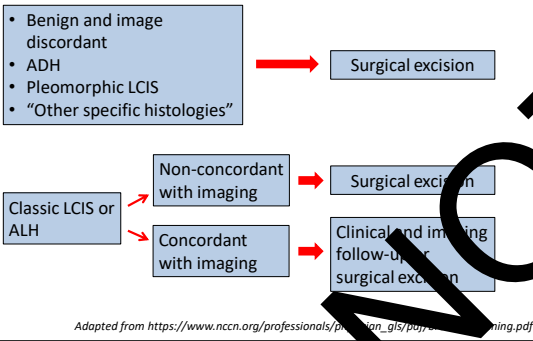


**Managing High Risk Lesions:
 A Pathologist's Perspective**

Megan E. Sullivan, MD
 Clinical Assistant Professor of Pathology,
 University of Chicago
 NorthShore University HealthSystem

- No disclosures to report.

NCCN Guidelines



Overview

- Atypical ductal hyperplasia (ADH)
- Flat epithelial atypia (FEA)
- Lobular neoplasia
 - Classic LCIS and ALH
 - LCIS variants
- Papillomas, radial scars & complex sclerosing lesions
- Mucocele-like lesions

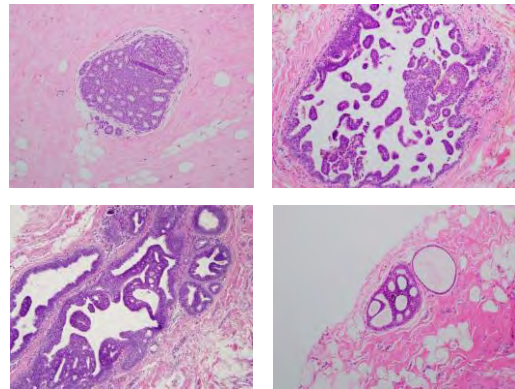
ADH vs. Low Grade DCIS

ADH

- Rigid bridges, micropapillae, cribriform spaces
- Monotonous nuclei, even cell placement, distinct borders
- Partial involvement
- Less than 2 spaces or ≤ 2 mm in greatest extent

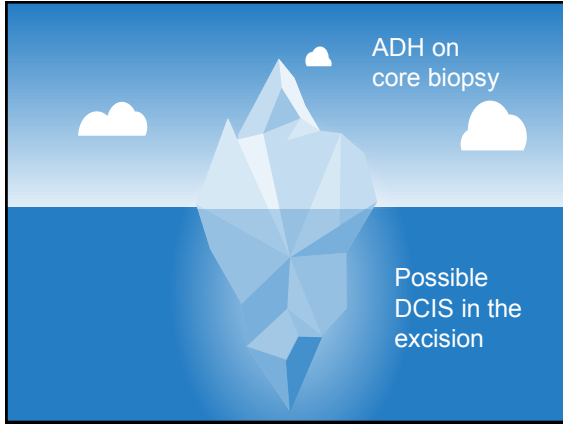
DCIS

- Rigid bridges, micropapillae, cribriform spaces
- Monotonous nuclei, even cell placement, distinct borders
- Complete involvement
- ≥ 2 spaces or > 2 mm in greatest extent





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My Perspective

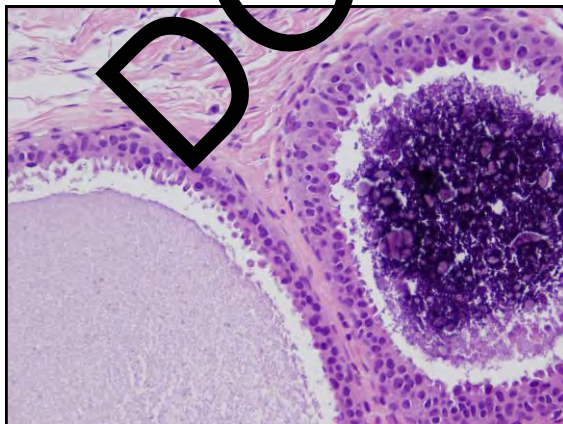
- Lots of morphologic overlap between ADH & low grade DCIS (criteria are subjective)
- Even cases pathologists are worried about ("borderline DCIS") only have a 50% upgrade rate at excision
- A conservative approach: diagnose as ADH on core and wait until excision for definitive categorization

Vanderlaschke et al. JCO 2013;23

FEA

- Increasingly detected because of association with microcalcifications
- Per NCCN may be "suitable for monitoring in lieu of surgical excision"
- Mayo Benign Breast Disease Cohort data
 - Incidence 2.4%
 - About half of FEA cases were associated with other atypia (ADH and/or ALH)
 - Relative risk of breast cancer is not elevated by FEA alone

Said SM et al. Cancer. 2015;121(10):1548-55.



	Pure FEA cases / # excised	Upgrade to DCIS or IC	Indication for biopsy	Residual lesion post-biopsy	Patients without excisions
Noel et al (2009)	62 / 20	0	Calcifications	Present in the 20 excised cases	No changes in mammogram at 6-12 months post biopsy
Uzoaru et al (2012)	145 / 95	3 (3%)	Calcifications, mass	Unknown	No changes in mammogram with mean follow-up of 5 years
Peres et al (2012)	128 / 95	9 (9%)	Calcifications, mass	Unknown	No changes in mammogram with median follow-up of 13 months
Khoumanis et al (2013)	104 / 94	10 (10%)	Calcifications, mass	Unknown	No changes in mammogram with mean follow-up of 36 months



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My Perspective

- I have a high diagnostic threshold for FEA on core biopsy
- Examination of deeper levels can be helpful
- Excision should be considered on a case by case basis to account for other risk factors

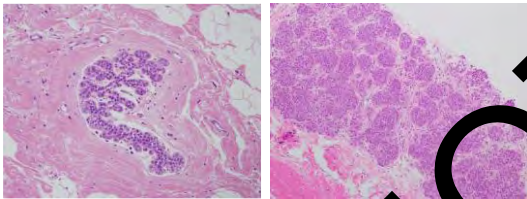
Martel et al. Virchows Arch;2007;451(5):883-91

ALH and classic LCIS

- Most often an incidental finding
- Never mass forming but can occasionally be associated with calcifications
- Multicentric in up to 85% of patients and bilateral in 30-67%

WHO Classification of Tumours of the Breast, 4th ed.

ALH vs. LCIS



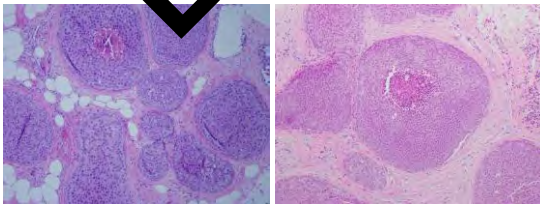
Prospective Excision of ALH/LCIS

Study	# of Upgrades	Upgrade Rate
Rendi (2012)	3/68	4.4%
Murray (2013)	2/72	3.0%
Nakhlis (2016)	2/77	3.0%
Susnik (2016)	7/180	3.9%
Total	14/397	3.5%

LCIS Variants

Pleomorphic LCIS

Florid LCIS with necrosis



Often associated with microcalcifications

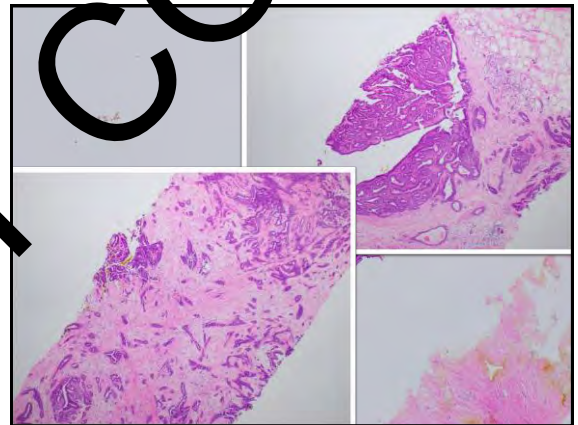
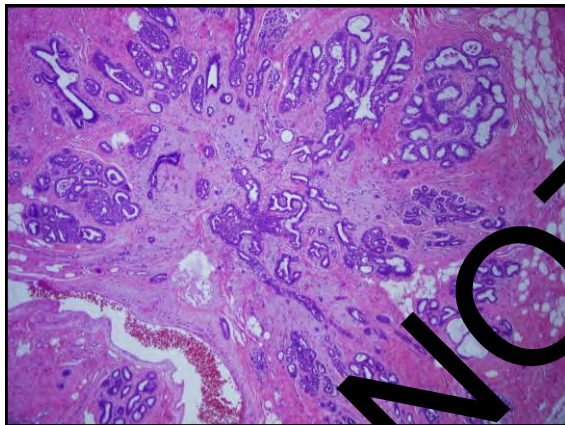
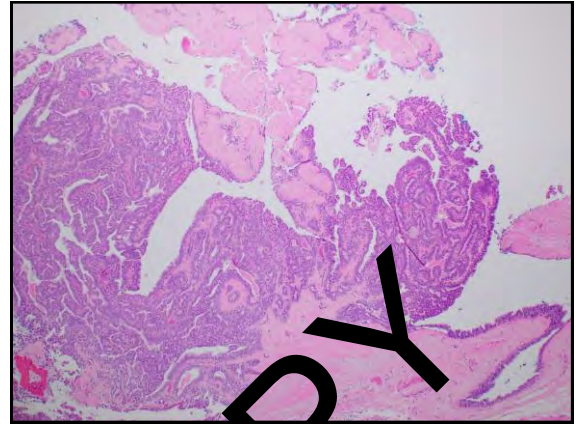
Although clinical significance is unclear, excision is warranted

My Perspective

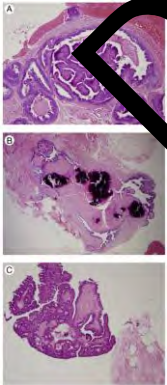
- Path-rads concordance is key with ALH and classic LCIS
- Upgrade rate is 3-4% so clinical and imaging follow-up is acceptable
- The above statements apply to classic LCIS only; LCIS variants should be excised

Papillomas & Radial Scars

- NCCN
 - Papillomas without atypia and “adequately sampled or incidental radial scars” may be “suitable for monitoring in lieu of surgical excision”
 - Also listed as lesions that may “require additional tissue”
- Complex sclerosing lesion (CSL)
- Mass forming vs. incidental



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“Incidental” Papilloma & RS

Microscopic and contained within a core

- Microscopic with calcifications
- Non-mass associated but fragmented

Weisman et al. *Human Pathology*; 2014 (45); 583-88

Concordant, non-atypical breast papillomas do not require surgical excision: A 10-year multi-institution study and review of the literature

Lats J. Grimm^{1,2}, Christine E. Bookhout³, Rex C. Bentley⁴, Sheryl G. Jordan⁵, Thomas J. Lawton⁶

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³ Department of Pathology, Duke University, DUMC Box 3722, Durham, NC 27710, USA
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⁵ Department of Pathology and Laboratory Medicine, University of California Los Angeles, 10833 Le Conte Ave, Los Angeles, CA 90095, USA

Table 1
Literature review of reported papilloma upgrade rates

Study	Upgrade rate (%)	Study	Upgrade rate (%)	Study	Upgrade rate (%)
Edin (2002)	0-8 (0)	Toak (2012)	0-83 (0)	Bentz (2007)	2-81 (4.9)
Liberatos (1996)	0-7 (0)	Avon (2007)	0-87 (0)	Pu (2012)	12-200 (3.6)
Liberatos (2006)	0-14 (0)	Swamy (2013)	0-77 (0)	Shankara (2013)	3-31 (5.6)
Pulgarin (2009)	0-15 (0)	Mosler (2013)	0-86 (0)	Laursen (2014)	1-17 (5.9)
Agarwal (2007)	0-16 (0)	Armen (2008)	0-120 (0)	Lindo (2012)	4-16 (6.3)
Lee (2012)	0-17 (0)	Chang (2010) ^a	1-109 (1)	Jaffe (2009)	3-104 (6.7)
Carli (2005)	0-17 (0)	Solis (2007)	1-174 (1.1)	Gilani (2012)	2-29 (6.9)
Hendawee (2004)	0-18 (0)	Altmanshah (2008) ^a	3-86 (1.2)	Heller (2012)	1-34 (2.1)
Schmittshals (2008)	0-17 (0)	Mosier (2014)	2-126 (1.2)	Sakr (2008)	4-48 (8.3)
Reiss (2002)	0-27 (0)	Wynn (2014)	2-126 (1.2)	Ali (2008)	6-68 (8.8)
Ruan (2004)	0-20 (0)	McGinn (2019)	1-45 (2.2)	Ruan (2012)	21-254 (9.2)
Strommen (2014)	0-27 (0)	Wynn (2014)	0-173 (3.3)	Shin (2006)	10-103 (9.7)
Jaffe (2013)	0-28 (0)	Berman (2012)	1-42 (2.4)	Shawler (2012)	6-59 (10.2)
Solbi (2013)	0-29 (0)	Silber (2007)	3-78 (2.6)	Reiss (2008)	9-64 (15.2)
Caputo (2008)	0-43 (0)	Kim (2015)	0-320 (2.6)	Baranovsky (2011)	5-47 (10.6)
Lee (2007)	0-43 (0)	Jalilian (2014)	2-75 (2.7)	Lee (2006)	1-7 (14.3)
Mercado (2006)	0-43 (0)	Tamargo (2014)	0-114 (3.3)	Almoud (2002)	1-6 (16.7)
Makani (2013)	0-45 (0)	Nayak (2013)	3-80 (3.8)	Skandjajaj (2008)	13-90 (14.8)
Chang (2011)	0-49 (0)	Cox (2011)	0-93 (4.1)	Tang (2005)	7-24 (29.2)
Yildiz (2013)	0-60 (0)	Gore (2014)	7-146 (4.8)	Shino (2015)	4-12 (33.3)

^a Studies met eligibility criteria as outlined in the table.

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Table 1 Literature review of reported papilloma upgrade rates

Study	Upgrade rate (%)	Study	Upgrade rate (%)	Study	Upgrade rate (%)
Ellis (2002)	0.0 (0)	Yoon (2012)	0.0 (0)	Banik (2009)	2.43 (4.9)
Uthman (1999)	0.0 (0)	Arora (2007)	0.0 (0)	Dra (2012)	12.20 (5.5)
Uthman (2006)	0.14 (0)	Wong (2013)	0.77 (0)	Ramakrish (2015)	3.51 (3.9)
Philpotts (2005)	0.13 (0)	Muster (2013)	0.00 (0)	Lorenson (2014)	1.72 (5.9)
Agar (2014)	0.14 (0)	Raman (2010)	0.120 (0)	Linda (2012)	4.94 (6.3)
Lee (2012)	0.17 (0)	Cheng (2014)	1.109 (1)	Jaffe (2006)	3.04 (6.7)
Carlier (2005)	0.17 (0)	Sohn (2007)	1.174 (1.1)	Ghani (2013)	3.29 (6.8)
Randall (1994)	0.18 (0)	Alimohamed (2009)	1.161 (1.0)	Holbe (2012)	1.74 (7.1)
Schmittner (2008)	0.19 (0)	Moore (2014)	3.296 (3.2)	Isikr (2006)	4.44 (5.3)
Raman (2002)	0.27 (0)	Wynn (2013)	2.156 (2.3)	Jil (2008)	0.99 (4.8)
Ryan (2004)	0.29 (0)	Mohar (2013)	1.85 (2.2)	Hiro (2012)	37.258 (9.8)
Wernms (2014)	0.37 (0)	Paras (2014)	6.173 (2.3)	Shin (2006)	16.103 (8.7)
Jaffe (2013)	0.58 (0)	Reisman (2013)	1.462 (2.0)	Shouval (2002)	6.509 (10.2)
Shin (2013)	0.59 (0)	Spencer (2007)	1.38 (2.6)	Rizzo (2008)	0.99 (10.2)
Dighe (2008)	0.61 (0)	Yoon (2014)	6.239 (5.6)	Rosenkrantz (2011)	3.47 (10.8)
Go (2007)	0.63 (0)	Talasila (2016)	2.79 (2.7)	Levi (2009)	1.7 (14.8)
Marandi (2006)	0.64 (0)	Tamaguchi (2014)	4.114 (3.1)	Marandi (2006)	1.6 (16.7)
Nahata (2013)	0.65 (0)	Nayak (2013)	3.90 (3.8)	Shankaraj (2008)	13.90 (13.8)
Chang (2011)	0.69 (0)	Cy (2011)	0.93 (4.1)	Tanig (2005)	7.24 (29.2)
Khal (2013)	0.69 (0)	Zhou (2014)	7.566 (4.8)	Shoun (2015)	4.12 (13.8)

* Studies met eligibility criteria as outlined in the table.

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- Their own cohort included 388 papillomas
- 35% were excised with no cancers found
- No cancers were diagnosed in the group that was followed by imaging
- Overall upgrade rate from lit review ~4%
 - Down to 1.8% when studies with confounders are excluded
 - Down to 0.6% with the addition of their data

Radial Scar at Image-guided Needle Biopsy Is Excision Necessary?

Niamh Conlon, MB, FRCPath,* Clare D'Arcy, MB, FRC Path,* Jennifer B. Kaplan, MD,†
Zenica L. Bowser, MS,* Anibal Cordero, BS,* Edi Brogi, MD, PhD,* and Adriana D. Corben, MD*

TABLE 3. Meta-analysis of Multigiant Upgrade Rate of NCB-confirmed RS at Surgical Excision

Study	Needle Gauge (G)	No. Cases	Total Cases (N)	Upgrade Rate Atypia on CNB (%)	Carcinoma Type in Upgraded Cases	Upgrade Rate of CNB RS With Atypia	Carcinoma Type in Upgraded Cases	Overall Upgrade Rate of RS on CNB (%)
Jackman et al ¹	14	30	5	2.5 (40)	1 DCIS, 1 IDC	NA	NA	2.5 (40)
Kirwan et al ²	14	8.5	34	0.34 (0)	NIL	NA	NA	0.34 (0)
Philpotts et al ³	14, 11	9	8	0.7 (0)	NIL	0.1 (0)	NIL	0.8 (0)
Bremner et al ⁴	14, 12	NS	103	5.74 (7)	3 DCIS, 1 IDC	8/29 (28)	3 DCIS, 3 IDC	13.10 (13)
Brodie et al ⁵	14	4	16	2.16 (13)	2 DCIS	NA	NA	2.16 (13)
Cawson et al ⁶	14	6	54	6.27 (0)	NIL	3/27 (11)	3 DCIS	6.27 (0)
Lee et al ⁷	NS	NS	32	1.23 (4)	1 DCIS	4/9 (44)	3 DCIS, 1 IDC	1.23 (4)
Dillon et al ⁸	16, 14	NS	63	2.41 (5)	2 DCIS	7/22 (32)	6 DCIS, 1 IDC	2.41 (5)
Lopez-Molina et al ⁹	14	6.4	43	6.38 (16)	1 DCIS, 3 TC, 1 IDC	2/7 (40)	1 DCIS, 3 TC	8.43 (19)
Leske et al ¹⁰	14	5	43	4.41 (9)	NS	NA	NS	4.41 (9)
Hayes et al ¹¹	NS	NS	57	4.42 (0)	4 DCIS	3/15 (20)	3 DCIS	7.97 (12)
El-Sayed et al ¹²	NS	NS	153	12.132 (9)	6 DCIS, 6 IC	5/21 (24)	1 DCIS	17.153 (11)
Rosenkranz et al ¹³	11, 9	39	19	8.01 (0)	NS	0/9 (0)	NS	8.01 (0)
Rajan et al ¹⁴	14	6	25	1.22 (5)	1 DCIS	0/10 (0)	NIL	1.22 (5)
Linda et al ¹⁵	14, 11	7	65	5.62 (6)	3 DCIS, 1 IDC, 1 IC	6/10 (6)	NS	8.65 (9)
Rakha et al ¹⁶	NS	NS	329	25.278 (9)	14 DCIS, 5 TC, 2 IC, 4 IC	20/31 (39)	9 DCIS, 8 IC	33.929 (13.7)
Rakha et al ¹⁷	NS	NS	42	1.39 (3)	1 IDC	0/3 (0)	NA	1.39 (3)
Bruncho et al ¹⁸	14	4	49	4.49 (8)	3 DCIS, 1 IC	NA	NA	4.49 (8)
Andreopoulos et al ¹⁹	11, 9	67	497	8.07 (6)	4 DCIS	8/8 (8)	NA	8.07 (6)
This study	11, 9	8	48	1.48 (2)	1 DCIS	NA	NA	1.48 (2)
Total	7	1255	29107 (7.5)	46 DCIS, 1 IDC, 3 TC, 4 IC, 10 IC, 4 NS	34 DCIS, 3 TC, 2 IC, 12 IC, 1 NS	11/25 (44)	NS	11.255 (10.4)

Radial Scar at Image-guided Needle Biopsy Is Excision Necessary?

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Rakha et al ¹⁶	NS	NS	329	25.278 (9)	14 DCIS, 5 TC, 2 IC, 4 IC	20/31 (39)	9 DCIS, 8 IC	33.929 (13.7)
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Total	7	1255	29107 (7.5)	46 DCIS, 1 IDC, 3 TC, 4 IC, 10 IC, 4 NS	34 DCIS, 3 TC, 2 IC, 12 IC, 1 NS	11/25 (44)	NS	11.255 (10.4)

Overall upgrade rate for RS without atypia 7.5% (with confounders)
Their data showed 2% upgrade rate

My Perspective

- These diagnoses encompass a range of lesions
 - If atypical and symptomatic, excision may be warranted
- The literature is plagued by confounding variables
 - When confounders are removed, the upgrade rate is very low (~2% for papillomas and RS)
- Small (<1 cm) or incidental papillomas, RS or CSLs can reasonably be followed

Conlon et al. AJP: 2015 (39): 779-785
 Neal et al. Mayo Clin Proc; 2014 (89): 536-47
 Grimm et al. Clinical Imaging; 2018 (51): 180-85

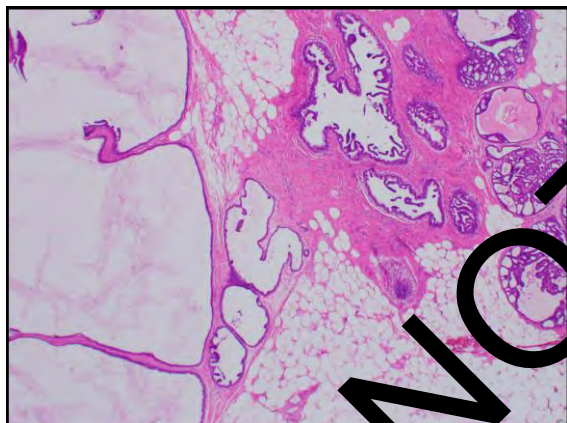
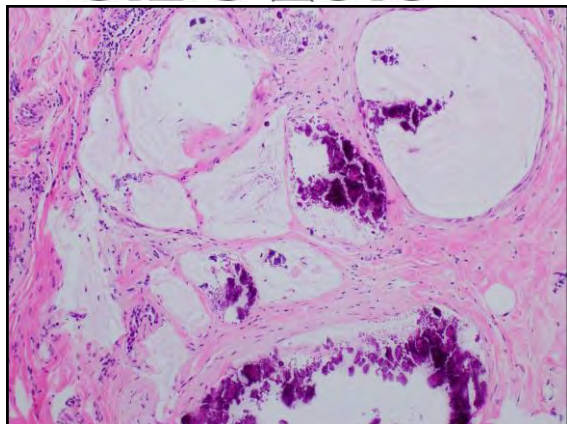
Mucocele-like lesions

- Range of imaging findings: mass forming, calcifications, or incidental
 - 70-80% associated with calcs
- NCCN “may require additional tissue”
- Arise in the setting of various pathologic processes



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Mucocyst-like lesions without atypia

Study	# of Upgrades	Upgrade Rate
Wentz (2011)	1/50	2%
Sutton (2012)	0/22	0
Rakha (2013)	2/54	3.7%
Ha (2015)	0/12	0
Park (2015)	0/21	0
Diorio (2016)	2/35	5.7%
Zhang (2018)	1/19	5.2%
Moseley (2019)	1/16	6.2%
Total	7/229	3%

My Perspective

- MLLs that are associated with atypia and/or a mass should likely be excised
- MLLs without atypia have an upgrade rate of about 3%

Harrison et al. Surg Path Clin; 2018 (11); 61-90

Take Home Points

- ADH can be found in isolation or in association with other high risk lesions and should be excised
- LCIS variants ≠ ALH/classic LCIS
- High risk lesions without atypia have a relatively low upgrade rate
 - ~2% for IDP, RS
 - ~3-4% for MLLs, classic LCIS/ALH
 - ~7% for FEA
- Imaging findings, concordance & clinical factors can help decide when excision is warranted



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