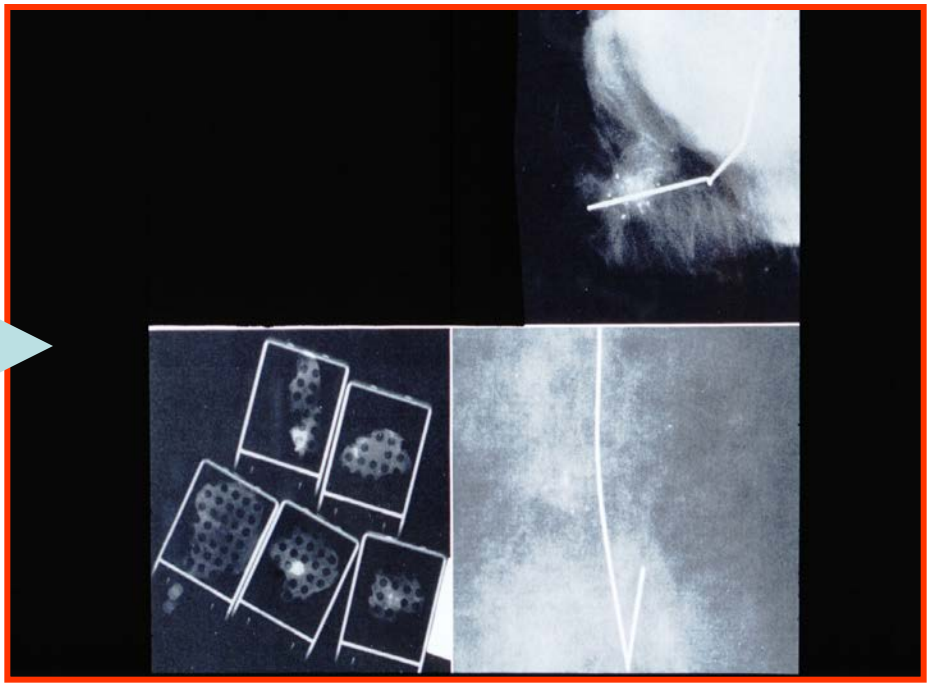
Atypical Lesions :
To Excise or Not To Excise?

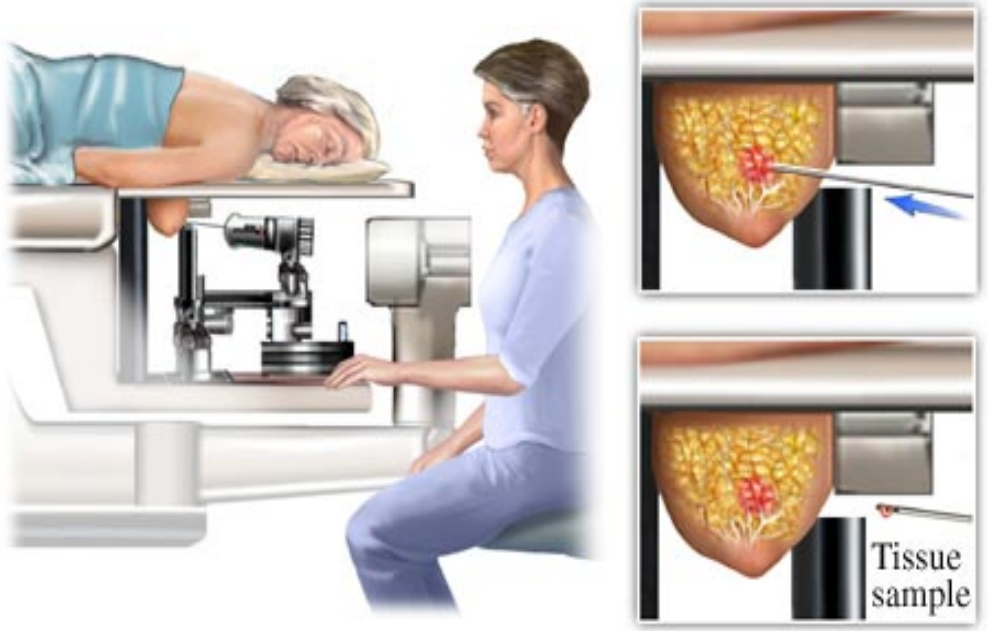
H. Evin Gulbahce MD

Needle Guided Biopsy



Excisional biopsy

Sterotactic Core Biopsy



Type	Used For	Needle	Anesthesia	Pros	Cons
Fine needle aspiration (FNA)	Cysts, masses	22 or 25 G	Local or none	Fast, no stitch, no scar	Small sample size, operator dependent
Core Needle	Solid mass, Ca++	10,11,14 G	Local	No stitch, no internal scar	Limited sample size
Vacuum Assisted (Mammotome)	Mass, Ca++	9, 11,14 G, 0.25 inch incision	Local	Excellent for Ca++, no stitches, min scar	Not good for hard to reach lesions
Large Core Surgical (ABBI)	Nonpalpable	5mm-20mm, size of wine cork	Local	Large tissue without sedation	Stitches, scar, may not have adequate margin
Open Surgical	Hard to reach	1,5-2 in incision, golf ball size	Heavy sedation or general anesthesia	Large tissue, accurate diagnosis	Permanent scar, stitches, longer recovery

BIRADS Breast Imaging Reporting and Data System

0: Incomplete
1: Negative
2: Benign finding(s)
3: Probably benign (≤2% risk of malignancy)
4: Suspicious abnormality
5: Highly suggestive of malignancy
6: Known biopsy – proven malignancy

Wire localization / excisional biopsy versus image guided / sterotactic core biopsy

Excisional Bx

- Surgical excision
- Done in OR, more $$
- 70% need second surgery

Core Bx

- Stab wound to insert needle
- Outpatient, local anesthesia, less $$
- 84% only one surgery
- No permanent effect in subsequent mammograms

Breast Needle Biopsy

- **Anything can turn up..**
- **What you see is what you have and it may not be all there is..**
- **What you have may be all there is..**

High Risk Lesions

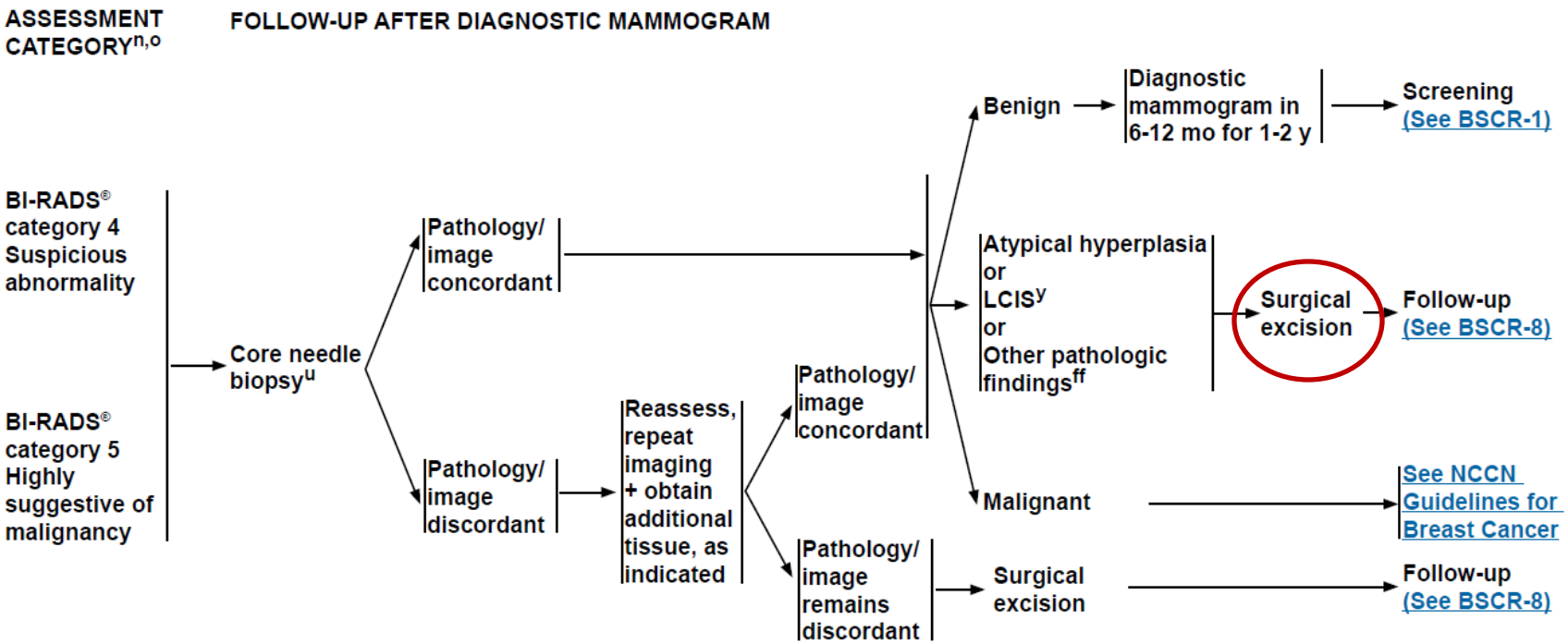
- Atypical Ductal Hyperplasia (ADH)
- Lobular Neoplasia (ALH + LCIS)
- Flat Epithelial Atypia (FEA)
- Radial Scar or Complex Sclerosing Lesions
- Papilloma

“Underestimation”
“Upgrade in excision”

Missing a lesion that would have otherwise required additional surgery

- **-Invasive cancers**
- **-DCIS**

NCCN



[y]Multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy may be associated with increased risk of invasive cancer on surgical excision.
[ff]Other histologies that may require additional tissue: mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar, or other histologies of concern to pathologist.

Predictors of Malignancy on Excision Depends on

- **As the technology to obtain image guided breast tissue changes, and the amount of breast tissue removed increases, the need for re-excision may be re-evaluated.**

- **Volume of breast tissue removed:**
  - **14 Gauge needle: 17 mg**
  - **14 Gauge vacuum-assisted device: 36 mg**
  - **11 Gauge vacuum-assisted device: 94 mg**

- **Complete removal**
  - **Related to biopsy type / needle size**

- **Underestimation for ADH**
  - **20-56% with 14G needle vs 0-38% vacuum assisted 11G or 14G**

Bauer, Breast J 2003
Liberman Rad Clin North Am, 2000

Studies Involving High Risk Lesions

- Retrospective, small numbers
- Coexistence of >1 high risk lesion
- Selection criteria for surgical excision unknown and / or not uniform
- Lack of follow up data from patients not referred to excision
- Variability in pathologic diagnosis of high risk lesions

Variation in Physician Recommendations for Surgery after Dx of High Risk Lesion

- Registrants to a Radiology Meeting given cases and responses were reported
- Information on radiologic findings , type/gauge of bx, number of bx cores, adequacy of sampling (e.g. adequate sampling of calcifications), pathologist Dx provided.
- Asked for recommendation

Georgian-Smith et al AJR 2012

Variation in Physician Recommendations for Surgery after Dx of High Risk Lesion

TABLE 2: Registrant Responses for Lobular Carcinoma In Situ (LCIS)

Response	2010 (86)	2011 (34)
Concordant; imaging follow-up	12 (14)	4 (12)
Concordant but because of LCIS; recommend surgery	57 (66)	19 (56)
Discordant because LCIS is incidental without imaging correlate; recommend surgery	17 (20)	11 (32)

Note—Data in parentheses are percentages.

Georgian-Smith et al AJR 2012

Variation in Physician Recommendations for Surgery after Dx of High Risk Lesion

They were updated in the literature asked what their management will be

Georgian-Smith et al AJR 2012

Variation in Physician Recommendations for Surgery after Dx of High Risk Lesion

They were updated in the literature asked what their management will be

TABLE 6: Summary of Options

Option	Respondent Answers (83)
Will not change	35 (42)
Definitely change	4 (5)
Will consider changing	16 (19)
Now completely confused	28 (34)

Note—Data in parentheses are percentages.

Georgian-Smith et al AJR 2012

Management Practice of Borderline Lesions on Needle Biopsy

Lesion	Routine excision, n (%)	Selective excision, n (%)	No further excision, n (%)
ADH	405 (85)	63 (13)	NA
Lobular neoplasia	270 (57)	144 (30)	52 (11)
Radial scar	273 (57)	192 (40)	NA
Papillary lesion	235 (49)	216 (45)	21 (4)
Flat epithelial atypia	274 (57)	148 (31)	47 (10)

NA = not applicable.

Nizri et al Am J Surgery 2012

Management Practice of Borderline Lesions (Margin)

Table 3 Management of ADH found on margin of specimen

Variable	No further surgery (n = 263), n (%)	Selective reexcision (n = 130), n (%)	Routine reexcision (n = 22), n (%)	*P*
Participation in tumor board				
Weekly	150 (68)	62 (28)	6 (3)	.006*
Biweekly	63 (65)	30 (31)	4 (4)	
Monthly	35 (48)	28 (38)	9 (12)	
None	15 (54)	10 (36)	3 (11)	
Fellowship training				
Surgical oncology	40 (68)	18 (31)	1 (2)	.03†
Breast	151 (60)	80 (32)	17 (7)	
Other	58 (73)	20 (25)	1 (1)	
None	14 (48)	12 (41)	3 (10)	
Annual volume of new breast patients				
<25	16 (38)	20 (48)	5 (12)	<.0001*
25–50	47 (48)	43 (44)	7 (7)	
51–100	67 (61)	37 (34)	5 (5)	
>100	133 (79)	30 (18)	5 (3)	
Percentage of practice dedicated to breast surgery				
<15%	8 (50)	6 (38)	1 (6)	<.001*
15%–50%	45 (46)	44 (45)	9 (9)	
>50%	210 (26)	80 (69)	12 (4)	
Type of practice				
Cancer center	32 (80)	8 (20)	0 (0)	.0009†
Private	124 (54)	92 (40)	12 (5)	
Academic	54 (72)	17 (23)	4 (5)	
Dedicated breast center	53 (72)	13 (18)	6 (8)	

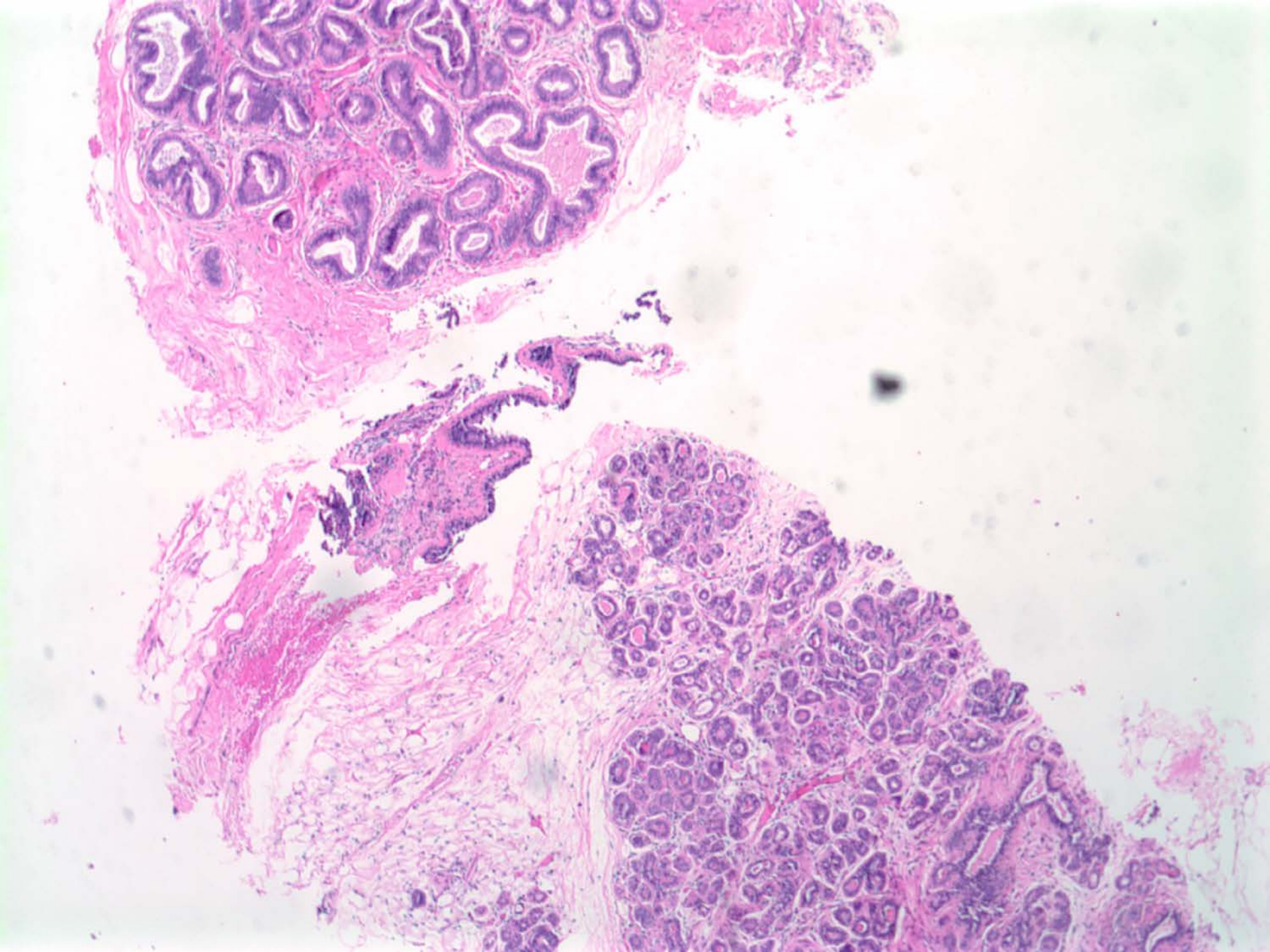
Nizri et al Am J Surgery 2012

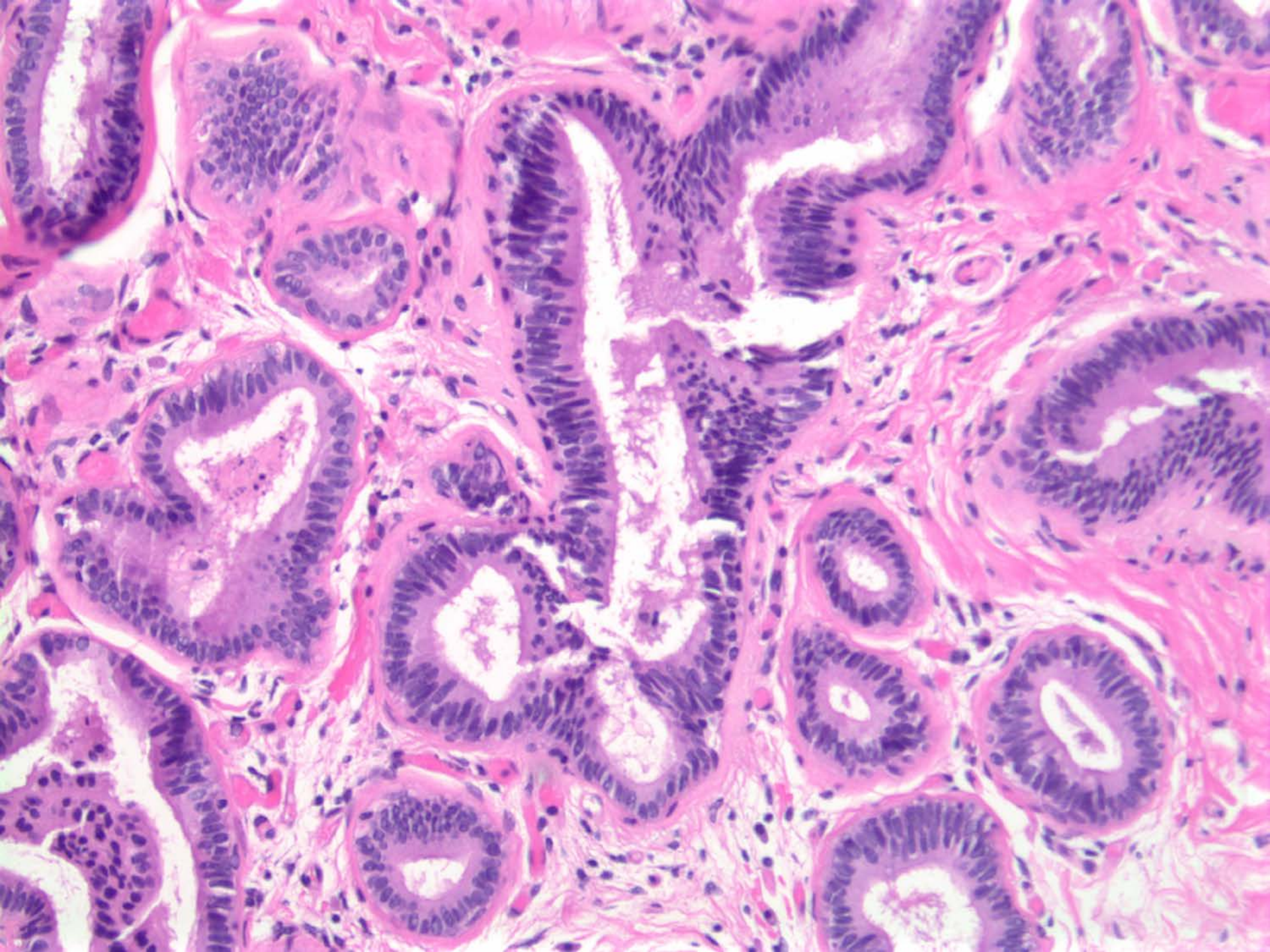
Management Practice of Borderline Lesions (Margin)

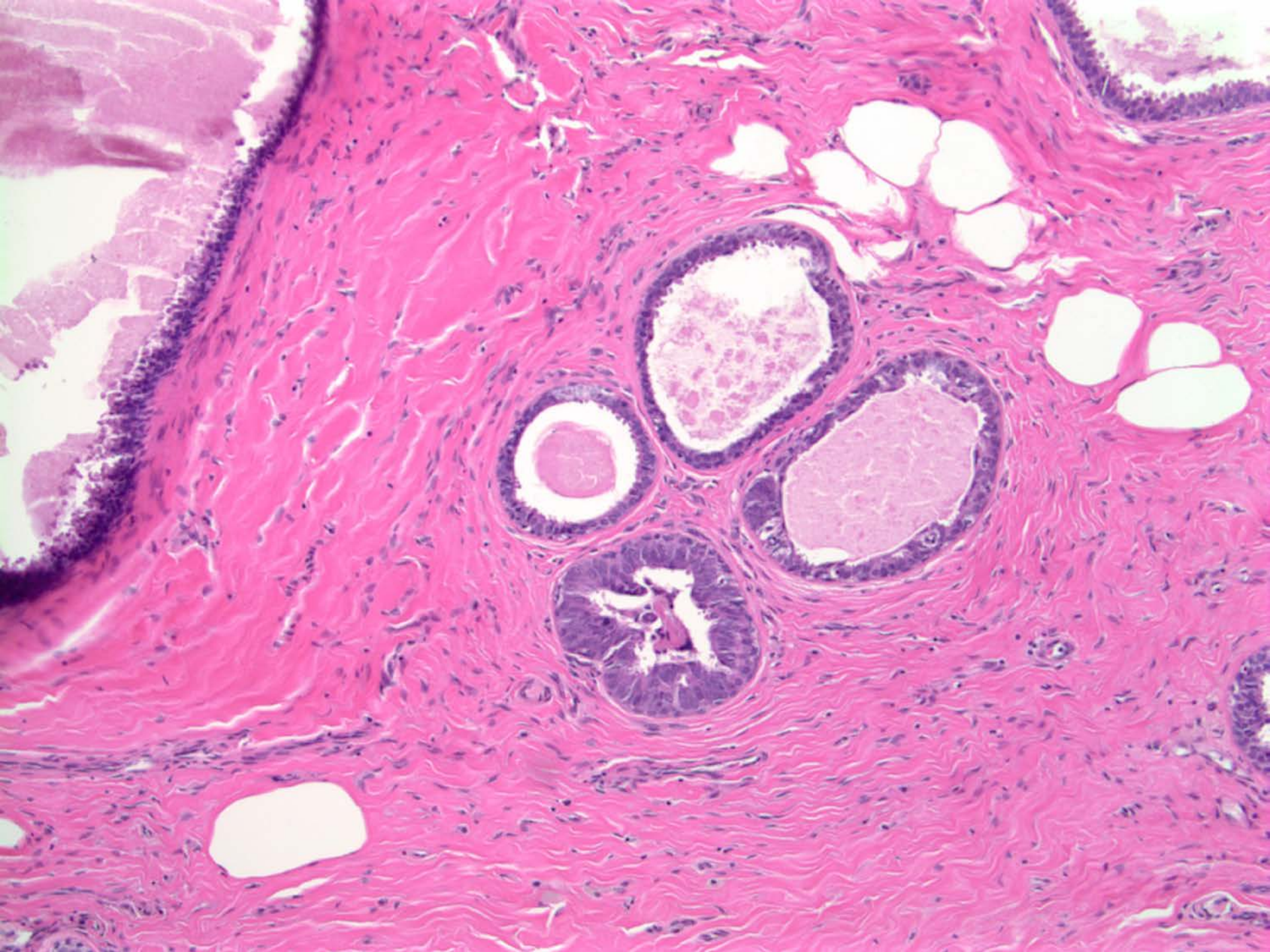
Table 4 Management of lobular neoplasia found at a margin of excisional specimen

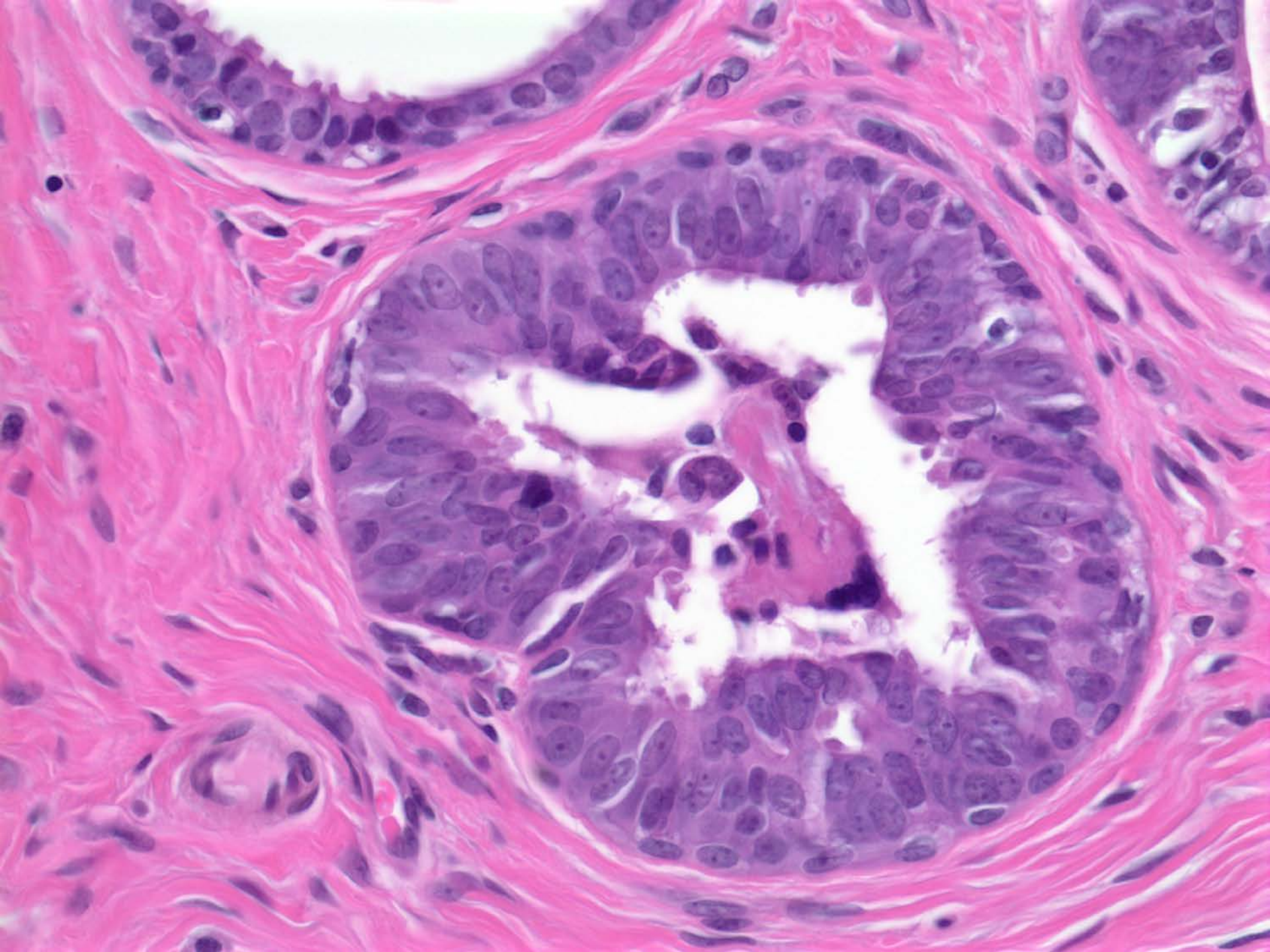
	No further surgery (n = 316), n (%)	Selective reexcision (n = 123), n (%)	Routine reexcision (n = 19), n (%)	*P*
Participation in tumor board				
Weekly	157 (72)	54 (25)	6 (3)	.02*
Biweekly	74 (76)	22 (23)	1 (1)	
Monthly	45 (62)	21 (29)	7 (10)	
None	15 (54)	10 (36)	3 (11)	
Fellowship training				
Surgical oncology	48 (81)	10 (17)	1 (2)	.008†
Breast	56 (71)	21 (27)	1 (1)	
Other	13 (45)	15 (52)	1 (3)	
None	174 (70)	61 (24)	14 (6)	
Annual volume of new breast patients				
<25	20 (48)	17 (40)	5 (12)	.002*
25–50	63 (65)	27 (28)	7 (7)	
51–100	80 (73)	29 (27)	0 (1)	
>100	128 (76)	34 (20)	5 (3)	
Percentage of practice dedicated to breast surgery				
<15%	9 (56)	4 (25)	3 (19)	.0001*
15%–50%	57 (58)	31 (32)	10 (10)	
>50%	225 (774)	72 (24)	4 (1)	

Nizri et al Am J Surgery 2012









Columnar Cell Lesions of the Breast and Flat Epithelial Atypia (FEA)

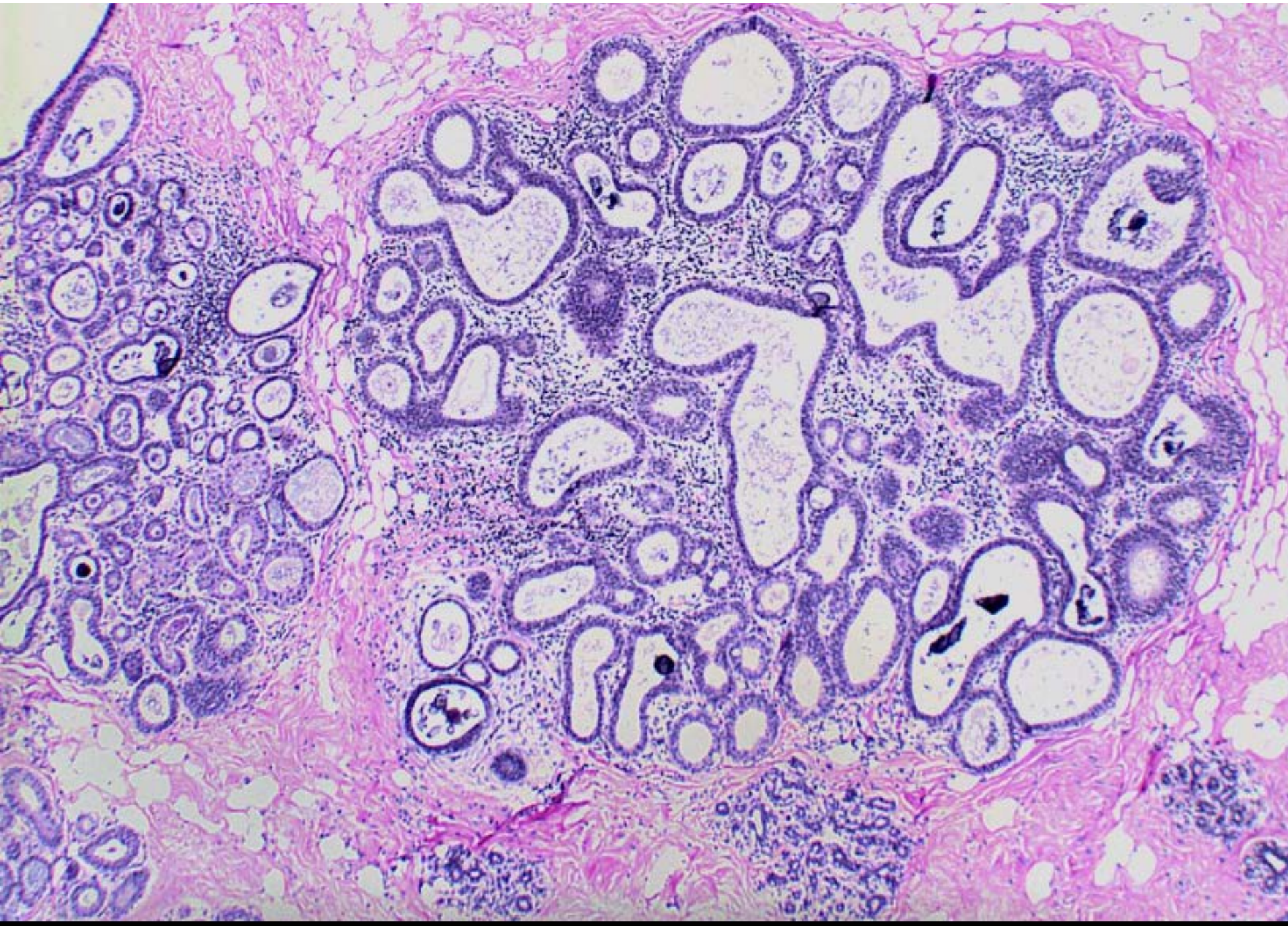
Currently Used Terminology for Columnar Cell Lesions of the Breast

- **Columnar Cell Change**
- **Columnar Cell Hyperplasia**
- **Columnar Cell Change with Atypia (Flat Epithelial Atypia)**
- **Columnar Cell Hyperplasia with Atypia (Flat Epithelial Atypia)**

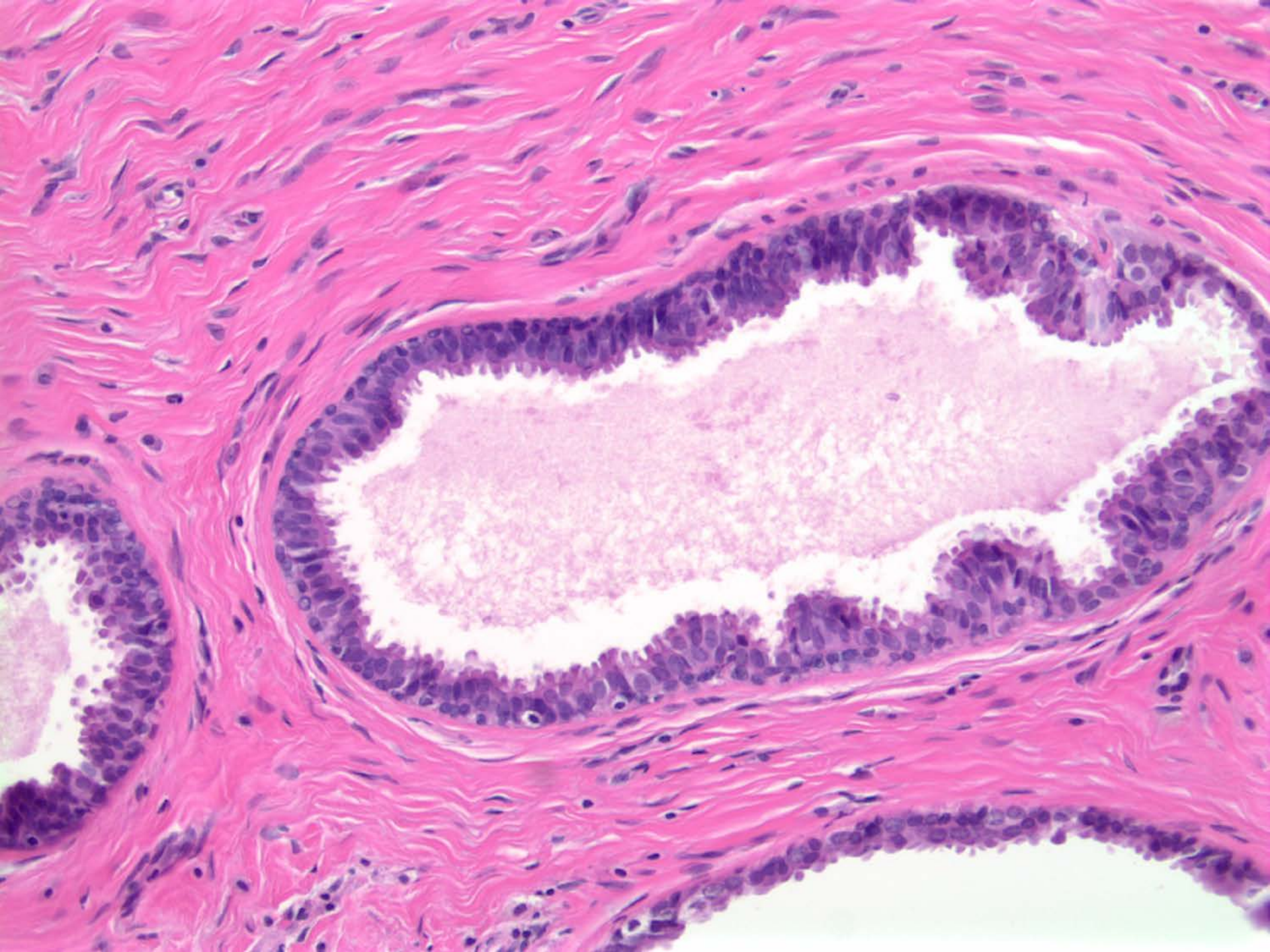
****Not uncommon to see a combination of these in a breast biopsy**

****These lesions also often coexist with areas that are diagnostic for ADH or DCIS and therefore, search for these significant findings should be conducted upon identification of columnar cell lesions.**

Schitt Adv Anat Pathol 2003
Turashvili Virchows 2008
Feeley Histopathology 2008



Schnitt et al

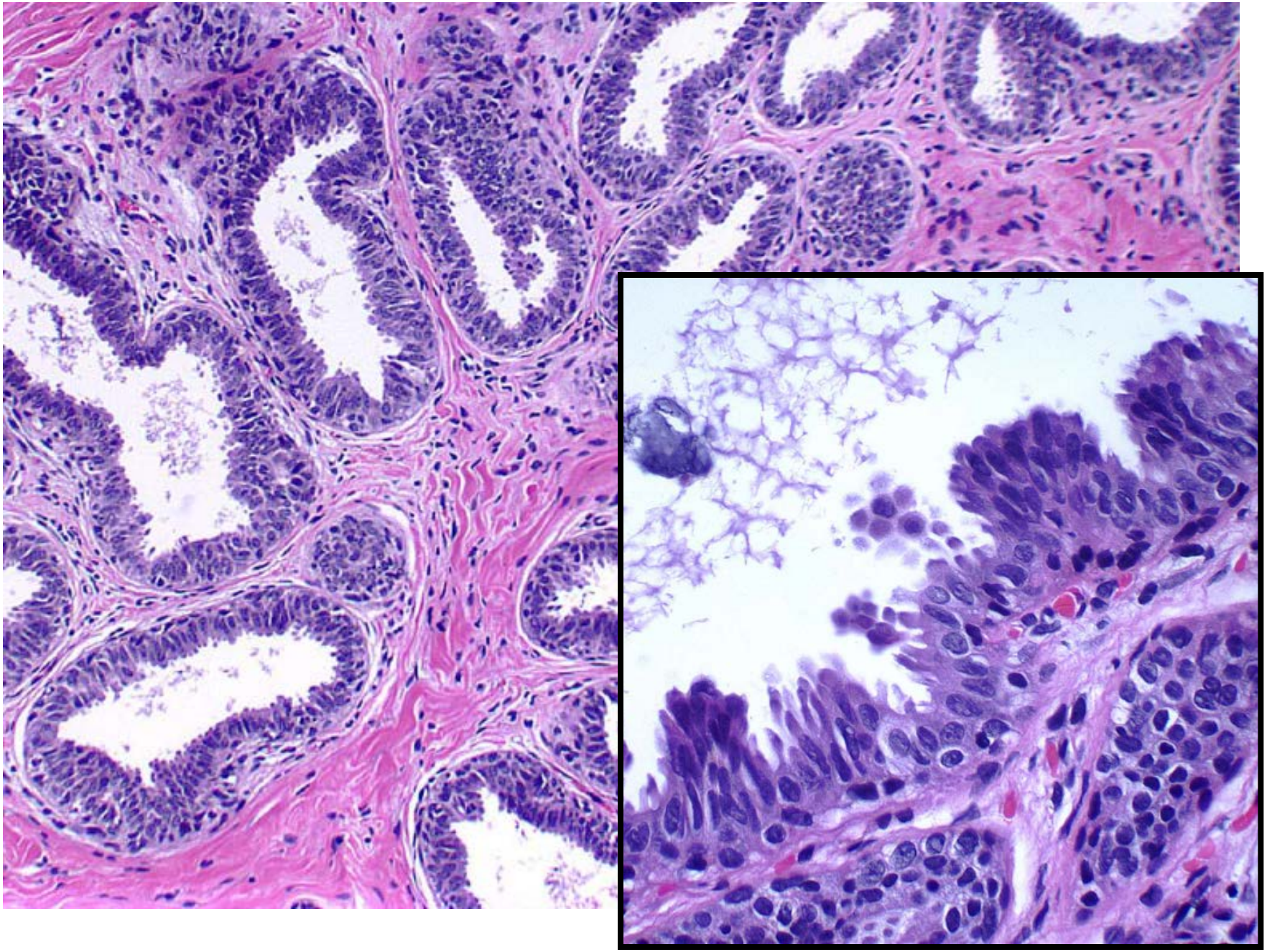


Columnar Cell Change

- **Terminal duct lobular units (TDLU) with dilated acini, usually with irregular contours.**
- **Lined by one or two layers of columnar epithelium with uniform, ovoid to elongated nuclei**
- **Apical cytoplasmic blebs often but not prominent at the luminal surface.**
- **Intraluminal secretions may be present in the lumina associated with luminal calcifications**

Columnar Cell Hyperplasia

- **TDLU with variably distended acini often with irregular contours.**
- **Cellular stratification more than two cell layers**
- **Apical snouts present, often exaggerated.**
- **Luminal secretions often present, associated with calcification which may be psammomatous.**
- **NO COMPLEX ARCHITECTURAL PATTERN**



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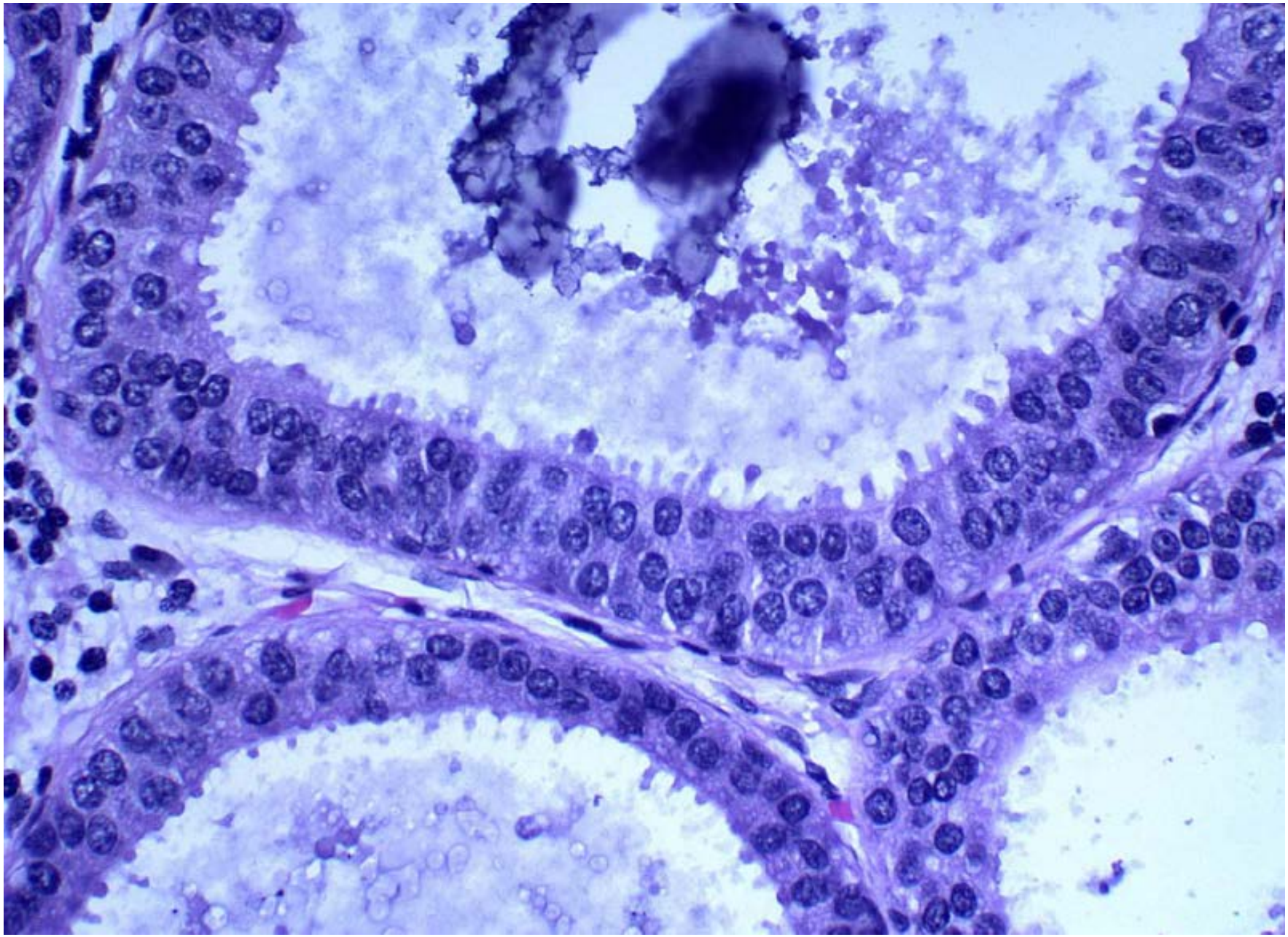


Schnitt et al

Flat Epithelial Atypia

- **Similar to architectural features of columnar cell change or columnar cell hyperplasia but with subtle cytologic atypia**
- **Round or ovoid (rather than elongated) nuclei that are not oriented perpendicular to the basement membrane with somewhat increased nuclear cytoplasmic ratio.**
- **Nucleoli may be variably prominent.**

Flat Epithelial Atypia
not allowed

Architecture

- **Complex architectural patterns**
  - **Well developed micropapillations**
  - **Bridges or sieve like fenestrations**
- **If present, these lesions should be characterized as ADH or DCIS depending on the severity and extent.**

Cytology

- **High grade cytologic atypia or nuclear pleomophism that is seen in high grade DCIS, even if only one cell layer thick**

Schnitt, Adv Anat Path 2003

Flat Epithelial Atypia

Differential Diagnosis

- ***Cytologic***
  - **Microcysts**
  - **Apocrine metaplasia**
  - **Columnar Cell Change / Hyperplasia**
- ***Architectural***
  - **ADH**
  - **Low grade DCIS**

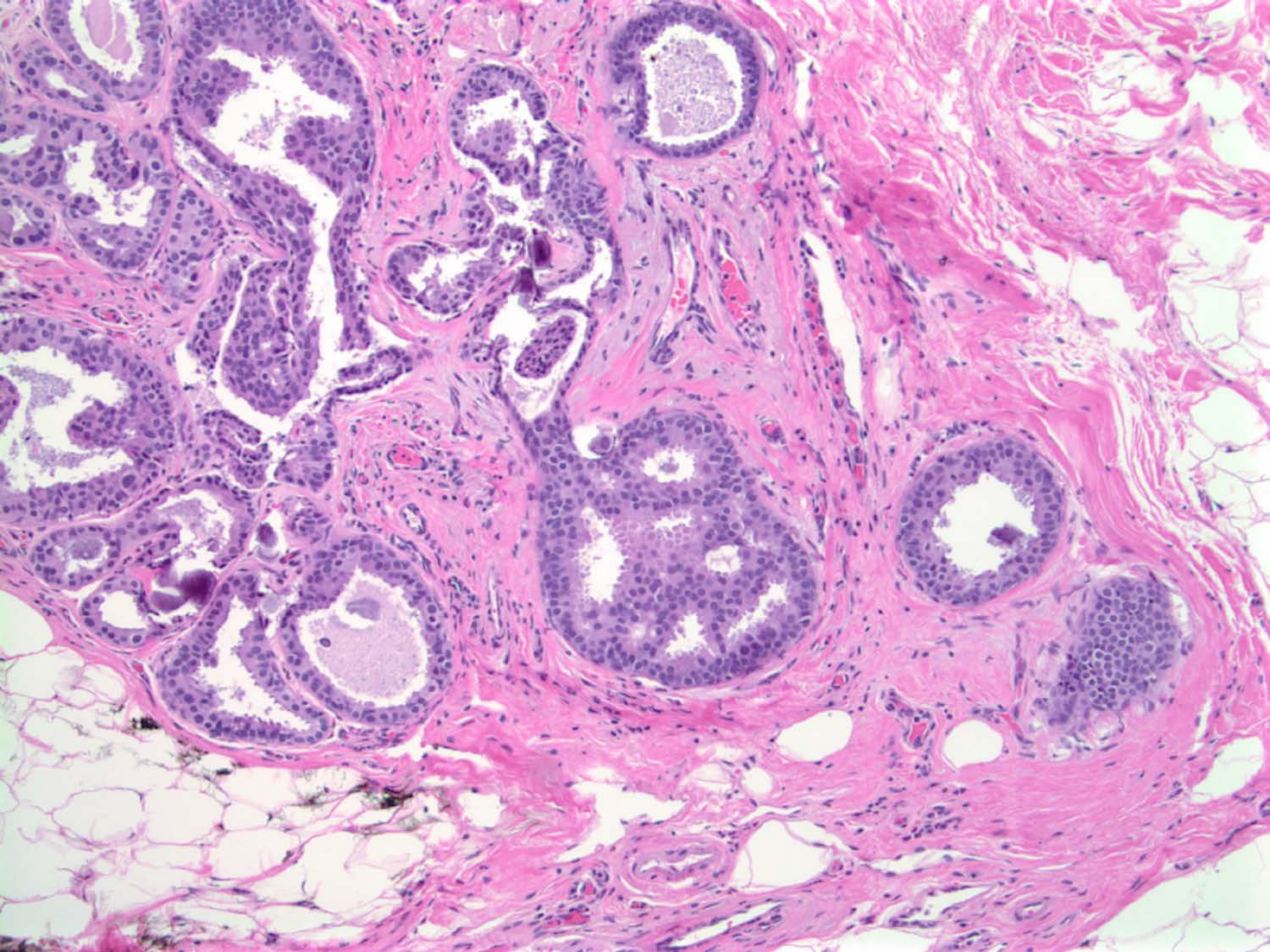
Need to go to High Power

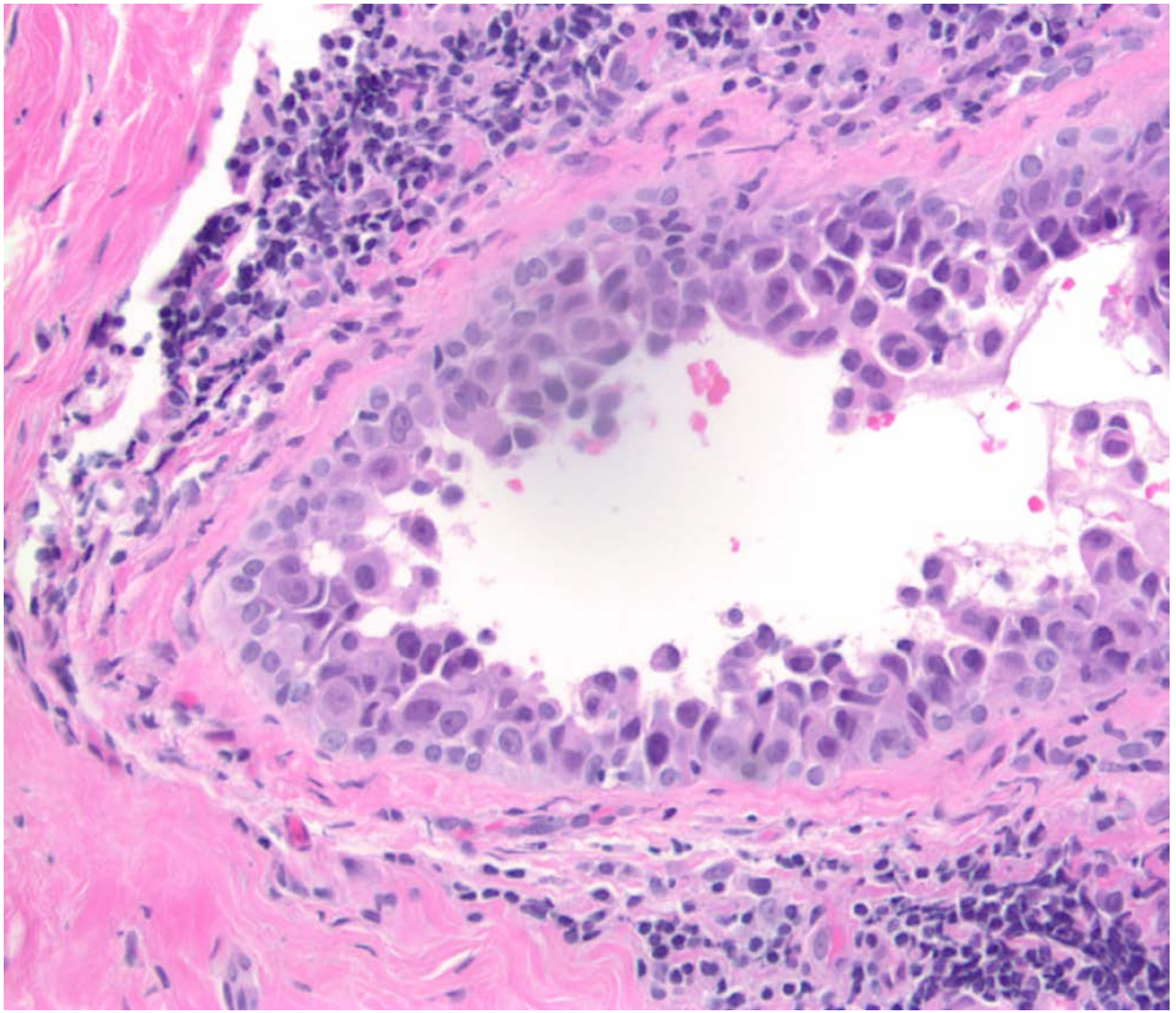
Low Power

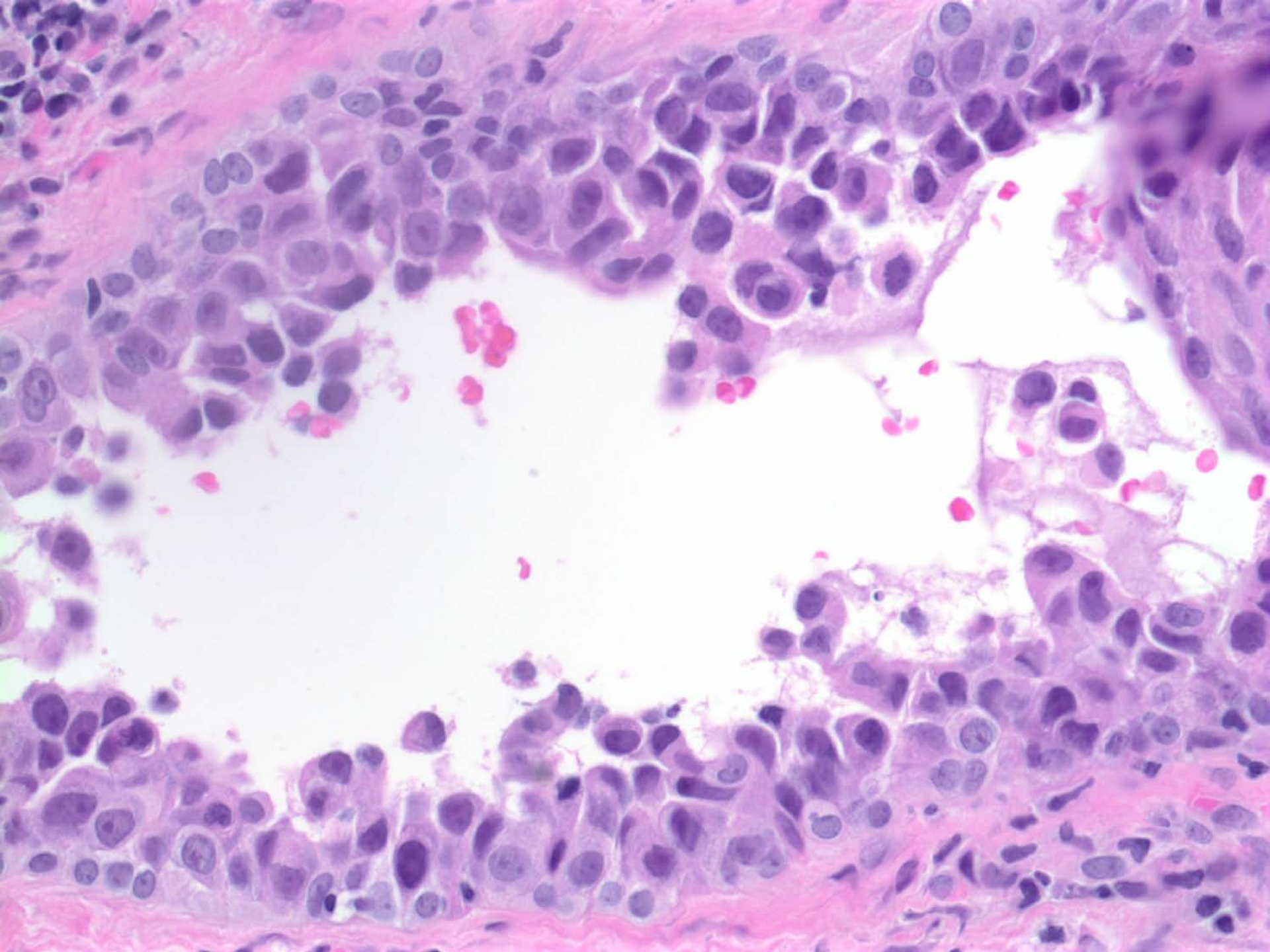
Schnitt, Adv Anat Path 2003

FEA vs ADH or DCIS

	FEA	ADH / DCIS
Low-grade cytologic atypia	+	+
Complex architectural patterns	NO	+
High-grade atypia	NO	-/+







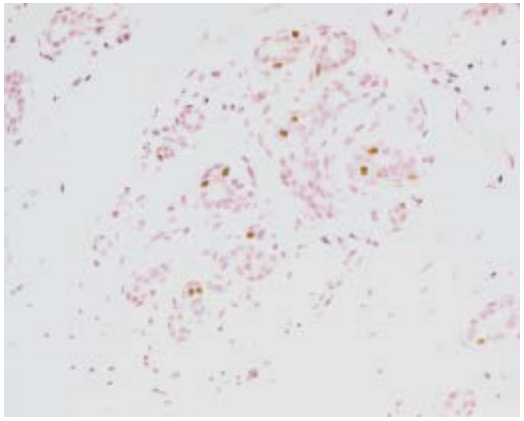
Biologic Markers of Columnar Cell Lesions of the Breast

- **Intense ER and PR positivity**
- **Rare mitosis and Ki-67 positivity, even in those with atypia**

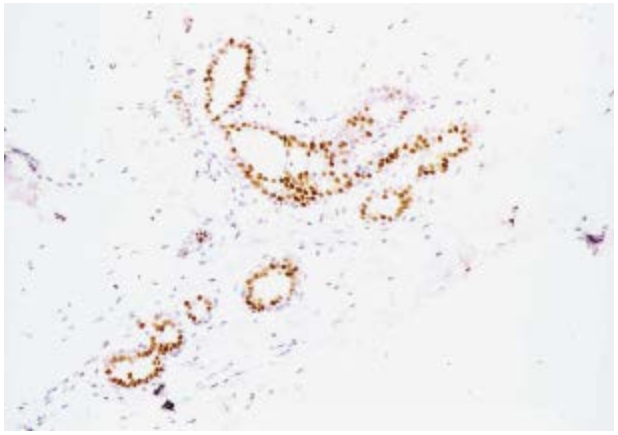
Tremblay , Breast Journal 2005
Oyama, Virchows 1999
Schnitt, Breast Cancer Research 2003

Simpson, AJSP 2005
Dessauvagie Human Path 2007
Aguilar Virchows 2005
Noel Virchows 2006

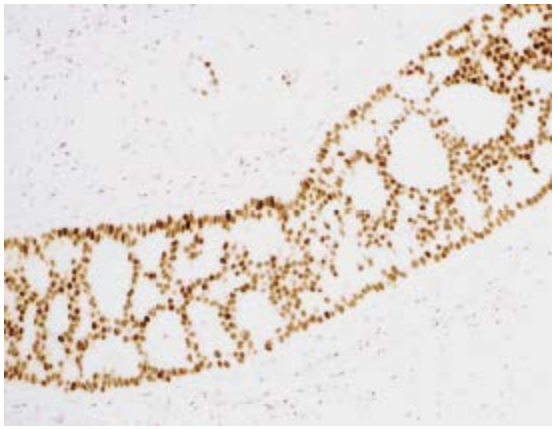
ER



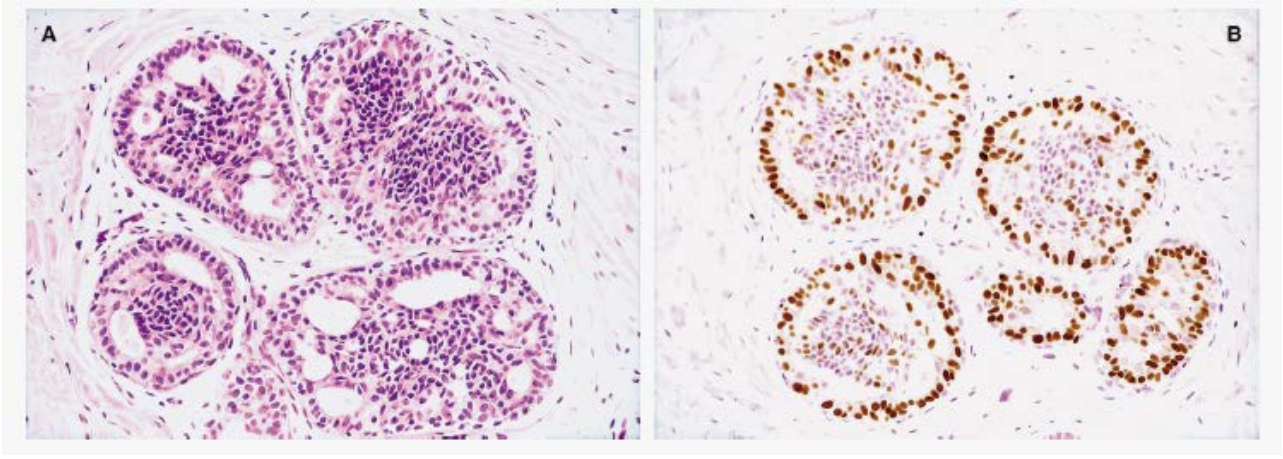
Premenopausal



Postmenopausal

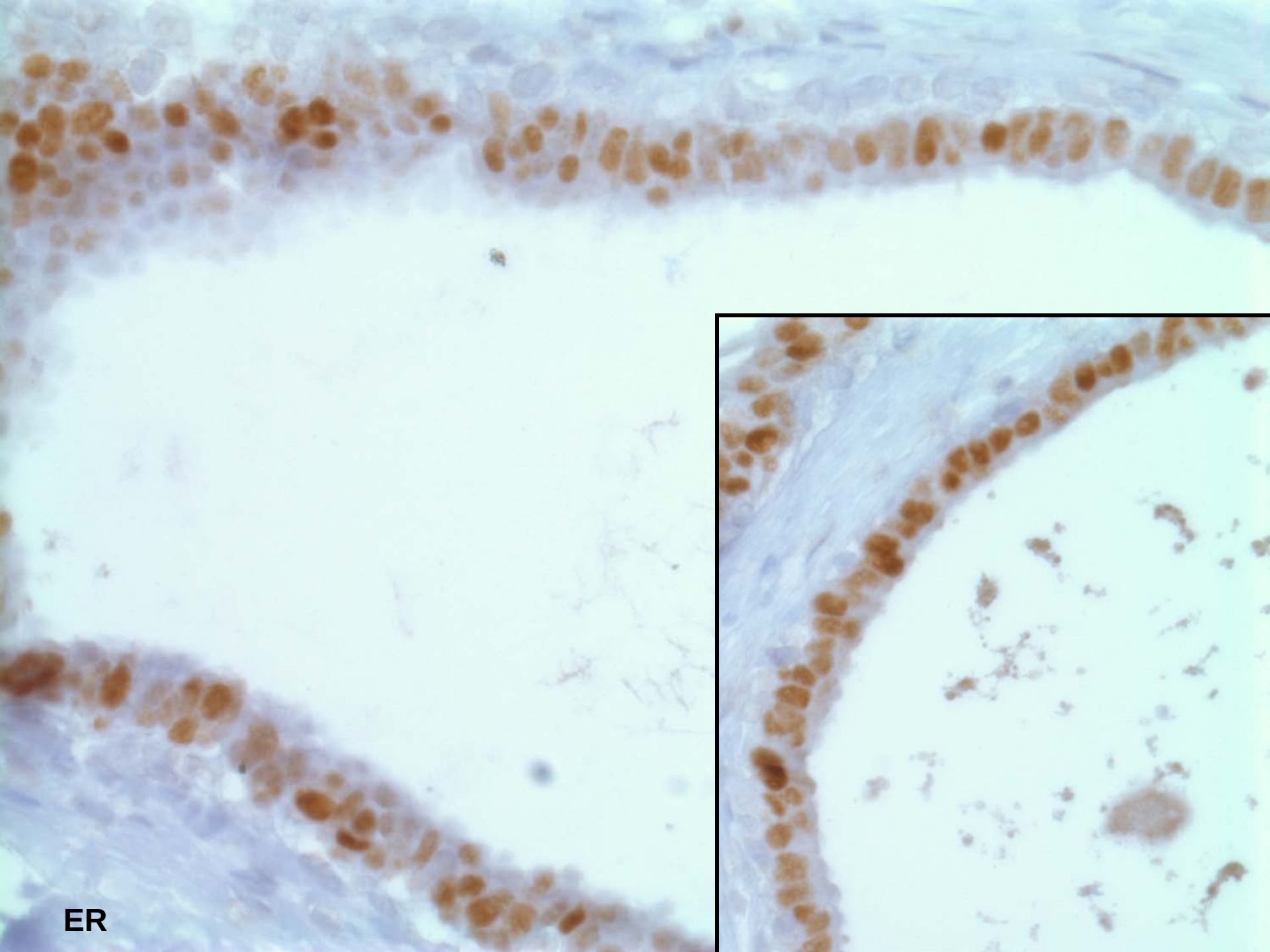


Low Grade DCIS



Usual Hyperplasia

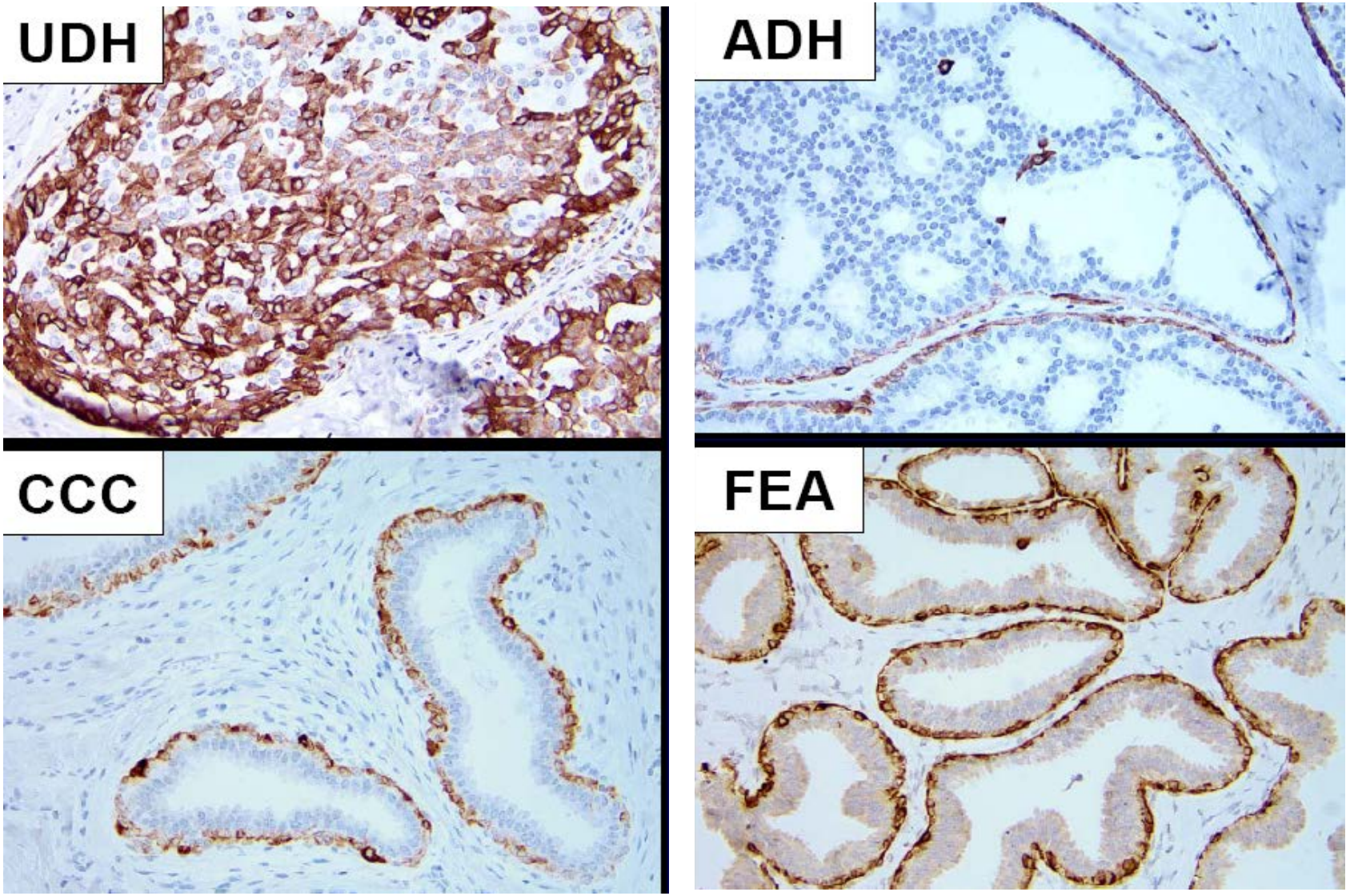
Also: normal breast in BrCa have higher ER


ER

Flat Epithelial Atypia

Separation of atypical columnar cell lesions (FEA) from non-atypical columnar cell lesions is important in immediate management decisions (ie excision or no excision after core needle biopsy)

CK 5/6



Not a good marker to differentiate CCC/CCH vs FEA

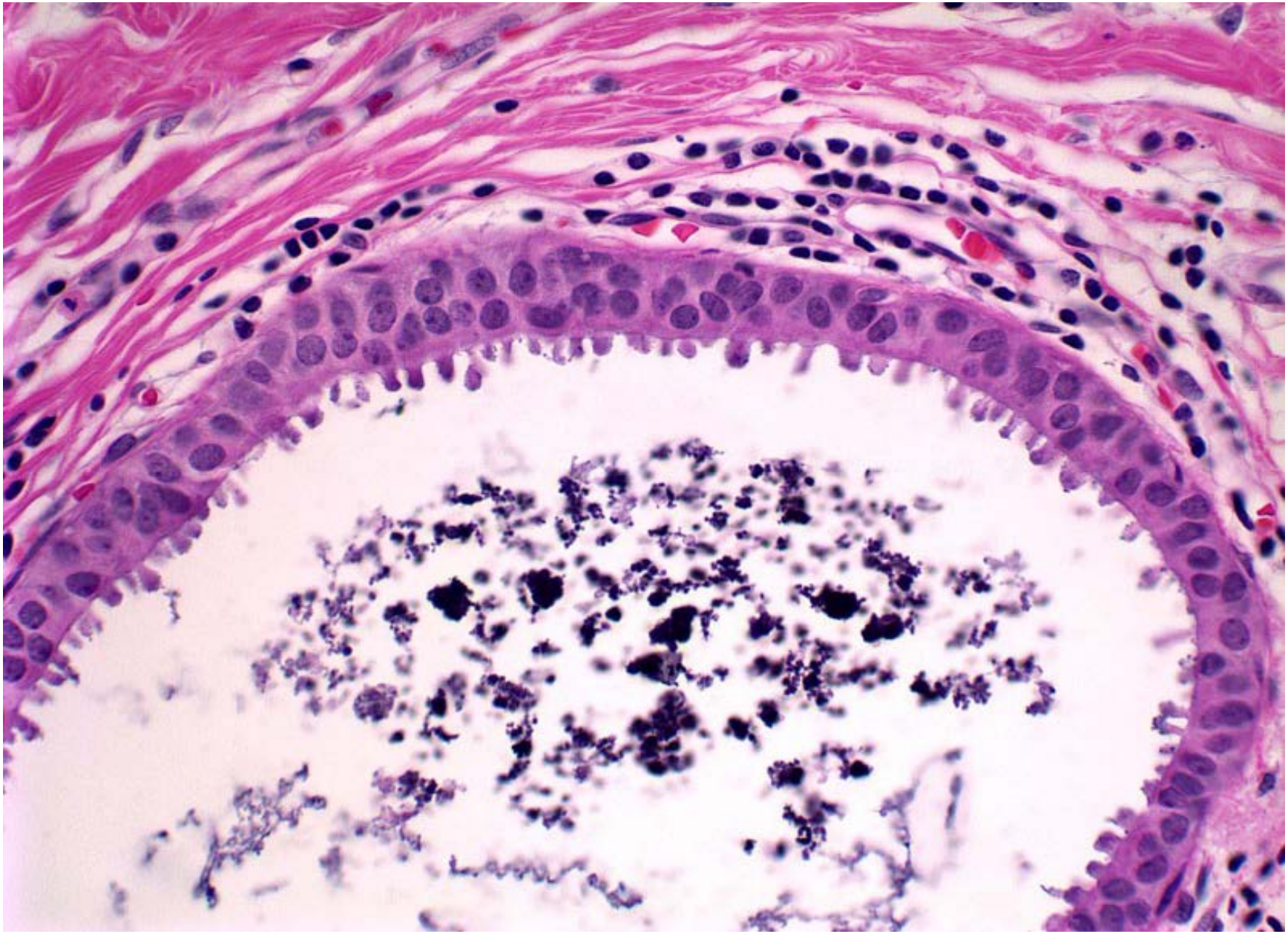
Schnitt et al

Interobserver agreement in diagnosis of FEA

- **Seven pathologist →power point tutorial**
- **Images of 30 columnar cell lesions : FEA / No atypia**
- **Multi-rater kappa value: 0.83**
- **However**
  - **All with interest in breast pathology**
  - **Images rather than real slides used**

**** Correct diagnosis / agreement on "Atypia" is important since it may make the difference between excision and no excision**

O'Malley, Mod Path 2006



Clinical Significance

More frequently seen nowadays because of mammographic screening (Ca^{++}).

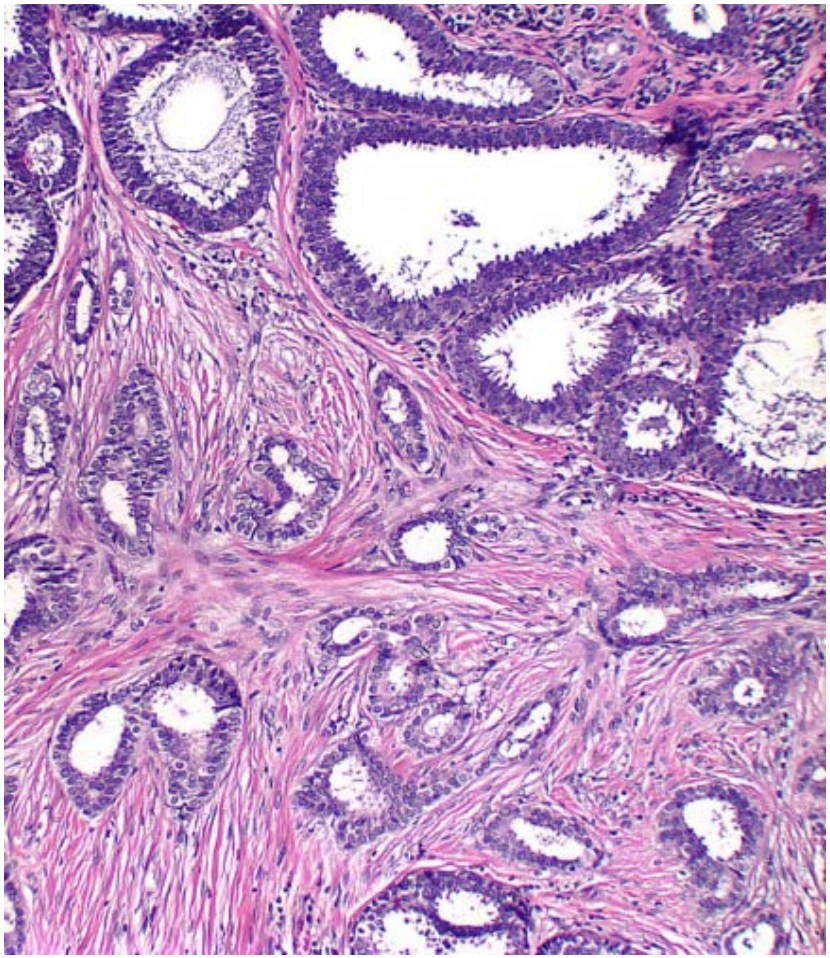
Fraser, AJSP 1998

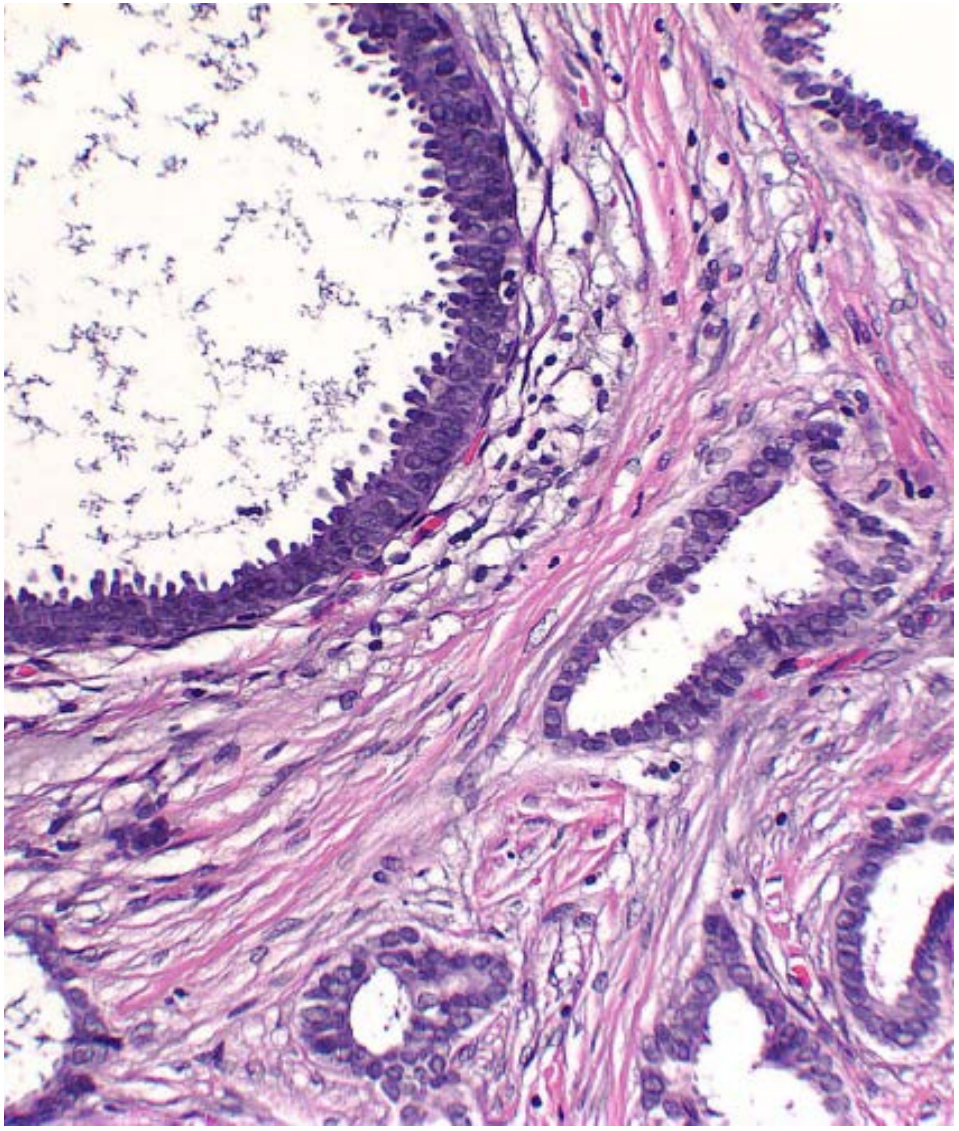
Clinical Significance

Often seen in association with

- **Tubular carcinoma**
- **ADH**
- **DCIS**
- **Lobular neoplasia (ALH/LCIS).**

Liebl, Histopathology 2007
Abdel-Fatah, AJSP 2007
Bratthauer, Virchows 2004
Goldstain, AJCP 1996





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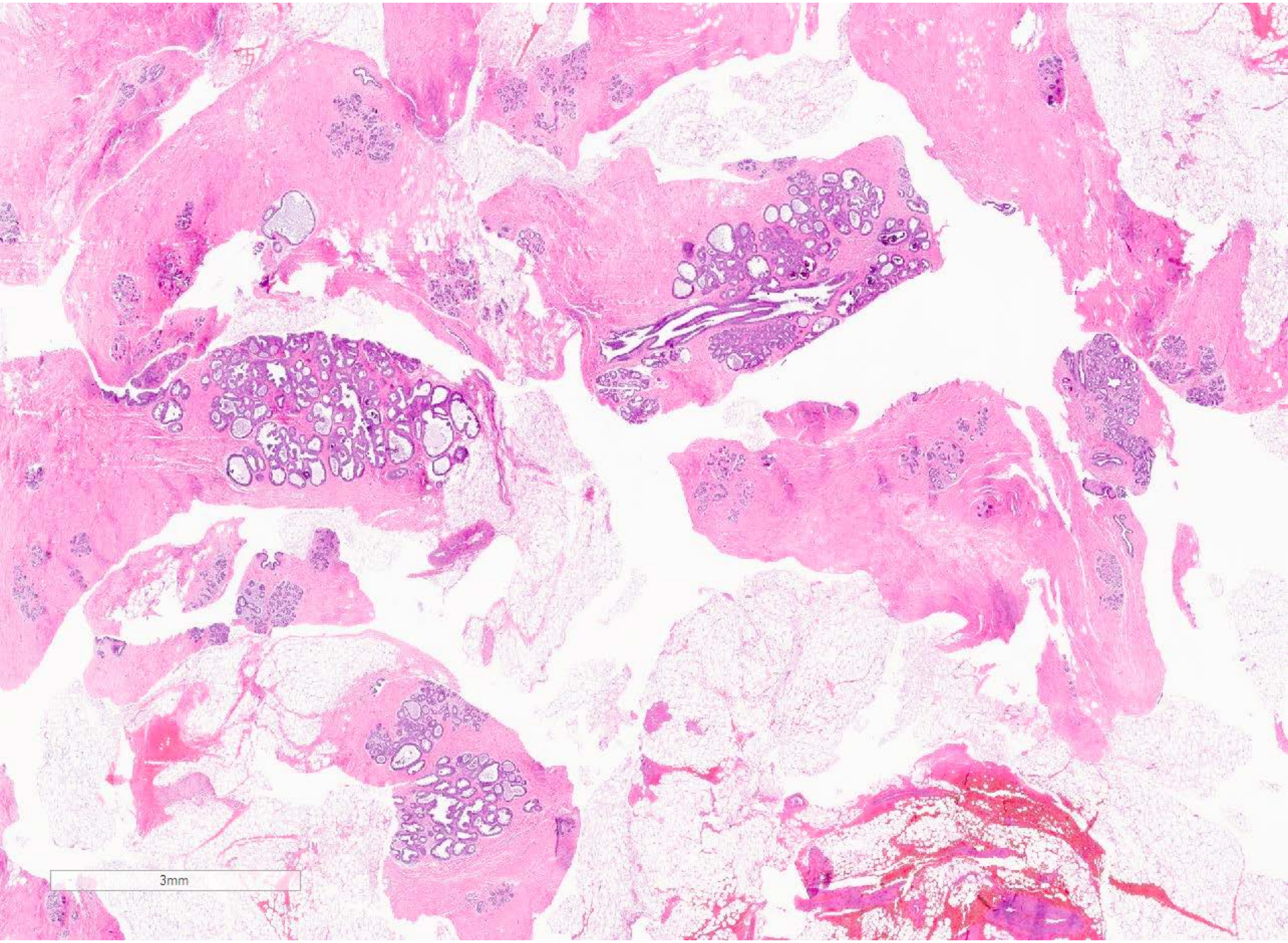
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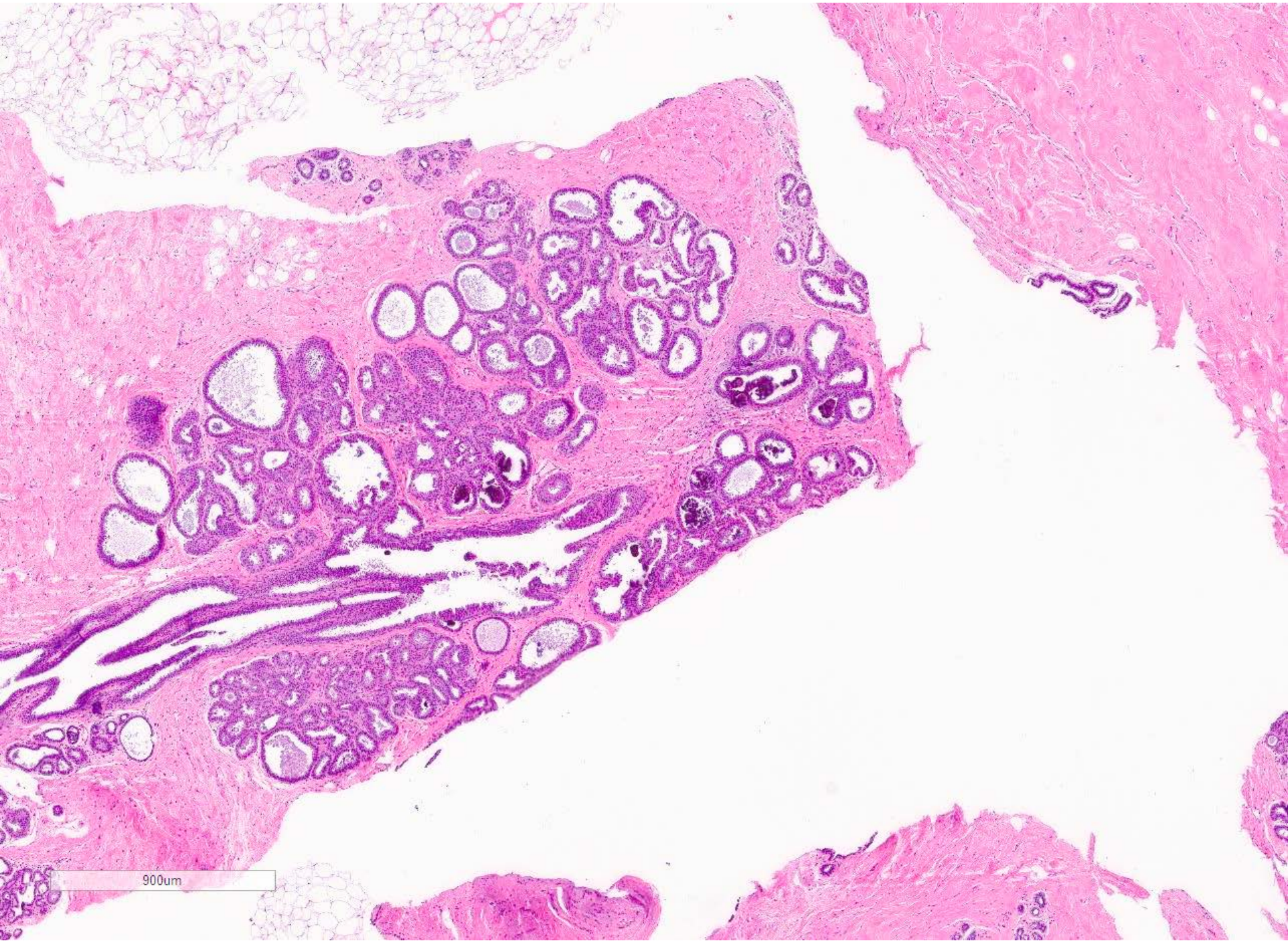
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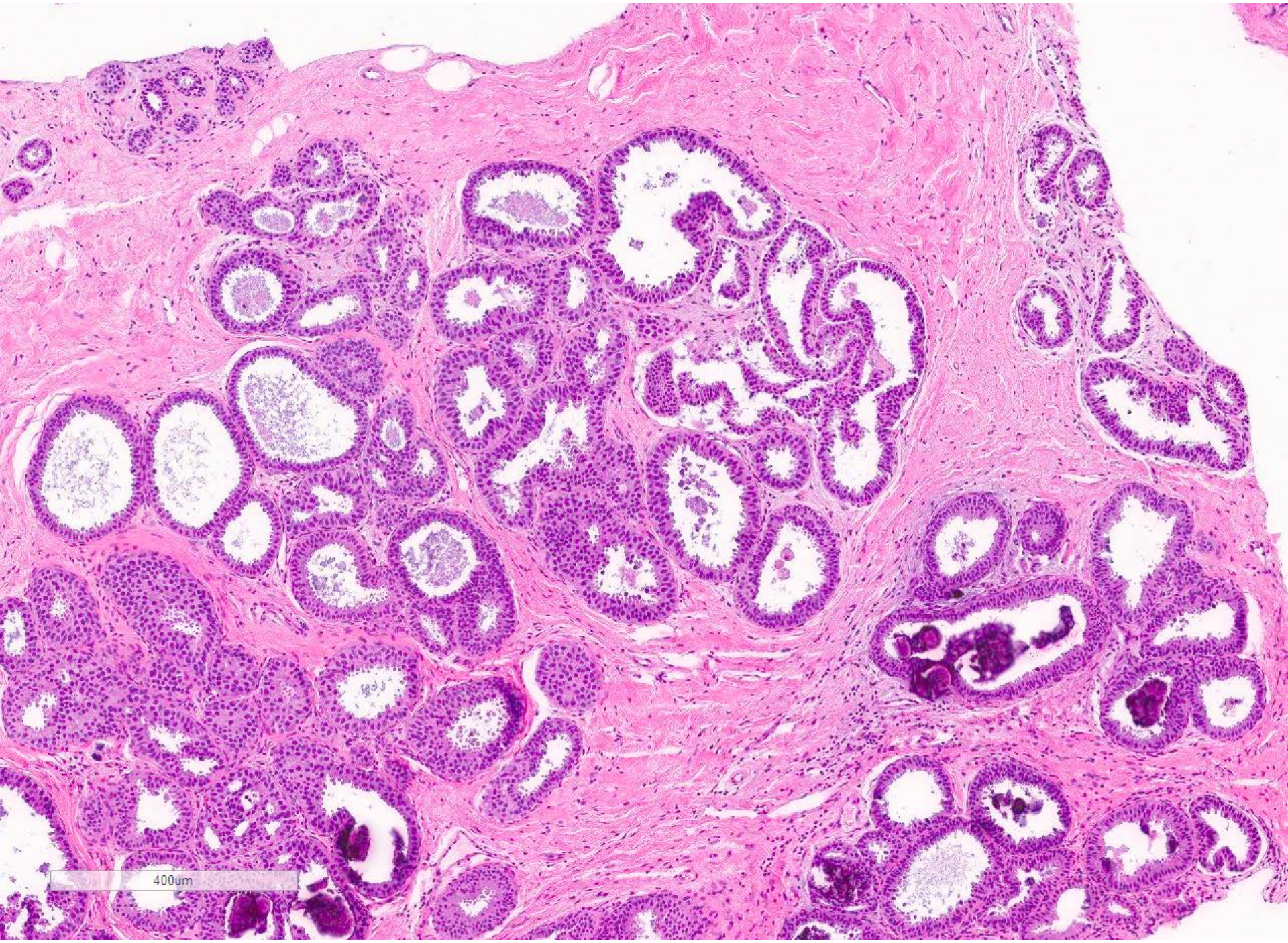
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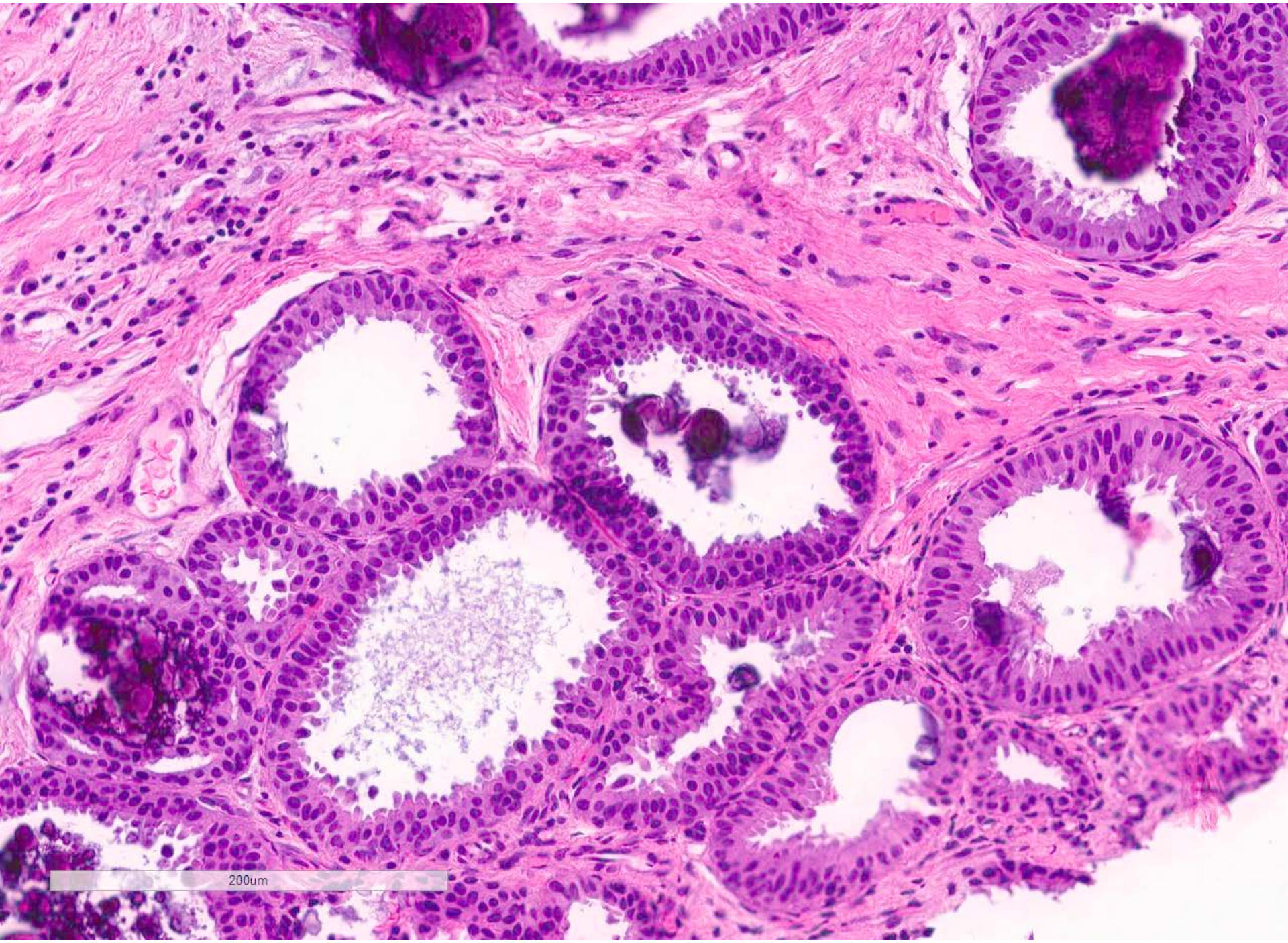
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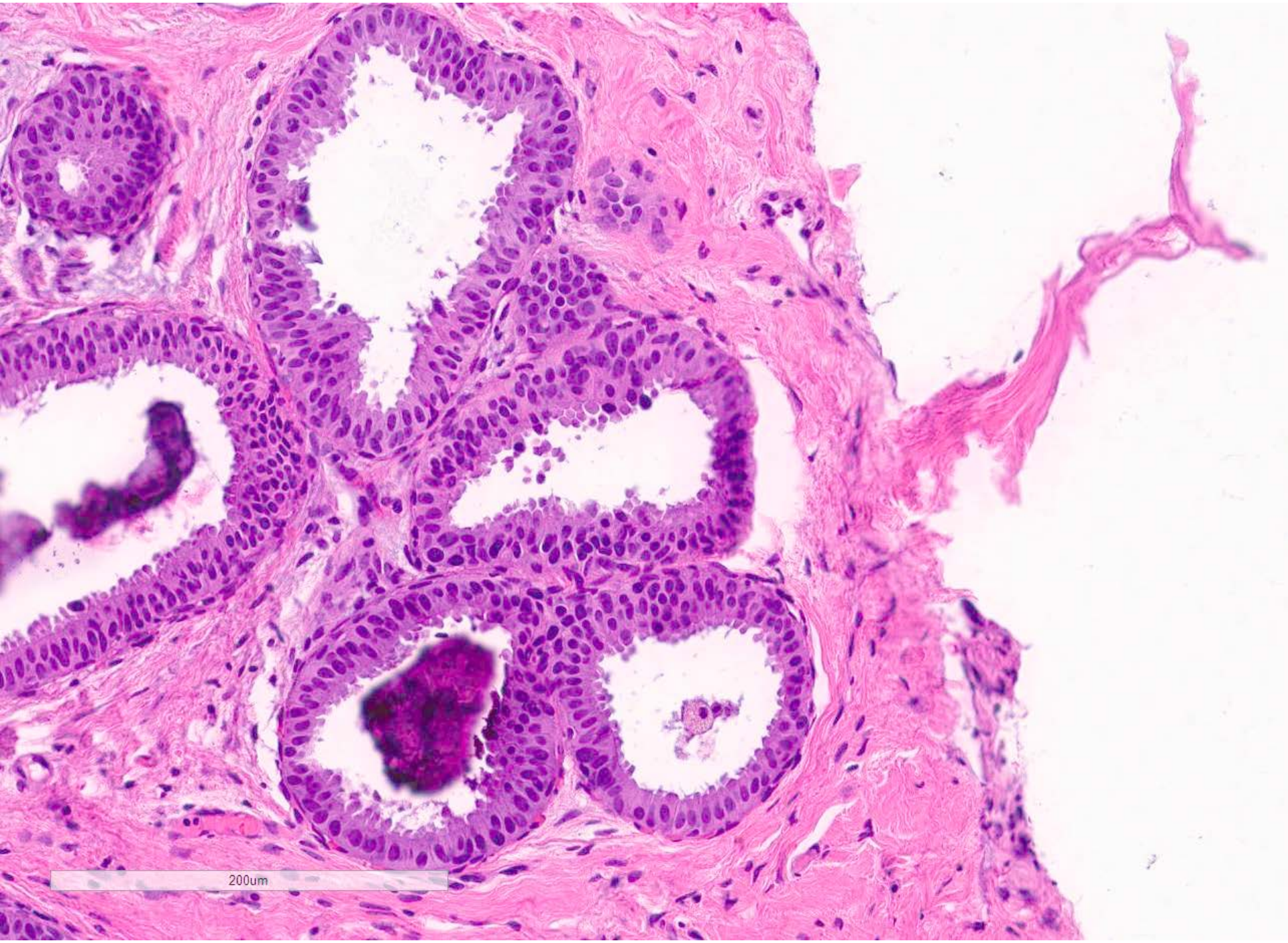

200um

Genetic Abnormalities in FEA

PCR done for Loss of Heterozygosity (LOH) (2p, 3p, 11q, 16q, 17q)

	LOH
Flat Lesions (n:22)	**17 (77%)**
Monomorphic (FEA) (n:13)	**9 (70%)**
Polymorphic (n:9)	**8 (89%)**
Tubular Carcinoma (n:10)	**9 (90%)**

Tubular Carcinoma and Flat lesions shared common LOH pattern (at least 1 locus) in 70% of the cases

Moinfar, Cancer 2000

Flat Epithelial Atypia

Synonyms

- **Columnar alterations with prominent, apical snouts and secretions (CAPSS) with atypia**
- **Columnar cell change with atypia**
- **Columnar cell hyperplasia with atypia**
- **Clinging carcinoma, monomorphic type**
- **DIN 1A, flat monomorphic type**
- **Atypical cystic duct**
- **Atypical cystic lobules**
- **Atypical lobules type A**
- **Hypersecretory hyperplasia with atypia**
- **Pretubular hyperplasia**

Flat Epithelial Atypia

Association with other lesions

- "Atypical cystic lobules" found more common in specimens with DCIS, than in specimens without DCIS (36% versus 3%) also there was geographic proximity between these lesions (Oyama et. al.).
- Association between "small ectatic ducts lined by atypical cells with apocrine snouts" with both low grade DCIS and tubular carcinoma (Goldstein et. al).
- Various associations found between "flat atypical lesions" and DCIS and/or invasive carcinoma (Page et.al, Rosen et. al).
- Weidner noted similarity between "small ectatic ducts lined by one or two layers of columnar cells with apical snouts" and tubular carcinoma and he considered these as low grade DCIS.

Page et. al. Pathology case reviews 1996, 1:36-40.
Rosen et. al. American Journal of Surgical Pathology 1999, 23:1561.
Oyama et. al. Breast Cancer 2000, 7:326-331.
Goldstein et. al. American Journal of Clinical Pathology 1997, 107:561-566.
Weidner. Seminars in Diagnostic Pathology 1995, 12:2-13

Flat Epithelial Atypia

Association with other lesions

- FEA seen in 48% of the tubular carcinoma vs 13% of Grade 1 invasive ductal carcinoma
- Lobular neoplasia coexisted in 86% with FEA.
- "Atypical Cystic Lesions" seen
  - In breast bx with LN: 56%
  - In 60% of cases with LCIS
  - In 46% of cases with ALH
- "Columnar Cell Lesions" seen in association with
  - ADH in 60% of cases
  - Low grade DCIS in 42% cases
- In 543 DCIS, FEA is significantly associated with
  - Low nuclear grade DCIS, micropapillary and cribriform architecture

Fernandez-Aguilar, Virchows 2005
Liebl Histopathology 2007
Brogi Int J Surg Path 2001
Abdel-Fatah AJSP 2007
Collins Mod Pathol 2007

Flat Epithelial Atypia

Association with other lesions

Grade	Invasive carcinoma	Lobular carcinoma (% of invasive carcinoma)	LIN
Low-risk DIN (UDH) *n*=426	10 (2%)	1 (10%)	43 (10%)
DIN 1-flat type (Flat epithelial atypia) *n*=1000	68 (7%)	19 (28%)	257 (26%)
DIN 1 (ADH/DCIS G1) *n*=538	116 (22%)	11 (9%)	116 (22%) Without DIN 1-flat type=85 (16%)
DIN 2 (DCIS G2) *n*=383	142 (37%)	11 (8%)	62 (16%) Without DIN 1-flat type=57 (15%)
DIN 3 (DCIS G3) *n*=281	102 (36%)	2 (2%)	26 (9%) Without DIN 1-flat type=22 (8%)

Bratthauer et al Virchows 2004

Flat Epithelial Atypia

Association with other lesions

- **"Rosen Triad": tubular ca + LCIS + "Columnar cell lesion" (includes non-atypical lesions)**
  - **All of 86 TC had CLL 79% of which were atypical (i.e FEA)**
  - **53% had all three ie TC, LCIS, CCL**
- **Core biopsies done for calcifications: 54% of the LN was associated with "Columnar cell alteration" (includes non-atypical lesions).**
  - **9.6% LN→ upgrade to cancer on excision**
  - **13% LN+ CCA→ upgrade to cancer on excision**
- **42 / 100 breast bx done for Ca++ had "CAPPS" (includes non-atypical lesions)**
  - **More commonly associated with low-grade DCIS**

Brandt Adv Anat Pathol 2008
Carley AJCP 2008
Fraser AJSP 1998

FEA in CNB: to excise not to excise

- **37 / 142 (20%) CAPSS (includes non-atypicals) →excised**
  - **1 / 6 (16%) CAPSS without atypia on excision →DCIS**
  - **4 / 31 (13%) CAPSS with atypia (ie FEA) on excision → 3 DCIS + 1 invasive**

- **3 / 12 (25%) pure FEA → cancer on excision**
  - **FEA coexisted with ADH 73% of the time**

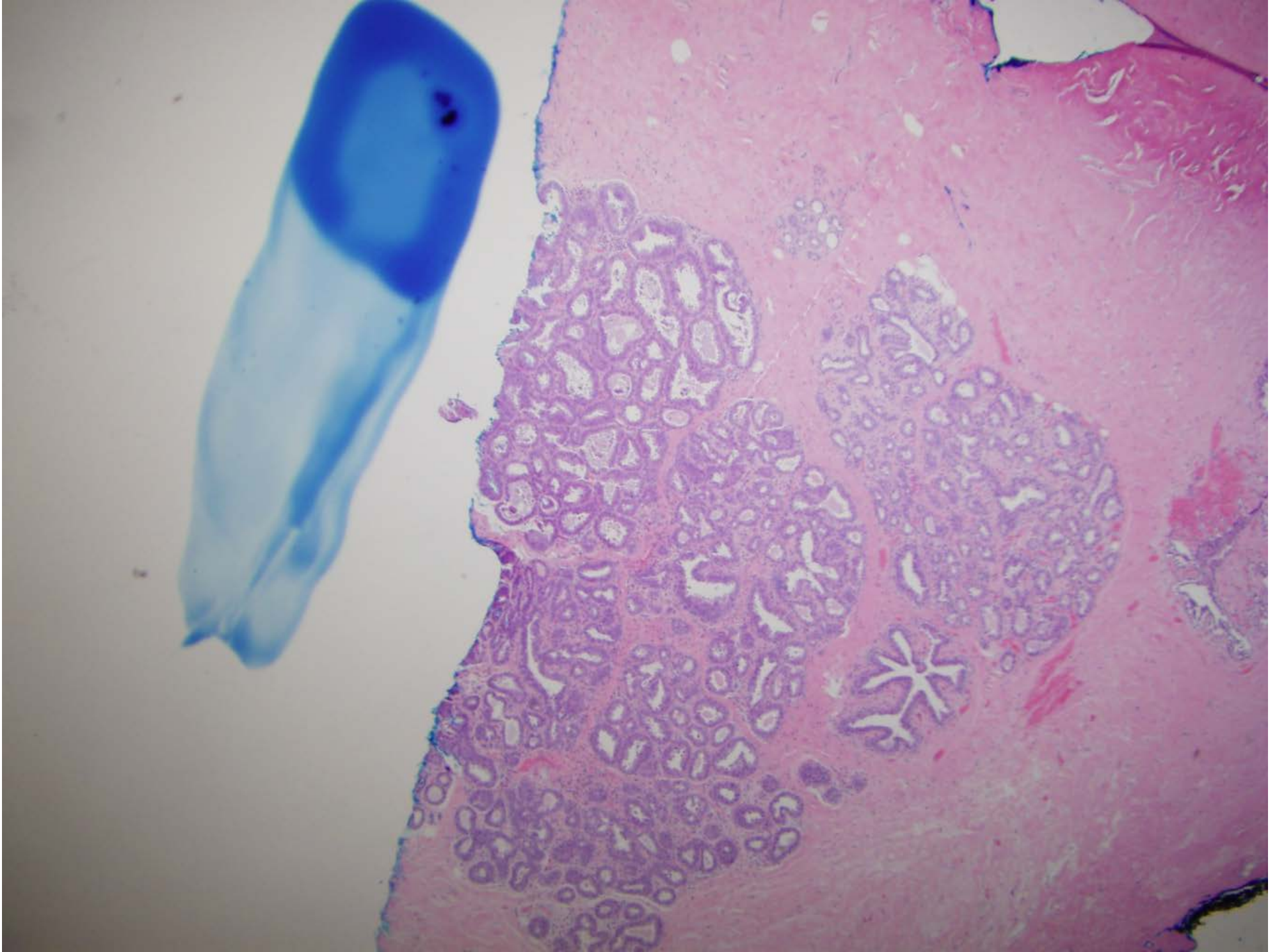
- **2 / 9 (22%) "columnar cell lesion with atypia" →cancer**

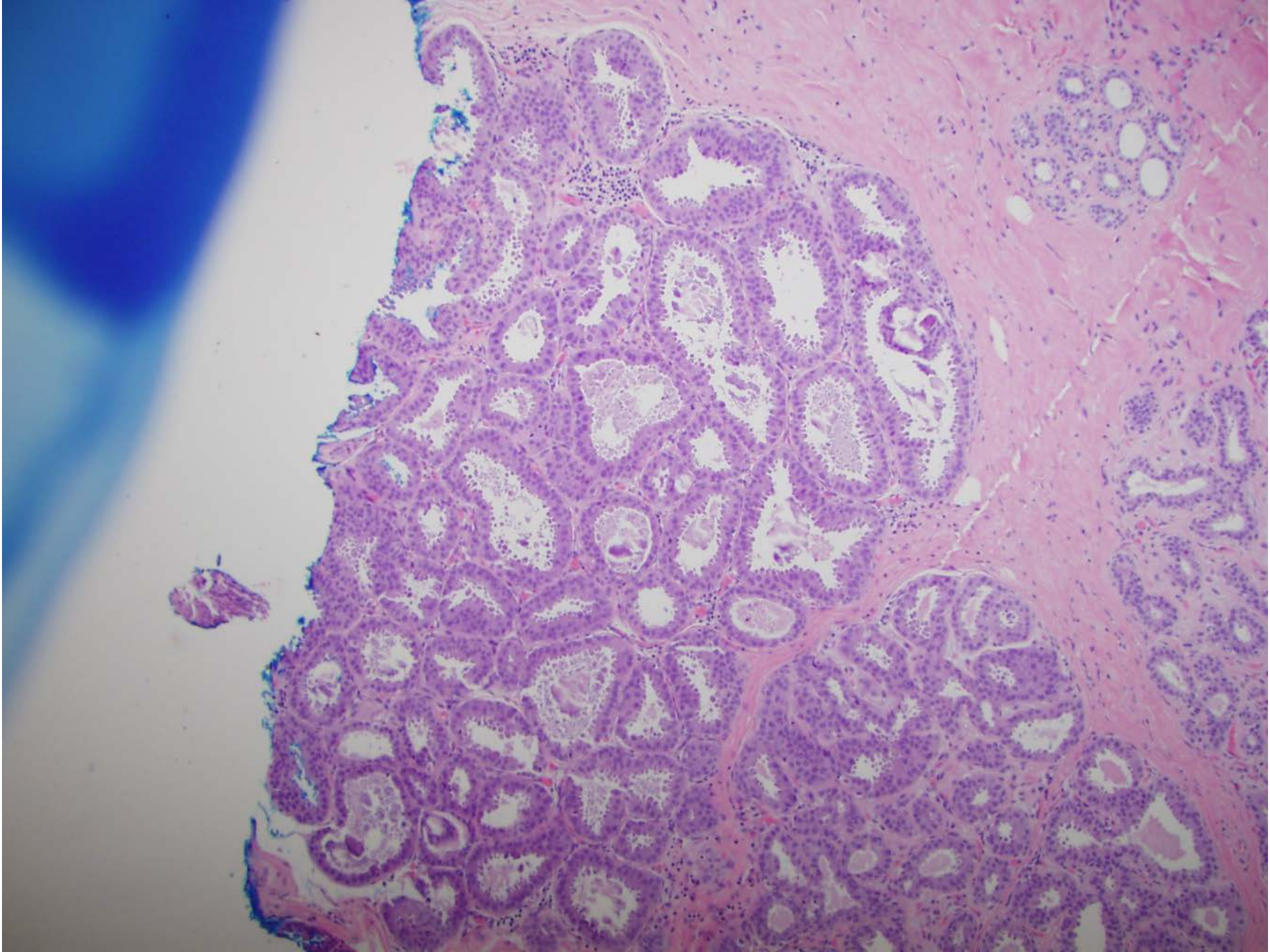
- **1 / 5 (20%) "columnar cell lesion with atypia"→ cancer**

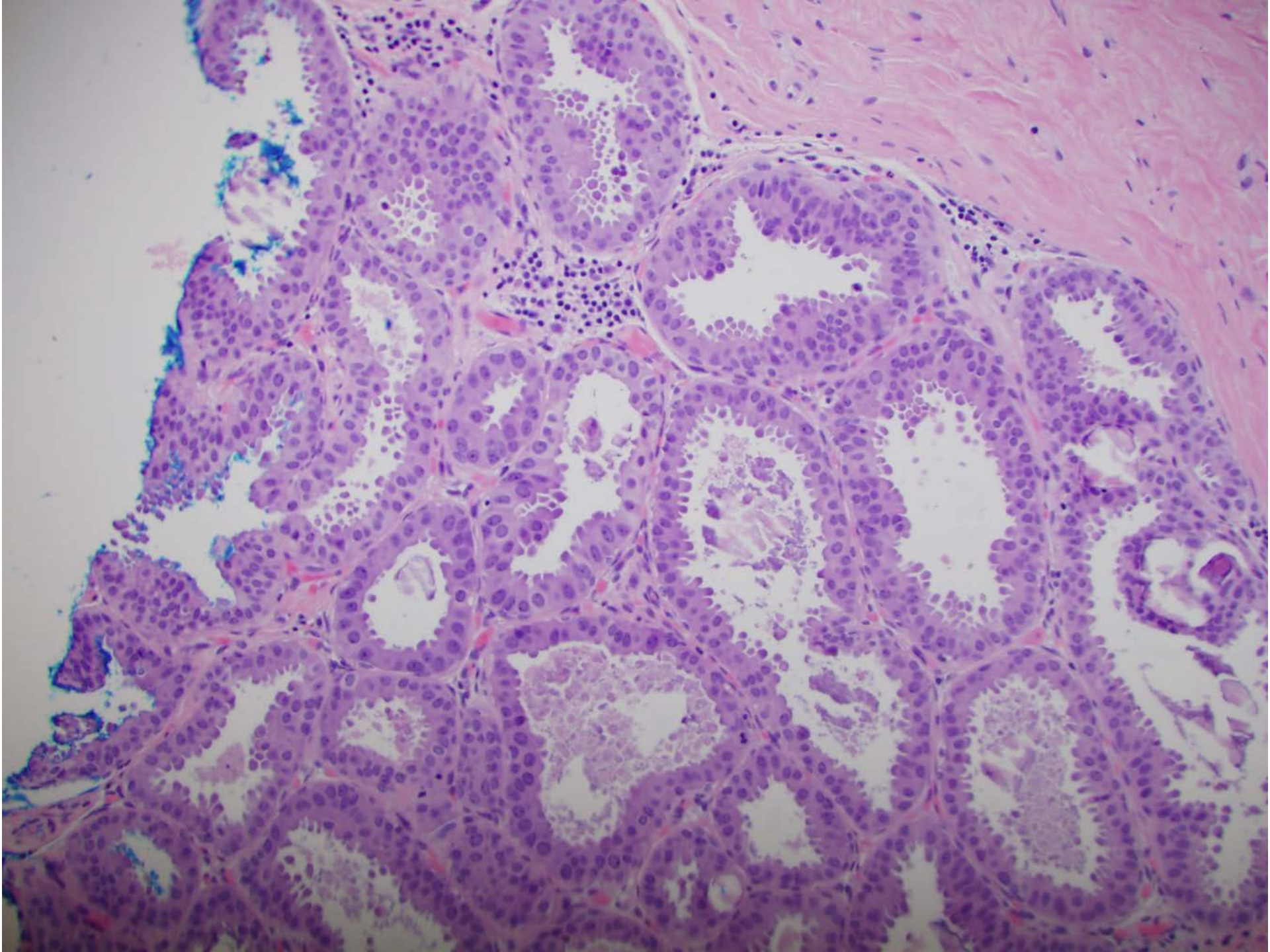
Guerra-Wallace Am J Surgery 2004
Kunju, Hum Path 2007
Bonnett Mod Path 2003
Lim J Clin Path 2006

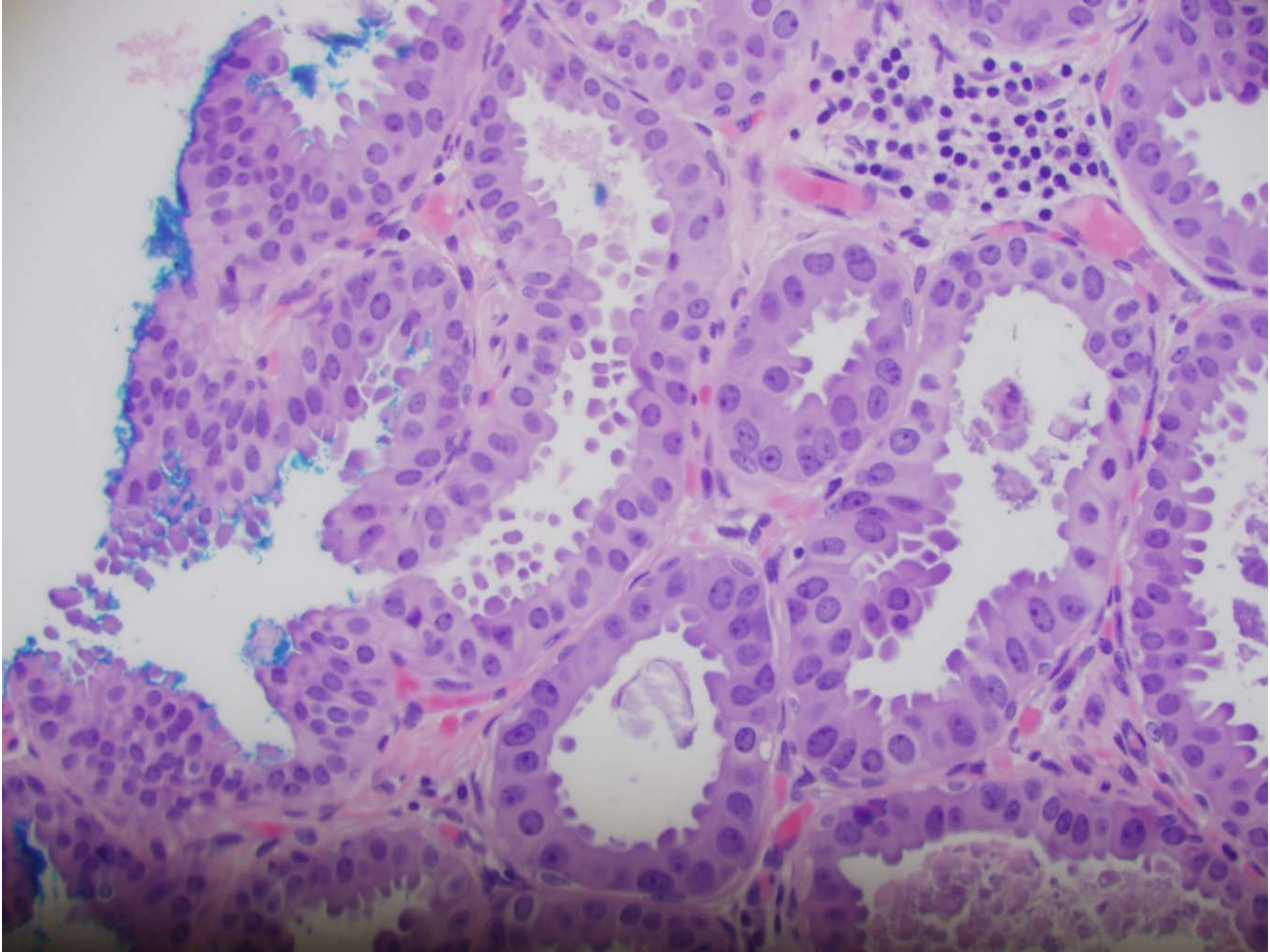
Problems with the literature

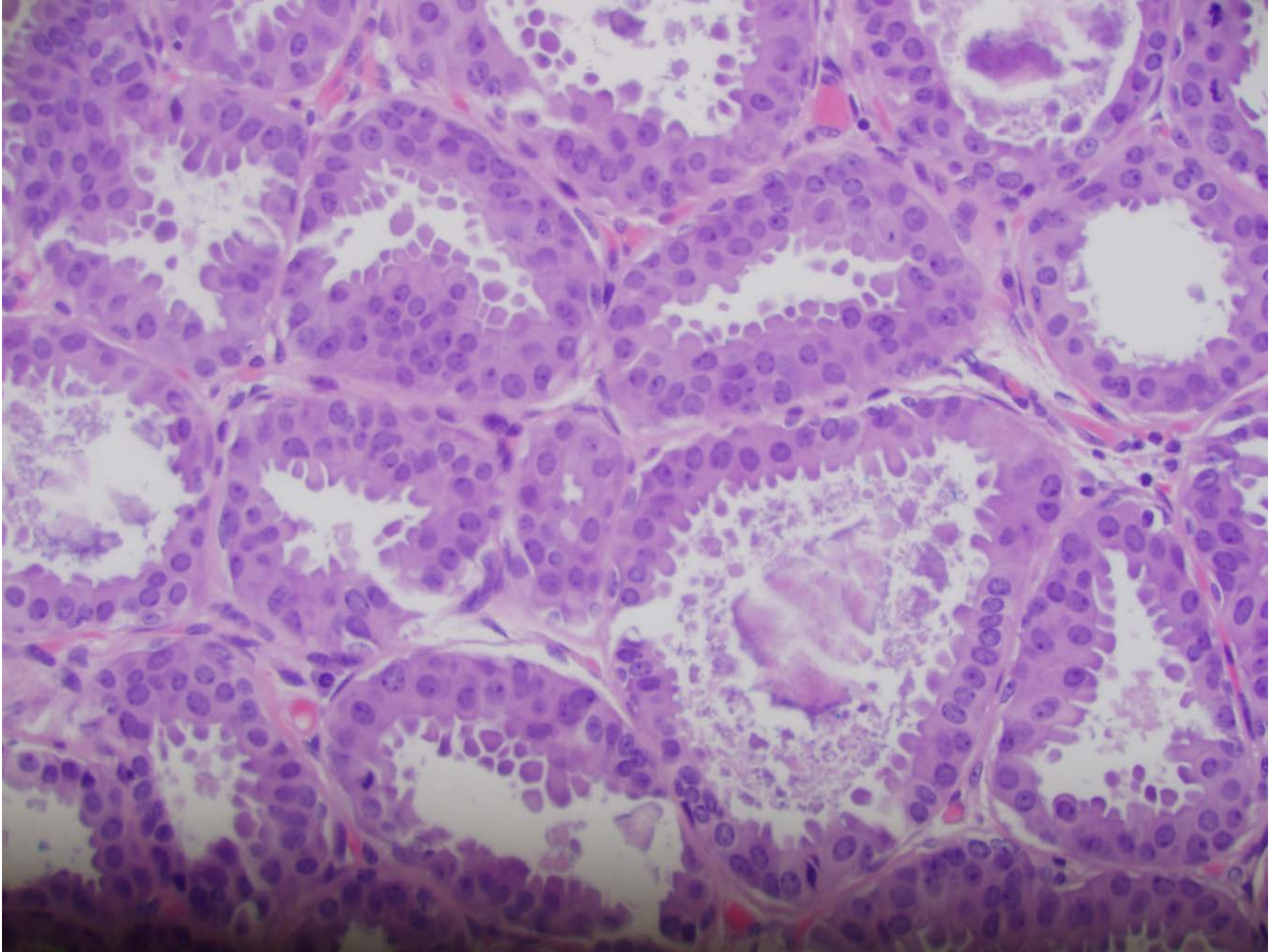
- **Lack of uniform terminology**
- **Lack of multidisciplinary approach**
- **Non-atypical and atypical columnar cell lesions analyzed together**
- **Most series include other, coexistent high risk lesions such as ADH**
- **No radiologic-pathologic correlation**
  - **No explanation why some FEA not excised (and in some studies why some non-atypicals are excised)**

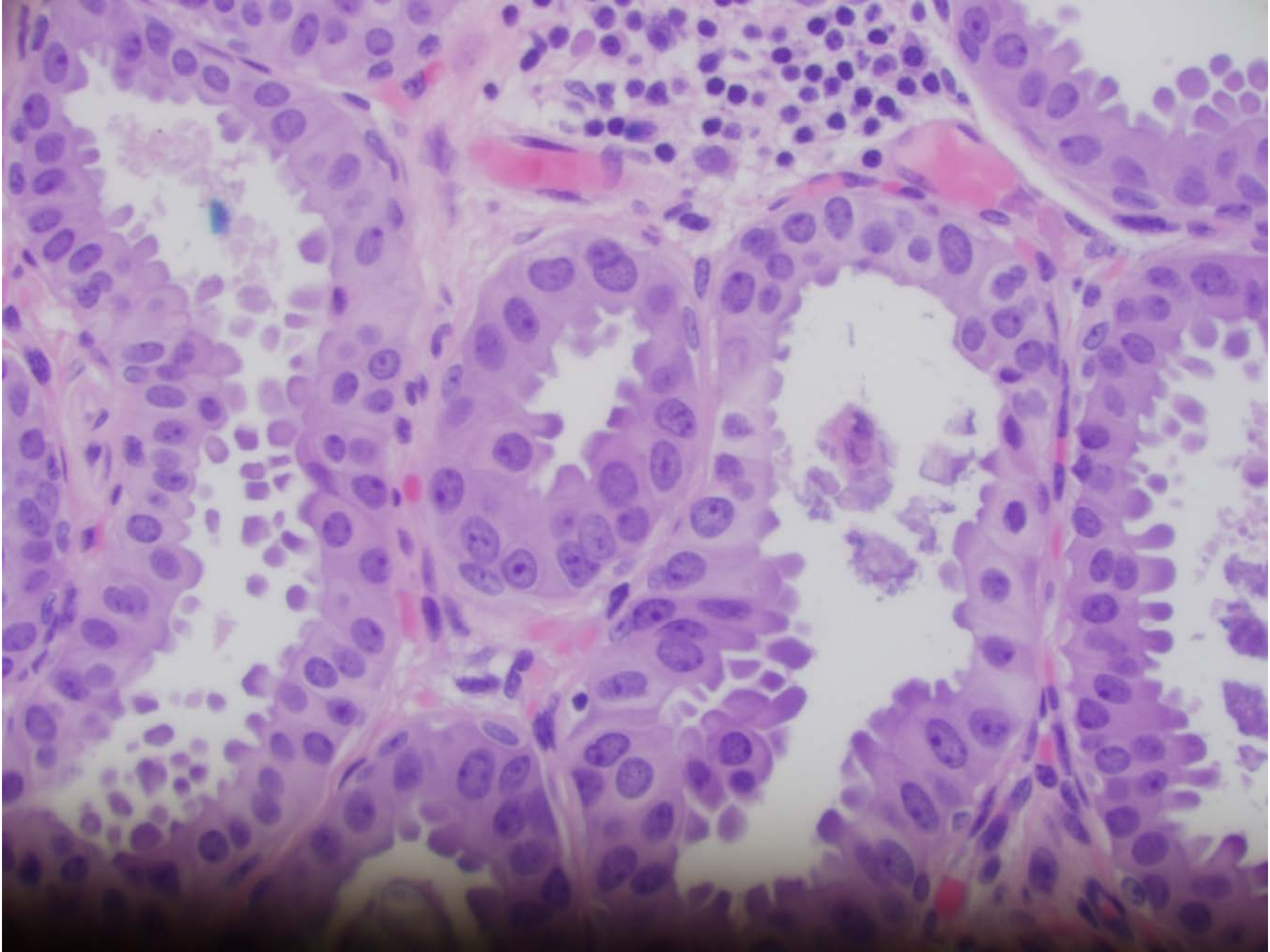












Morphologic Parameters of FEA as Predictors of Malignancy on Excision

859 VANCB from 14 institutions in Italy with follow up excision

Bianchi et al Virchows Arch 2012

Morphologic Parameters of FEA as Predictors of Malignancy on Excision

Mention of FEA at VANCB	Diagnosis at surgical excision				Total
	Benign, *N*	Atypia, *N*	Malignancy		
			N	%	
Pure FEA	73	99	18	9.5	190 (32.2 %)
FEA + ADH	72	128	75	27.3	275 (46.7 %)
FEA + LIN	17	60	13	14.4	90 (15.3 %)
FEA + ADH + LIN	5	21	8	23.5	34 (5.8 %)
Total	167 (28.4 %)	308 (52.3 %)	114 (19.4 %)		589 (100 %)

Bianchi et al Virchows Arch 2012

Morphologic Parameters of FEA as Predictors of Malignancy on Excision

Pure FEA:

- No association with any variables including extent of FEA, degree of atypia (mild vs moderate), BIRADS category, number of cores
- Trend for mild vs moderate atypia and incomplete removal of microcalcifications

Bianchi et al Virchows Arch 2012

Pure FEA on CNB: Is There a Place for Excision?

3,948 Breast CNB

145 (3.7 %)
Pure FEA
- 46% Calcification
- **66% Excision**
  - 3.2% Upgrade
- 0.2% Upgrade

58 (1.5%)
FEA and ADH
- 86% Calcification
- 74% Excision
  - 18.6% Upgrade
- 13.8% Upgrade

Not all excised, patient decision

Uzoaru et al Virchows Arch 2012

Pure FEA: Is There a Place for Excision?

1,678 CNB (VABB)

52 (3%) Pure FEA

- 86% Calcification
- 12% Mass
- **>90% excised**
- 12% BI-RADS 5
- 3 (6%) Upgrade

(2/3 BI-RADS 5)

Ceugnart Diagnostic & Interventional Imaging 2013

FEA on Core Bx: Management may be Individualized

Table 1 Flat epithelial atypia and co-existing lesions on core biopsy

Total	*FEA only*	*ADH*	*ALH*	*ADH & ALH*	*LCIS*	*DCIS*	*Invasive*
210	94 (45%)[a]	60 (29%)	19 (9%)	9 (4%)	2 (1%)	14 (7%)	12 (6%)

Calhoun Mod Pathol 2014

FEA on Core Bx: Management may be Individualized

Table 2 Excision after flat epithelial atypia alone on core biopsy

Total	*No atypia*	*FEA*	*ADH*	*ALH*	*DCIS*	*Invasive*
73	20 (27%)[a]	31 (42%)	14 (19%)	3 (4%)	3 (4%)	2 (3%)

Pure FEA upgrade 7%
No upgrades if all calcifications removed

Calhoun Mod Pathol 2014

Pure FEA on Core Bx: Management may be Individualized

	Core biopsies	*Excisions*	*Carcinoma (%)*	*DCIS*	*Invasive*	*Recommendation*
Lavoue *et al*[38]	60	60	8 (13%)[a]	6	2	Excision
Guerra-Wallace *et al*[21]	39	31	4 (13%)	3	1	Excision
Bianchi *et al*[27]	190	190	18 (10%)	NR	NR	Excision
Chivukula *et al*[33]	39	35	5 (14%)	3	2	Excision
Noske *et al*[39]	43	30	2 (7%)	2	0	Excision
Senetta *et al*[40]	41	36	0 (0%)	0	0	Case by case
Ceugnart *et al*[41]	63	52	2 (4%)	2	0	Case by case
Biggar *et al*[42]	51	51	3 (6%)	2	1	Excision
Khoumais *et al*[43]	104	94	10 (11%)	5	5	Excision
Uzoaru *et al*[44]	145	95	3 (3%)	1	2	Case by case
Peres *et al*[45]	128	95	9 (10%)	5	4	Excision
Villa *et al*[46]	142	121	7 (6%)	NR	NR	Case by case
This study	94	73	5 (7%)	3	2	Case by case
Total	1139	963	76 (8%)	32	19	

Studies including 30 or more excisions from 2010-2014

Calhoun Mod Pathol 2014

Epithelial Atypia in Excisional Bx performed for Calcifications: Long term follow up

- **971 of 2,833 (34%) Surgical biopsy done for calcifications had "Epithelial Atypia" (included ADH, FEA, LN) .**
- **670/971 without accompanying carcinoma**
- **101/2,833 (3.5%) of all surgical Bx had FEA**
  - **84/101(83%) of FEA was isolated**
  - **17/101 (17%) FEA had concomitant cancer**
  - **None of the FEA developed subsequent carcinoma (mean follow up 160 months)**

De Mascarel et al Virchows 2007

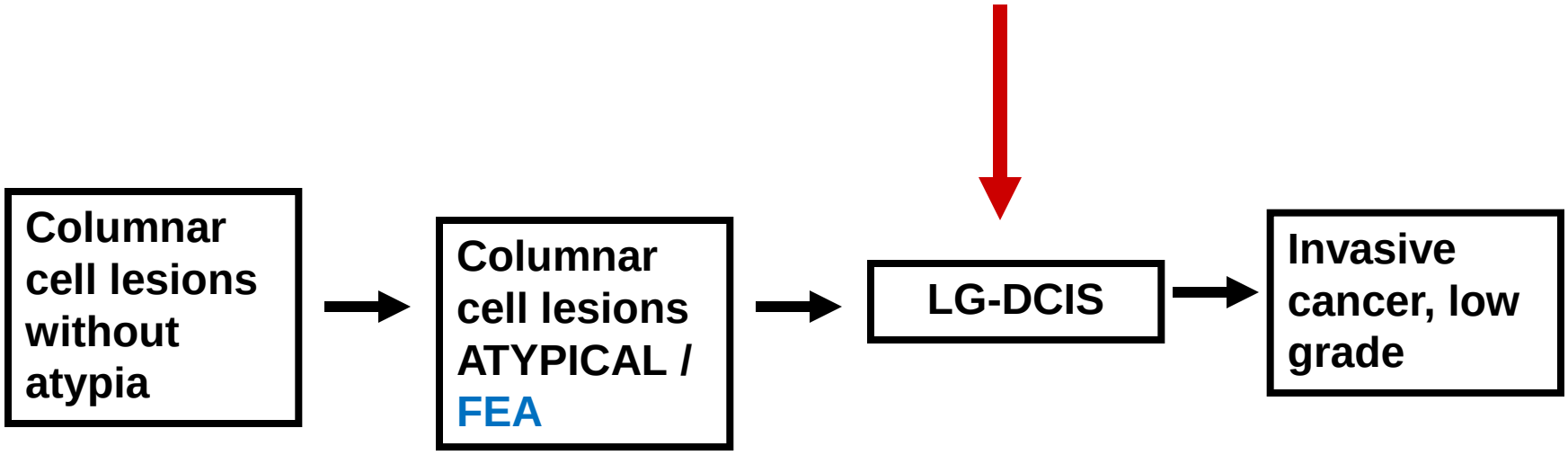
FEA

Risk of progression to cancer is very low when isolated lesion

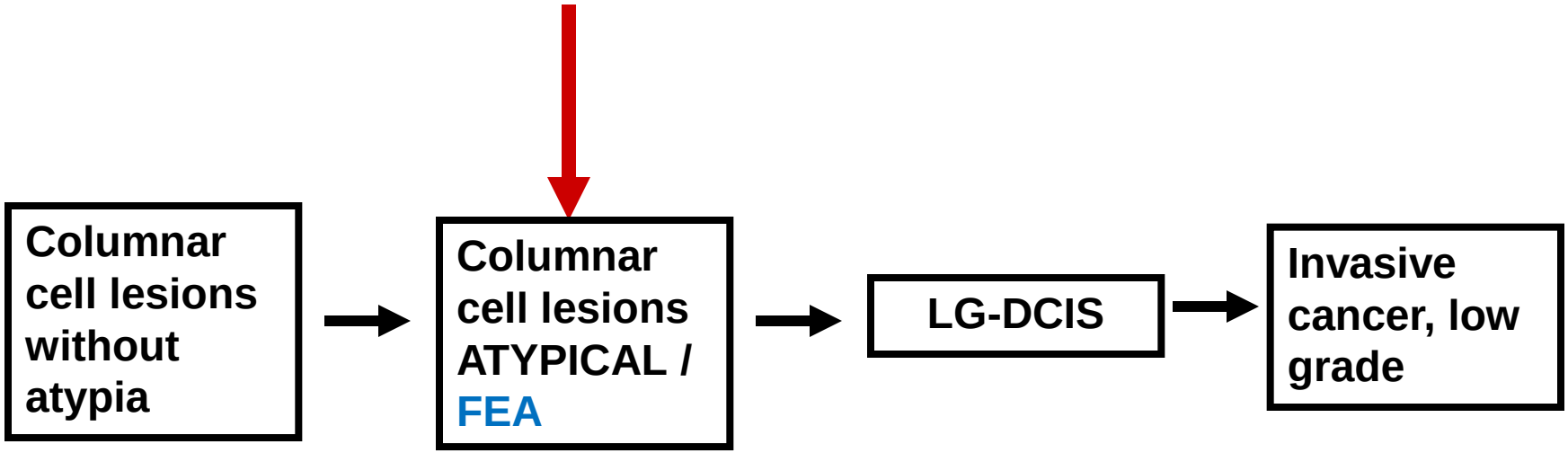
Current recommendation:

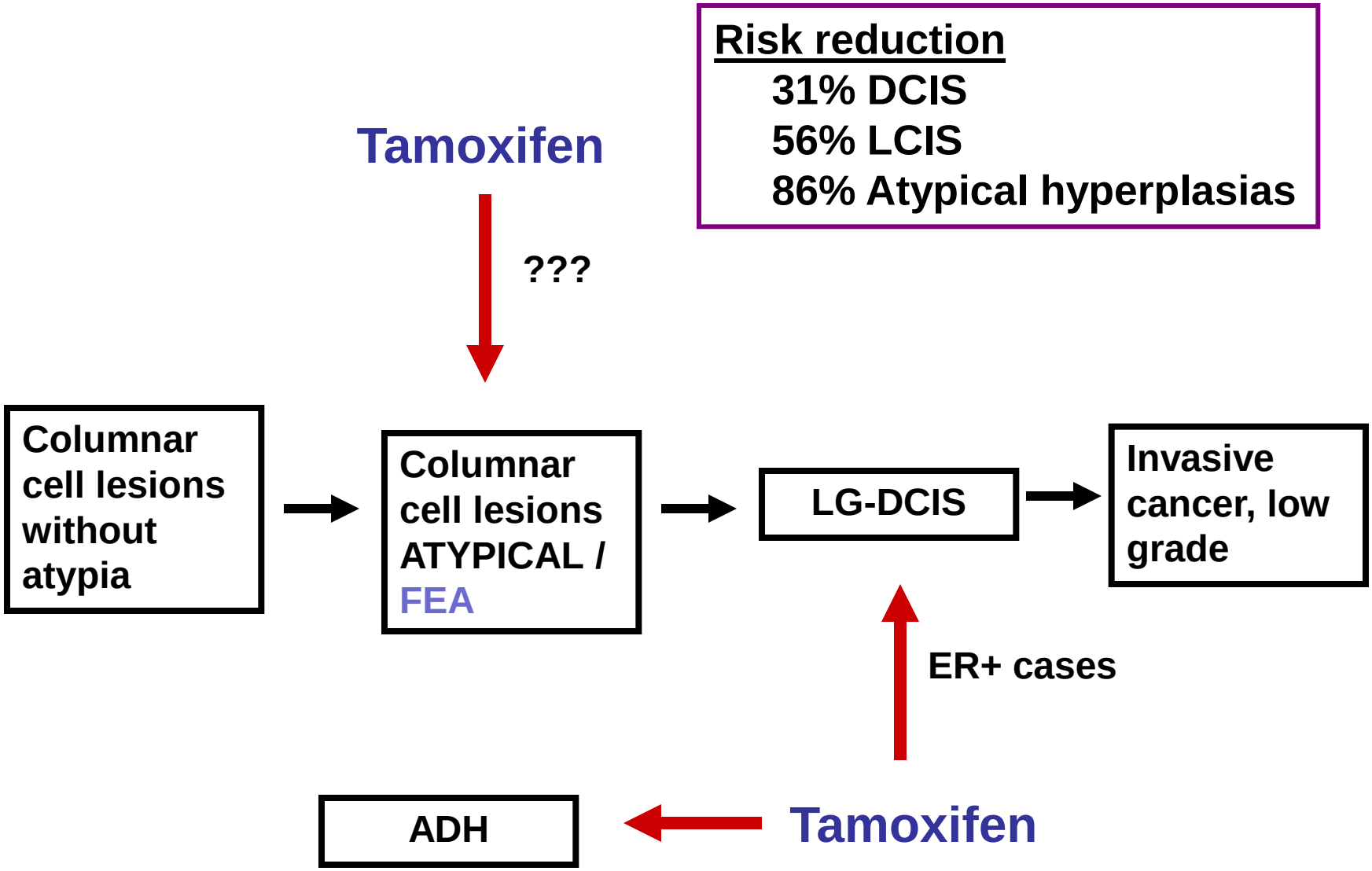
- **Not to re-excise if FEA is at the margin of a lumpectomy**
- **Not include FEA when determining the size of DCIS**

Re-excise if margins positive



To excise or not to excise after core biopsy




Risk reduction
31% DCIS
56% LCIS
86% Atypical hyperplasias
Tamoxifen
???
Columnar cell lesions without atypia
Columnar cell lesions ATYPICAL / FEA
LG-DCIS
Invasive cancer, low grade
ER+ cases
ADH
Tamoxifen

Flat Epithelial Atypia

Atypical and non-atypical columnar lesions may be biologically related, may represent spectrum of changes and in future both may be proven to be risk factors for breast cancer requiring similar follow up and treatment

Lobular Neoplasia (LCIS/ALH)

Lobular Neoplasia (LCIS/ALH)

- **Rare lesions 0.5%-3.8% of breast biopsies**
- **Incidence has been increasing in all ages**
  - **Hormone replacement therapy (up to 2002)**
  - **Use of larger gauge needles and VABB**
  - **Calcifications in 20-25% of LCIS (upto 42% of LCIS in Karabakhtsian et al)**
- **Multicentric (48%), bilateral (>50%)**

Hanby , Histopathology 2008
Collins, Cancer 2007

Lobular Neoplasia (LCIS/ALH)

- **Similar (?) risk for ipsilateral and contralateral breast**
- **The risk of development of breast carcinoma after LCIS is about 1-2% / year with a life-time risk of 30-40% (RR x8-10). RR x4 for ALH**
- **Nurses Health Study: both ALH and ADH ~60% ipsilateral. ALH in premenopausal women RRx7.3**
- **Risk of subsequent carcinoma after ALH and/or LCIS is 3 x more likely in ipsilateral breast**

Hanby , Histopathology 2008
Collins, Cancer 2007
Page, Lancet 2003

Lobular Neoplasia (LCIS/ALH)

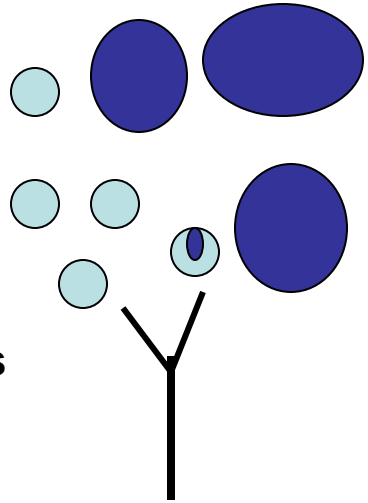
- **ALH: partial involvement**
- **LCIS: >1/2 lobule involved and must be filled and distended (Page: at least 8 cells within its cross sectional diameter)**
- **Difficulties differentiating ALH from LCIS:**
  - **Core biopsy**
  - **Underlying lesion such as sclerosing adenosis**
  - **When only Pagetoid spread is present**

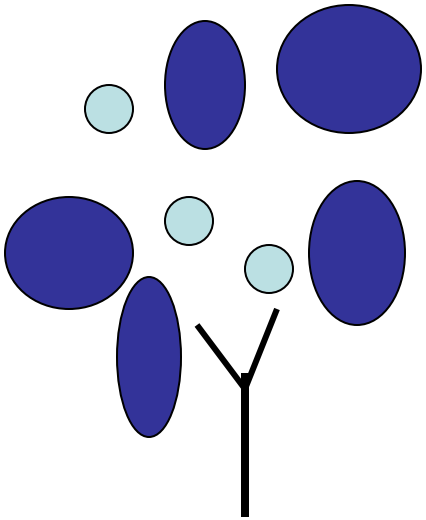
Pinder et al Pathology 2008
Page et al Hum Path 1991

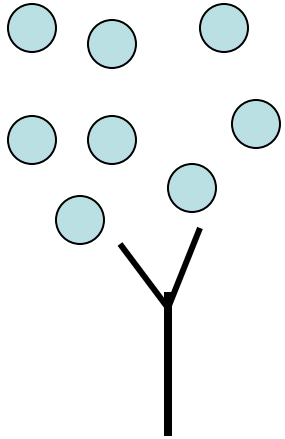
ALH

LCIS

Normal







Page

*50%

*likes distention

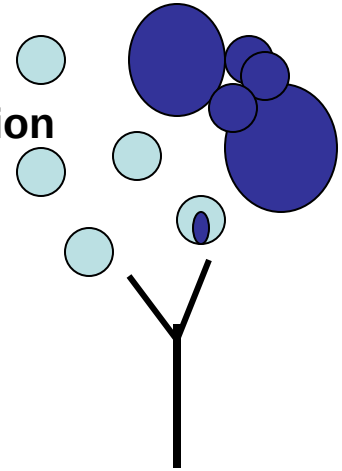
*doesn't like lumens/spaces in LCIS

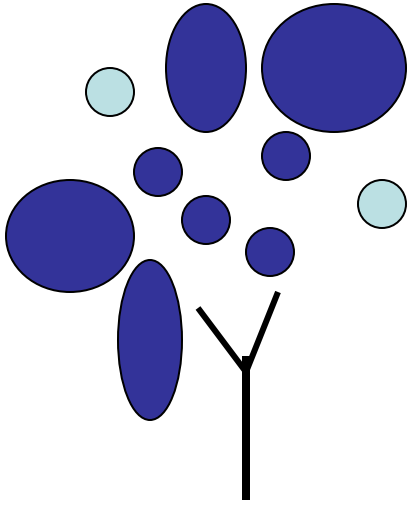
Rosen

*75%

*doesn't care about distention

*OK with lumens/spaces in LCIS

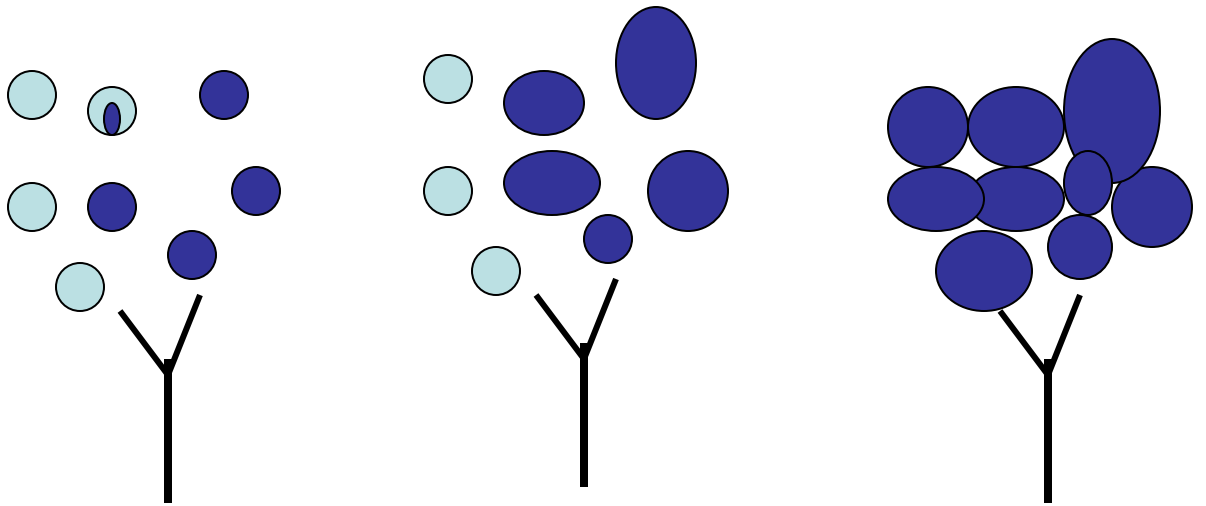




LIN1

LIN2

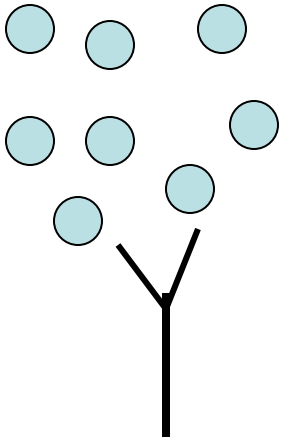
LIN3

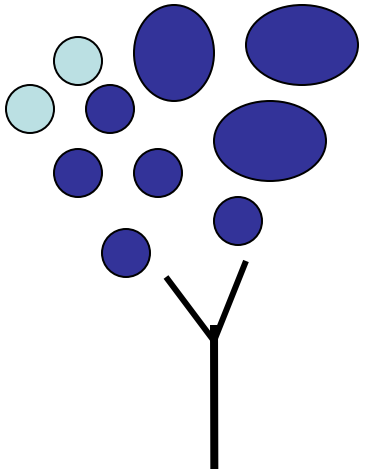


Tavassoli

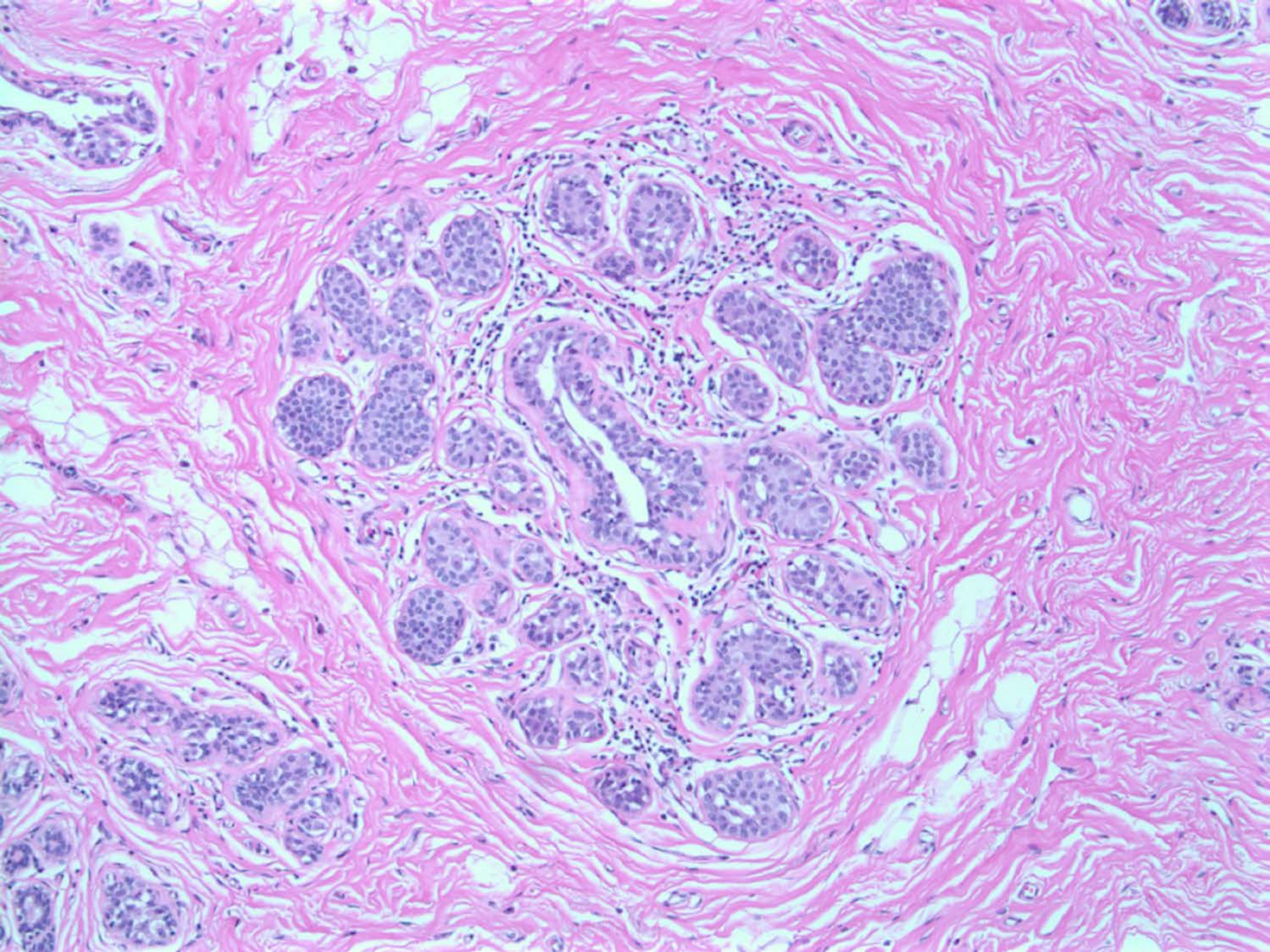
***residual lumens OK in LIN 2 but Not in LIN 3**

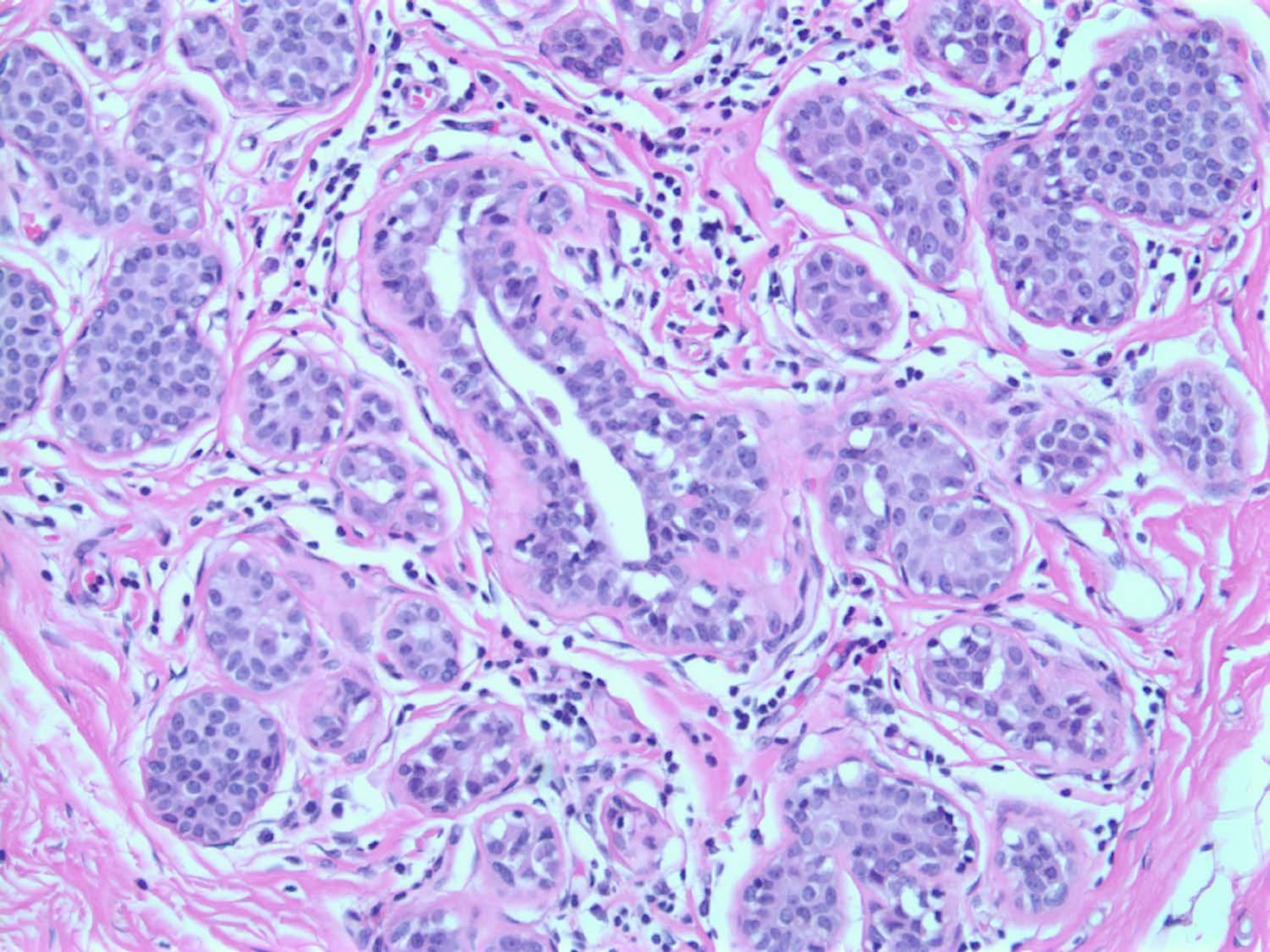
Normal

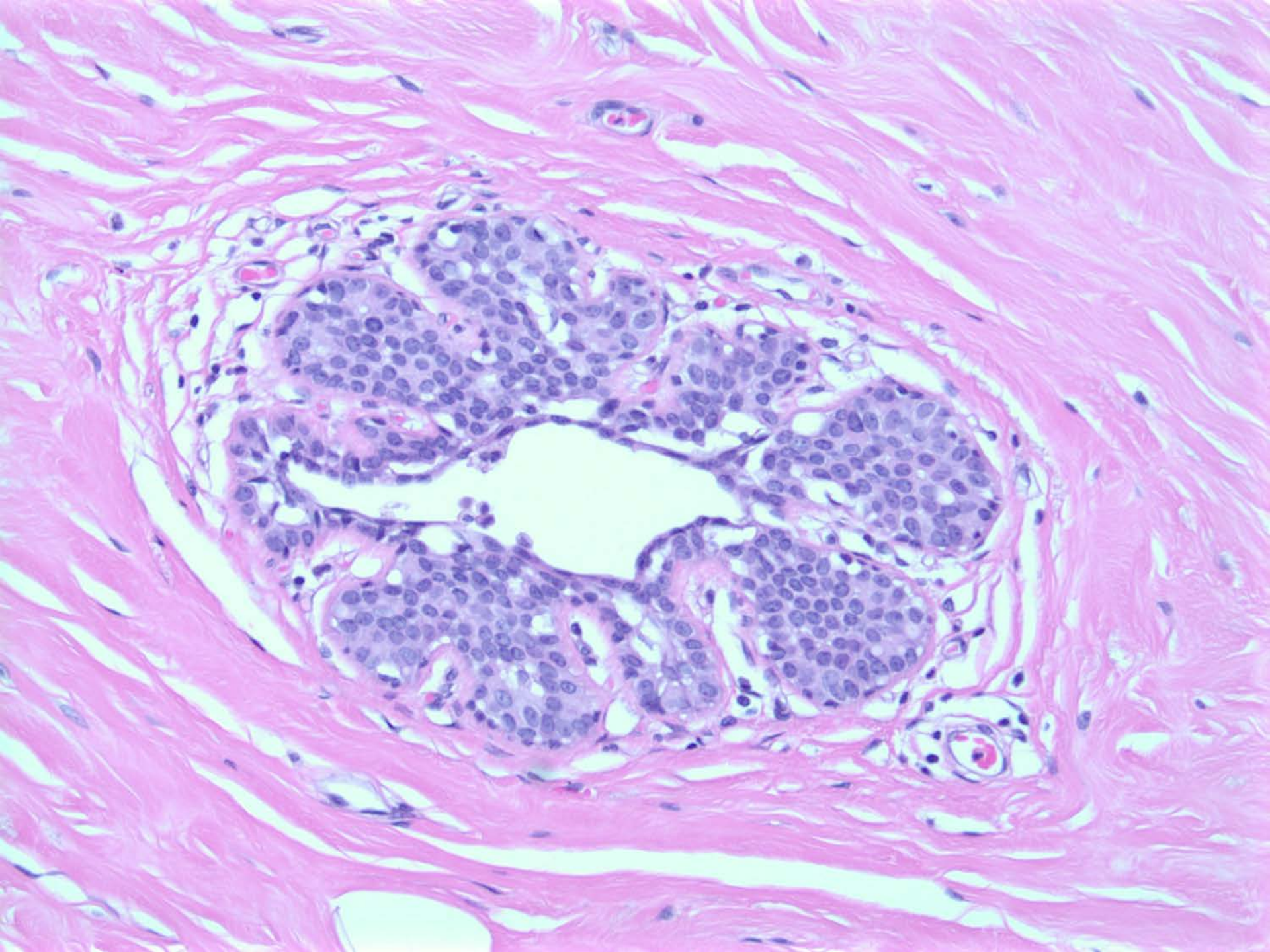


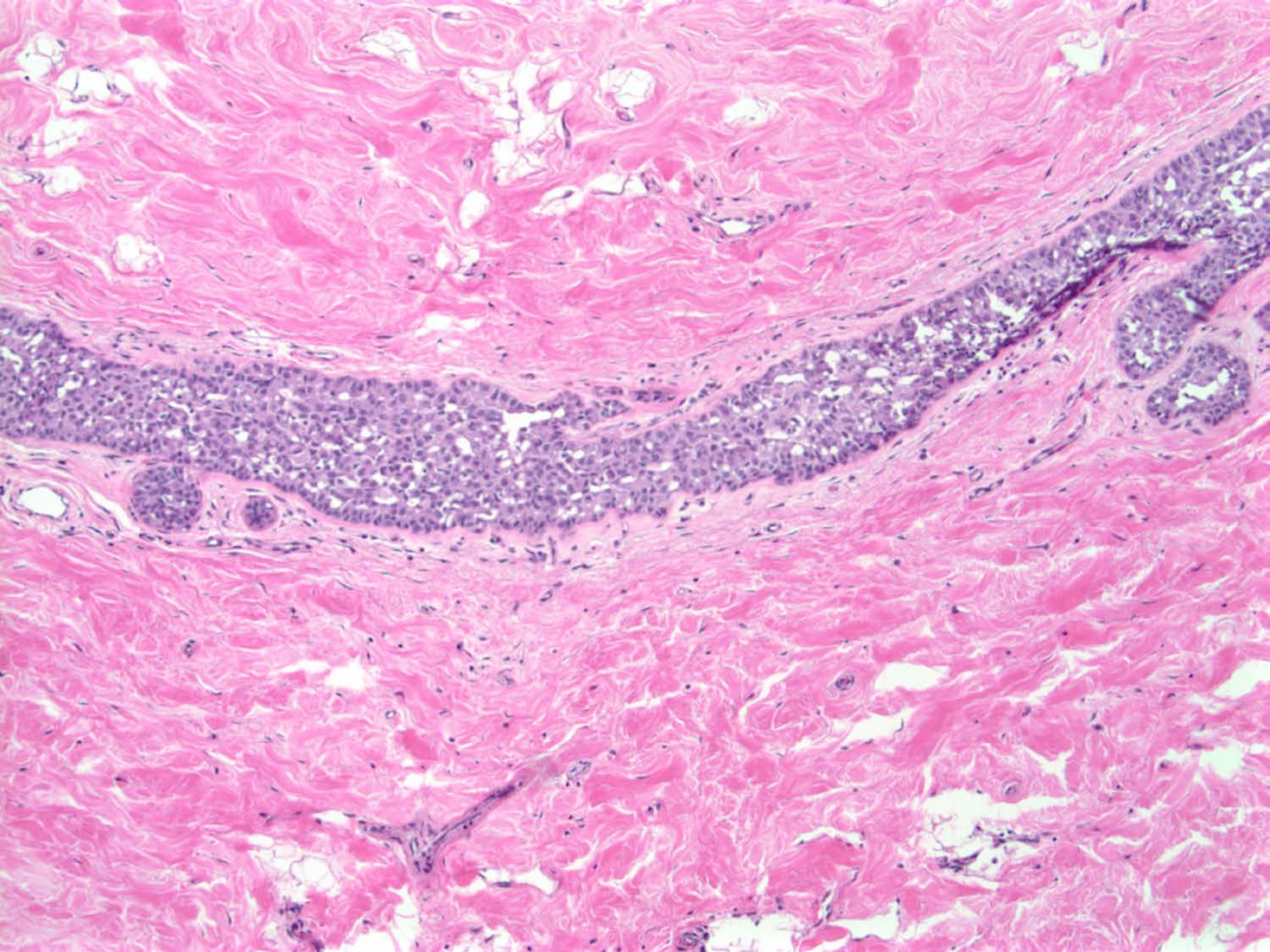


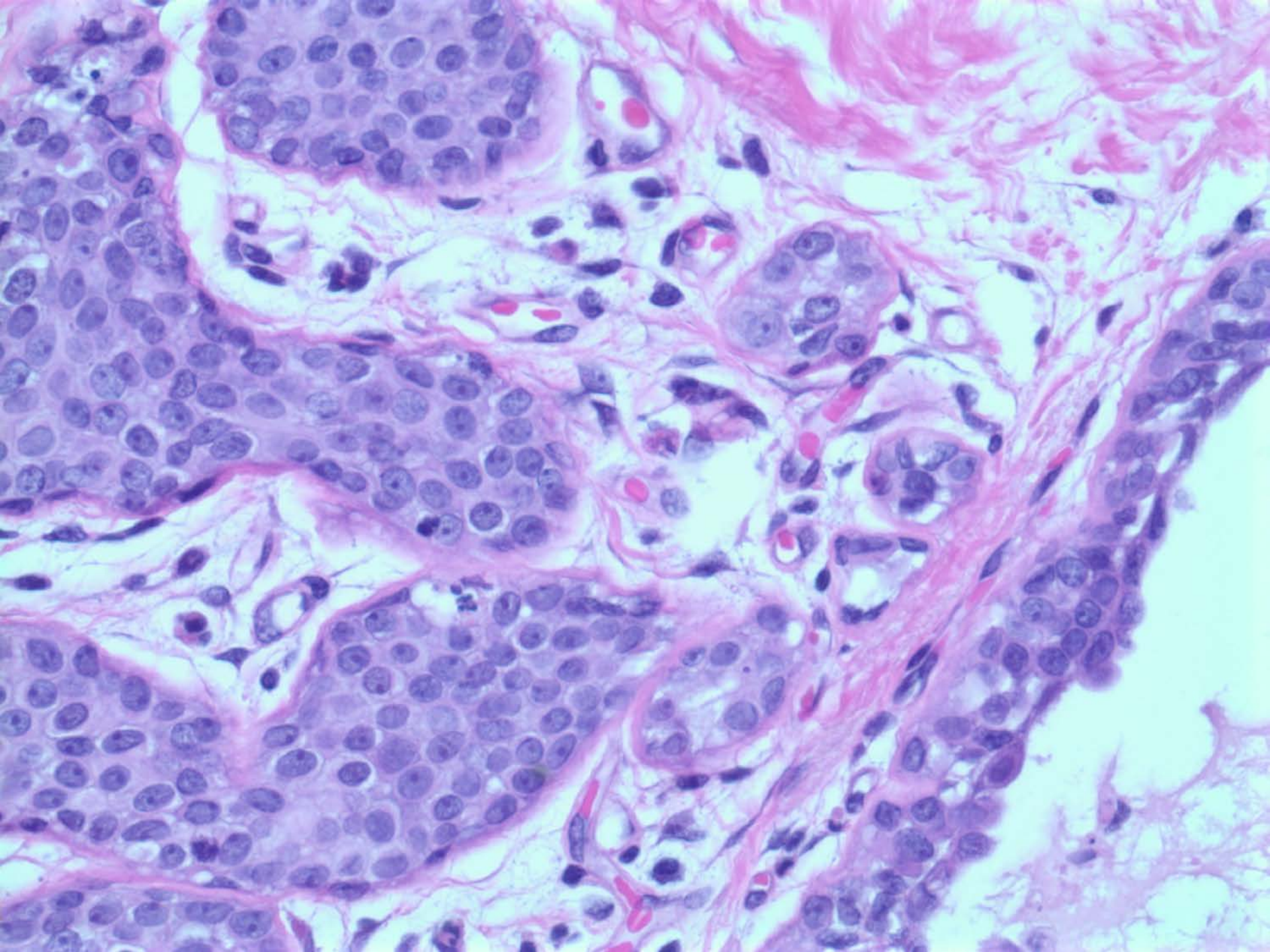
Page: **ALH because less than 50% distended**
Rosen: **LCIS because >75% involved**
Tavassoli: **LIN 2**

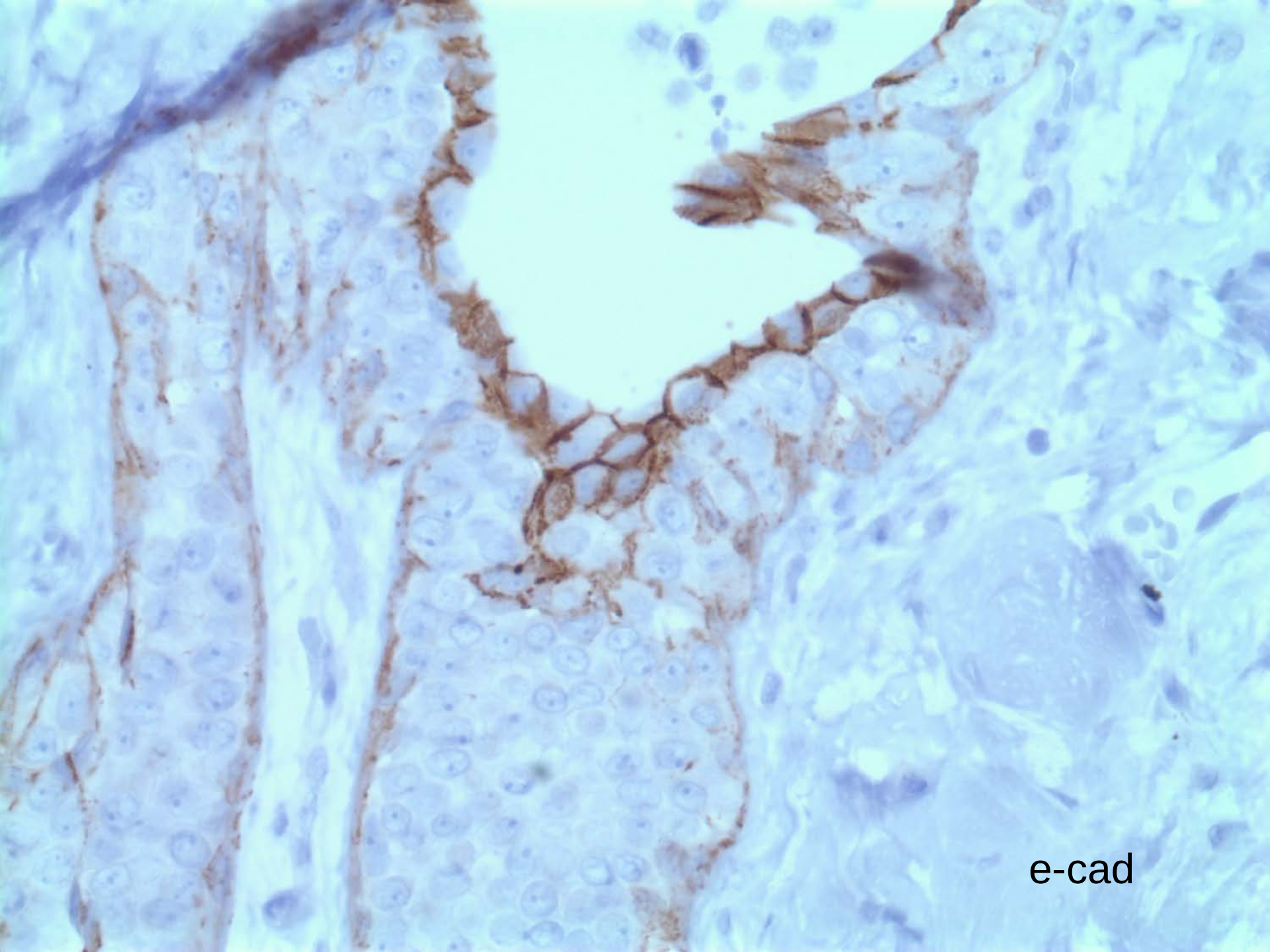











e-cad

Lobular Neoplasia (LCIS/ALH)

- **Lacks: E-cadherin, ß- and α-catenin**
- **P120: cytoplasmic staining (rather than membranous staining)**
- **Poor fixation may mimic discohesion in TDLU (less of a problem in core biopsies)**

E-cadherin

- **Helpful in difficult cases but should not be the magic tool to differentiate ductal vs lobular neoplasia**
- **Aberrant E-cadherin staining in 15% ductal and lobular lesions**

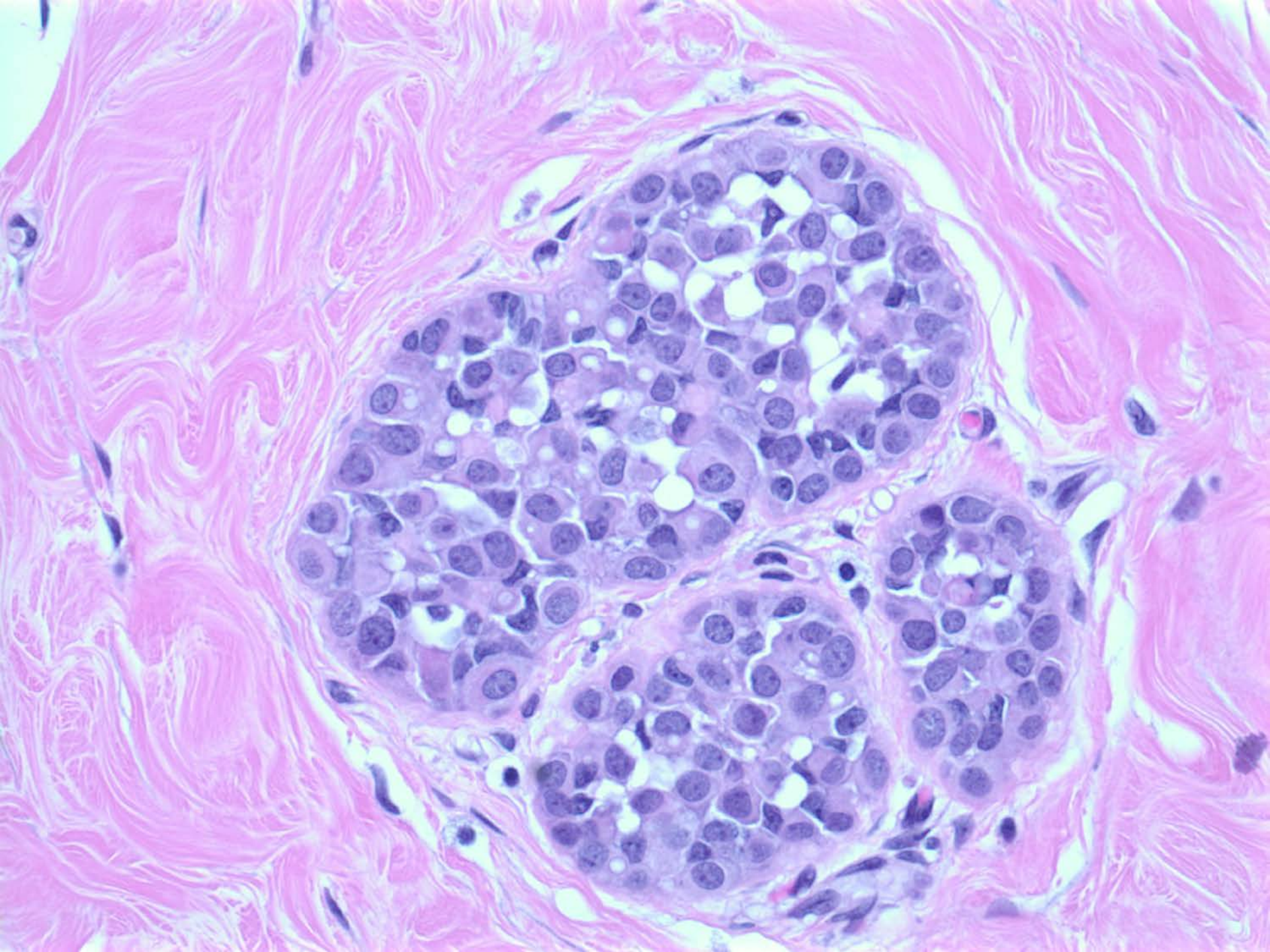
Table 1 E-cadherin immunoreaction in duct and lobular neoplasia (E-cadherin immunostaining)

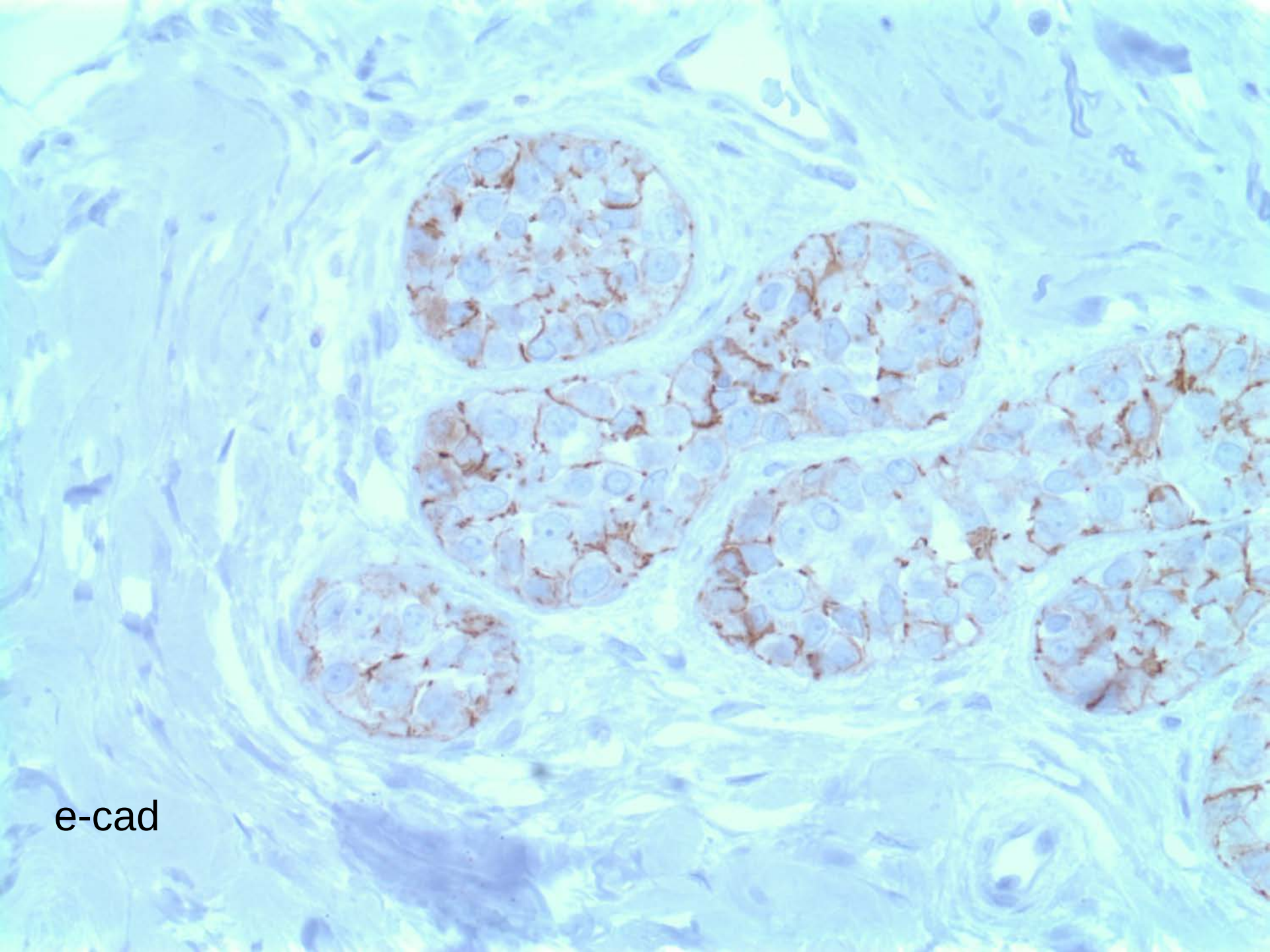
Cases/ diagnoses	*Complete absence*	*Weak/partial fragmented*	*Focal/dot-like cytoplasm*	*Complete membrane*	*Reduced/weak membrane*	*Antibody clone/dilution*	*IHC staining technique*
140 LN/ILC	121 (86.4%)	**16 (11.5%)**	**3 (2.1%)**			ECH-6 clone Cell Marque, prediluted	HIER Citrate, pH 6.0 EnVision Plus
21 DCIS/IDC				15 (71.4%)	**6 (28. 6%)**		

CIS, carcinoma *in situ*; DCIS, duct carcinoma *in situ*; HIER, heat-induced epitope retrieval; IDC, infiltrating duct carcinoma; ILC, infiltrating lobular carcinoma.
Bold number and percentage: cases with aberrant E-cadherin reaction.

- **Interobserver variability, variation with the Ab used**

Choi et al Mod Path 2008

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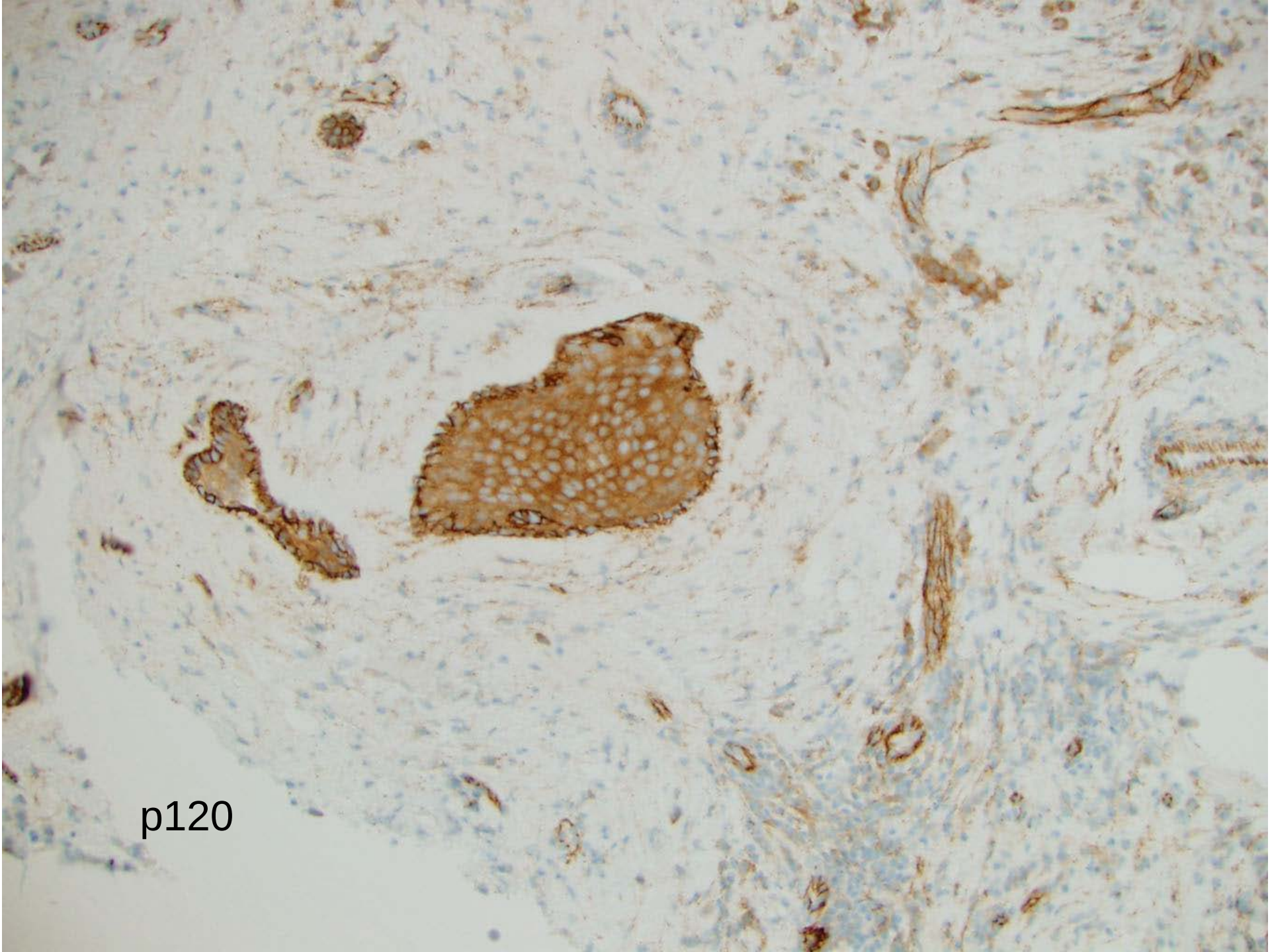
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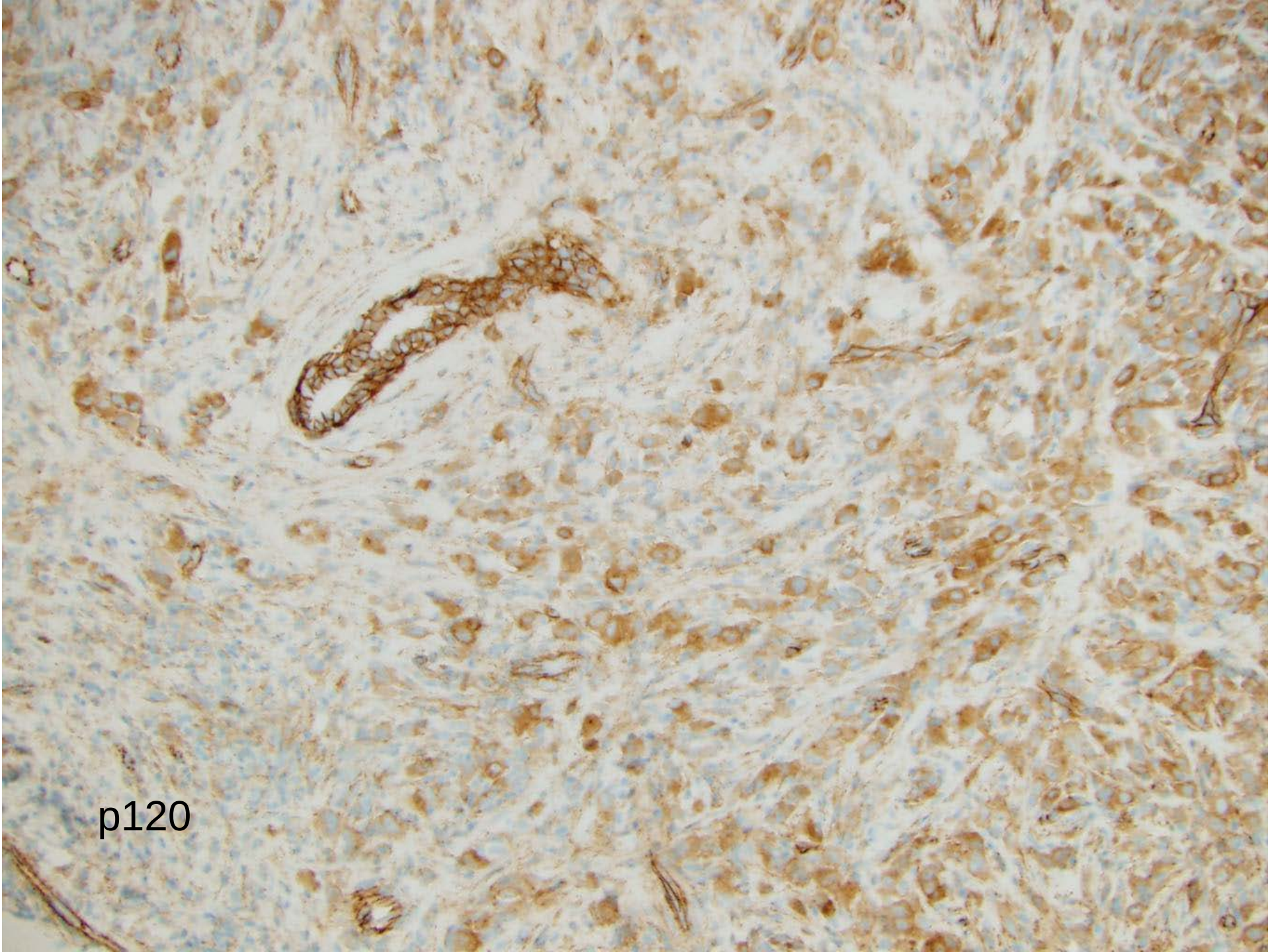
p120

LCIS

- **1941 Foot and Stewart**
  - **concluded LCIS is premalignant and recommended mastectomy**
- **After 3 decades it was noticed that LCIS do not uniformly progress to invasive cancer and risk is bilateral**
- **In 1978 Haagensen coined the term lobular neoplasia to discourage surgeons form performing mastectomy because of low risk of subsequent breast cancer and that unilateral mastectomy would not address the nearly equal risk of contralateral breast cancer**

LCIS

- **Many was reluctant to re define LCIS as purely non malignant lesion as:**
  - **LCIS is associated with greater risk for subsequent cancer than is ALH**
  - **LCIS may be occasionally be direct precursor of invasive lobular cancer (such as same truncating e cadherin mutations seen in invasive locular cancer adjacent to LCIS (Berx et al 1996)**
- **Nomenclature has not changed the recommendations that LCIS should not be treated with surgery**
- **1990s consensus was LCIS is a risk factor but not precursor for BrCa →no further surgical treatment after Bx diagnosis**

Is the Management of LCIS the Same as DCIS?

- LCIS in core bx→??
- LCIS in excisional bx→no further excision
- LCIS at lumpectomy margin →noted but not re-excised
- Post-excision radiotherapy not recommended
- Hormonal therapy recommended

- DCIS on core bx→lumpectomy
- DCIS in excisional biopsy may need re-excision if margins positive
- DCIS at lumpectomy margin→re-excised
- Post lumpectomy radiotherapy required in most cases
- Hormonal therapy recommended in ER+ DCIS

Is the Management of LCIS the Same as DCIS?

- LCIS in core bx→??
- LCIS in excisional bx→no further excision
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- DCIS on core bx→lumpectomy
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- DCIS at lumpectomy margin→re-excised
- Post lumpectomy radiotherapy required in most cases
- Hormonal therapy recommended in ER+ DCIS

Is re-excision needed after LCIS at lumpectomy or excisional biopsy margin ?

Did local recurrence vary with co-existing LCIS in women with breast cancer

TABLE 3
Comparison of Reports with LCIS as a Component of Breast Carcinoma Treated with BCS and RT

Reporting institution	Stage of disease	No. of control patients	No. of patients with LCIS	Median follow-up in mos	Risk of local failure		*P*-value
					+LCIS	−LCIS	
Fox Chase[21]	I–II	1209	65	76	5% 29%	3% After 5 yr 6% After 10 yr	0.003
Yale[22]	0–II	1045	51	127	23%	16%	NS
Harvard[23]	I–II	1062	137	161	13%	12%	NS
University of Michigan (current study)	0–II	121 matched	64	45	1.7%	1.6%	NS

LCIS: lobular carcinoma in situ; BCS: breast-conserving surgery; RT: radiotherapy; +LCIS: with lobular carcinoma in situ; −LCIS: without lobular carcinoma in situ; NS: not significant.

Ben-David et al Cancer 2006

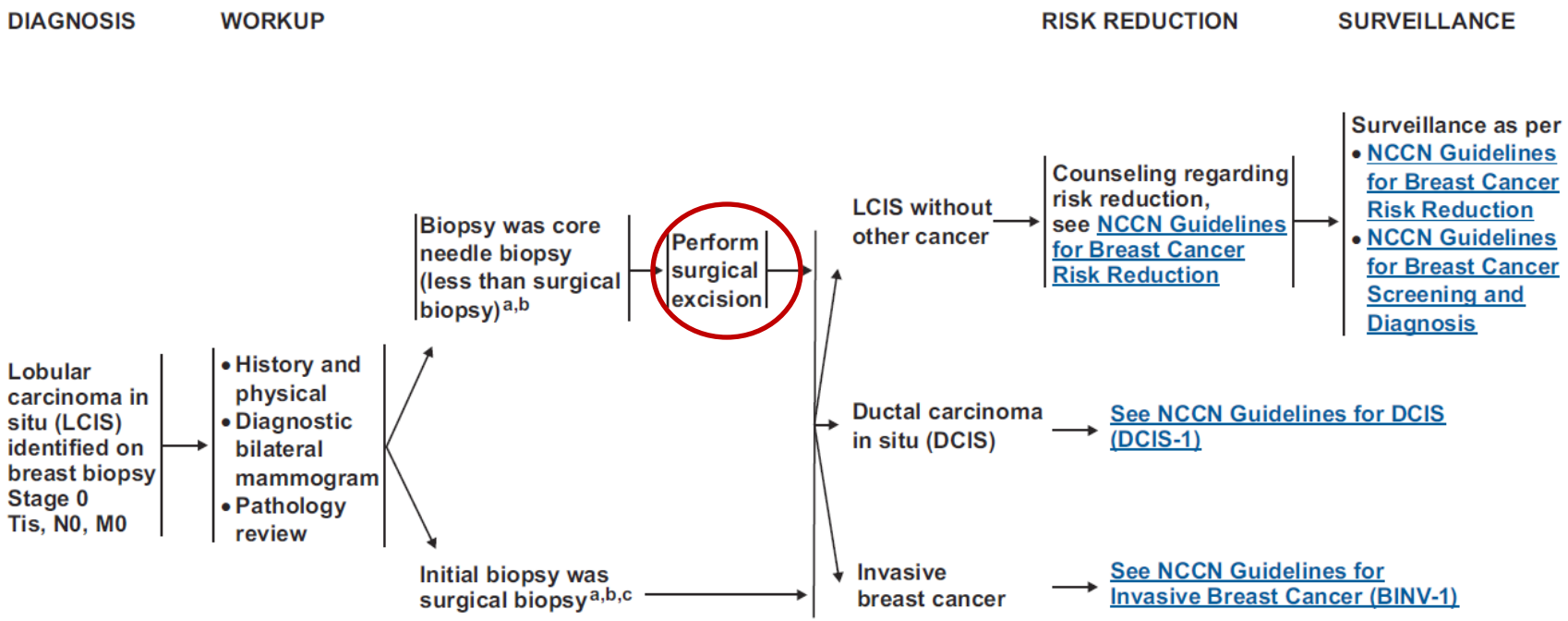
Is re-excision needed after LCIS at margin ?

Extent of LCIS or its presence at the margins did not effect excellent local control with breast conserving surgery and RT

Ben-David et al Cancer 2006
Adepoju et al Cancer 2005

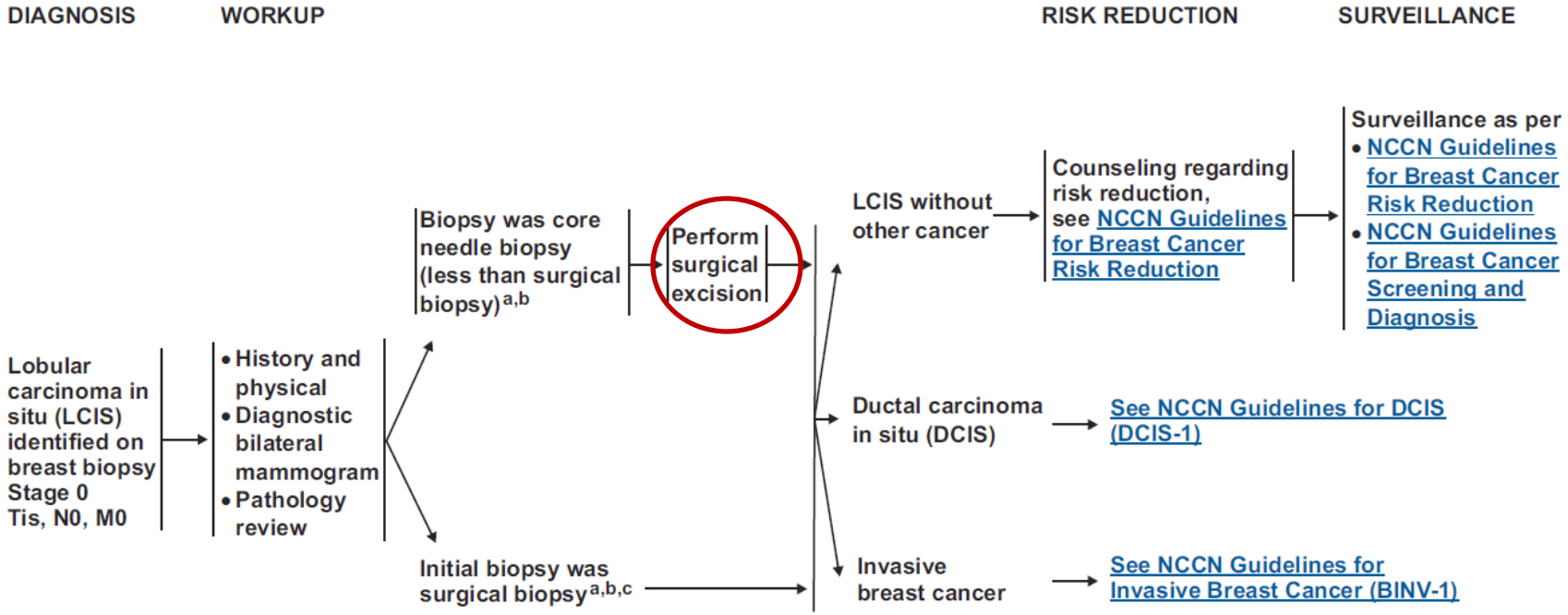
Lobular Neoplasia
To Excise or Not to Excise After Core Needle Biopsy

NCCN / LCIS



[c]Multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy may be associated with increased risk of invasive cancer on surgical excision.

NCCN / LCIS



[c]Multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy may be associated with increased risk of invasive cancer on surgical excision.

Therefore, according to the NCCN Panel, it is reasonable to perform surgical excision of LCIS found in a core biopsy to exclude an associated invasive cancer or DCIS. More than 4 foci of LCIS may also increase the risk for upstaging on surgical biopsy.[38] The NCCN Panel recommends that LCIS of the usual type (involving <4 terminal ductal lobular units in a single core) found on core biopsy, as a result of routine screening for calcifications and without imaging discordance, may be managed by imaging follow-up.

Morphologic Parameters of LN as Predictors of Malignancy on Excision

	Diagnosis at surgical excision				
			Malignancy		
LN, pure or associated with other lesions at VANCB	Benign, no.	Atypia/LCIS, no.	No.	%	Total, *N* (%)
Pure LN (ALH + LCIS)	25	99	25*	16.8	149 (52.1)
Pure ALH	18	59	13	14.4	90 (31.5)
Pure LCIS	7	40	12	20.3	59 (20.6)

Bianchi et al Histopathology 2013

Morphologic Parameters of LN as Predictors of Malignancy on Excision

– Significant association with BiRADS 4-5
– NO association with extent of LN

Bianchi et al Virchows Arch 2012

Recommendations for Excision

- **Despite removal of calcifications some cases may still have cancer on excision**
- **Unable to identify particular mammographic, technical findings or features that would indicate LN more likely to be upgraded**

Elsheikh, AJCP 2002
Foster, Radiology 2004
Mahoney, AJR 2006

Dr Rodman: “ Any attempt to make the diagnosis more exact is certainly praiseworthy. Being a surgeon, however, I am not sure but that sometimes *x-ray men have somewhat vivid imaginations*. The clinical diagnosis of carcinoma of the breast and chronic cystic mastitis is not ordinarily difficult, and therefore until we have x-ray evidence of a more positive value we had best go a little slow in accepting evidence which is contrary to clinical findings”

Philadelphia Academy of Surgery 1931

Findings at Surgical Excision of LN

Reference	Cases With Follow-Up Excision	Findings at CNB			Mention of Imaging-Histologic *Concordance*	Findings at EXB			No. of Upgrades/ Total (%)	Comments on Cases With Upgrade
		ALH	LCIS	LN		Total Cases. With Invasion and/or DCIS	Cases. With DCIS	Cases. With Invasion		
Shin & Rosen, 2002[7b]	13	5	8	NA	No	2	1	1	2/13 (15)	—
Middleton,2003[8b]	17	6	9	2	No	6	0	6	6/17 (35)	All mass lesions
Renshaw, 2006[30b]	92	NA	NA	92	No	7	1	6	7/92 (8)	Carcinoma away from CNB site in 5 cases; 1 case was not cLN at CNB
Cangiarella, 2008[28b]	38	18	20	NA	No	3	1	2	3/38 (8)	Two mass lesions
Elsheikh & Silverman, 2005[22c]	33	20	13	NA	Yes	9	4	5	9/33 (27)	Two mass lesions; 1 case was not cLN at CNB
Liberman, 1999[6b]	13	9	4	NA	Yes	2	1	1	2/13 (15)	All non-cLN
Hwang, 2008[21b]	87	48	39	NA	Yes	4	1	3	4/87 (5)	Three cases were not cLN at CNB
Nagi, 2008[20b]	45	NA	NA	45	Yes	2	1	1	2/45 (4)	—
Rendi, 2011[27c]	68	20	48	NA	Yes	2	2	0	3/68 (4)	All in high-risk women; 1 mass lesion
Current study[c]	72	42	30	NA	Yes	2	1	1	2/72 (3)	One in a high-risk woman

Murray Cancer 2013

Lobular Neoplasia
Outcomes of Prospective Excision

All pure LN excised (n=80)

- 72/80 (90%)→ concordant Rad-Path
  - 2/72 **(3%)** upgrade

    Calcs in benign glands

- 8/80 (10%)→ discordant Rad-Path
  - 3/8 **(38%)** upgrade

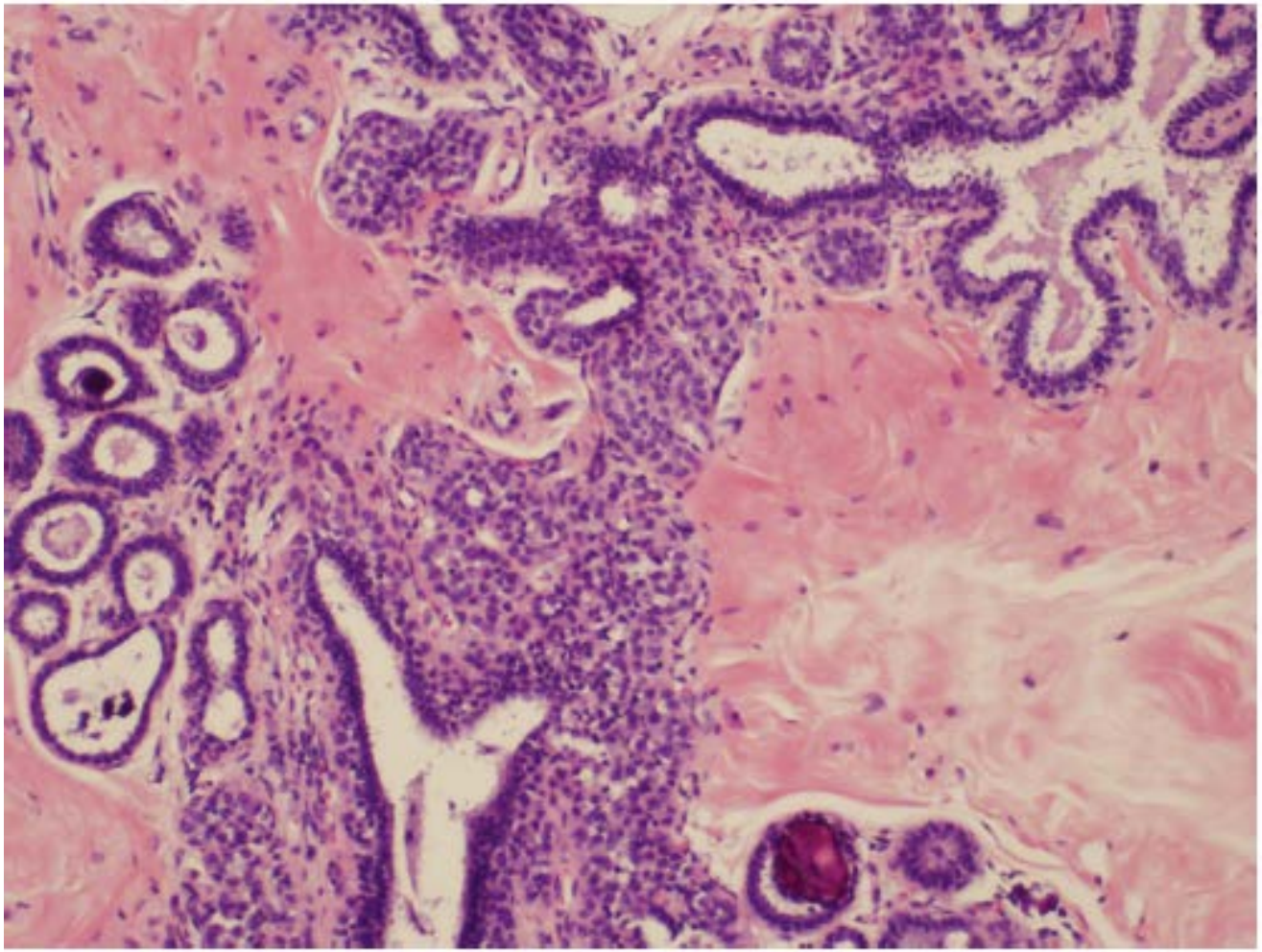
    Upgrades: insufficient explanation for mass

Murray et al Cancer 2013

Multidisciplinary approach LN

- Retrospective study with long f/u
- 124 LN
- 104 patients were clinically and or radiologically monitored
- Median follow up 3.4 years (range: 0.44-8.6 years)

Middleton, Cancer Medicine 2012



Multidisciplinary approach LN

Variable	Levels	Upgrade		*P* value
		Yes (*n* = 8)	No (*n* = 81)	
Focal (<3 TDLU) vs. extensive (≥3 TDLU)	Extensive	8 (32%)	17 (68%)	<0.0001
	Focal		64 (100%)	
Targeted vs. incidental	Incidental	1 (1.6%)	61 (98.4%)	0.0008
	Targeted	7 (25.9%)	20 (74.1%)	
Percentage of lesion removed during biopsy	<Half excised		17 (100%)	1
	>Half excised	2 (5.6%)	34 (94.4%)	

Middleton, Cancer Medicine 2012

BIRADS Breast Imaging Reporting and Data System

Bx

0: Incomplete

1: Negative

2: Benign finding(s)

Family history
Patient and/or physician concern

3: Probably benign (≤2% risk of malignancy)

4: Suspicious abnormality

5: Highly suggestive of malignancy

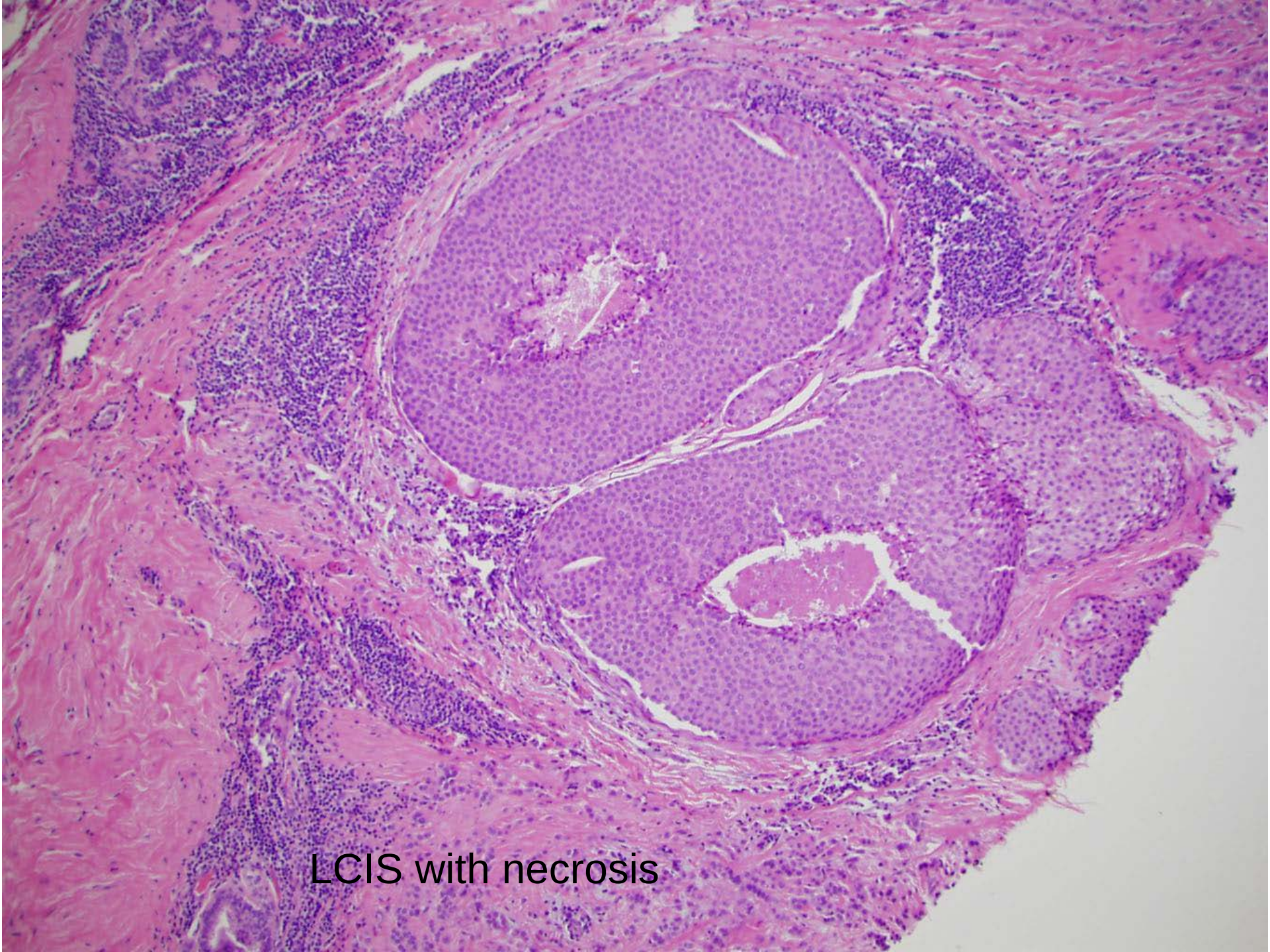
6: Known biopsy – proven malignancy

Major goal of CNB is to reduce number of open surgical biopsies. As such the threshold for proceeding to open biopsy should be relatively low particularly in the absence of firm data on which to base management decisions.

Recommendations for Excision

- **Co-existing high-risk lesions such as ADH**
- **Morphologic overlap with DCIS**
- **Mixed E-cadherin staining**
- **Pleomorphic LCIS**
- **Radiologic-pathologic discordance**
- **Mass or architectural distortion**
- **Calcifications associated with LN**
- **h/o breast cancer**
- **Necrosis**
- **“Extensive” LN**

Pinder Pathology 2007
Reynolds AJR 2000
Reis-Filho JCP 2006
Karabakhtsian, AJSP 2007
Shin, Arch Path 2002
Cangieralla, Arch Path 2008


LCIS with necrosis

Pleomorphic LCIS (PLCIS)

- **Large, pleomorphic, discohesive cells with eccentric nuclei and eosinophilic cytoplasm**
- **Comedo necrosis is common and makes it difficult to differentiate from high-grade DCIS**
- **E-cadherin negative , cytoplasmic p120 catenin +, GCDFP15 +**
- **PLCIS found more commonly with invasive lobular cancer compared to usual LCIS about 45% of the time, especially pleomorphic invasive lobular carcinoma**

Chivukala et al. AJSP 2008
Dabbs et al Appl Immuno 2007
Middleton et al AJSP 2000

Pleomorphic LCIS

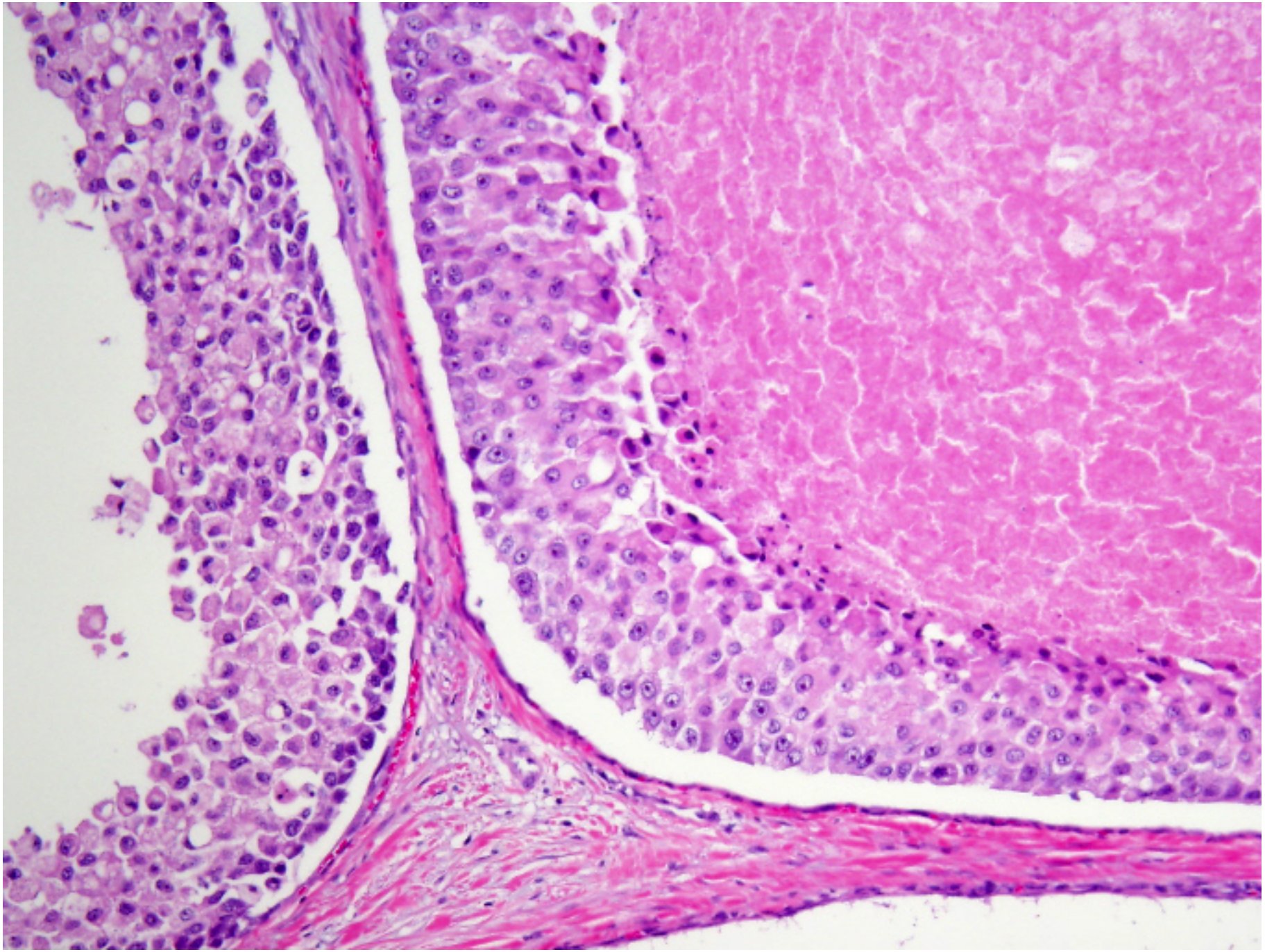
- **12 PLCIS in core biopsy→ excised**
  - **10/12 (83%) residual PLCIS**
  - **3/12 (25%) invasive lobular carcinoma**
- **11/12 (92%) ER + ; 6/12 (50%) PR +**
- **3/12 (25%) HER2 +**
- **High Ki-67 staining in 11/12 cases**

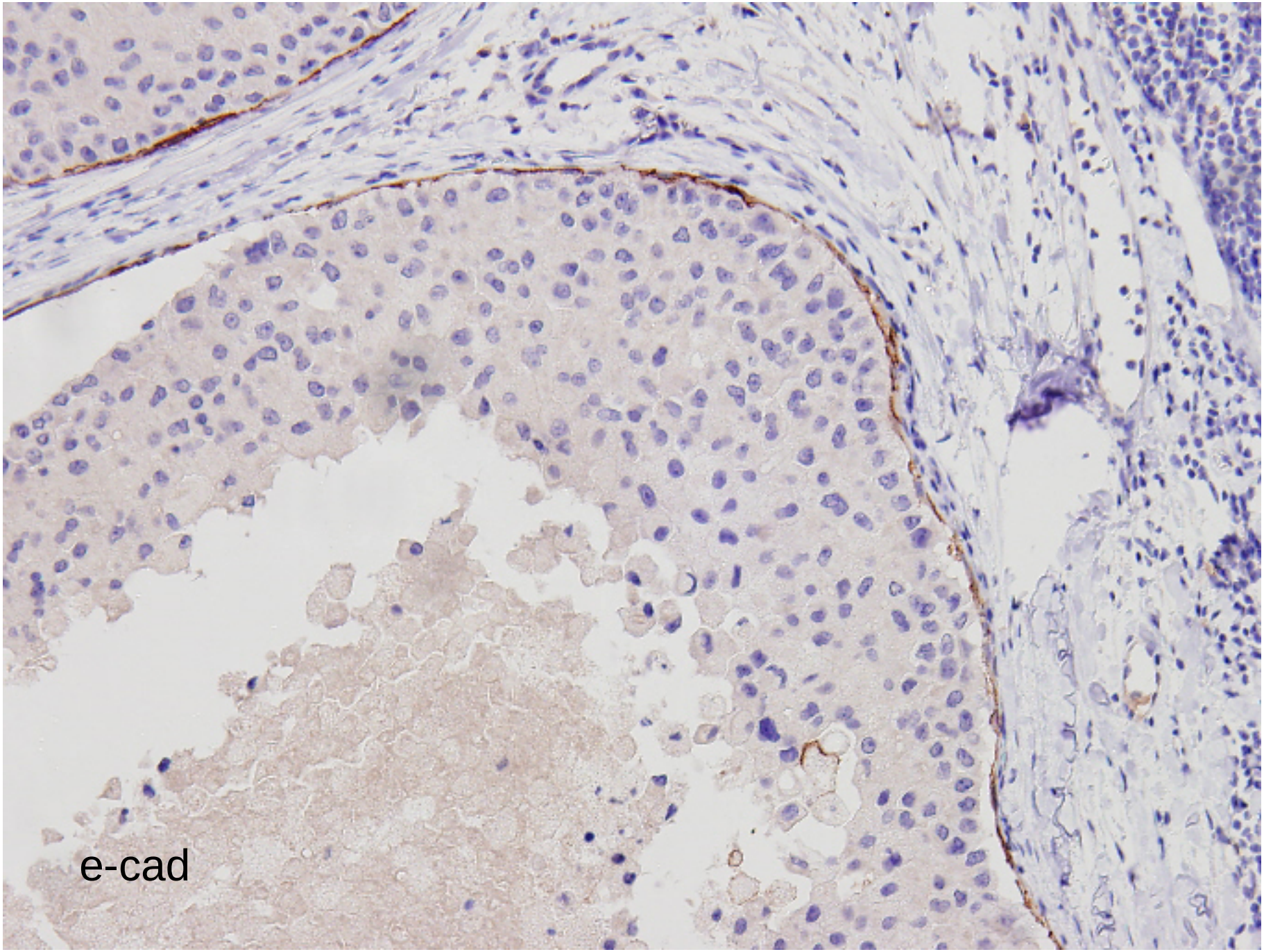
Chivukala et al. AJSP 2008

PLCIS

- **6/26 PLCIS with positive margin**
- **1/26 (3.8%) locally recurred at 19 months similar to recurrence rates after DCIS**

Downs-Kelly et al Arch Pathol 2011



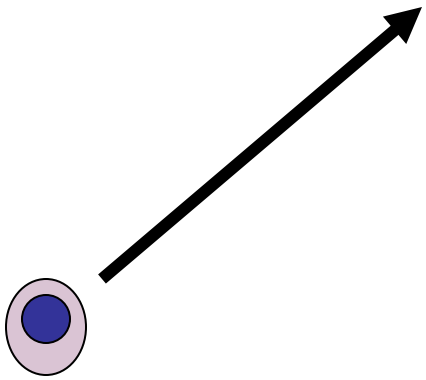

e-cad

What is the biological relationship between “incidental” lesions and high risk lesions ?

Association between LN and FEA

- **80% of the 111 breast biopsy specimens which contained LN (excluded DCIS and invasive cancer) had FEA**
- **42% of LN and ADH also harbored FEA**

Leibl et al Histopathology 2007
Bratthauer et al Virchows 2004



Stem cell(s)

Low Nuclear Grade Breast Neoplasia

*Columnar cell lesions/FEA
*ADH/low grade DCIS
*LN
*Invasive tubular, lobular and tubulo-lobular carcinoma

High Nuclear Grade Breast Neoplasia

Breast Neoplasia

Low Nuclear Grade

- Diploid/near diploid
- Recurrent loss of 16q
- Gains of 1q
- Negative basal and myoepithelial markers
- Positive CK19/18/8
- Positive ER, bcl-2,cyclinD1

High Nuclear Grade

- Aneuploid
- Complex genetic profiles
- Infrequent deletion of 16q
- More likely to be positive for basal, myoepithelial markers
- More likely to be triple negative

Abdel-Fatah et al AJSP 2008
Abdel-Fatah et al AJSP 2007

Low Grade Pathway

Chromosome 16q loss:

UDH = Random chromosome alterations similar to normal breast

Excision Recommended after ADH Diagnosed in MRI or US Guided Bx

ADH in VAB of Breast Microcalcifications

140 ADH VABB

EXCISION (n= 121)

Upgrade 16 (13%)

Ass'ed with:

> 2 TDLU

removal of <95% calcs

FOLLOW UP (n= 19)

No new lesions

Nguyen Ann Surg Oncol 2011

Benign Solitary Intraductal Papillomas

- Close imaging follow up unless
  - Discordance between imaging and pathology
  - Papillary lesion associated with mass

Thank you