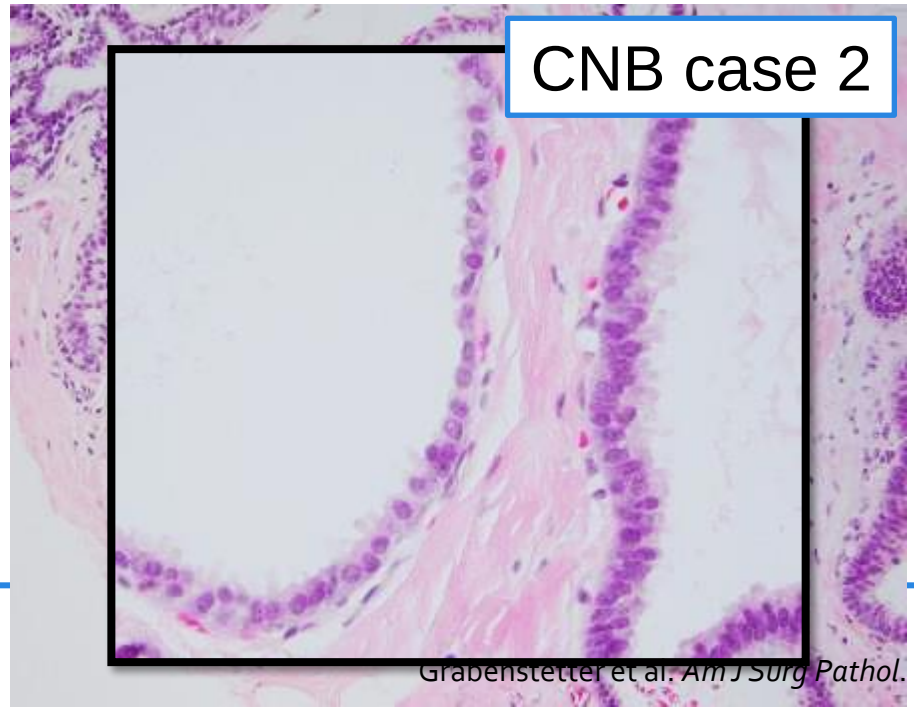
Two CNBs reclassified as “Benign”

Excision

ADH

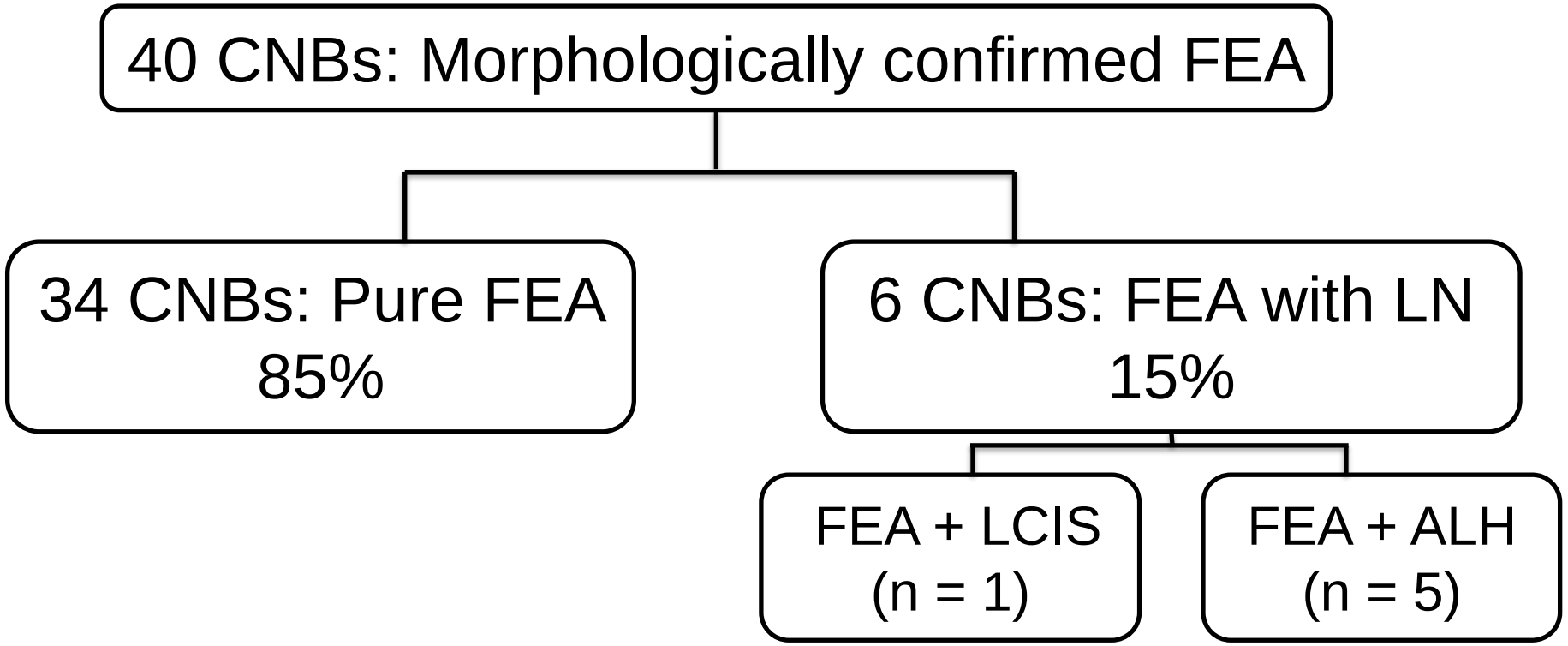
Benign breast





Grabenstetter et al. *Am J Surg Pathol*. 2020; 44 (2): 182-190.

MSK Study: Final FEA Study Cohort



40 CNB from 40 women, median age: 52 years (range 35-73)

Grabenstetter et al. *Am J Surg Pathol*. 2020; 44 (2): 182-190.

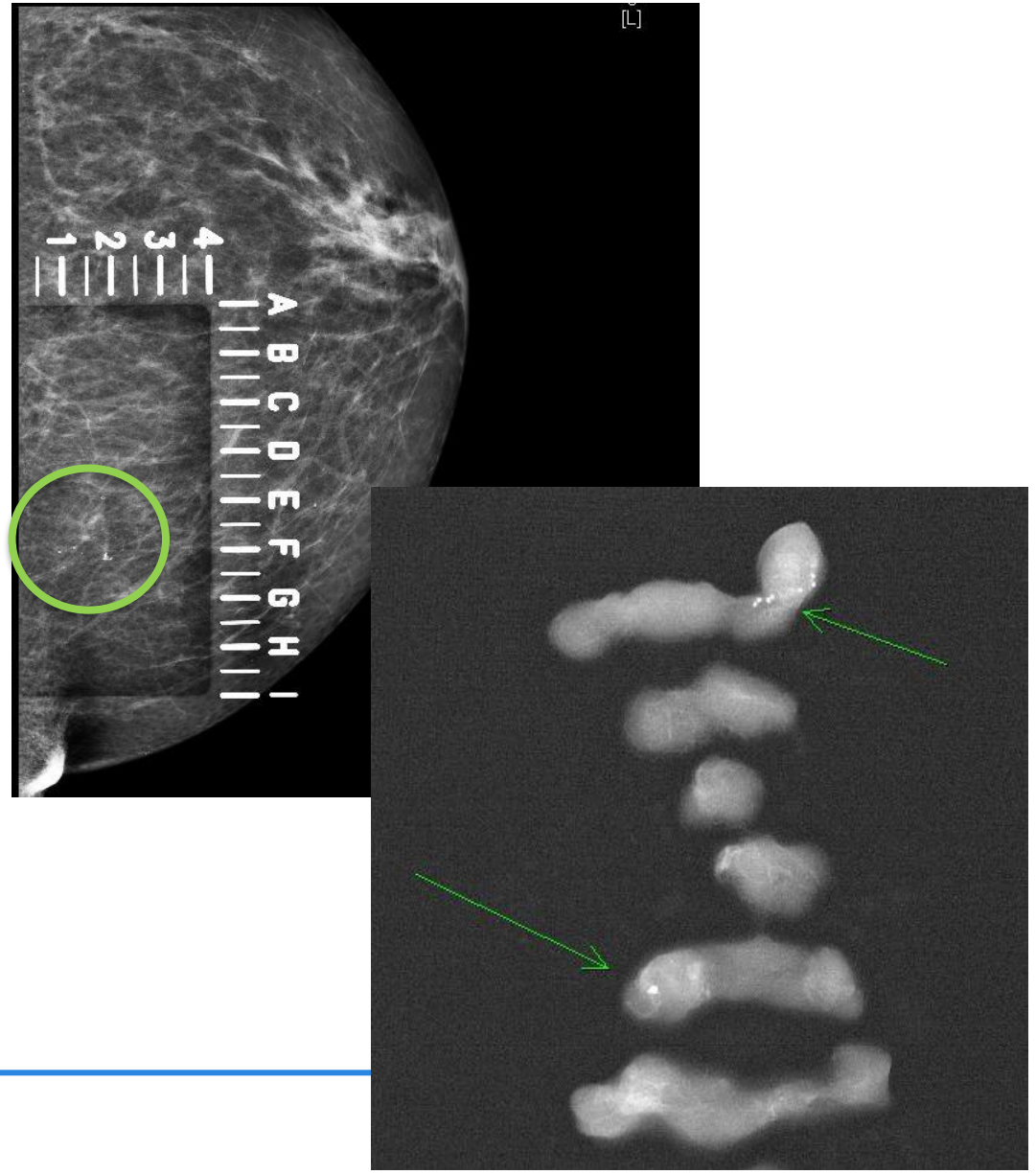
Final FEA Study Cohort – Imaging Findings

- Target
  - Calcifications: 36 (90%)
  - MRI NME: 3 (8%)
  - US mass: 1 (2%)

- Average lesion diameter: 8.98 mm (range 2-31)
  - Calcifications: 8.98 mm (2-22)
  - NME: 8.74 mm (6-31)
  - US mass: 11 mm

- Average # cores removed: 8.22 (range 4-14)

- Gauge
  - 9G: 37 (93%)
  - 8G, 11G, 12G: 1 each



Grabenstetter et al. *Am J Surg Pathol*. 2020; 44 (2): 182-190.

FEA on CNB: Upgrade rate

- Upgrade rate to carcinoma was **5% (2/40)**

Case	Age	Mammographic calcifications	CNB Findings	Excision Findings	Cancer associated with Biopsy site
1	73	15 mm coarse heterogenous	2 FEA foci largest 3 mm	IDC, grade II/III 2.2 mm	No
2	46	22 mm amorphous	1 FEA focus 3.7 mm	Tubular carcinoma 2.0 mm and 1.0 mm	No

All upgrades consisted of minute, incidental low grade invasive carcinoma not associated with the biopsy site

ORIGINAL ARTICLE – BREAST ONCOLOGY

Incidence of Adjacent Synchronous Ipsilateral Infiltrating Carcinoma and/or Ductal Carcinoma In Situ in Patients Diagnosed with Flat Epithelial Atypia by Core Needle Biopsy (TBCRC 034)

Faina Nakhlis, MD[1,2,3], Gabrielle M. Baker, MD[3,4], Tianyu Li, MS[5], Priscilla F. McAuliffe, MD[6], George Plitas, MD[7], Kandice K. Ludwig, MD[8], Marc Boisvert, MD[9], Laura H. Rosenberger, MD, MS[10], Kristalyn K. Gallagher, DO[11], Lisa Jacobs, MD[12], Suniti N. Nimbkar, MD[1,2,3], Sheldon Feldman, MD[13], Paulina Lange, BS[1,2], Victoria Attaya, BS[1,2], Michelle DeMeo, BS[1,2], Ashton Fraettarelli, BA[1,2], Stuart J. Schnitt, MD[2,3,14], and Tari A. King, MD[1,2,3]

[1]Division of Breast Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, MA; [2]Breast Oncology Program, Dana-Farber Brigham Cancer Center, Boston, MA; [3]Harvard Medical School, Boston, MA; [4]Beth Israel Deaconess Medical Center, Boston, MA; [5]Department of Data Sciences, Dana-Farber Cancer Institute, Boston, MA; [6]UPMC Hillman Cancer Center, Pittsburgh, PA; [7]Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; [8]Indiana University Cancer Center, Indianapolis, IN; [9]Georgetown University Cancer Center, Washington, DC; [10]Duke University Medical Center, Durham, NC; [11]University of North Carolina, Chapel Hill, NC; [12]Johns Hopkins University, Baltimore, MD; [13]Montefiore Medical Center, New York, NY; [14]Department of Pathology, Brigham and Women's Hospital, Boston, MA

Ann Surg Oncol 2025; 32: 2578-2584.

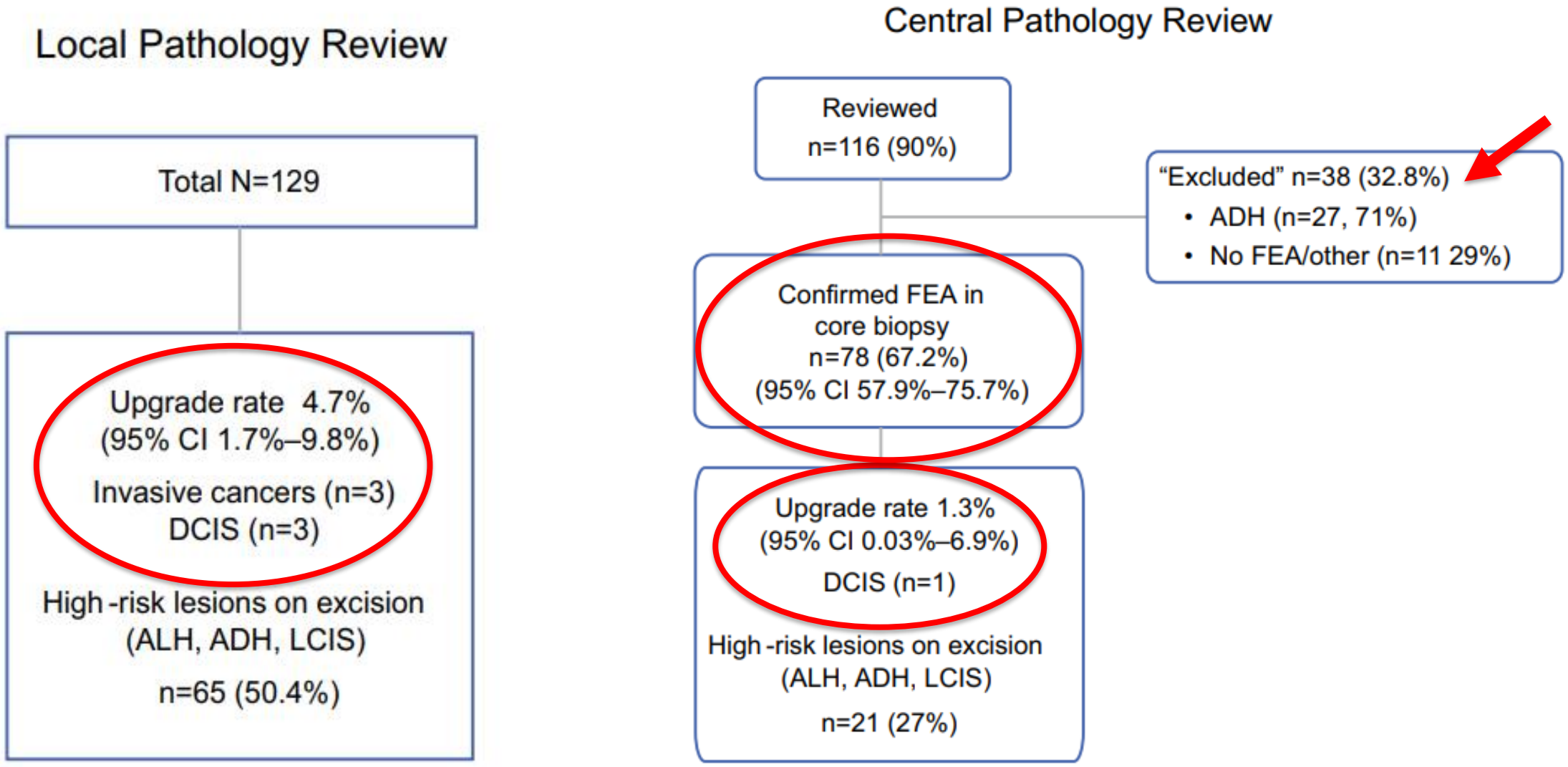
Prospective multicenter study (9 sites)

Inclusion: women with FEA on a rad-path concordant core biopsy

Exclusion: clinical concern (e.g. palpable mass, nipple discharge), ADH or non-classic LCIS in same biopsy, history of DCIS and/or invasive breast cancer

Primary objective: evaluate the frequency with which FEA diagnosed on core needle biopsy was upgraded to DCIS or invasive breast cancer upon surgical excision

TBCRC 034: Results



Nakhlis et al. *Ann Surg Oncol* 2025; 32: 2578-2584.

TBCRC 034: Results

TABLE 3 Lesions associated with an increased future breast cancer risk found on excision of FEA

	Local pathology (n = 129)	Central pathology (n = 78*)
ADH	27 (20.9%)	18 (23.1%)
ALH and/or LCIS	33 (25.6%)	3 (3.9%)
ADH and LCIS	5 (3.9%)	0
Total	65 (50.4%)	21 (27%)

FEA flat epithelial atypia, *ADH* atypical ductal hyperplasia, *ALH* atypical lobular hyperplasia, *LCIS* lobular carcinoma in situ

*Central pathology review confirmed FEA core biopsy diagnosis in 78 of 129 cases

High risk lesions were found in 50.4% of cases by local pathology review and in 27% by central review

Nakhlis et al. *Ann Surg Oncol* 2025; 32: 2578-2584.

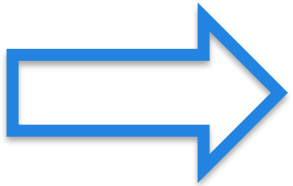
TBCRC 034: Conclusions

- Central review confirmed FEA in only 78/116 (67.2%) cases
  - Recommend obtaining second opinion to confirm
- FEA diagnosis is rare and robust prospective data demonstrating the safety of observation are not yet available however shows similar upgrade rates as those seen in classic lobular neoplasia
  - Reasonable to infer the safety of observation from the data on ALH and classic LICS
- High prevalence of high risk lesions (ADH, ALH, classic LCIS)
  - Referral for comprehensive risk assessment may be considered for patients with FEA

Observation may be clinically acceptable, depending on patient's risk factors. Management discussion with multidisciplinary treatment team is advised.

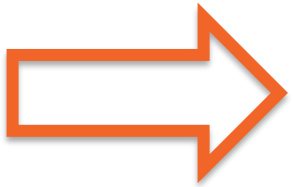
Management of FEA on CNB

FEA
IF no prior/concurrent carcinoma
AND
Rad-path concordance



No Excision
Routine imaging

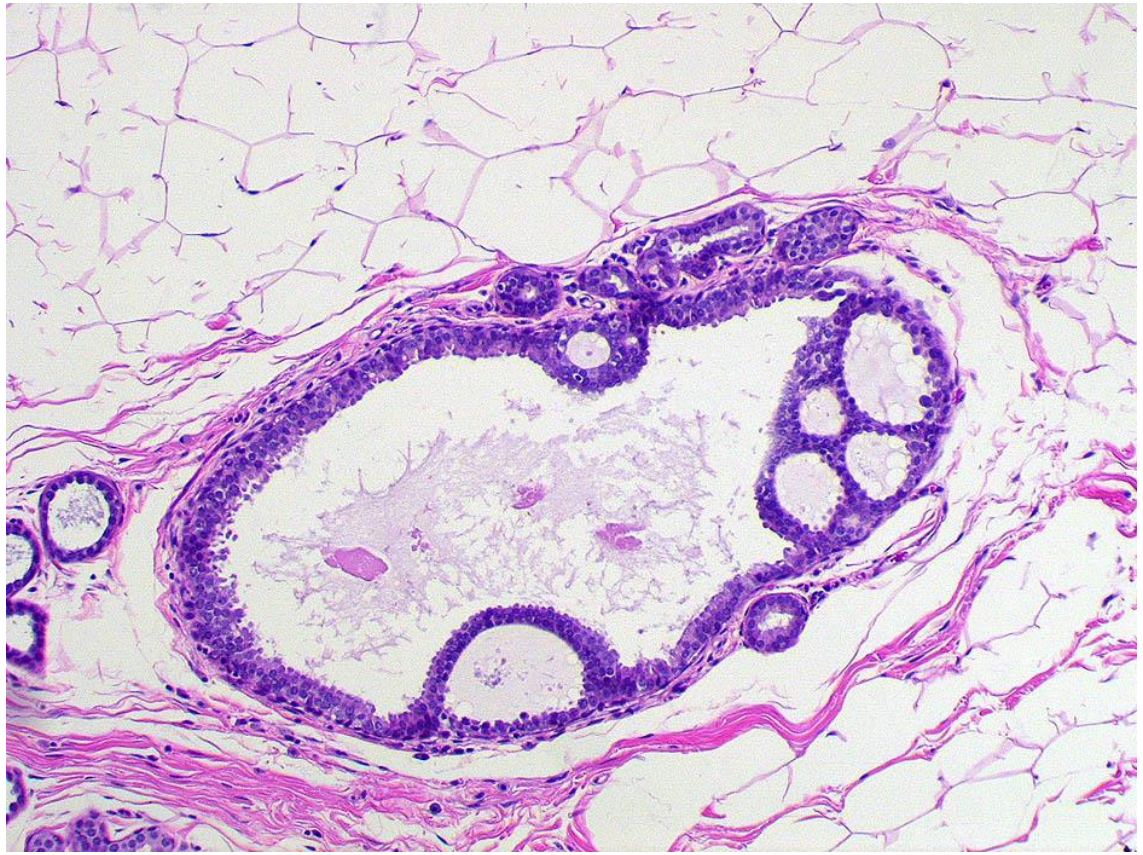
FEA
WITH prior/concurrent carcinoma
OR
Rad-path discordance



Surgical Excision

Atypical Ductal Hyperplasia (ADH)

Atypical Ductal Hyperplasia (ADH)



- Increased risk: 3-5x
- Absolute risk of breast cancer: 1% per year for at least 25 years
- Mean latency period: 8-12 years
- ~30% are "upgraded" on excision
  - Reported range: 0-80%

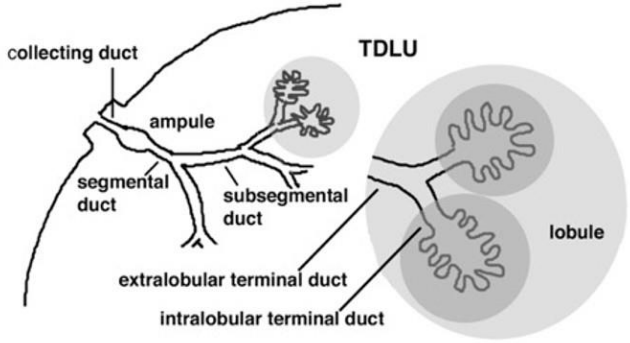
Core Biopsy of the Breast With Atypical Ductal Hyperplasia

A Probabilistic Approach to Reporting

Kim A. Ely, M.D., Beverley A. Carter, M.D., Roy A. Jensen, M.D., Jean F. Simpson, M.D., and David L. Page, M.D.

Am J Surg Pathol. 2001; 25 (8): 1017-1021.

47 CNB with ADH



Extent of ADH

1 or 2 foci: 24 (51.1%)	3 foci: 8 (17%)	≥4 foci: 15 (31.9%)
NO upgrades 0%	4 upgrades 50%	13 upgrades 86.6%
	3 DCIS, 1 IC	12 DCIS, 1 IC

Overall upgrade rate: 36%

Conclusion: Limited ADH probably do not require further surgical intervention, particularly if the mammographic abnormality has been removed.

ADH in Directional VAB of Breast Microcalcifications: Considerations for Surgical Excision

- Cohort: 140 patients
  - 121 excised, 19 observed
- Extent of ADH, histologic pattern, significant atypia, presence of necrosis
- Upgrade rate: **13.2% (16/121)**
  - 14 DCIS, 2 Invasive

Variable	Patients	Upgrades	*P* value
≤95% Ca^{++} removed	94	14 (14.9%)	.0371
>95% Ca^{++} removed	42	1 (2.4%)	
≤2 TDLU	81	5 (6.2%)	.0306
>2 TDLU	59	11 (18.6%)	
Cytologic atypia	20	12 (60%)	<.0001
No Cytologic atypia	120	4 (3.3%)	
Necrosis	5	4 (80%)	.0006
No Necrosis	135	12 (8.9%)	

Adapted from Nguyen et al. *Ann Surg Oncol*. 2011; 18: 752-761.

TABLE 2 Comparison of histologic findings (number of TDLU involved by ADH and presence of significant cytologic atypia and/or necrosis) in relation to rate of upgrade to carcinoma

Extent of ADH on DVAB	Presence of significant cytologic atypia and/or necrosis	Corresponding surgical excision/mammographic follow-up		Univariate *P* value (Fisher exact test)
		No carcinoma ($n = 124$)	DCIS/invasive carcinoma ($n = 16$)	
≤2 TDLU	No	72 (97.3%)	2 (2.7%)	.0038
	Yes	4 (57.1%)	3 (42.9%)	
>2 TDLU	No	42 (97.7%)	1 (2.3%)	<.0001
	Yes	5 (33.3%)	10 (66.7%)	

ADH atypical ductal hyperplasia, *DCIS* ductal carcinoma in situ, *DVAB* directional vacuum-assisted biopsy, *TDLU* terminal duct-lobular unit or large duct

ADH with significant cytologic atypia and/or necrosis should be excised

Cases involving ≤2 TDLUs, with >95% removal of targeted Ca^{++} and no significant atypia/necrosis may undergo imaging follow up

Nguyen et al. *Ann Surg Oncol*. 2011; 18: 752-761.

Long-term safety of observation

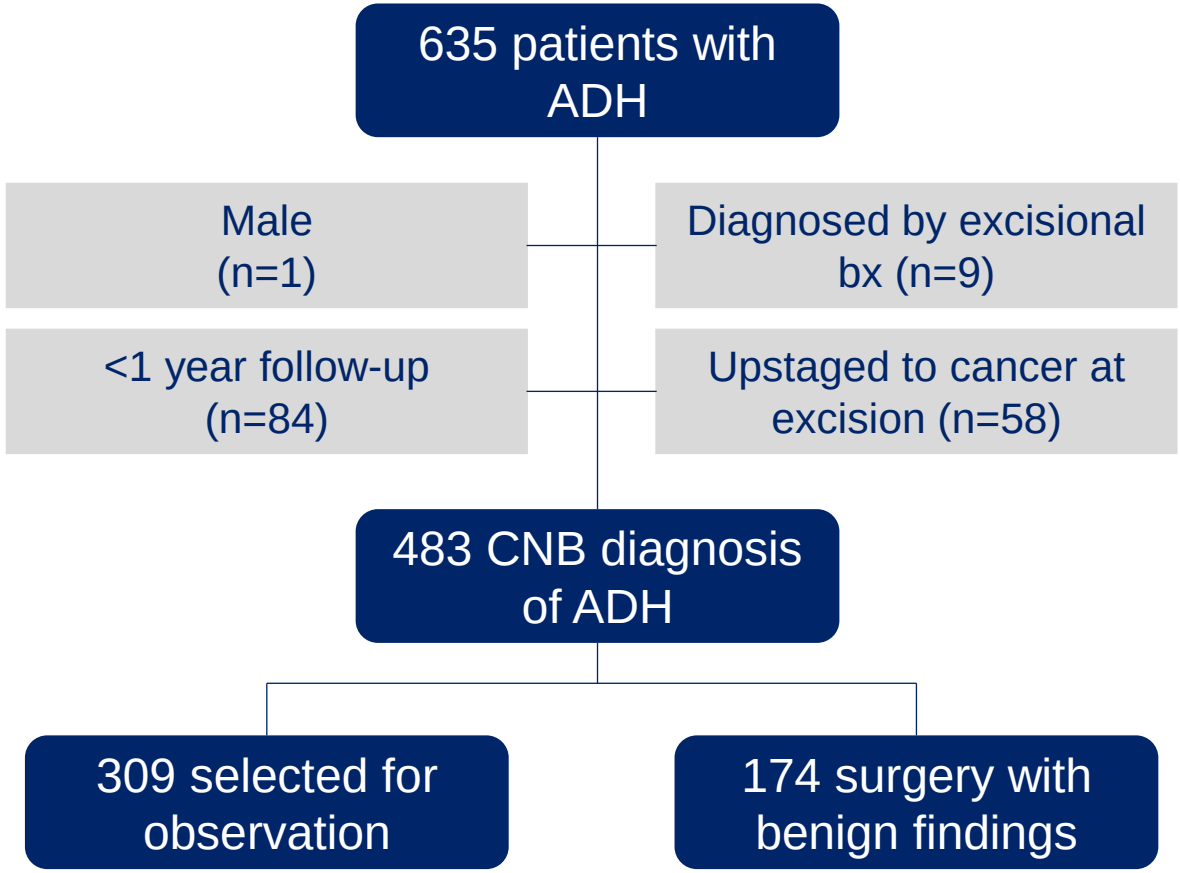
Expanded criteria: <3 TDLUs, >90% Ca^{++} removed, no necrosis/atypia, no mass lesion or architectural distortion, >50% Ca^{++} removed of well-sampled target

96 had personal hx of breast cancer

Median follow-up: 5.2 years (range 1.1-15.3)

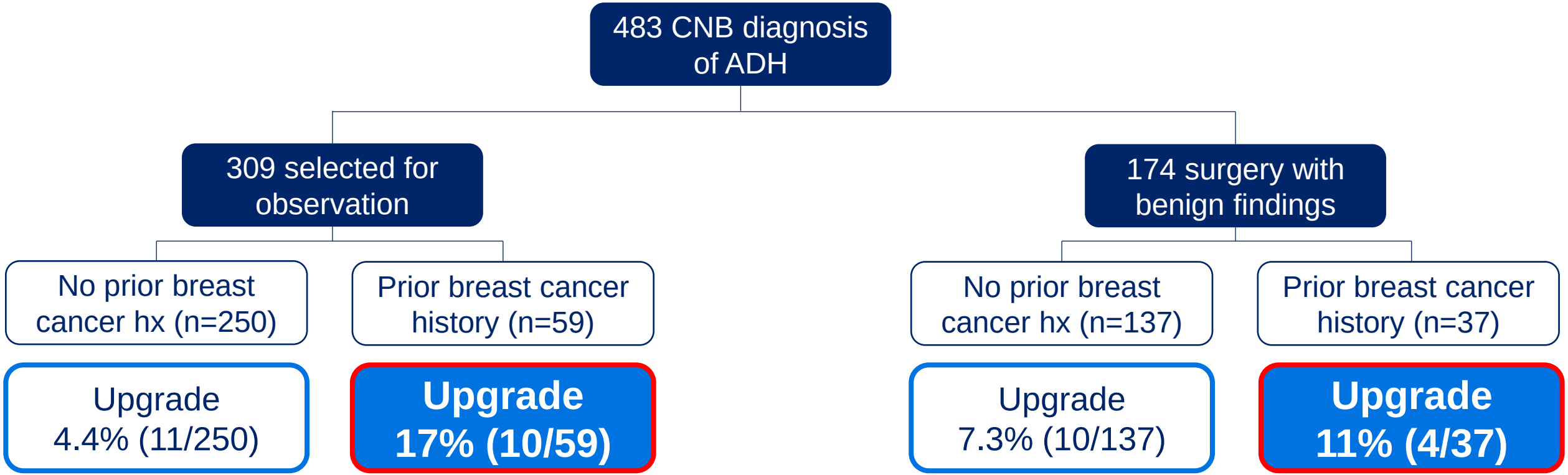
Women ≤ 50 y more likely to have surgery (42.4% vs 33.2%, *p*=0.04)

Women dx by stereotactic bx more likely to be observed than if dx by US or MRI bx (67.2% vs 43.1%, *p*=0.001)



Kilgore et al. *Ann Surg*. 2022; 276(6): e932-e936.

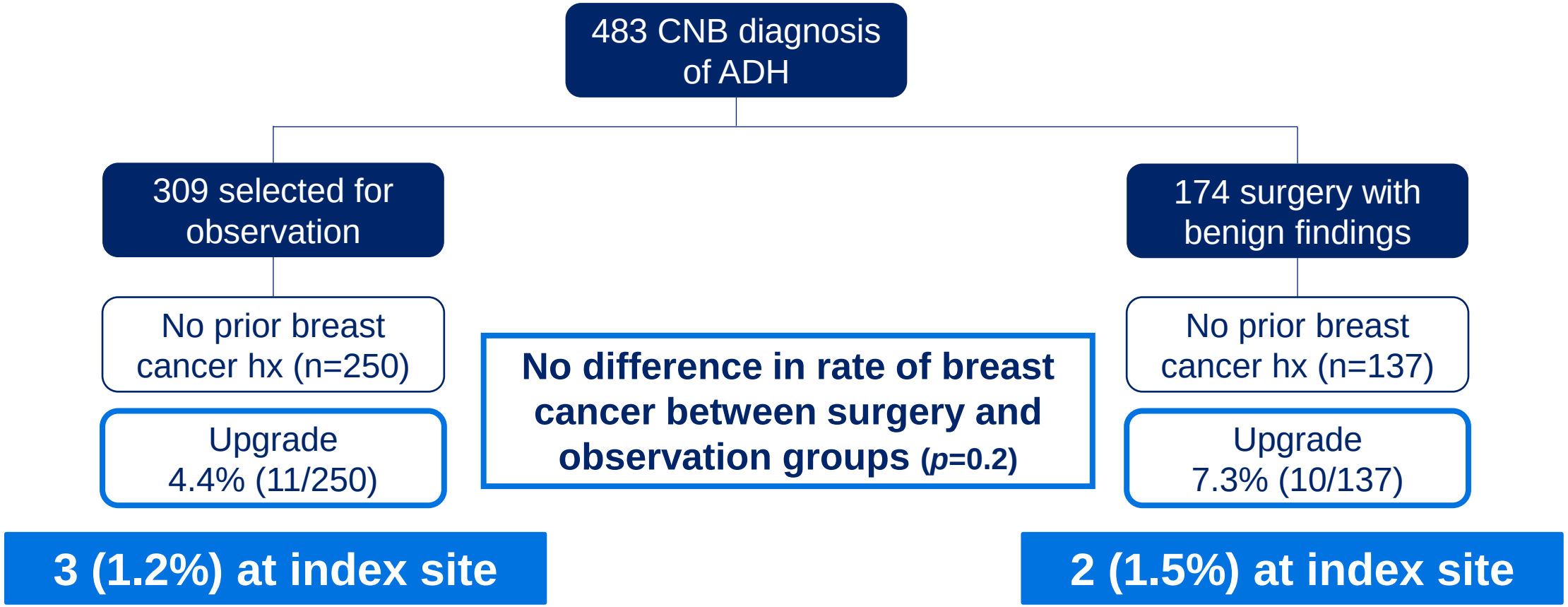
Long term safety of observation



Prior history of breast cancer was only factor associated with subsequent breast cancer risk (p=0.04)

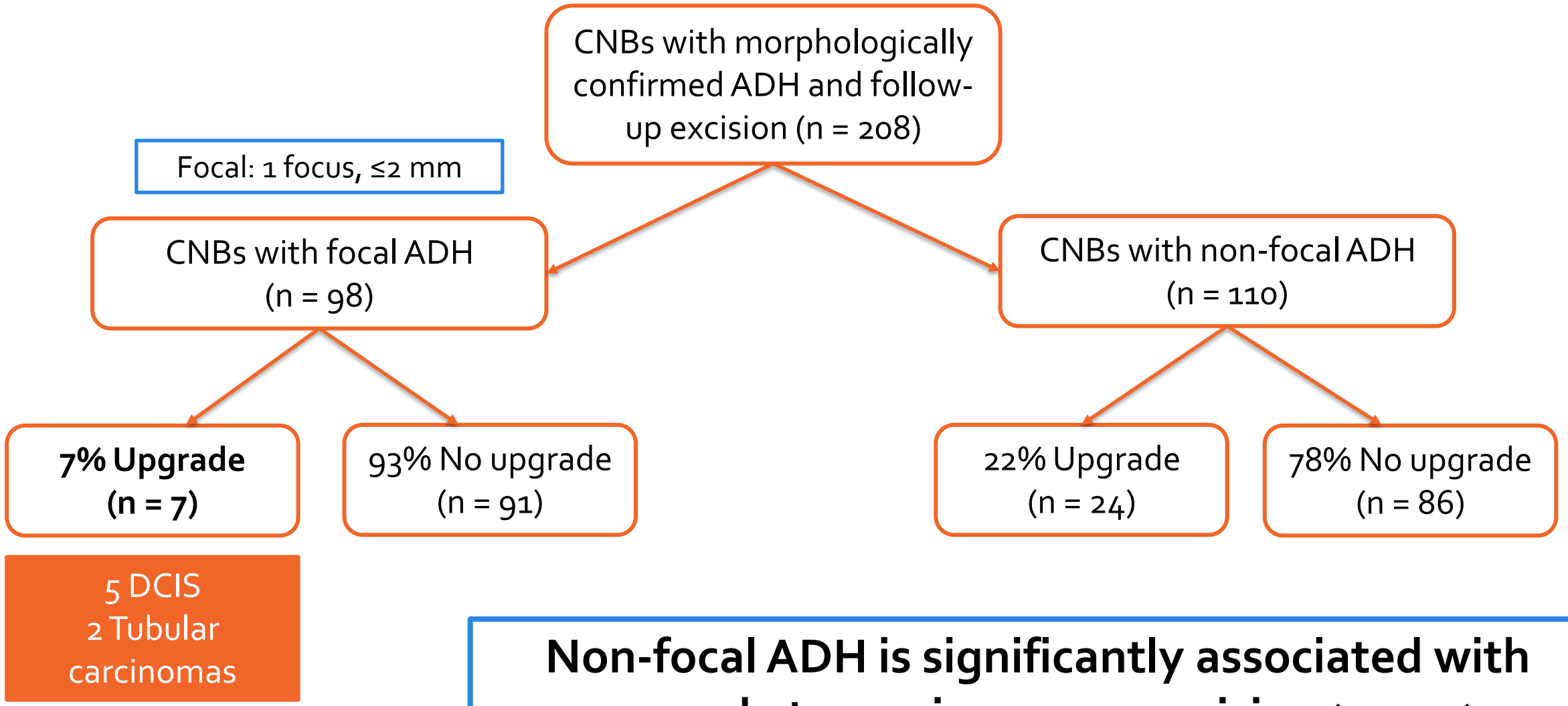
Kilgore et al. *Ann Surg*. 2022; 276(6): e932-e936.

Long term safety of observation



Conclusion: Risk of cancer at index site (i.e. site of ADH biopsy) is exceedingly low. Observation, rather than surgical excision, is safe in selected women that have a core biopsy diagnosis of ADH.

MSK Study: Focal ADH on CNB



Non-focal ADH is significantly associated with upgrade to carcinoma on excision (*p*=0.01)

Memorial Sloan Kettering Cancer Center

Grabenstetter et al. *Ann Surg Oncol.* 2023; 30 (7): 4087-94.

Upgraded cases showing focal ADH on core biopsy

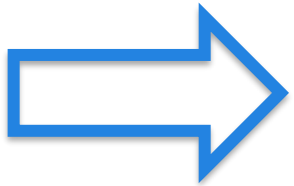
Imaging Findings					Excision Findings			
Case	Imaging modality	Lesion type	Lesion diameter (mm)	Target removed by CNB	DCIS at excision	DCIS grade	Invasive carcinoma at excision	Invasive carcinoma type
1	MMG	Ca^{++}	7	No	Yes (3 mm)	Intermediate (with Ca^{++})	No	-
2	US	Mass	8	No	Yes	Low	No	-
3	MMG	Ca^{++}	5	No	Yes (2.1 mm)	Low (with Ca^{++})	No	-
4	MMG	Ca^{++}	8	No	Yes (30 mm)	Intermediate (with Ca^{++})	No	-
5	MMG	Ca^{++}	4	Yes	Yes (12 mm)	Intermediate (with Ca^{++})	No	-
6	MMG	Ca^{++}	7	Yes	No	-	Yes (4.5 mm)	Tubular * carcinoma
7	MMG	Ca^{++}	6	No	No	-	Yes (6 mm)	Tubular * carcinoma

*Not associated with biopsy site

Grabenstetter et al. *Ann Surg Oncol*. 2023; 30 (7): 4087-94.

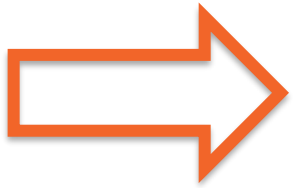
Management of ADH on CNB

Focal ADH
WITH
Rad-path concordance



In select clinical cases:
No Excision
Close imaging follow up

ADH



Surgical Excision

Core Needle Biopsy Lesion	MSK Upgrade Rate	Excision Recommended	Exceptions
Intraductal papilloma without atypia	2.3%	No*	Concurrent ipsilateral breast cancer (upgrade rate 16.6%)
Intraductal papilloma with atypia	Up to 41% (non-MSK data)	Yes	
Radial scar/complex sclerosing lesion without atypia	1%	No*	
Radial scar/complex sclerosing lesion with atypia	11-33% (non-MSK data)	Yes	
Mucocele-like lesion without atypia	0%	No*	Consider excision if mass lesion found on ultrasound
Mucocele-like lesion with atypia	22%	Yes	
Classic LCIS and ALH	3%	No*	
Non-classic LCIS	19%	Yes	
Flat epithelial atypia (FEA)	5%	No*	Personal history of breast cancer
Atypical Ductal Hyperplasia (ADH)	22%	Yes	Focal ADH (1 focus, <2 mm): if clinical need arises imaging follow up can be considered (upgrade rate 7%)

*Radiologic-pathologic concordance is required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