Lobular Carcinoma In Situ (LCIS) and Invasive Lobular Carcinoma:

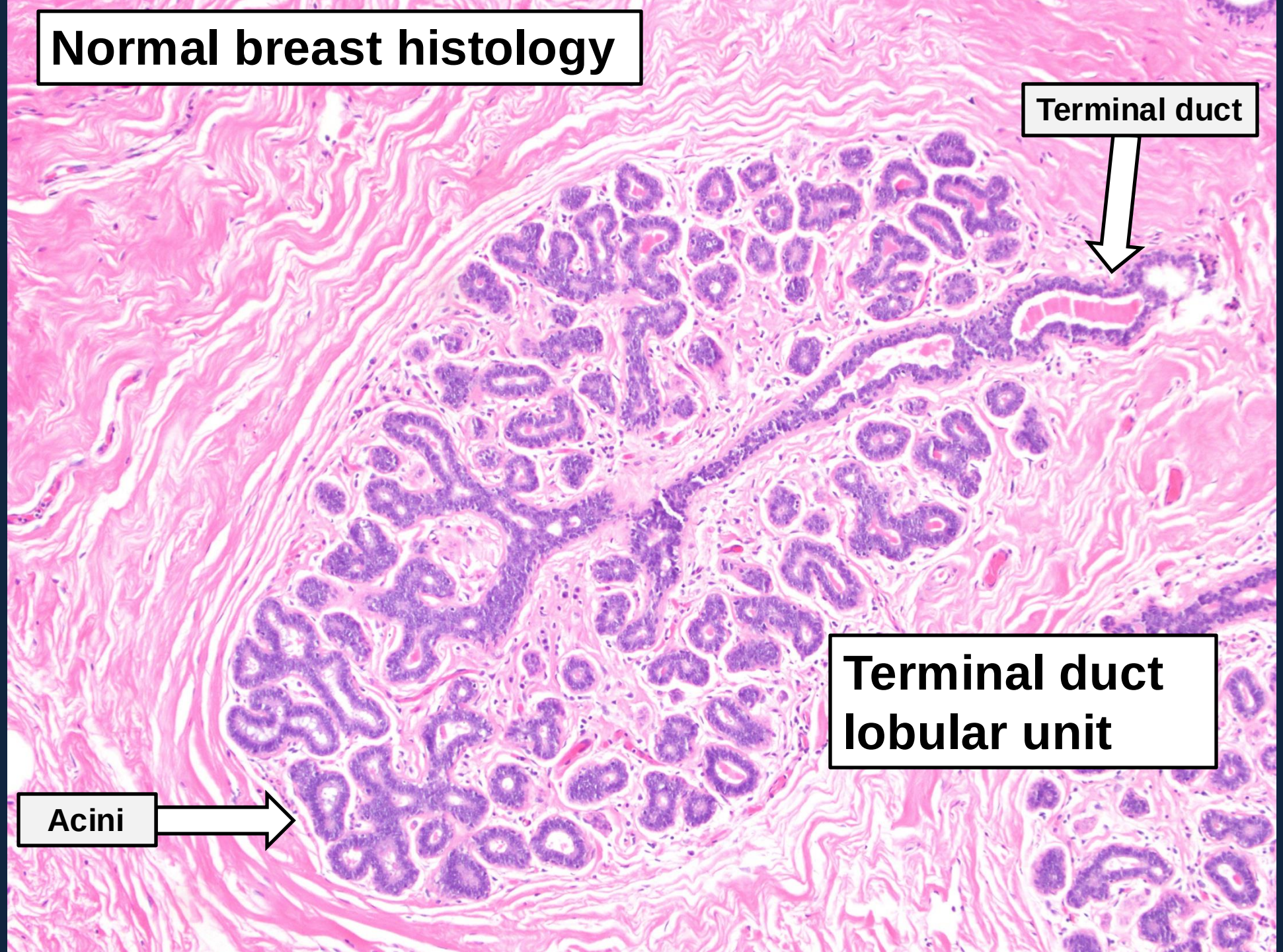
Old Story with New Concerns

6th Annual Breast Cancer Symposium
October 18, 2024

Timothy M. D'Alfonso, MD
Chief of Breast Pathology
Northwell Health

For this session…

- LCIS
  - Histopathologic features/classification
  - Clinical management
- Invasive lobular carcinoma
  - Distinction from invasive carcinoma, NST (ductal)
  - Pathologic classification


Normal breast histology
Terminal duct
Terminal duct lobular unit
Acini

LOBULAR CARCINOMA IN SITU *

A RARE FORM OF MAMMARY CANCER

FRANK W. FOOTE, JR., M.D., and FRED W. STEWART, M.D.
(From the Pathological Laboratories of the Memorial Hospital, New York, N.Y.)

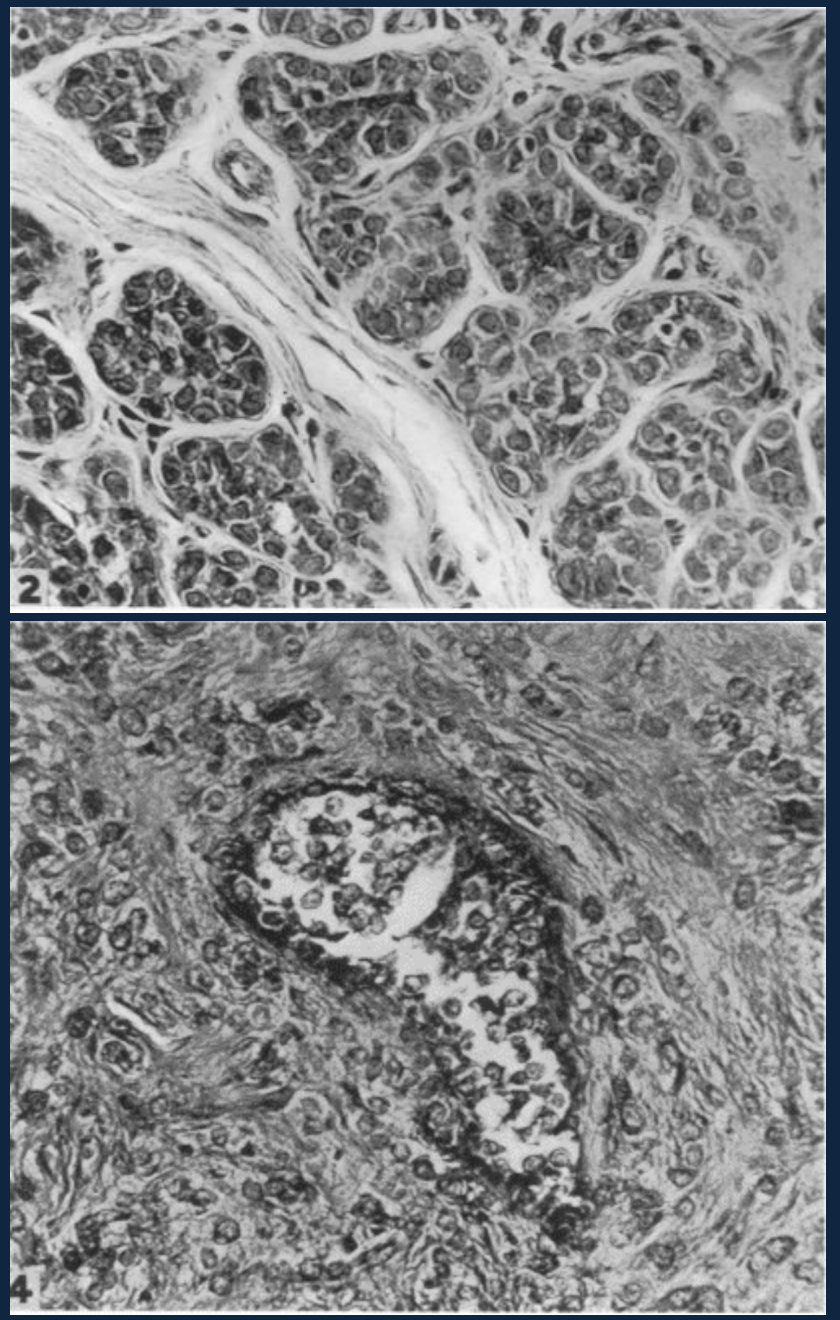
Foote and Stewart, 1941

"lobular carcinoma in situ" and its infiltrative phase characterized by loss of cohesion of cells

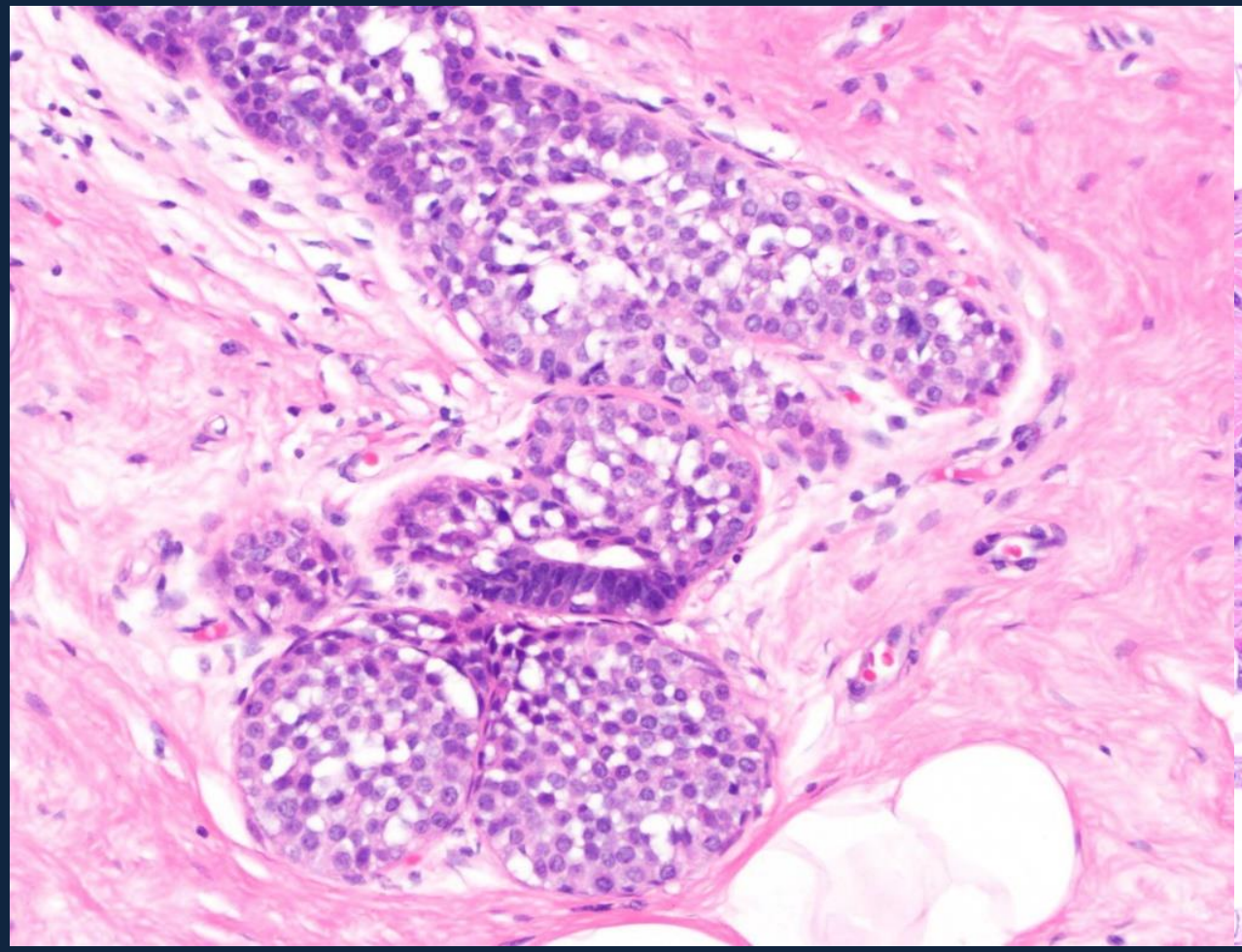
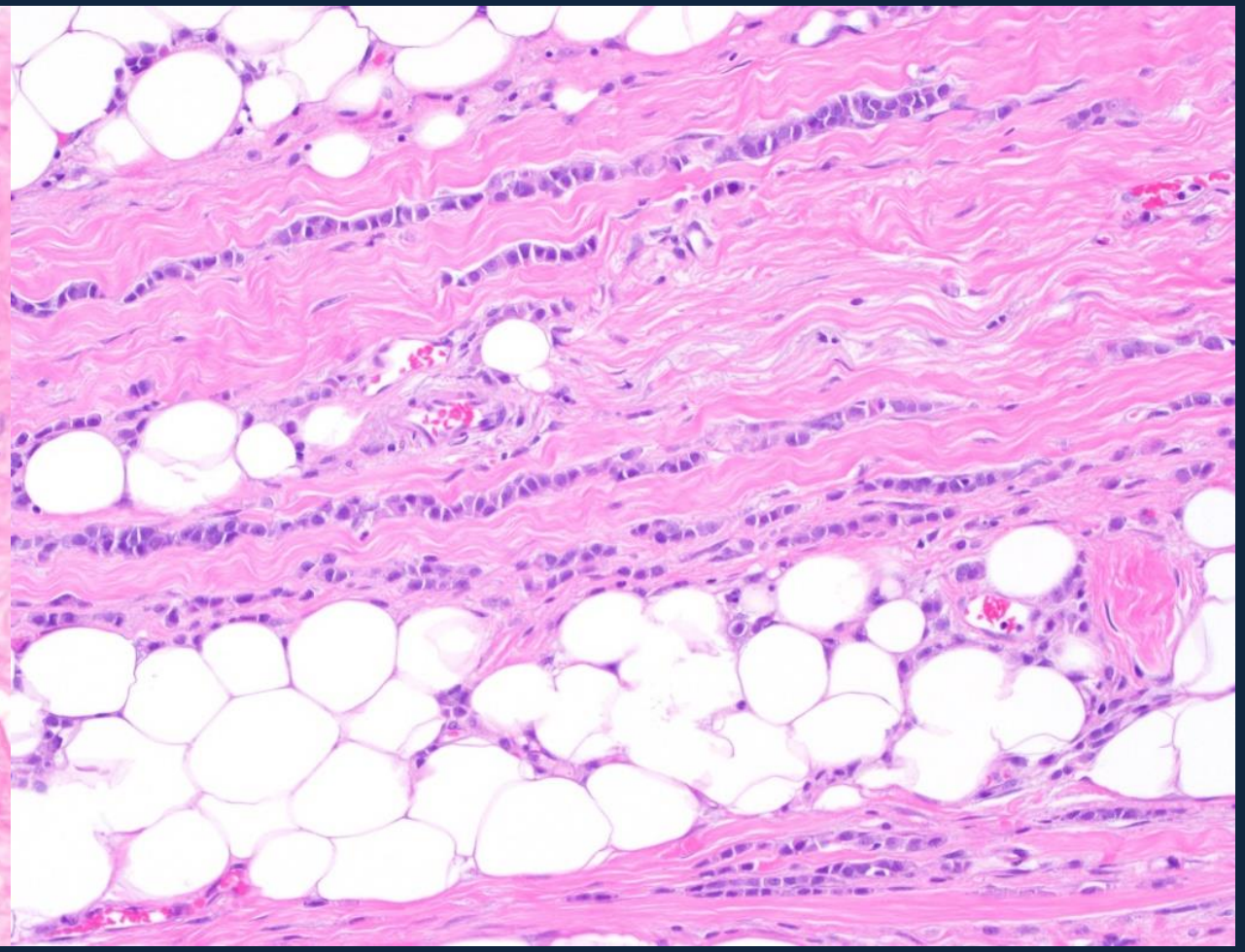
"pagetoid" growth

"disease of multiple foci"

"simple mastectomy is essential"



Am J Pathol 1941;17(4):491-496.3

Loss of E-cadherin expression is the defining feature of lobular lesions that leads to loss of cellular cohesion

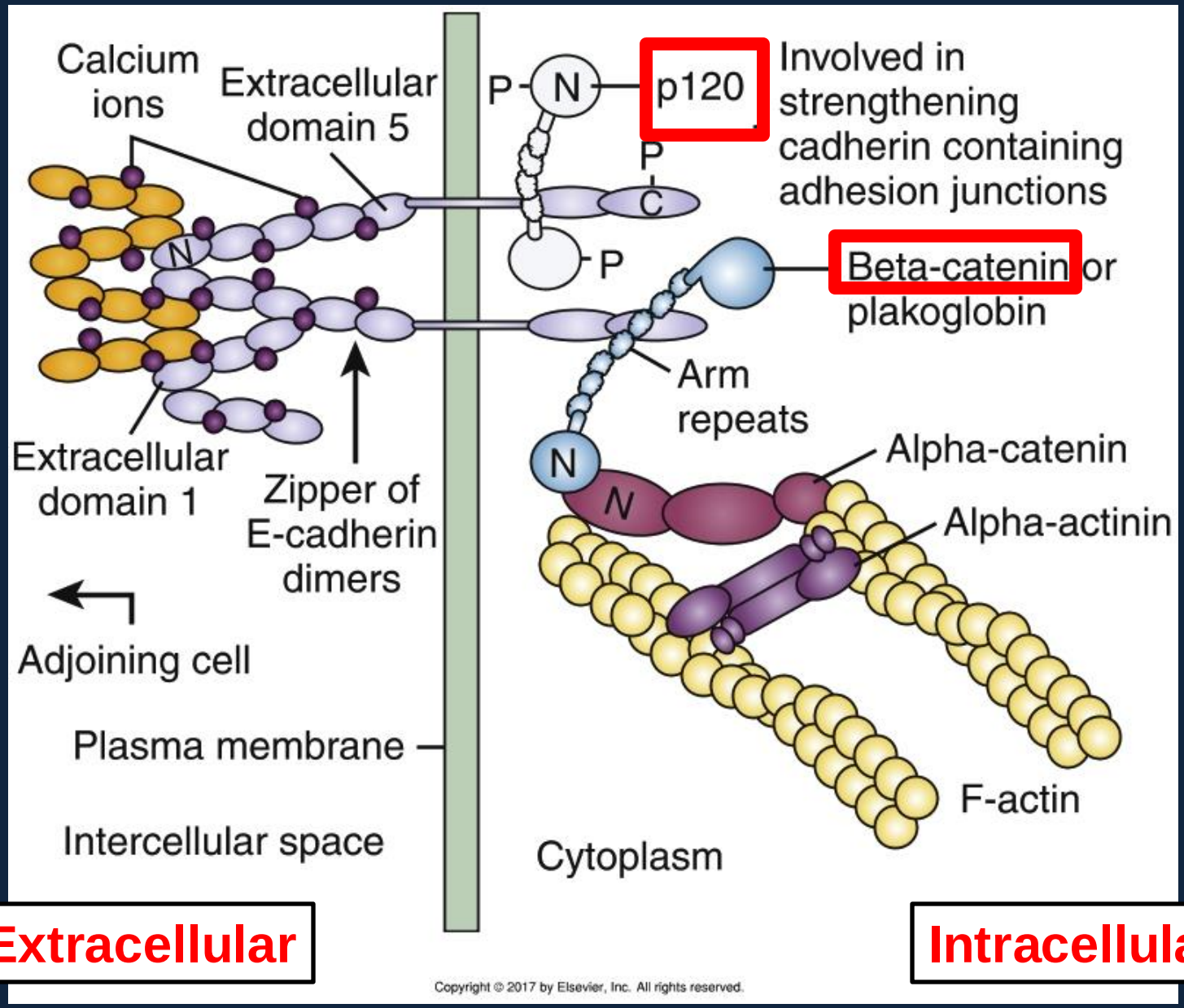
E-cadherin is cell-to-cell adhesion protein encoded by *CDH1* (16q.22.1)

CDH1 alterations in lobular carcinoma

- Biallelic inactivation of *CDH1* in majority (>80%)
  - Mutations
  - Deletions
  - Promoter methylation

- LCIS clonally related to co-existing ILC

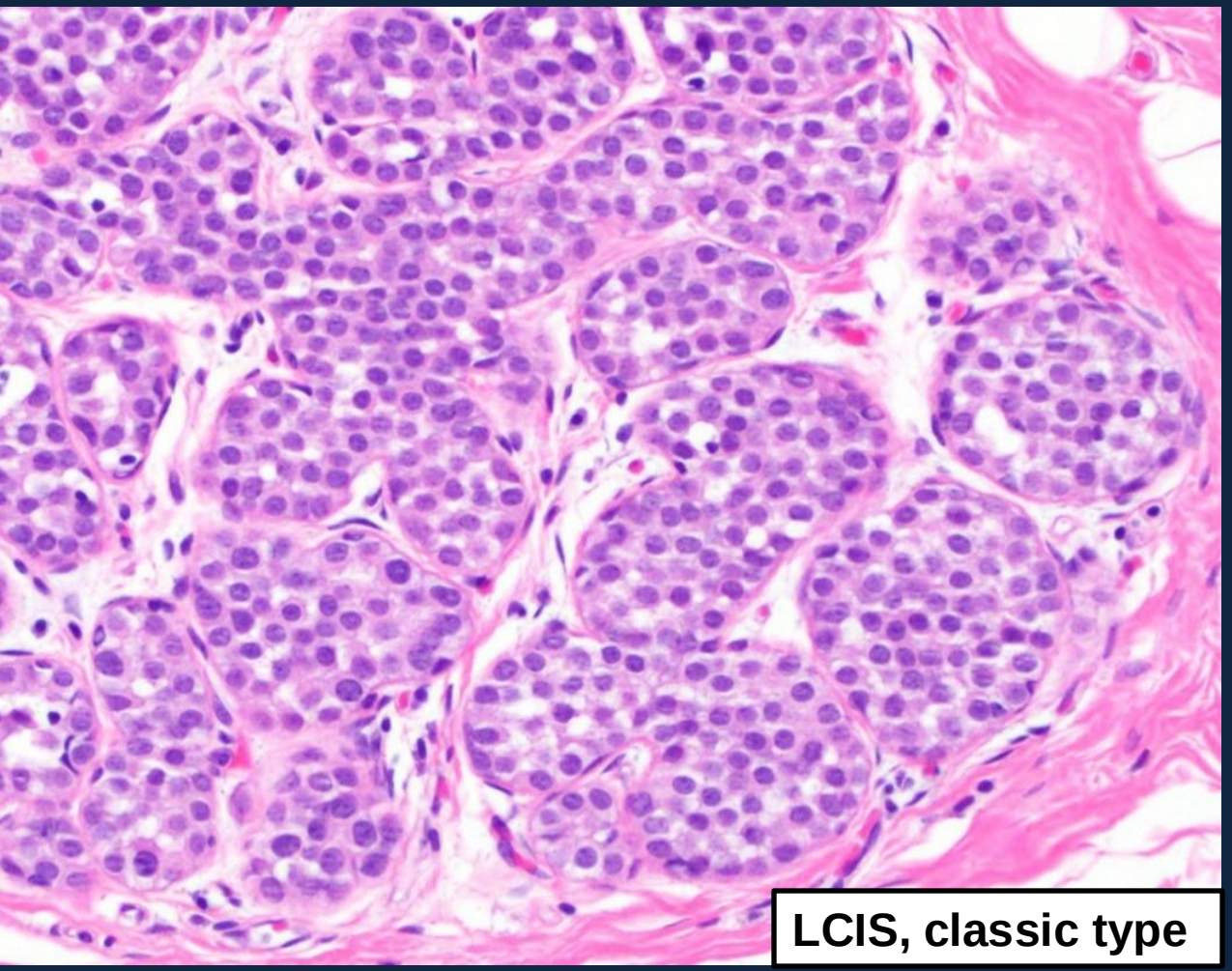
J Pathol 2010; 220(1):45-57
NPJ Precis Oncol 2024;8(1):33
Clin Cancer Res 2019;25(2):674-686.



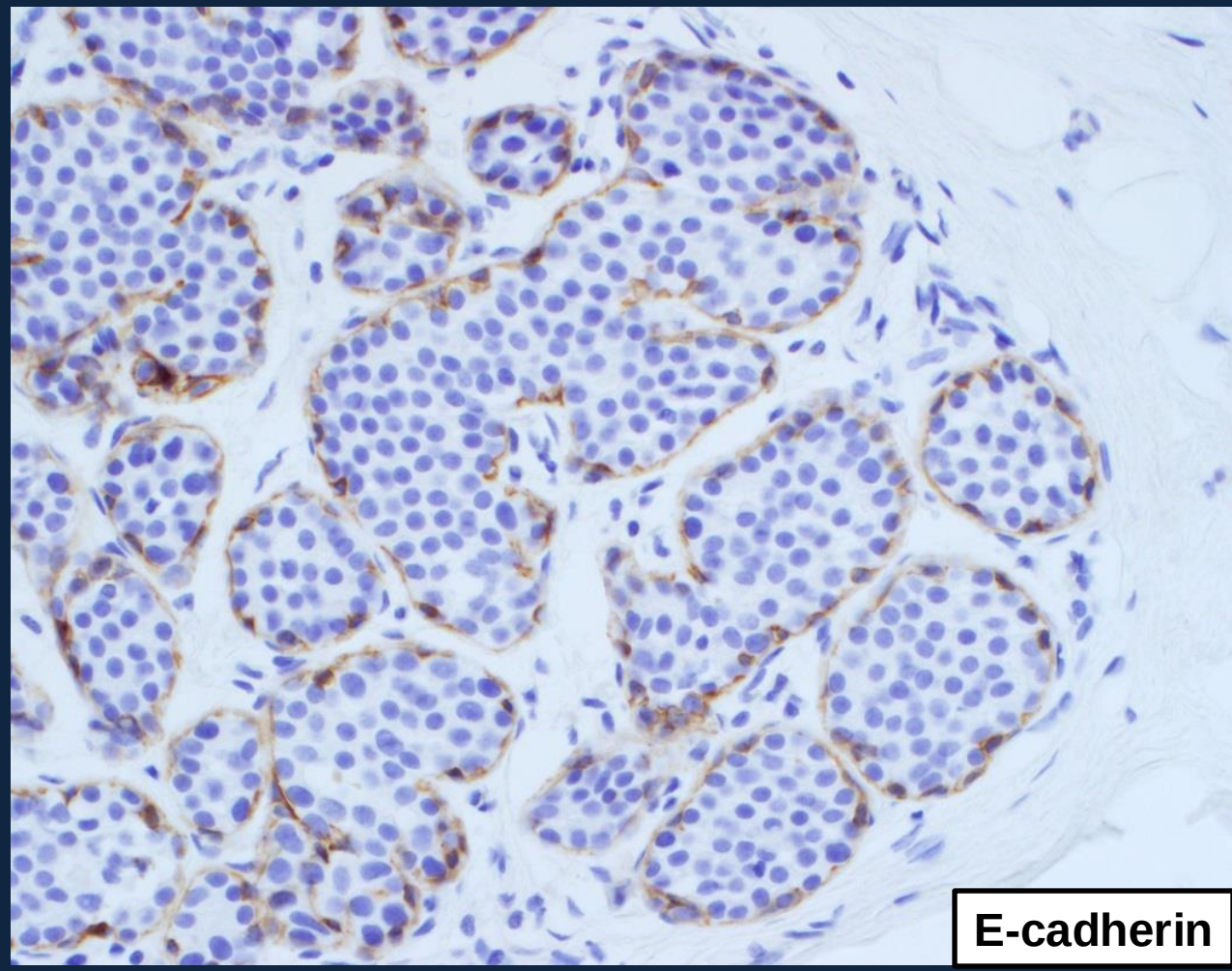
Proteins we can stain by IHC:

- **E-cadherin**
- **p120**
- **Beta-catenin**

Dabbs, DJ. Breast Pathology. 2nd Ed. Elsevier 2017



LCIS, classic type

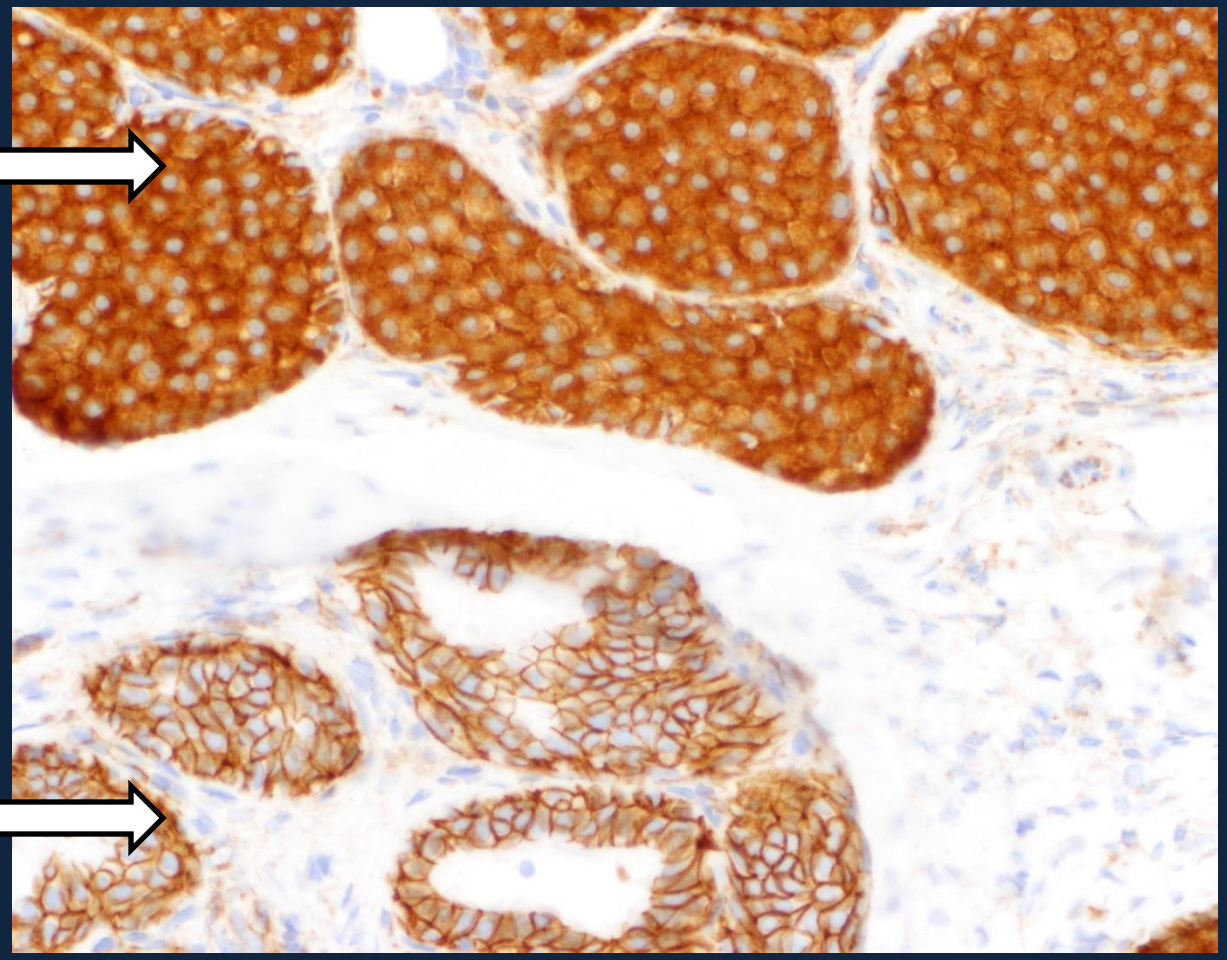


E-cadherin

Inactivation of E-cadherin results in accumulation of p120 in the cytoplasm

LCIS – cytoplasmic staining with p120

Benign glands – membranous staining with p120



Lobular carcinoma in situ (LCIS)

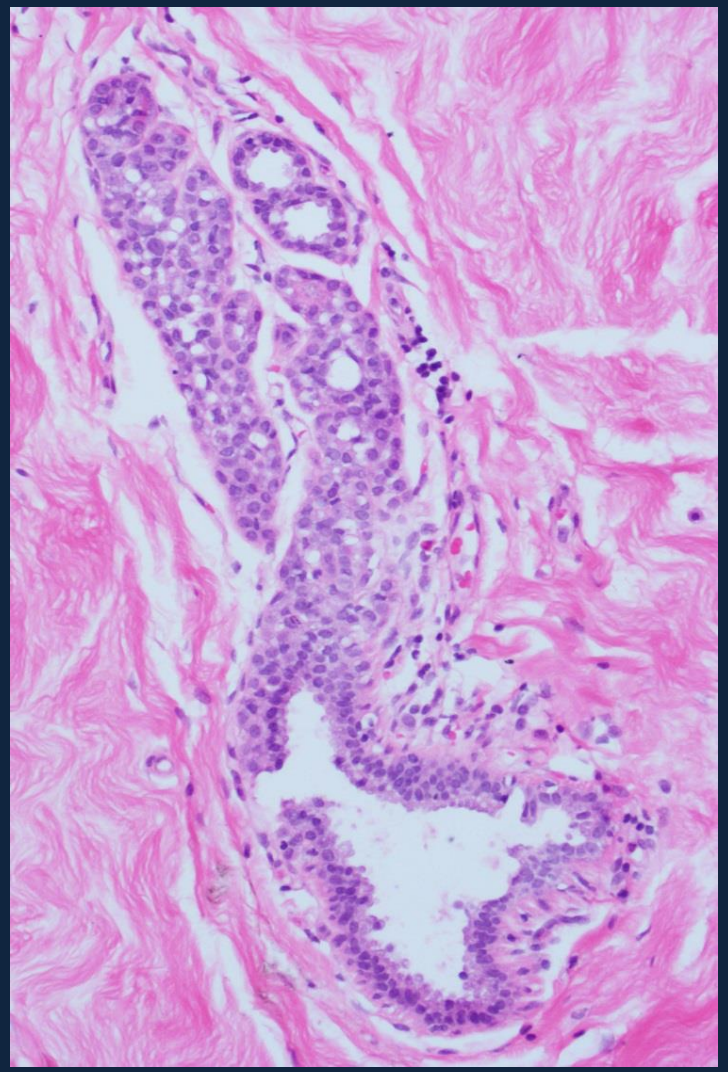
Lobular carcinoma in situ (LCIS)

- Premenopausal (mean 45 yrs)
- Multicentric, bilateral
- Often incidental finding
- Marker for increase in risk of invasive cancer (8-10x)
- Non-obligate precursor to invasive carcinoma

Arpino et al. *Cancer* 2004;101
Page et al. *Lancet* 2003;361

Atypical lobular hyperplasia (ALH)

- Less developed
- Distension of less than 50% acini in lobule
- Grouped with classic LCIS: “lobular neoplasia”



LCIS – morphologic classification

Classic

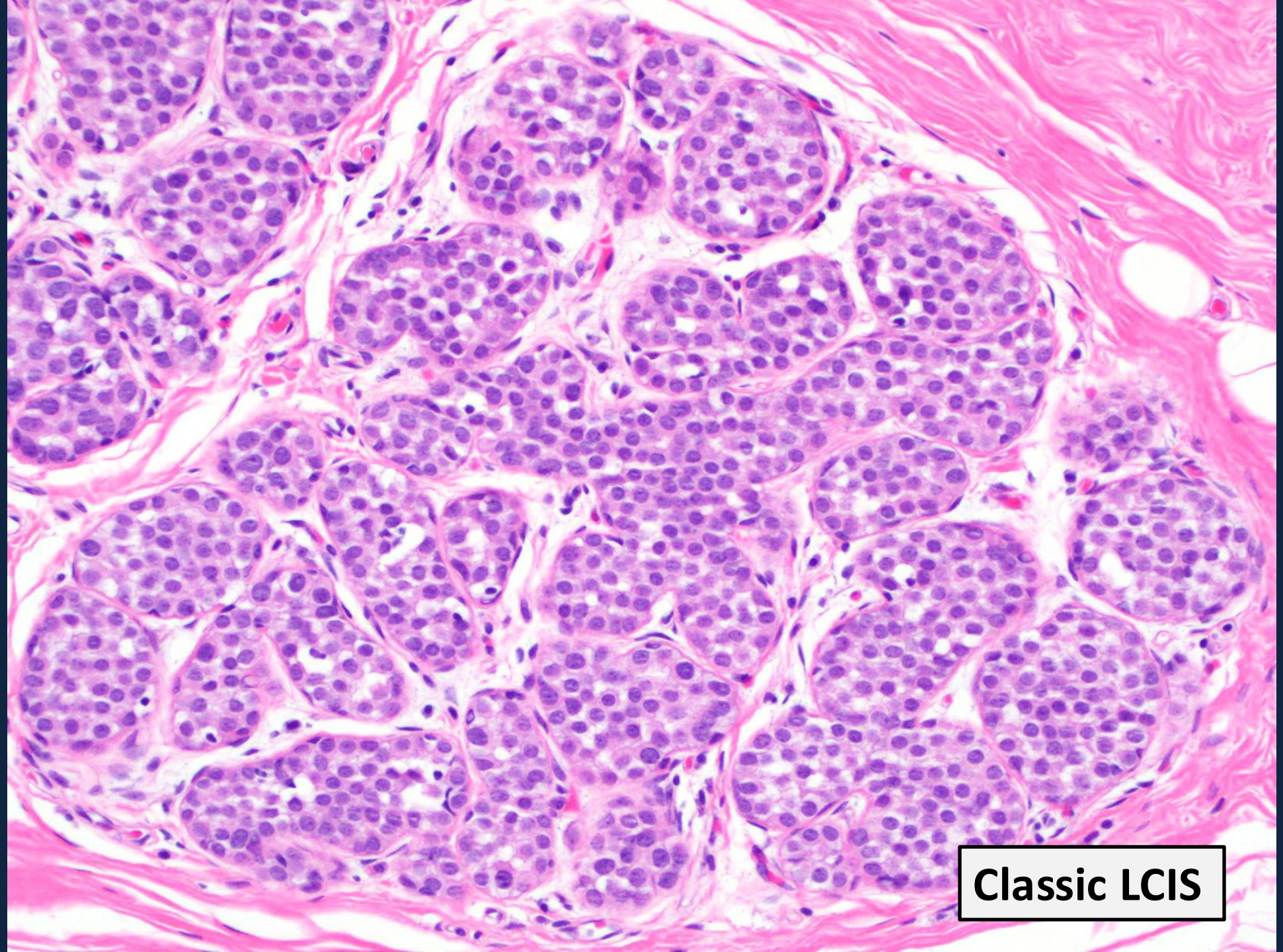
- Low to intermediate nuclear grade

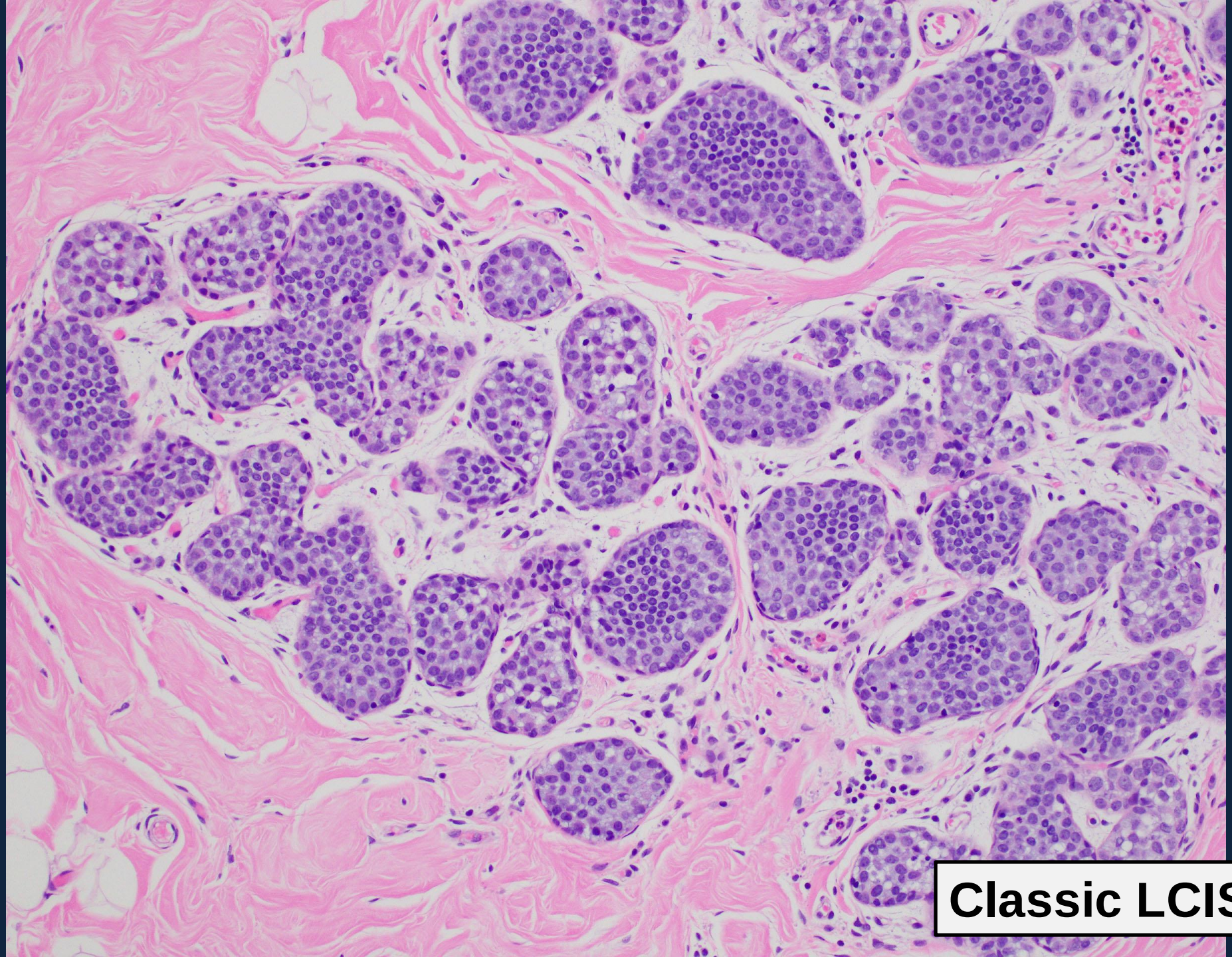
Florid

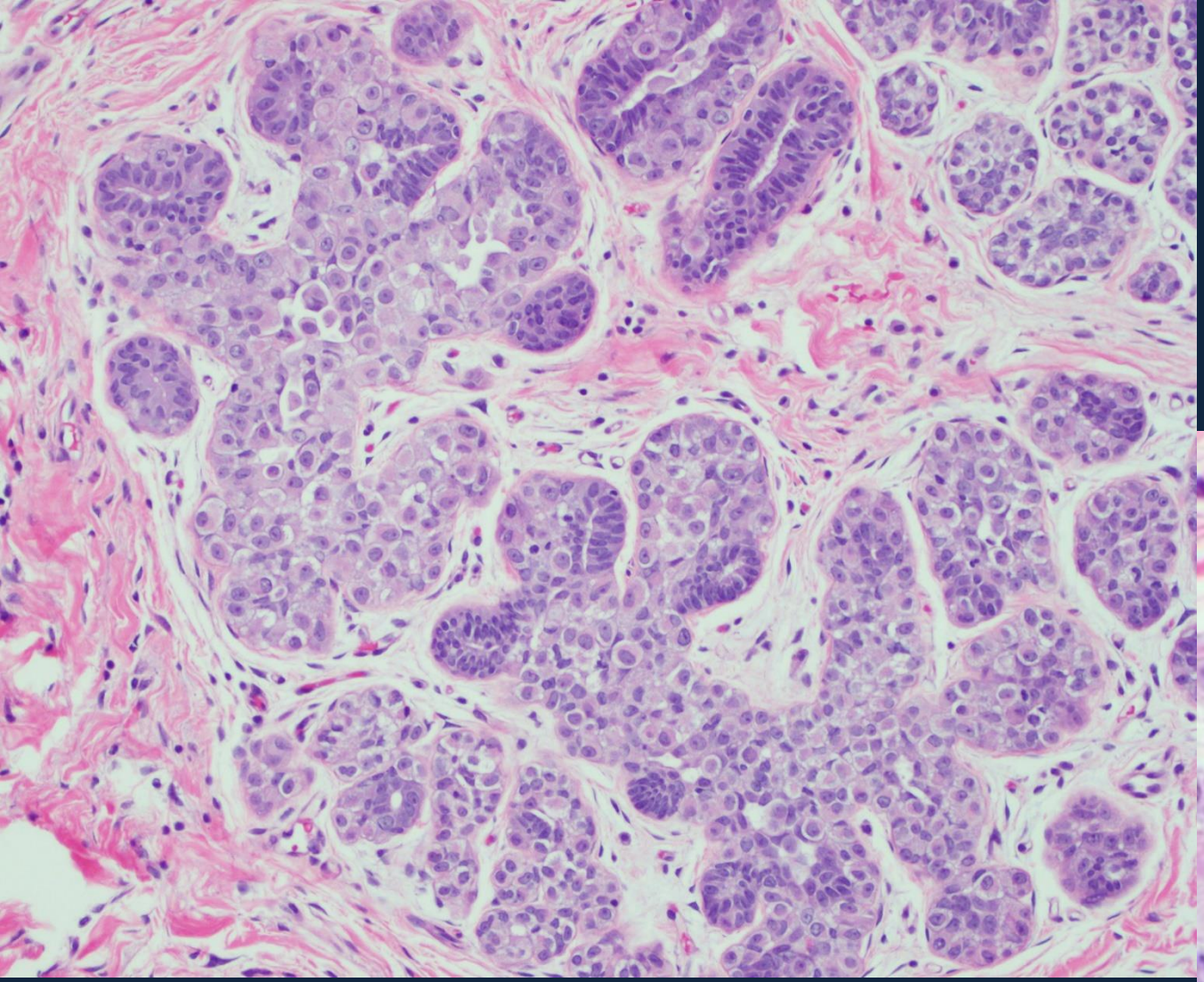
- Low to intermediate nuclear grade
- Expansion of ducts (“macroacinar distension”)

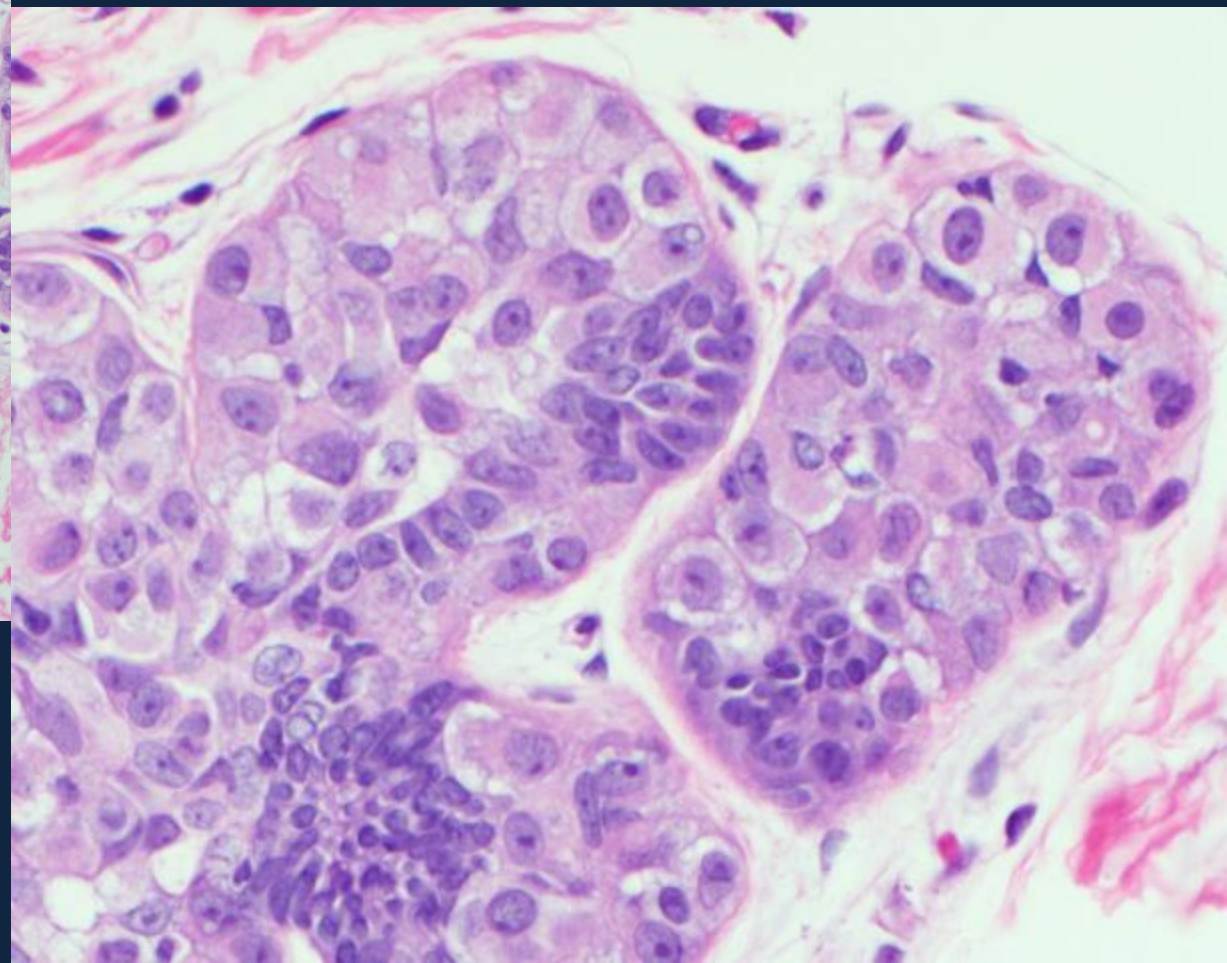
Pleomorphic

- High-grade cytology

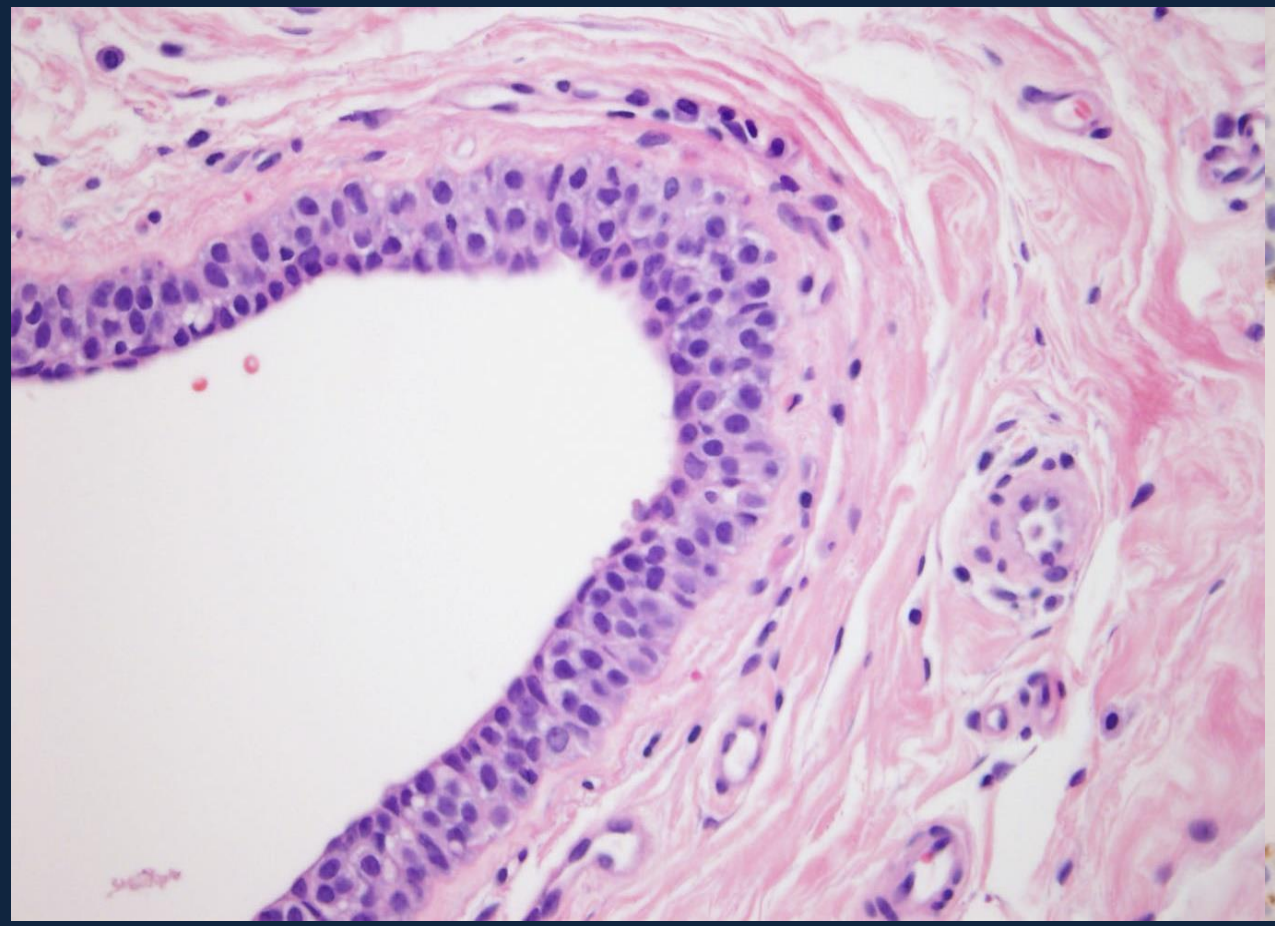

Classic LCIS


Classic LCIS

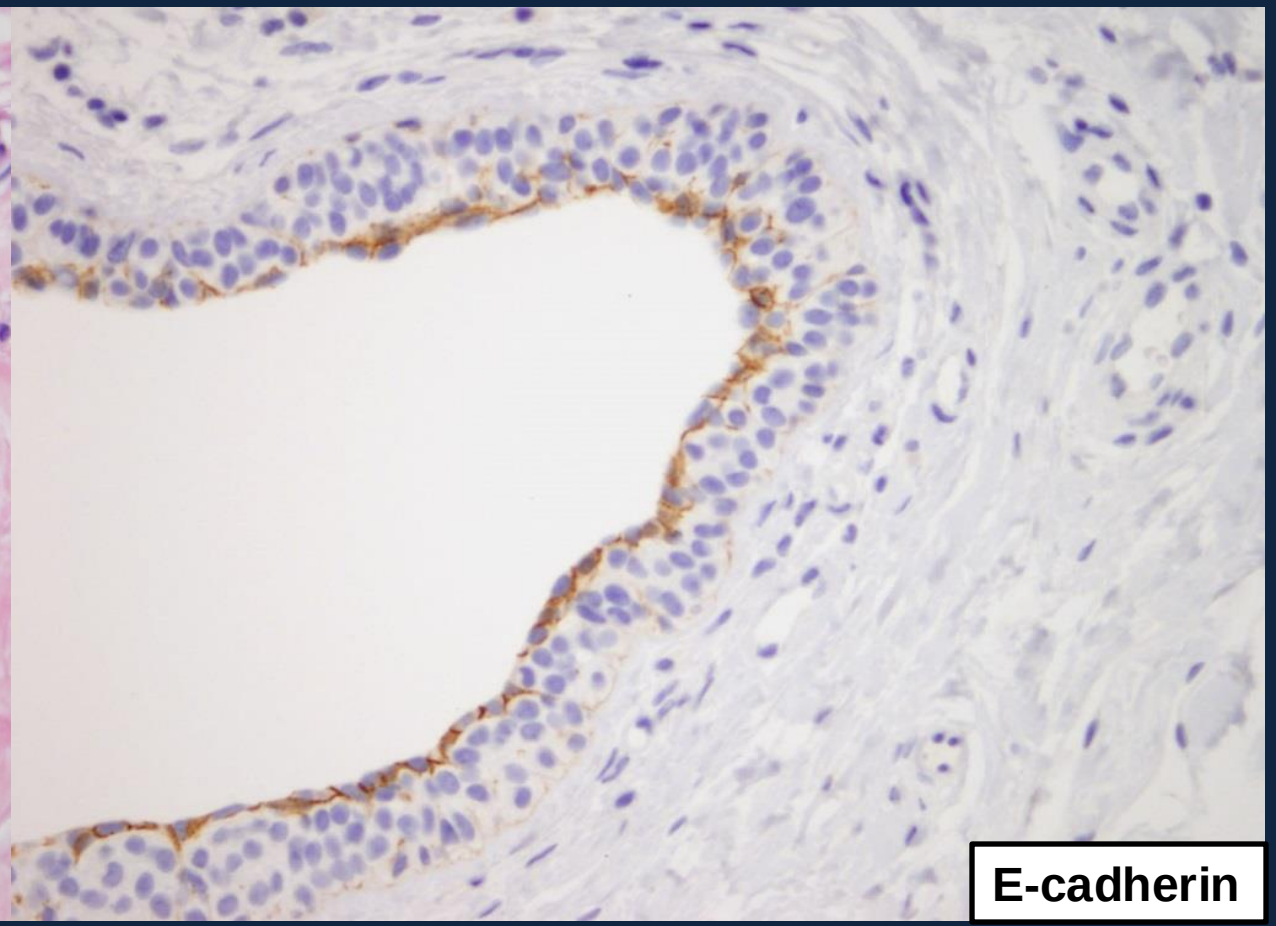




Classic LCIS “type B” cells



Pagetoid growth

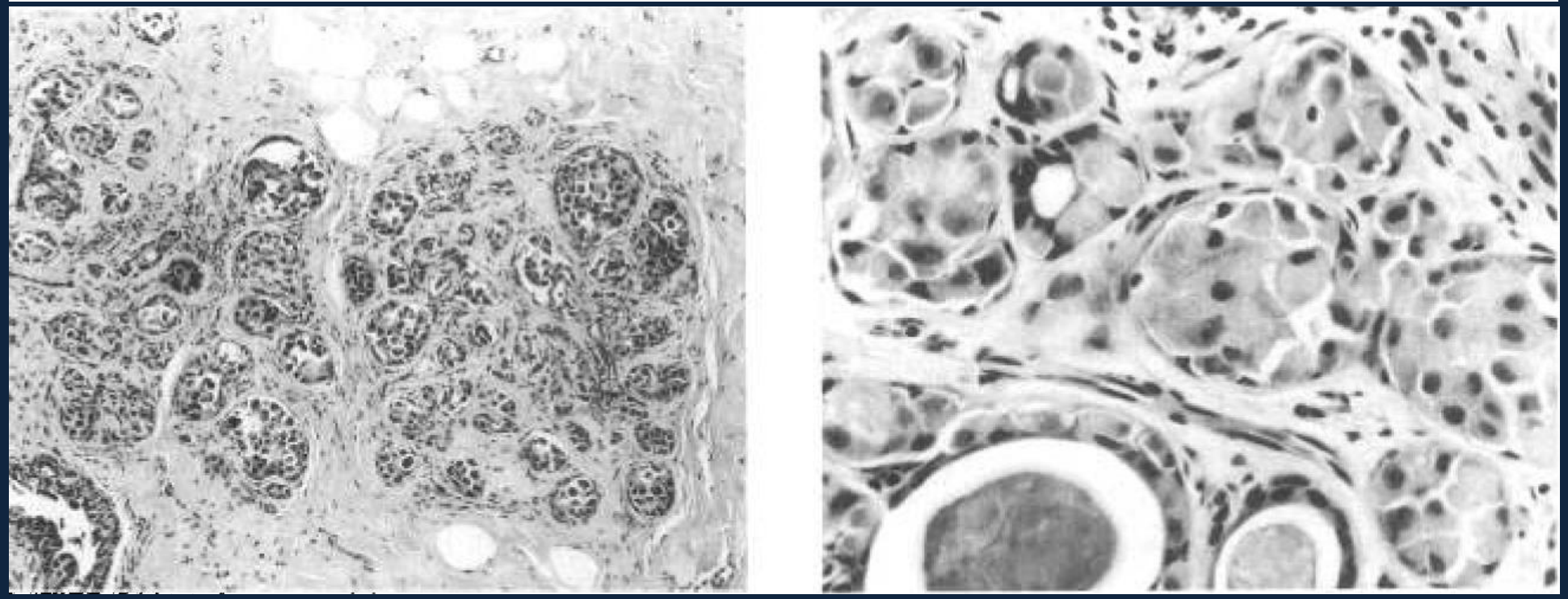


E-cadherin

CASE REVIEW

Pleomorphic Lobular Carcinoma In Situ

Andra R. Frost, MD,* Theodore N. Tsangaris, MD,†
and Steven G. Silverberg, MD*



"…The in situ carcinoma was cytologically identical to the infiltrating carcinoma and was interpreted as the *in situ* counterpart of infiltrating pleomorphic lobular carcinoma."

Pathol Case Rev. 1996;1:27-30.

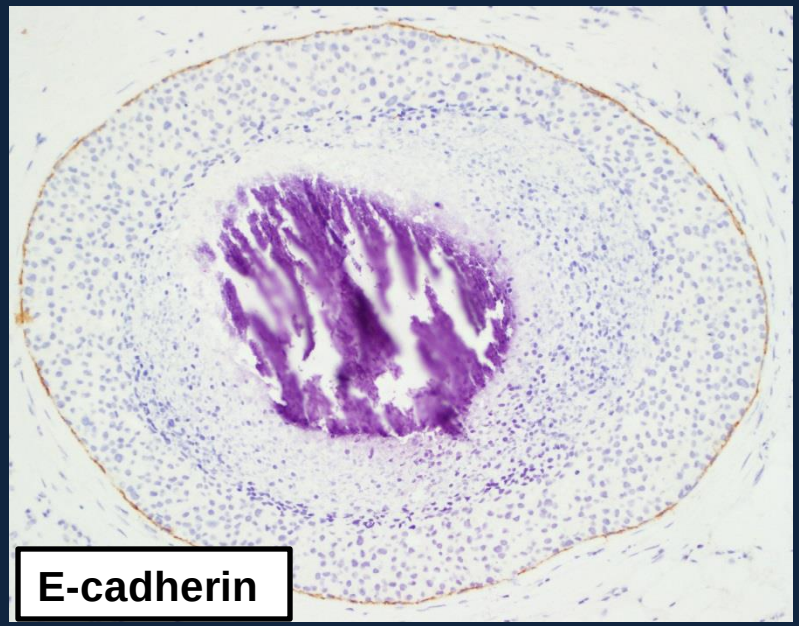
A variety of terms have been used for non-classic LCIS

- Large cell LCIS
- LCIS with pleomorphic features
- Pleomorphic apocrine LCIS
- LCIS with comedonecrosis
- LCIS with massive acinar expansion
- Signet ring cell LCIS

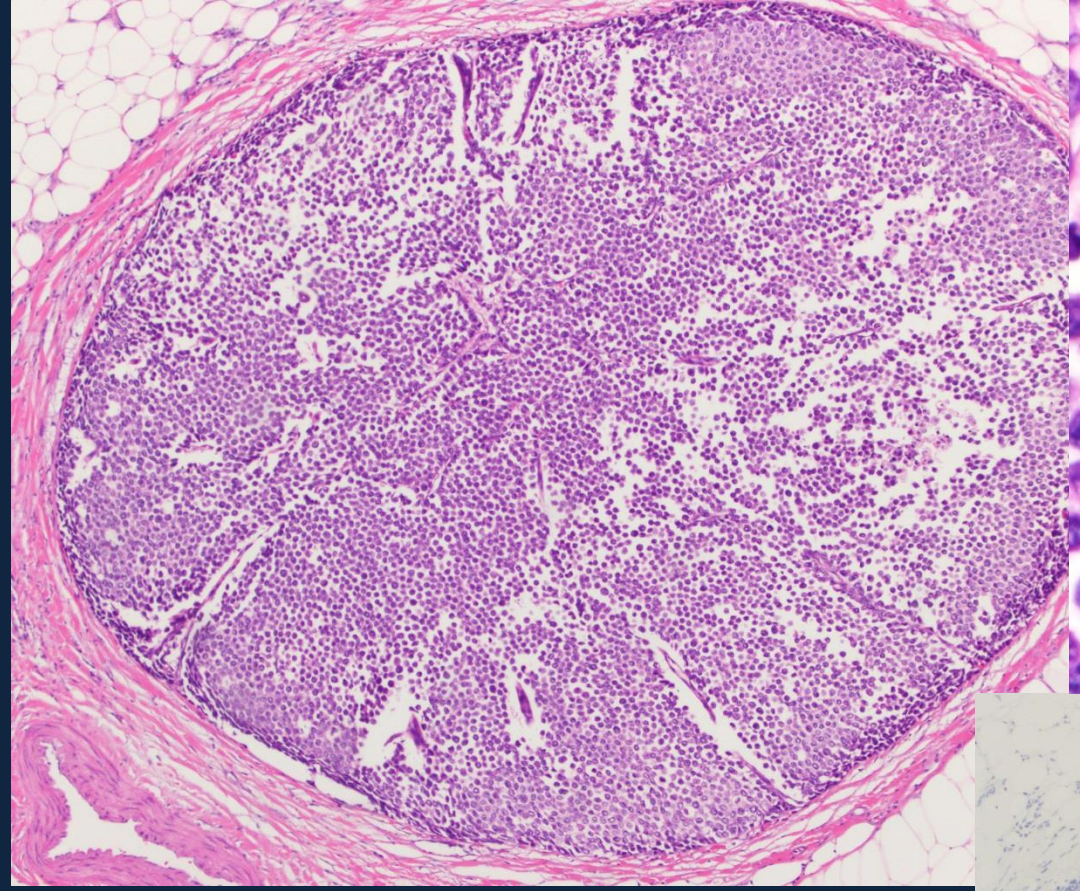
Expansion of ducts with low to intermediate grade LCIS cells

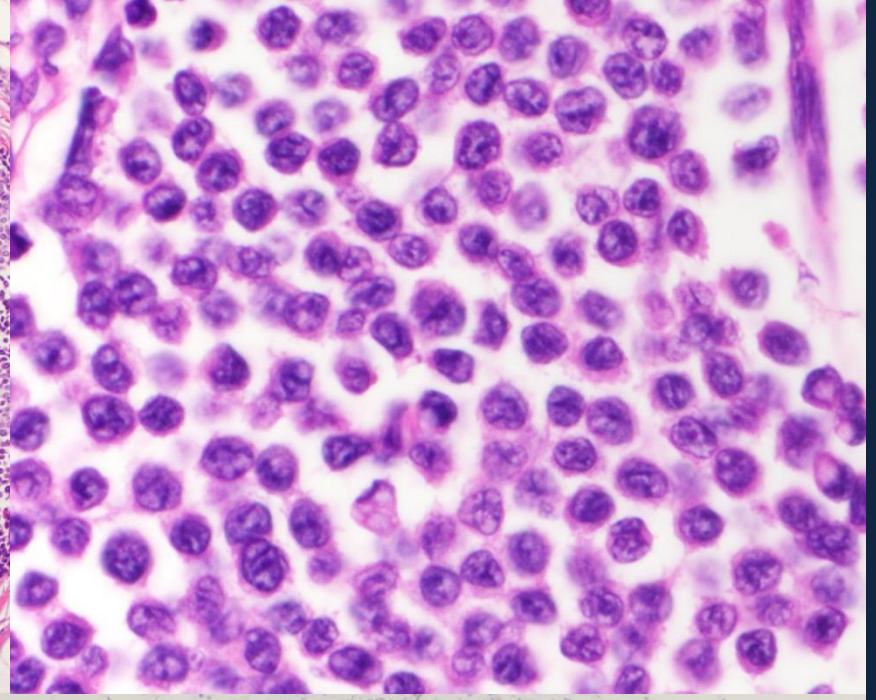
Necrosis, calcs

Florid LCIS



E-cadherin



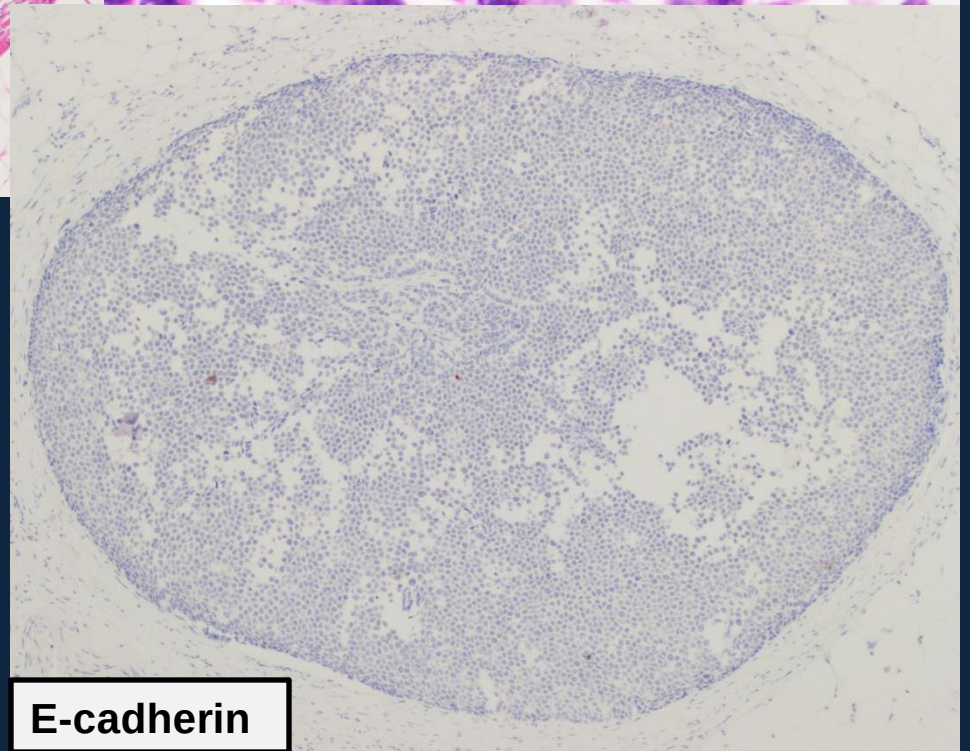


Florid LCIS

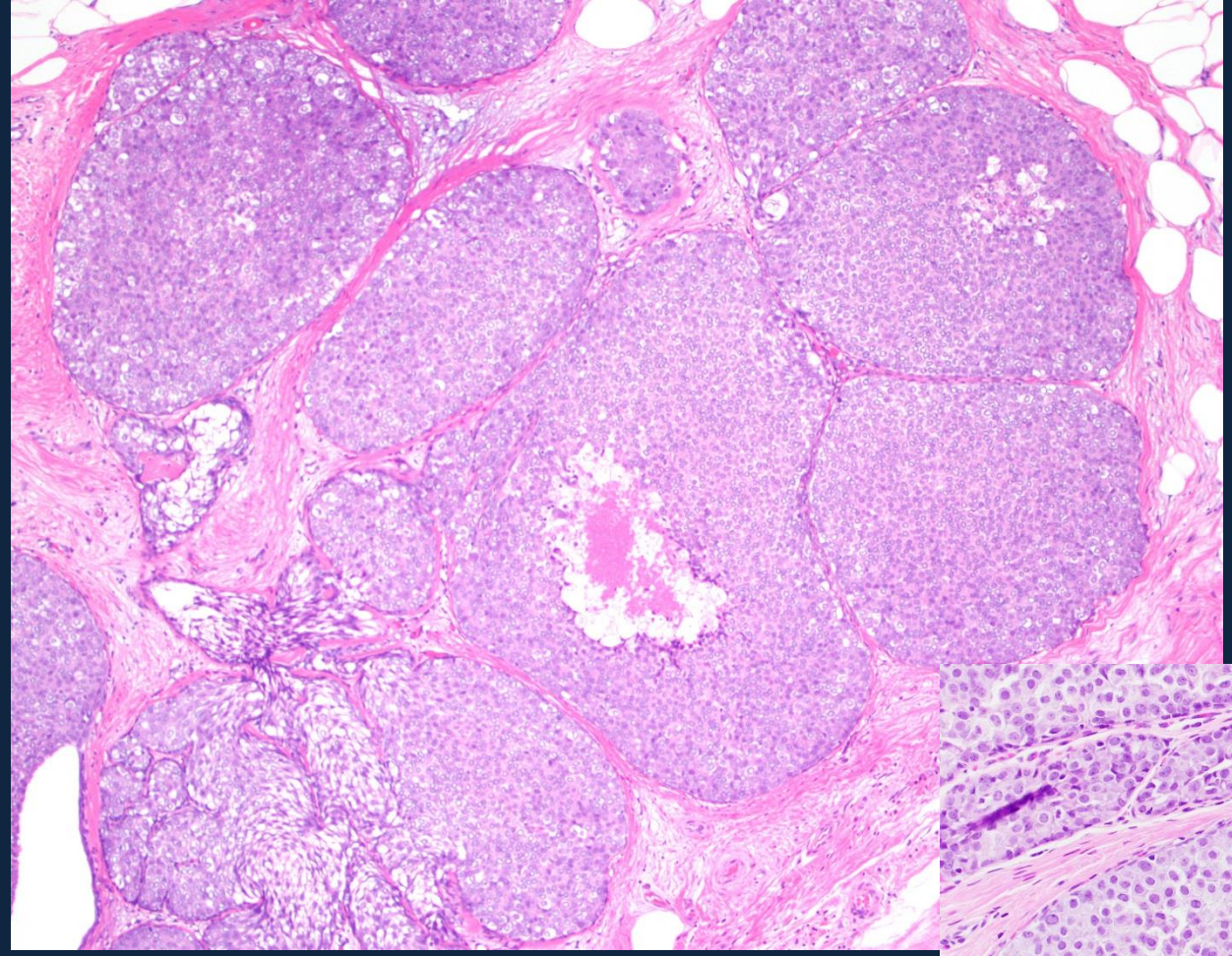
Distension of ducts

Low to intermediate-grade nuclei

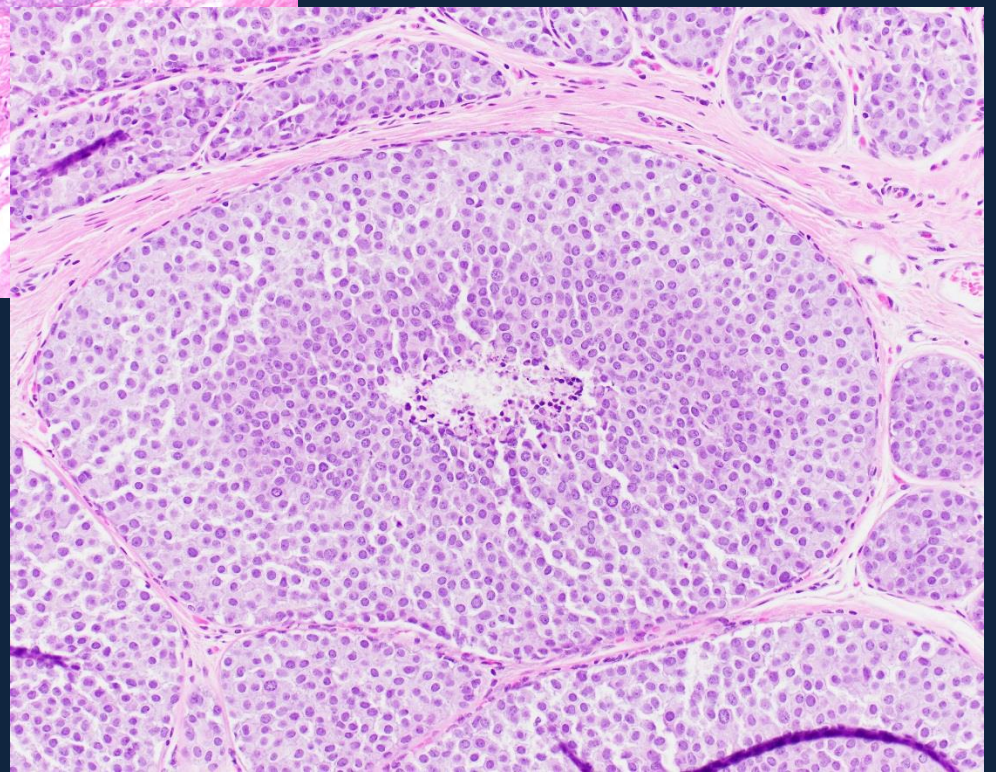
+/- necrosis and calcification



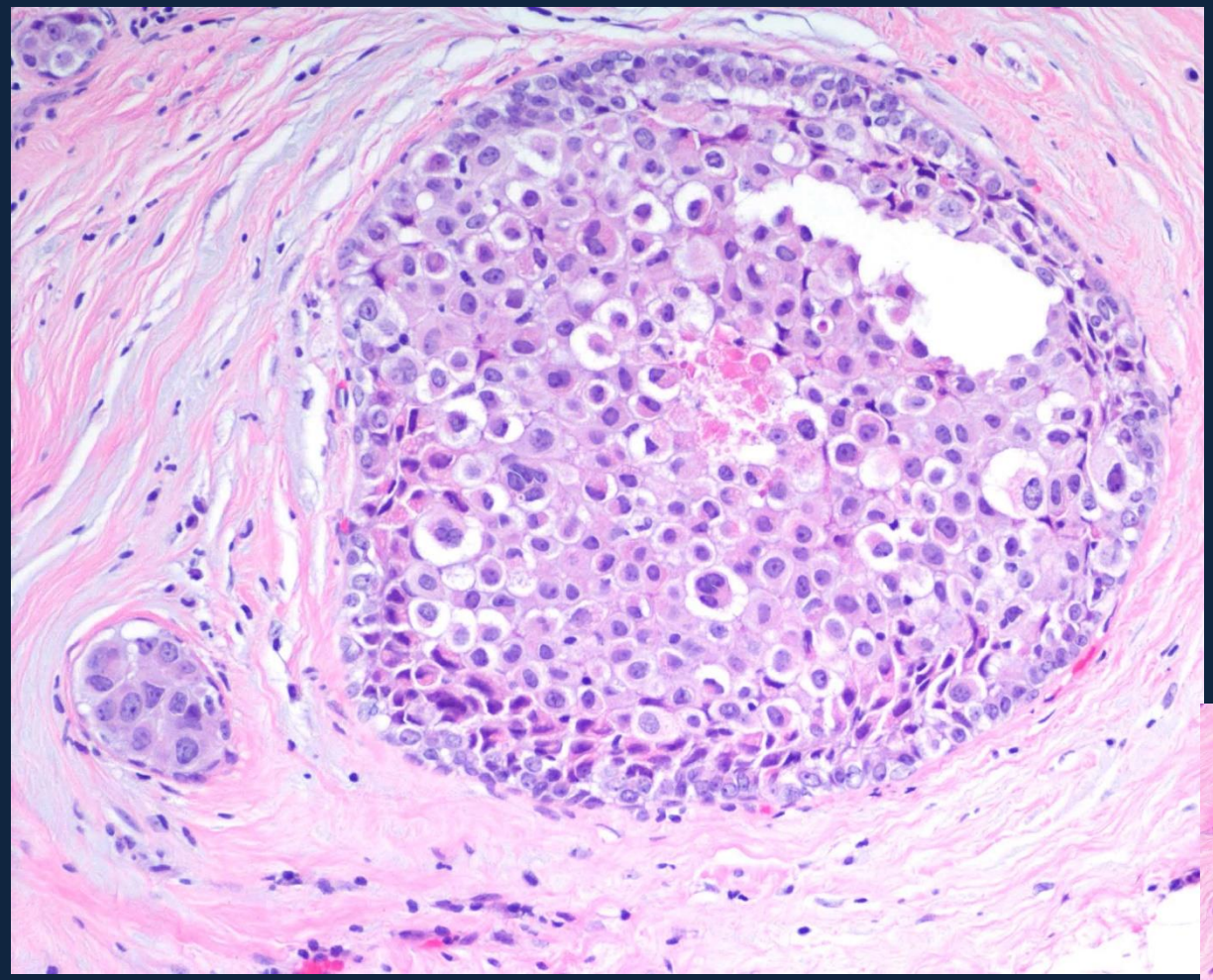
E-cadherin



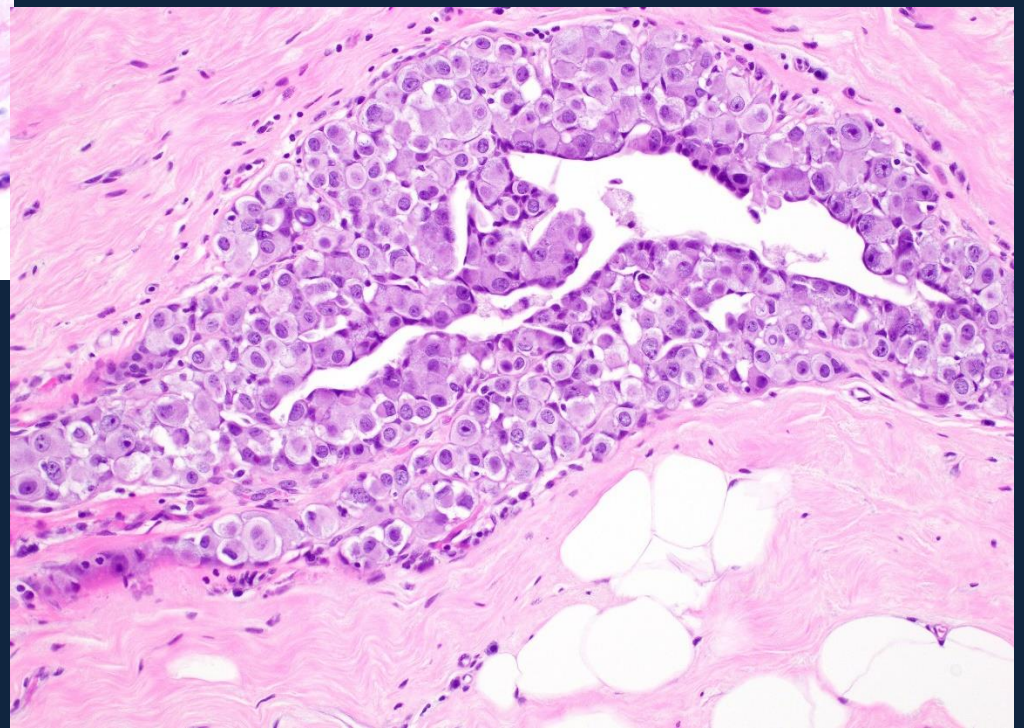
Florid LCIS



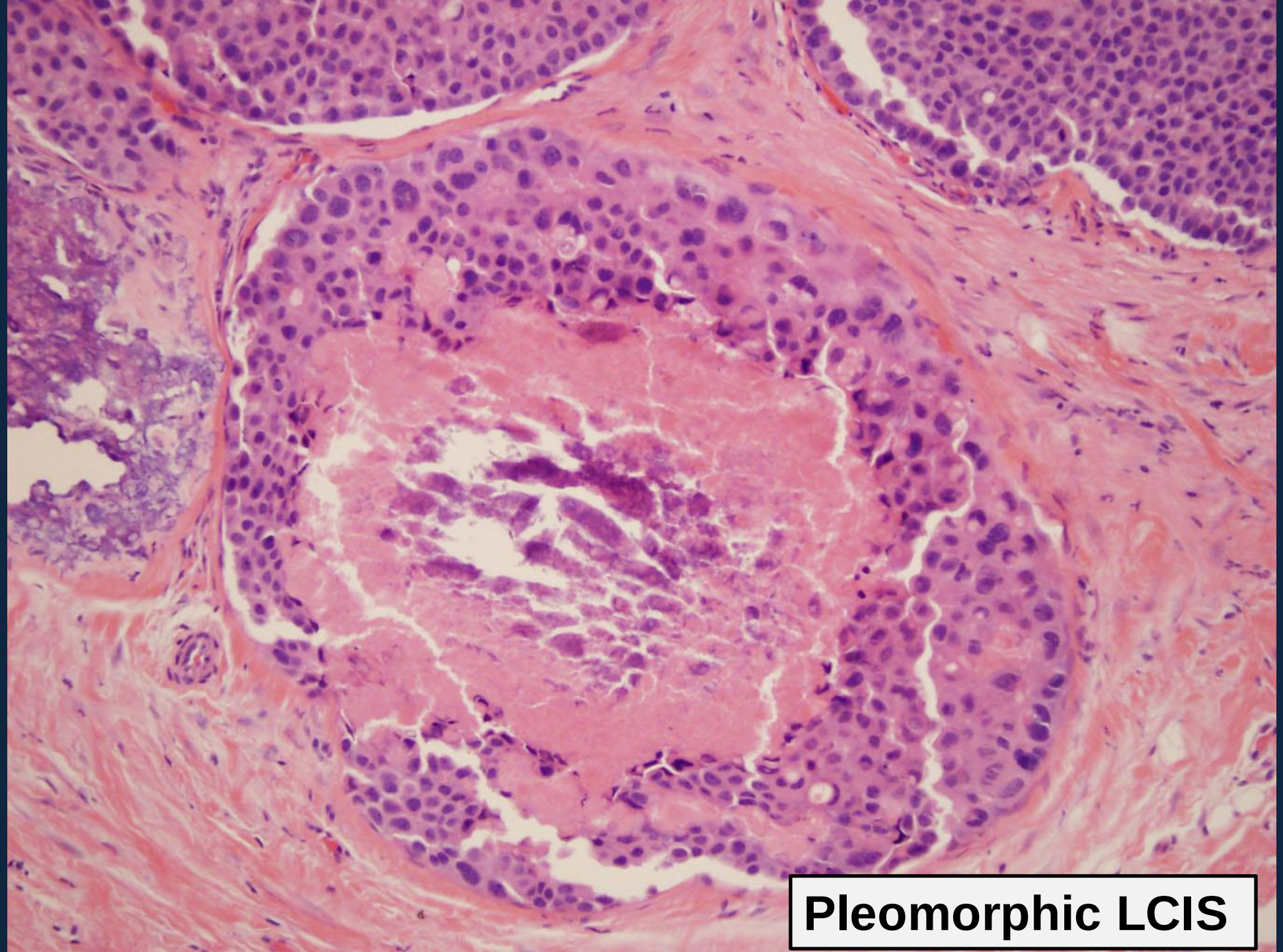
Little to no intervening stroma between expanded ducts

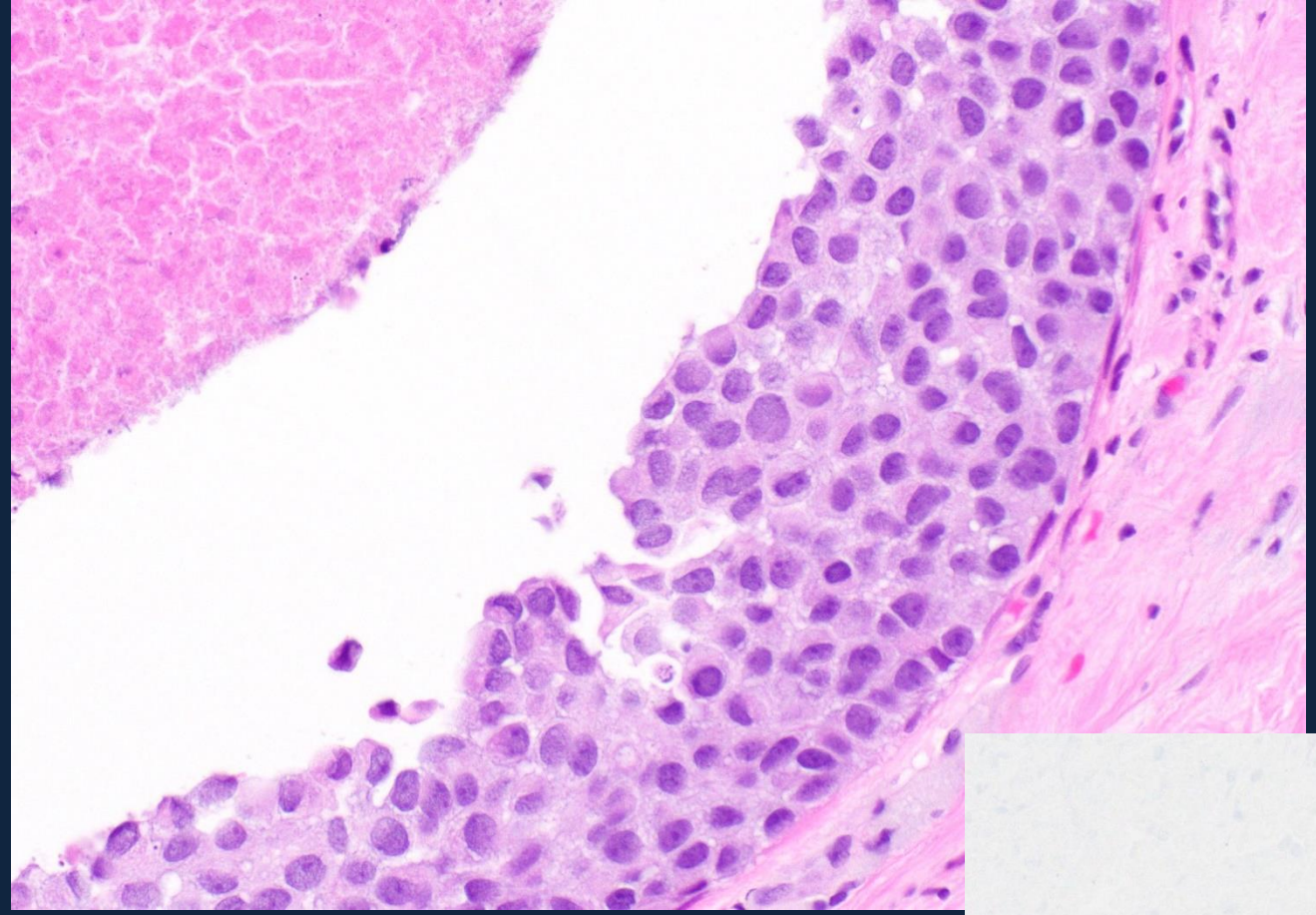


- High-grade nuclei
- Necrosis

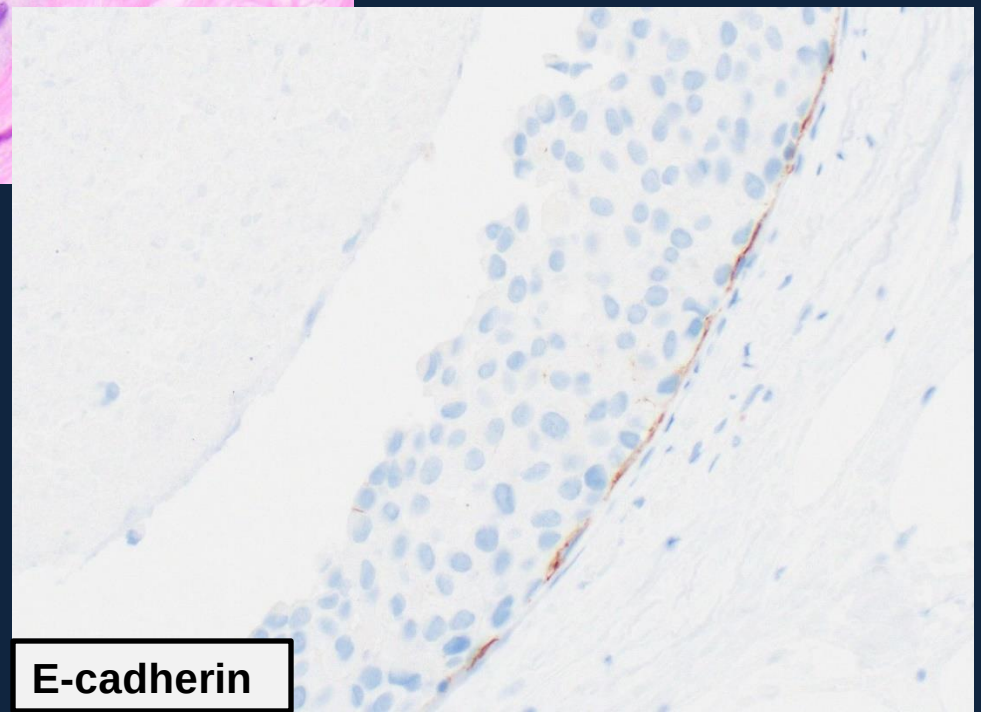


Pleomorphic LCIS


Pleomorphic LCIS



Pleomorphic LCIS



E-cadherin

Clinical presentation

Classic LCIS:

- Premenopausal, mean ≈ 45 yrs
- Incidental, less commonly bx'd due to calcs
- Multifocal, multicentric

Florid and pleomorphic LCIS:

- Postmenopausal, mean ≈ 60 yrs
- Usually imaging target – calcs or mass
- Unifocal
- Commonly seen in association with classic LCIS

Biomarker profile (stains not routinely performed)

Classic LCIS:

- Virtually all ER-positive, HER2-negative

Florid LCIS:

- Majority ER-positive, HER2-negative

Pleomorphic LCIS:

- Majority ER-positive
- HER2 overexpression in about 20%, particularly apocrine type

LCIS: Molecular features

Classic LCIS:

- 16q loss, gain of 1q
- *CDH1* alterations
- *PIK3CA* mutations

Florid LCIS:

- 16q loss, gain of 1q
- Greater genomic instability
- Increased copy number alterations

Pleomorphic LCIS:

- 16q loss, gain of 1q
- Greater genomic instability
- Increased copy number alterations
- *HER2* amplification

Mol Oncol 2016;10(2):360-70
Hum Pathol 2013;44(10):1998-2009
Breast Cancer Res 2017;19(1):7
Mod Pathol 2020;33(7):1287-1297

Genomic profiling of pleomorphic and florid lobular carcinoma in situ reveals highly recurrent *ERBB2* and *ERRB3* alterations

Beth T. Harrison[1] · Faina Nakhlis[2,3] · Deborah A. Dillon[1,3] · T. Rinda Soong[4] · Elizabeth P. Garcia[5] · Stuart J. Schnitt[1,3] · Tari A. King[2,3]

N=19: 17 pleomorphic, 2 florid

- ***CDH1* mutations, 16q loss, 1q gain (lobular hallmarks)**

- **Recurrent *ERBB2* alterations – mutations (13), amplifications (6)**
- **Recurrent *PIK3CA, RUNX1, CBFB* mutations**

***Mod Pathol* 2020;33(7):1287-1297**

LCIS: Clinical questions

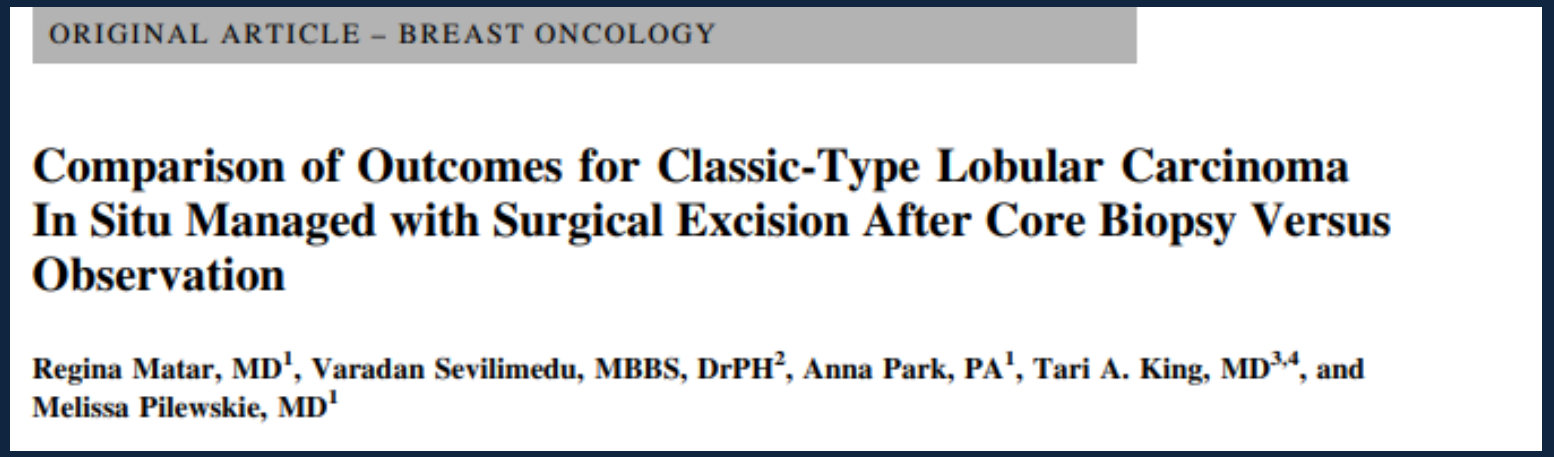
Excise when diagnosed in core biopsy?

Incidence of Adjacent Synchronous Invasive Carcinoma and/or Ductal Carcinoma In-situ in Patients with Lobular Neoplasia on Core Biopsy: Results from a Prospective Multi-Institutional Registry (TBCRC 020)

Faina Nakhlis, MD[1,8], Lauren Gilmore, MD[2], Rebecca Gelman, PhD[1], Isabelle Bedrosian, MD[4], Kandice Ludwig, MD[5], E. Shelley Hwang, MD[6], Shawna Willey, MD[7], Clifford Hudis, MD[3], J. Dirk Iglehart, MD[1,8], Elizabeth Lawler, BA[1], Nicole Y. Ryabin, BS[1], Mehra Golshan, MD[1,8], Stuart J. Schnitt, MD[9], and Tari A. King, MD[10]

- Prospective with central path review
- Diagnosis of lobular neoplasia in core bx
- Rad-path concordance in all cases
- BIRADS 4 or lower
- Upgrade: 1 of 74 (1.4%)
  - DCIS

Ann Surg Oncol 2016;23:722-728


ORIGINAL ARTICLE – BREAST ONCOLOGY

Comparison of Outcomes for Classic-Type Lobular Carcinoma In Situ Managed with Surgical Excision After Core Biopsy Versus Observation

Regina Matar, MD[1], Varadan Sevilimedu, MBBS, DrPH[2], Anna Park, PA[1], Tari A. King, MD[3,4], and Melissa Pilewskie, MD[1]

n= 312 w/ classic LCIS in core

- 54% - excision w/o upgrade
- 46% - observation

No diff. in breast cancer development between groups

No diff. in 5-year cancer development between concordant LCIS group and observation group

Ann Surg Oncol 2022;29(3):1670-1679

Classic LCIS:
Upgrade on excision s/p core biopsy

- Upgrade rates range from 1-35%
- Lower upgrade rates (1-4%) with rad-path concordance and incidental LCIS/ALH
- Upgrades small ER+ cancers, often incidental

Should classic LCIS be excised?

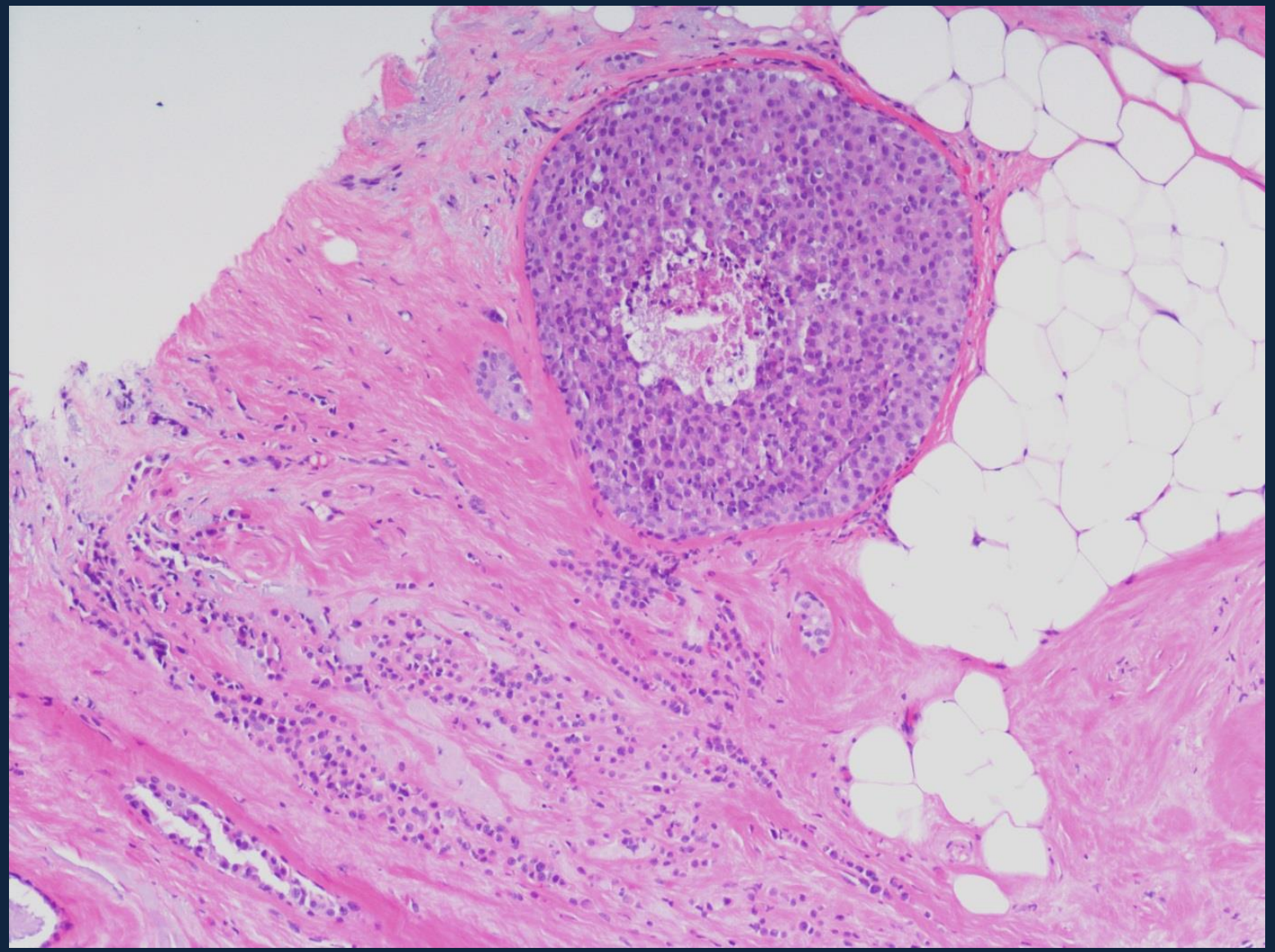
- Routine excision of incidental ALH/LCIS on core bx not indicated
- Multidisciplinary approach necessary
- Pts should undergo excision when:
  - Associated atypical hyperplasia
  - Radiologic-pathologic discordance
  - Residual mammographic abnormality after core bx

Management issues for LCIS variants

Excise after core biopsy diagnosis?

Re-excision of positive margins

Adjuvant radiation?



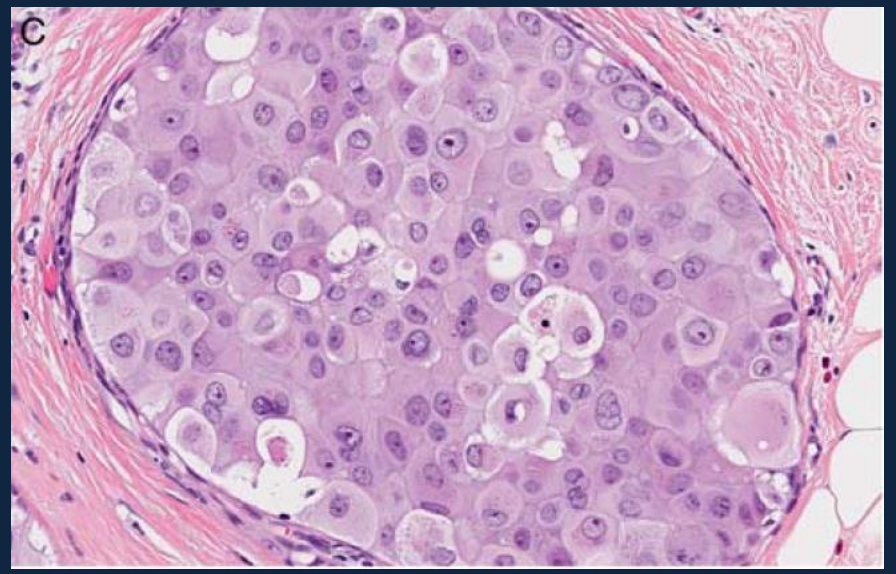
LCIS variants (florid, pleomorphic) are frequently associated with invasive carcinoma

Pleomorphic and Florid Lobular Carcinoma in Situ Variants of the Breast

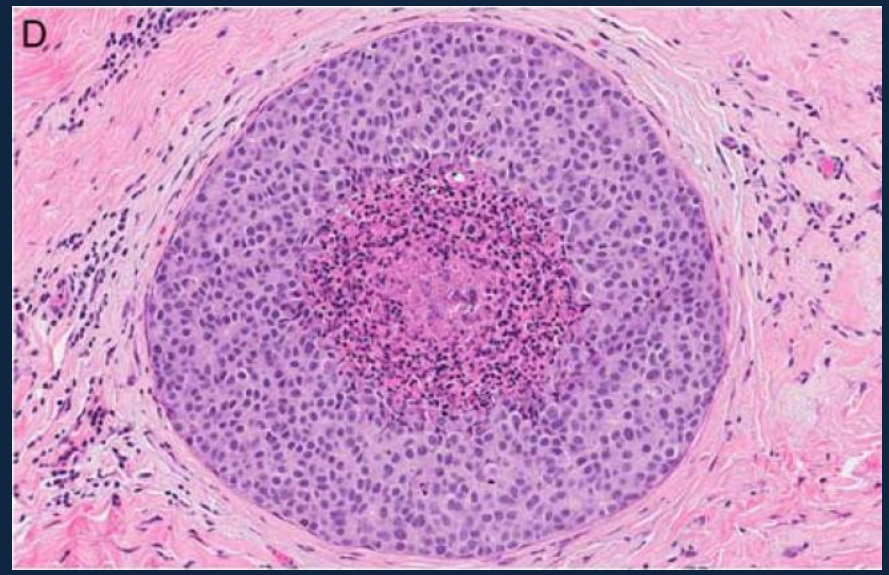
A Clinicopathologic Study of 85 Cases With and Without Invasive Carcinoma From a Single Academic Center

Eliah R. Shamir, MD, PhD, Yunn-Yi Chen, MD, PhD, Tianming Chu, Melike Pekmezci, MD, Joseph T. Rabban, MD, MPH, and Gregor Krings, MD, PhD

- **Pleomorphic + florid LCIS variants over 20-year period**
- **n = 85 (pleomorphic: n = 61, florid: n = 24)**
- **Overall, 77% were associated with invasive ca**
  - **84% were invasive lobular ca**



Apocrine pleomorphic LCIS



Florid LCIS

***Am J Surg Pathol.* 2019;43(3):399-408.**

Pleomorphic and Florid Lobular Carcinoma in Situ Variants of the Breast

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Pleomorphic LCIS (n=61):

- **44 (77%) associated with invasive ca**
  - **64% pleomorphic ILC)**
  - **79% HR+, 14% HER2+ (5 of 6 apo PLCIS), 12% triple-negative**
- **Core bx: 3/8 (38%) cases upgraded: 1 PILC, 1 ILC**

Florid LCIS (n=24):

- **18 (75%) assoc. w/ invasive ca**
  - **95% classic ILC or mixed ductal-ILC**
  - **All HR+, one case (6%) HER2+, none triple-negative**
- **Core bx: 2/6 (33%) cases upgraded: 1 ILC, 1 DCIS**

Am J Surg Pathol. 2019;43(3):399-408.

Evaluating the Rate of Upgrade to Invasive Breast Cancer and/or Ductal Carcinoma In Situ Following a Core Biopsy Diagnosis of *Non-classic* Lobular Carcinoma In Situ

Faina Nakhlis, MD[1,5,6], Beth T. Harrison, MD[2,5], Catherine S. Giess, MD[3,5], Susan C. Lester, MD, PhD[2,5], Kevin S. Hughes, MD[4,5], Suzanne B. Coopey, MD[4,5], and Tari A. King, MD[1,5,6]

- 76 cases pure non-classic LCIS (75 pts)
- 61 (80%) biopsied for mammographic calcs

- 27/76 (36%) showed upgrade
  - 17 (63%) upgraded to invasive ca: 9 ILC, 5 IDC, 3 mixed
    Median size: 2 mm (range: 0.6 to 11 mm)
    15 (88%) HR+, 1 (6%) HER2+

- No clinical/imaging findings associated with upgrade

Ann Surg Oncol. 2019;26(1):55-61.

References	NC-LCIS subtype	No. of excisions	No. of upgrades (%)
Georgian-Smith and Lawton[10]	P-LCIS	5	2 (40)
Lavoue et al.[11]	P-LCIS	10	3 (33)
Chivukula et al.[12]	PLCIS	12	3 (25)
Carder et al.[13]	P-LCIS	8	2 (25)
Sullivan et al.[9]	V-LCIS	11	4 (36)
	P-LCIS	17	3 (18)
Niell et al.[14]	P-LCIS	4	4 (100)
Meroni et al.[15]	P-LCIS	12	6 (50)
Flanagan et al.[16]	P-LCIS	21	11 (52)
Susnik et al.[17]	V-LCIS	15	4 (27)
Guo et al.[18]	P-LCIS	23	14 (60)
This report	CIS	19	4 (21)
	CIS/DLF	37	16 (43)
	V-LCIS	16	4 (25)
	P-LCIS	4	3 (75)
Total		214	83 (39)

CIS carcino… …*S* pleomorphic lobular carc… …na in situ, *NC-LCIS* non-cl…

Upgrade rates range from 18 – 100%
Mean: 39%

Ann Surg Oncol. 2019;26(1):55-61.

NCCN: Clinicians should consider complete excision with negative margins for non-classic LCIS (pleomorphic or florid LCIS) However, outcomes data regarding treatment of individuals with non-classic LCIS are limited, due in part to a paucity of histologic categorization of variants of LCIS.

The WHO Editorial Board recommends excision for both florid and pleomorphic LCIS diagnosed in a core biopsy.

NCCN Guidelines Breast Cancer Screening and Diagnosis – Version 2.2024
WHO Classification of Tumours, 5th Edition

Optimal management of patients with LCIS variants following excision is uncertain.

Few retrospective studies of small number of “pure” LCIS cases with variable inclusion criteria

Lack of uniform treatment, limited follow-up

ORIGINAL ARTICLE – BREAST ONCOLOGY

Does Non-Classic Lobular Carcinoma In Situ at the Lumpectomy Margin Increase Local Recurrence?

Anna C. Beck, MD[1], Solange Bayard, MD[2], George Plitas, MD[1], Varadan Sevilimedu, MBBS, DrPH[3], M. Gabriela Kuba, MD[4], Paula Garcia, MHA[1], Monica Morrow, MD[1], and Audree B. Tadros, MD, MPH[1]

MSKCC study:

511 pts with non-classic LCIS (NC-LCIS) in lumpectomies with invasive carcinoma and/or DCIS

No difference in rates of IBTR or LRR based on margin status

XRT (86% of pts) associated with decreased IBTR and LRR

Ann Surg Oncol 2023;30:6061-6069.

Clinical Implications of Margin Involvement by Pleomorphic Lobular Carcinoma In Situ

Erinn Downs-Kelly, DO; Diana Bell, MD; George H. Perkins, MD; Nour Sneige, MD; Lavinia P. Middleton, MD

- N = 26, including 6 with T1mi or T1a invasive ca
- 4 pts (15%) received XRT
- PLCIS at margin in 6 cases, <2 mm from margin in 11 cases
- 1 (3.8%) recurrence of PLCIS at lumpectomy site
  - Pt had positive margin at lumpectomy, no XRT

Pleomorphic lobular carcinoma *in situ* of the breast: clinicopathological review of 47 cases

Thaer Khoury, Rouzan G Karabakhtsian,[1] David Mattson,[2] Li Yan,[3] Susanna Syriac, Fadi Habib, Song Liu[3] & Mohamed M Desouki[4]

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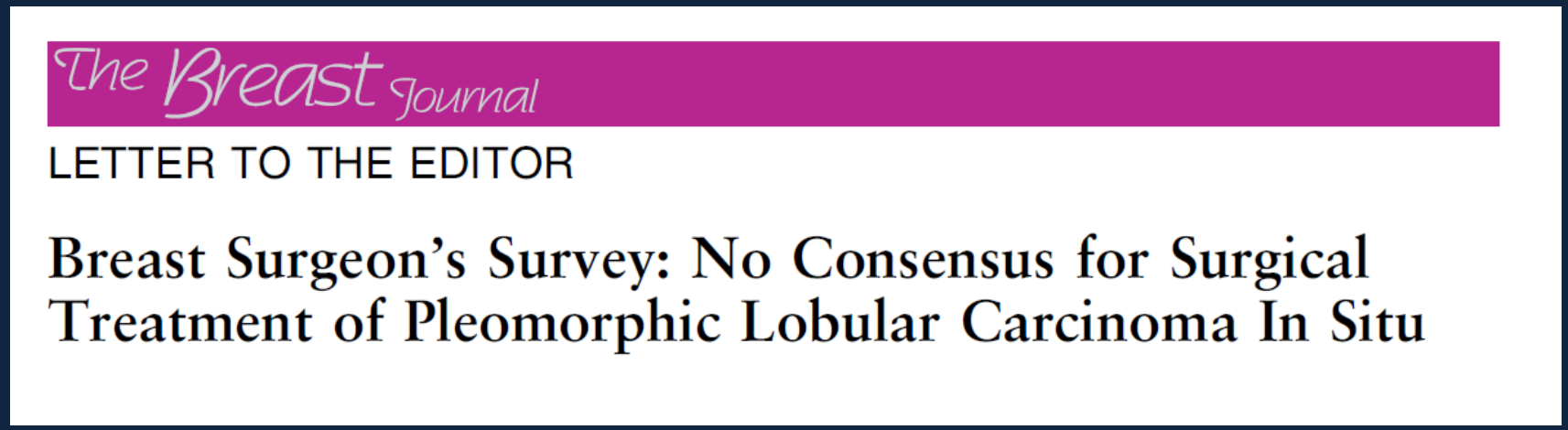
- Local recurrence in 6 of 31 (19.4%) pts with pure PLCIS
  - 4 invasive, 2 PLCIS
  - 2 had margins positive for PLCIS
  - All had BCT and XRT

Arch Pathol Lab Med. 2011;135(6):737-743.
Histopathology. 2014;64(7):981-993.



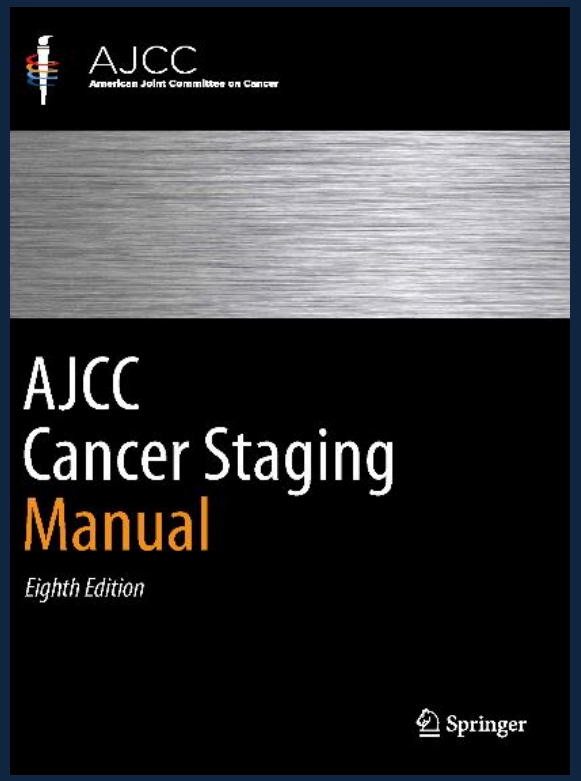
Survey of 351 breast surgeons

Would you re-excise pleomorphic LCIS at the margin?

- **53% no**
- **24% always excise**
- **23% sometimes excise**

Breast J. **2013;19(1):116-118.**

Staging per AJCC



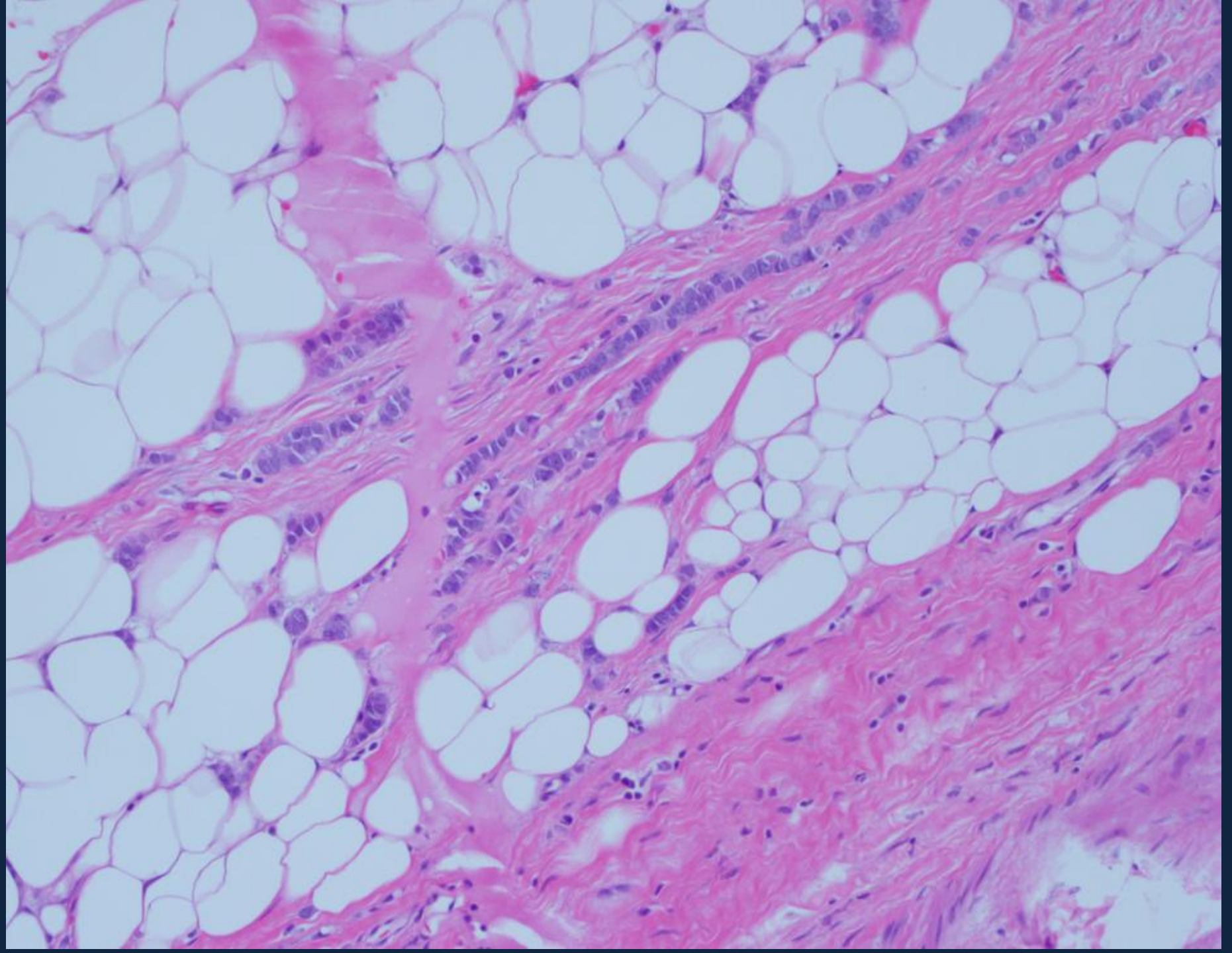
LCIS, including pleomorphic and florid types, <u>no longer staged as Tis</u> in current 8th Edition

LCIS
Take home points…

- Classic LCIS is morphologically and genetically different from variant (florid, pleomorphic) LCIS
- Classic LCIS in core bx does not require excision in most cases
- Pleomorphic LCIS (high-grade) and florid LCIS (expansion of ducts with classic-type cells) require excision

LCIS
Take home points…

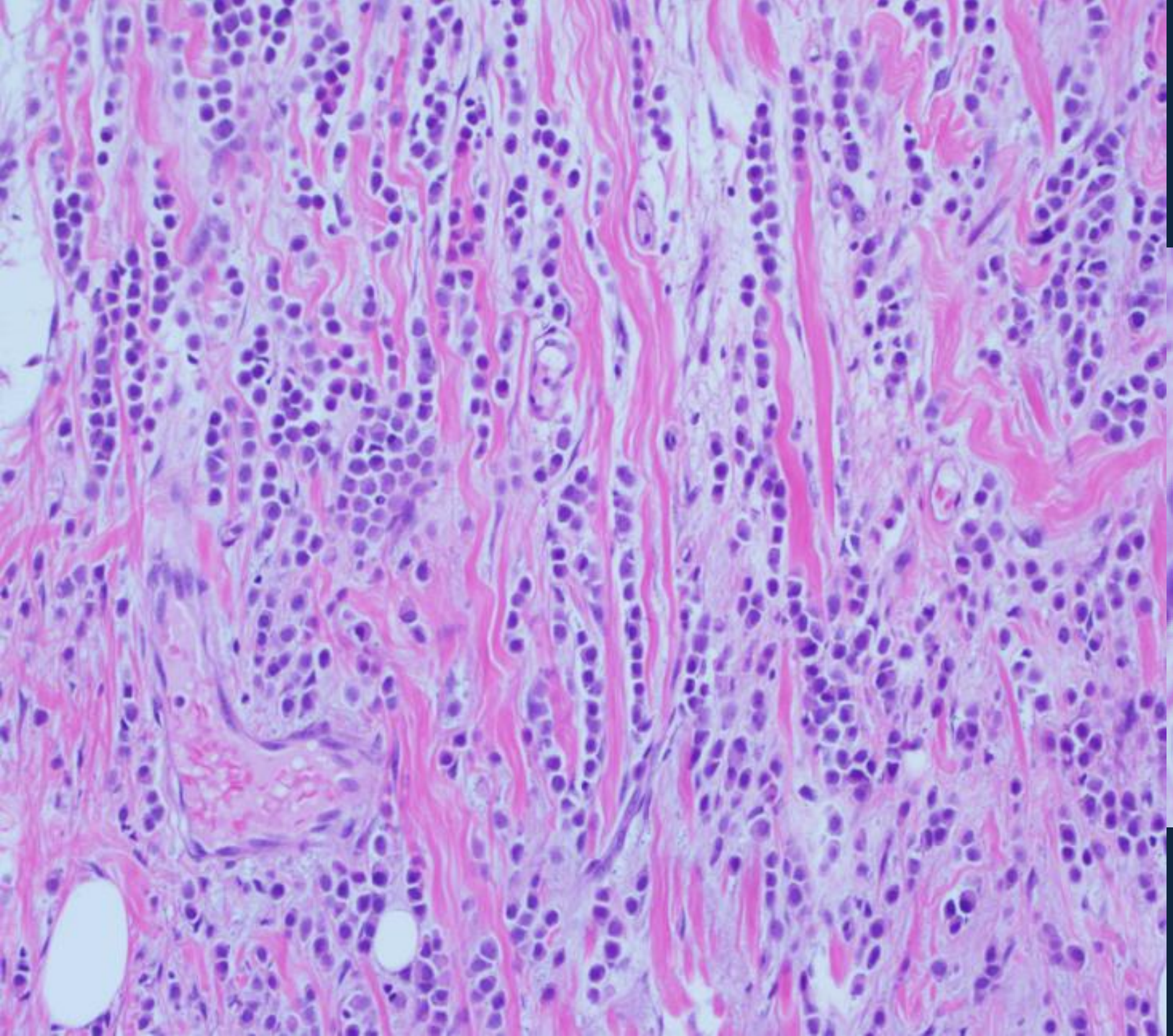
- Local recurrence rates for LCIS variants vary (0-57%)
- Uncertain impact of positive margins on recurrence, no consensus on surgical management of margins or what is adequate margin
- Insufficient data to support adjuvant radiation

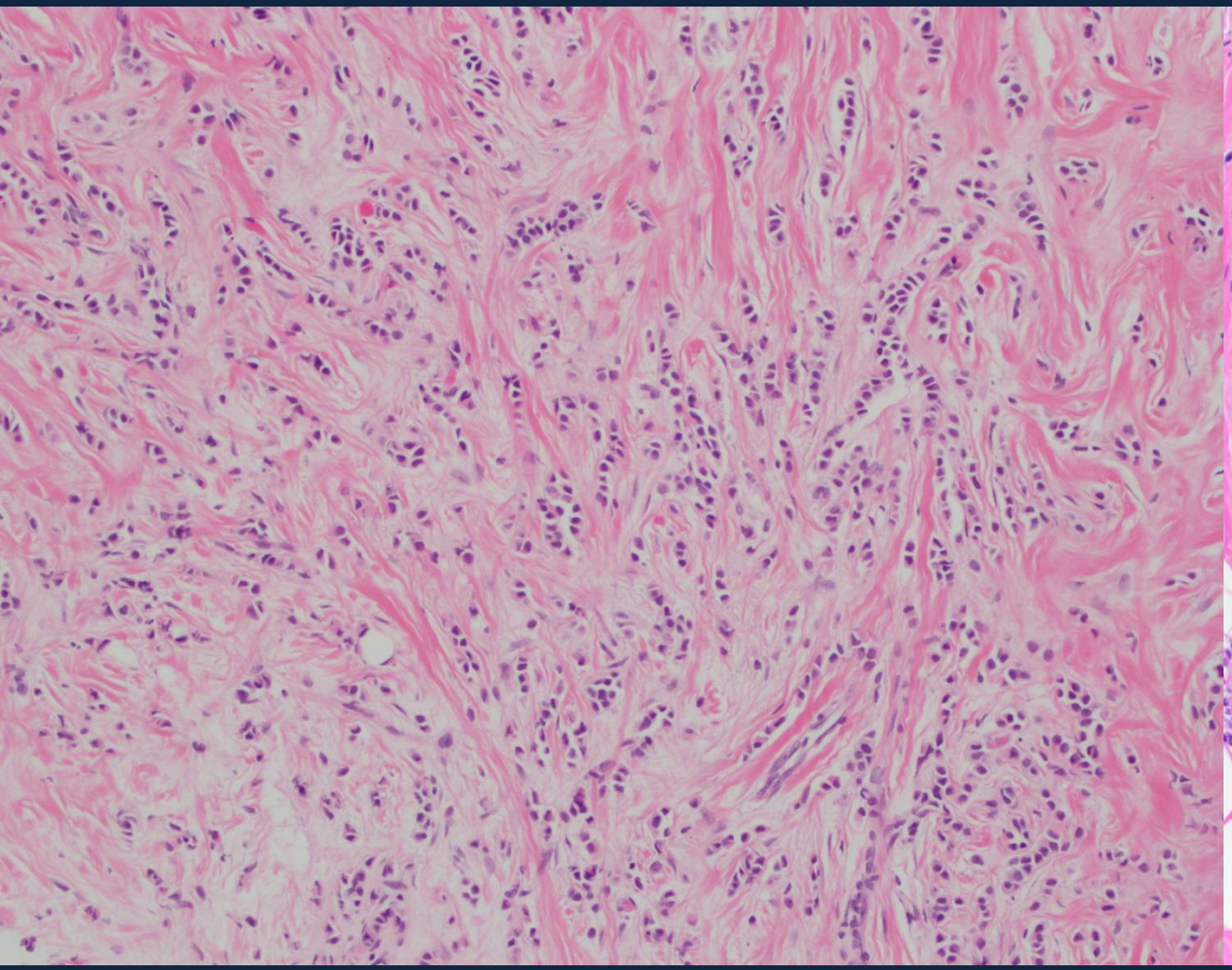


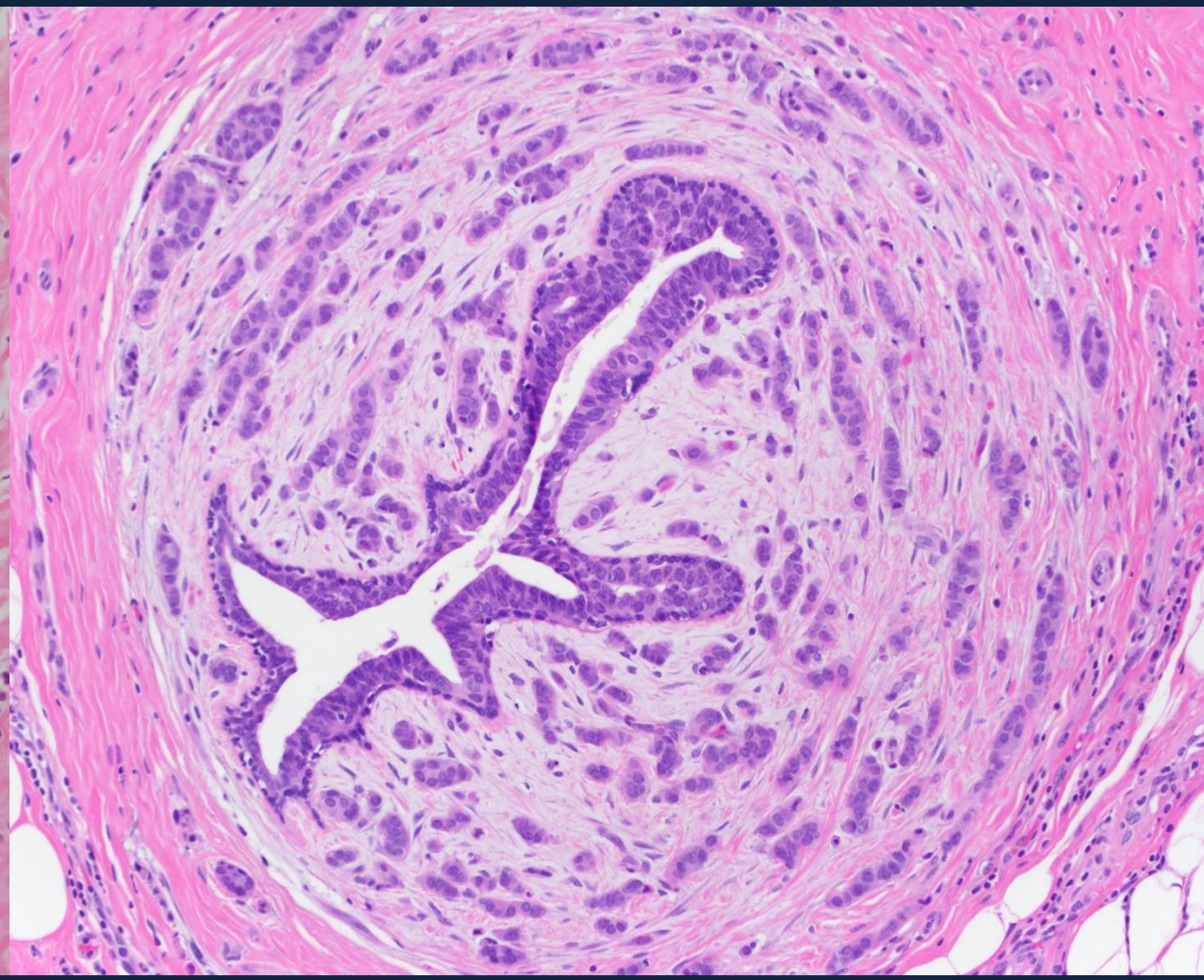
Invasive lobular carcinoma (ILC)

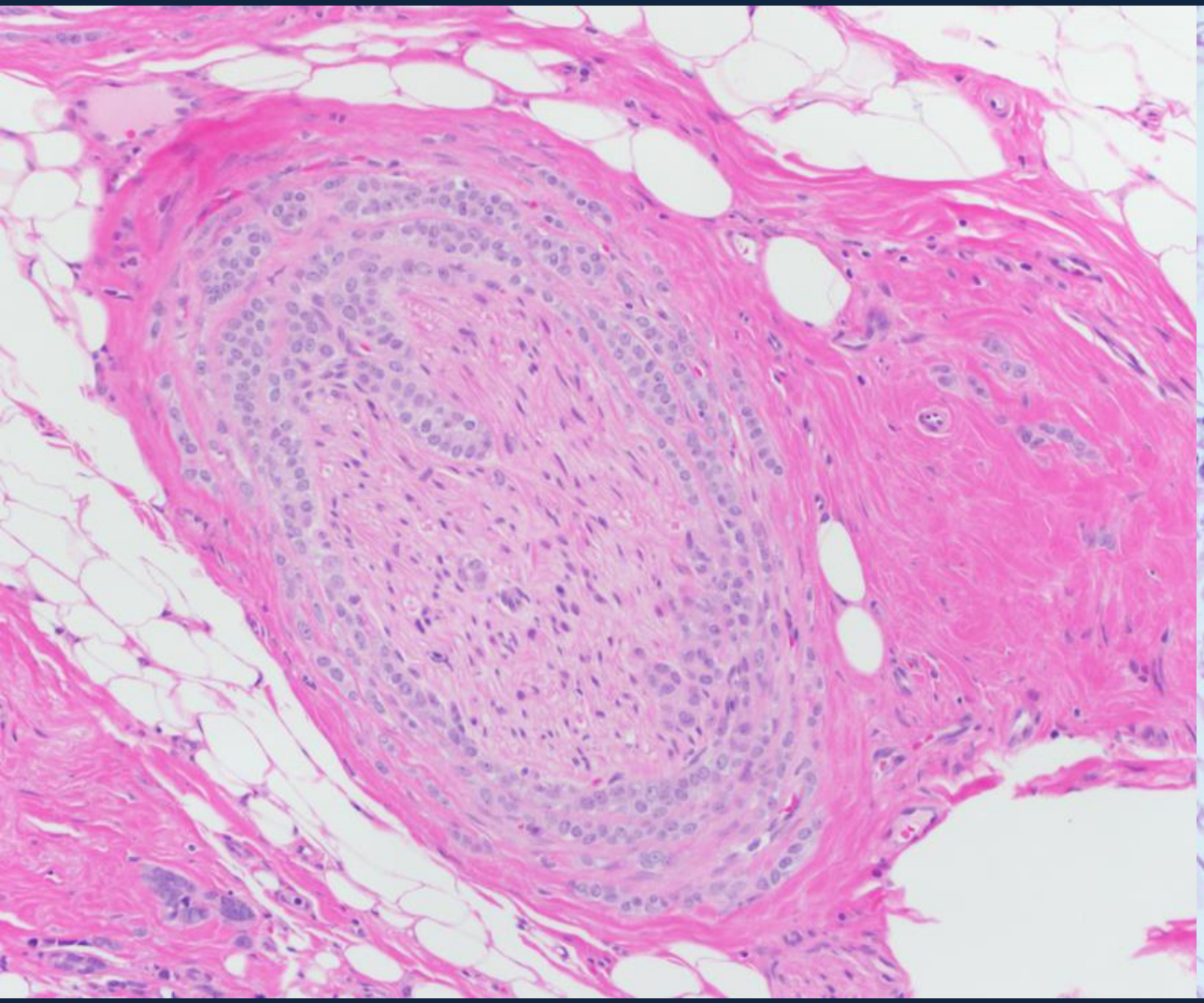
Invasive lobular carcinoma - overview

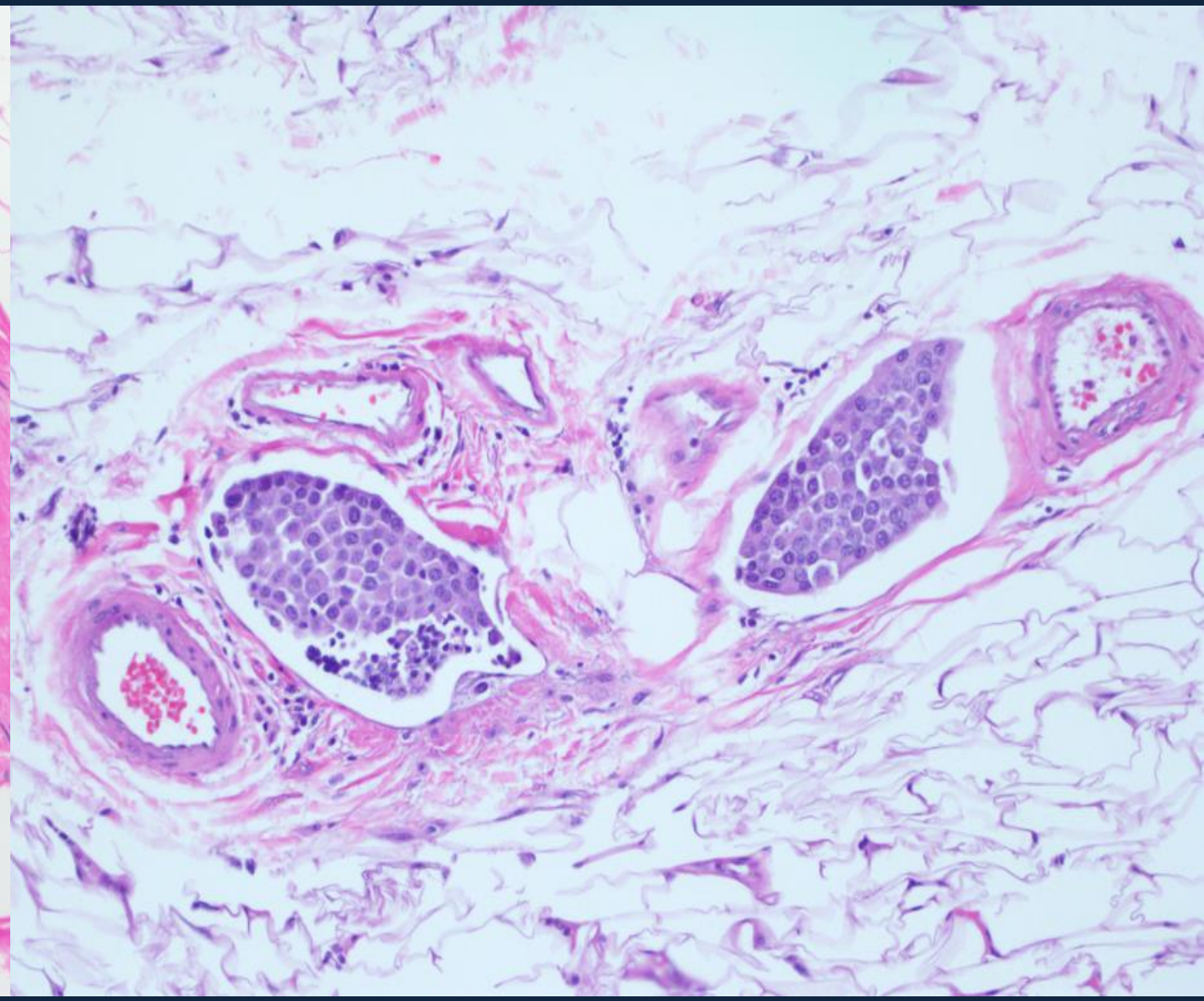
- Most common special type, approx. 10- 15% of invasive breast carcinomas
- Classic and variant morphologies
- Loss of E-cadherin expression, loss of cellular cohesion







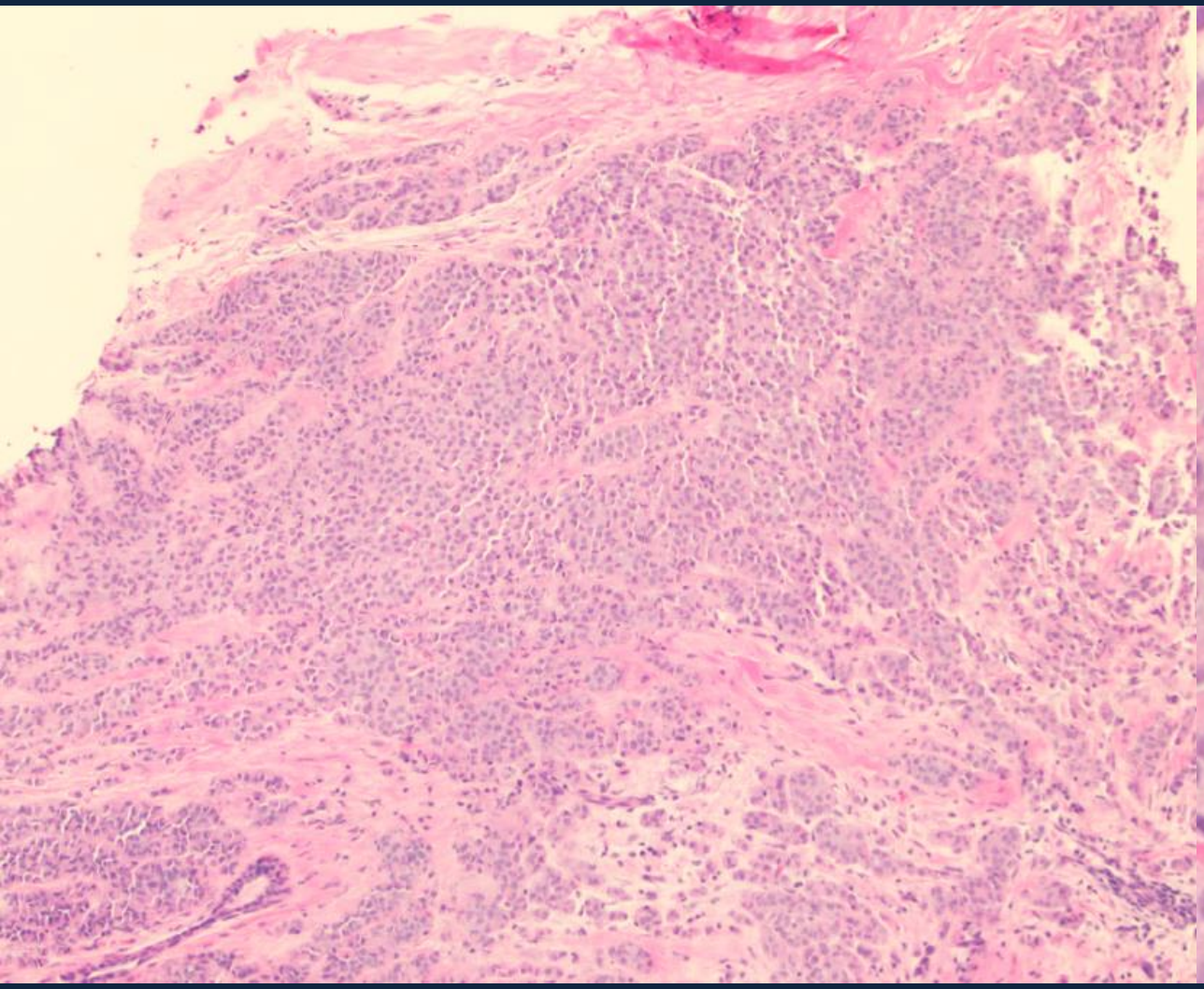


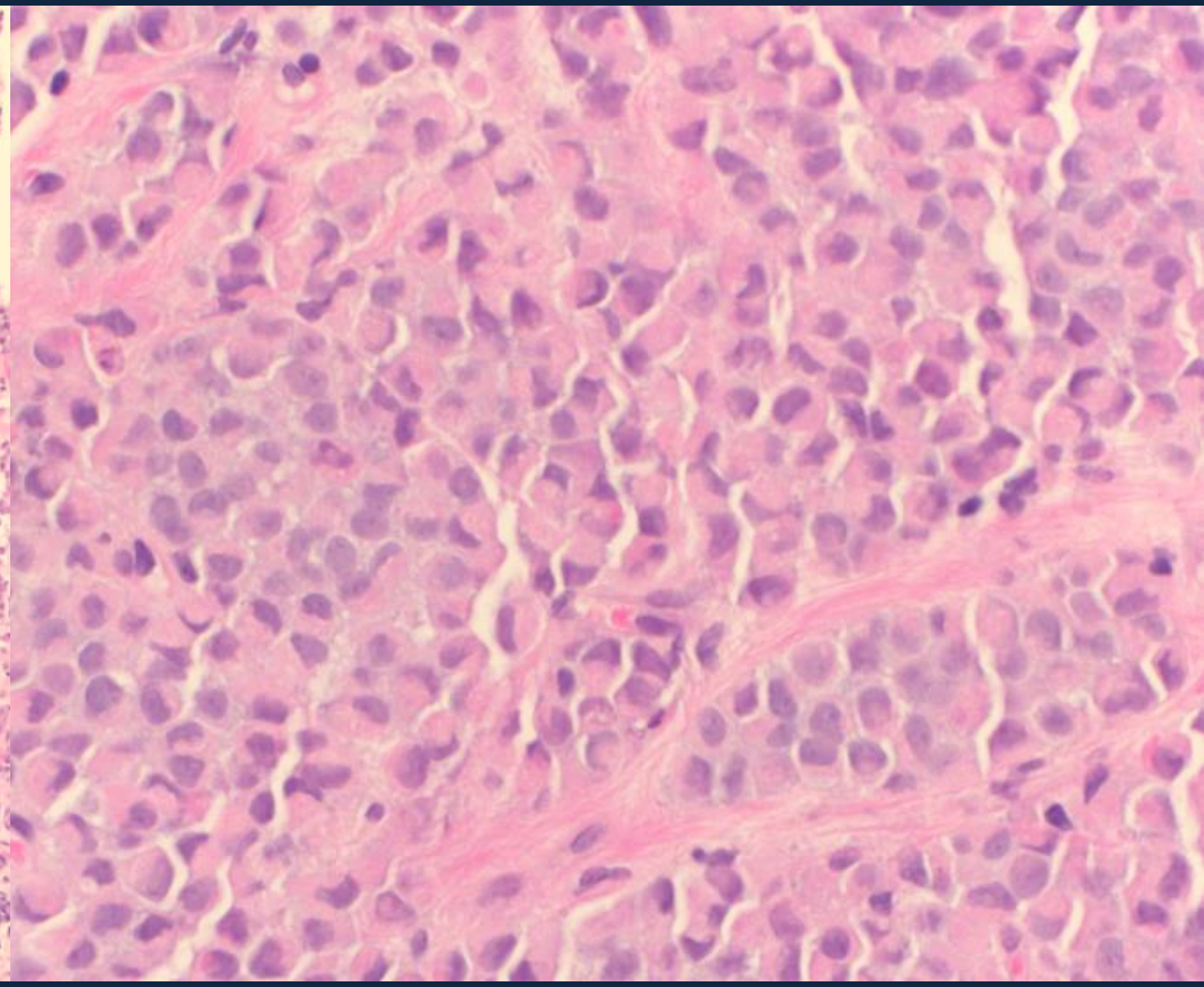


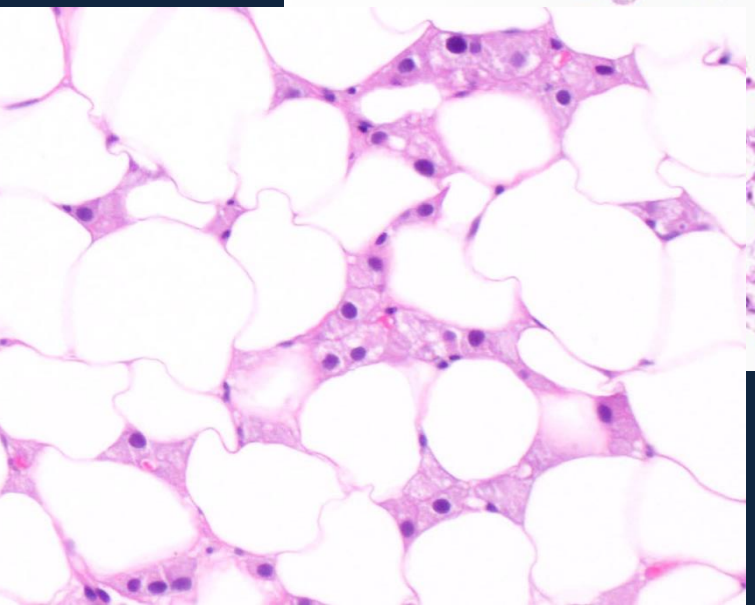
Growth patterns

- Classic
- Solid
- Alveolar
- Pleomorphic
- Mixed
- With extracellular mucin

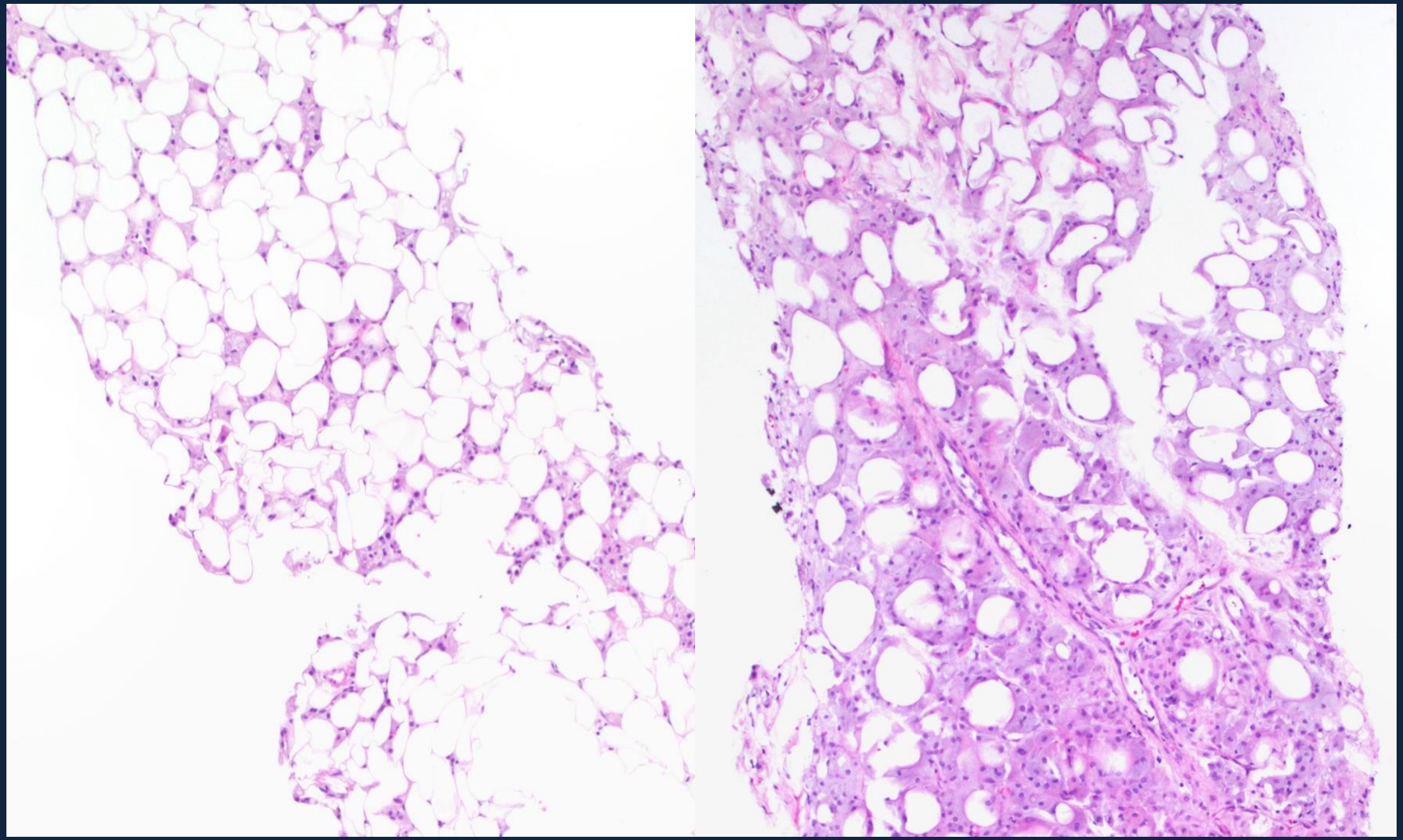
*All may exhibit signet ring and/or apocrine features







CK (AE1/AE3)



Classic type invasive lobular carcinoma diagnostic criteria

WHO:

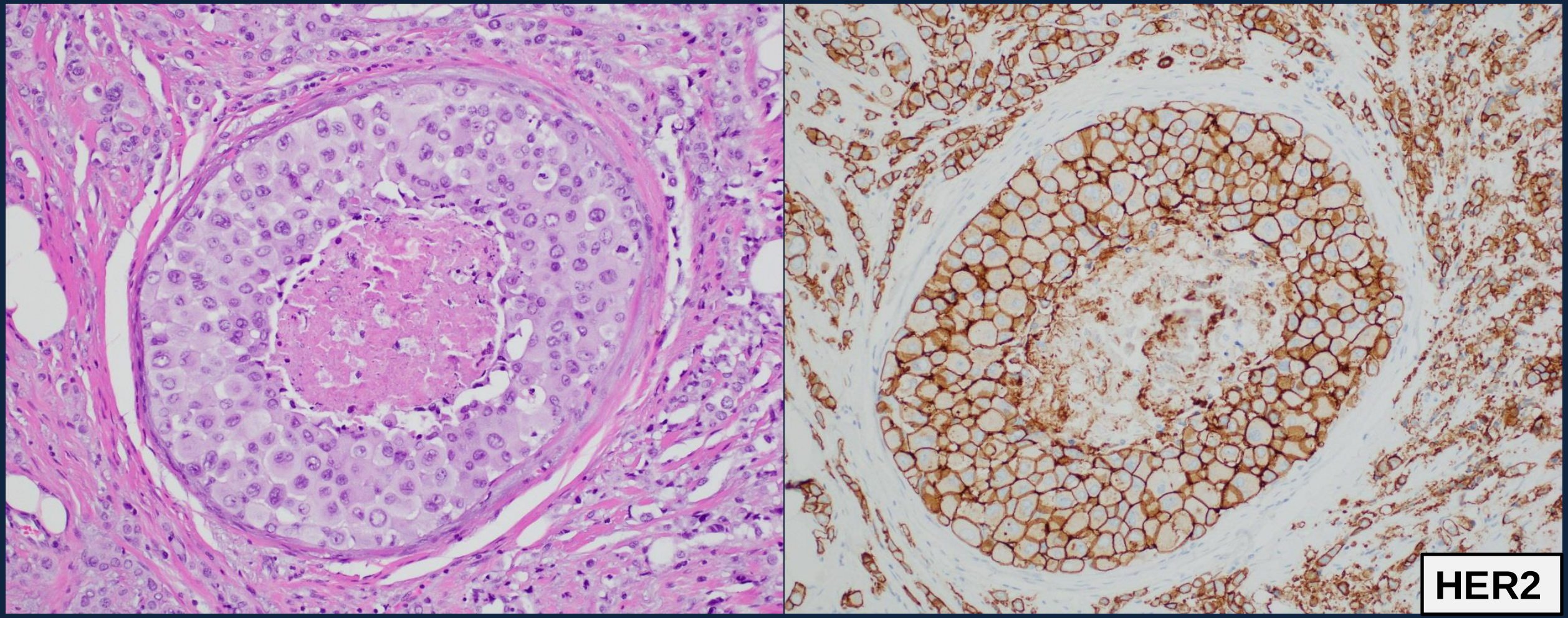
“Invasive carcinoma composed of dispersed or linear dyscohesive cells with low to intermediate nuclear grade morphology and low mitotic count”

***E-cadherin loss not necessary for diagnosis**

Invasive lobular carcinoma biomarker profile

- Most (>90%) ER-positive and HER2-negative
- Triple-negative and HER2-positive tumors uncommon and seen in pleomorphic and/or apocrine ILC

J Clin Oncol 2008;26(18):3006-14.



Pleomorphic invasive lobular carcinoma and LCIS with apocrine differentiation

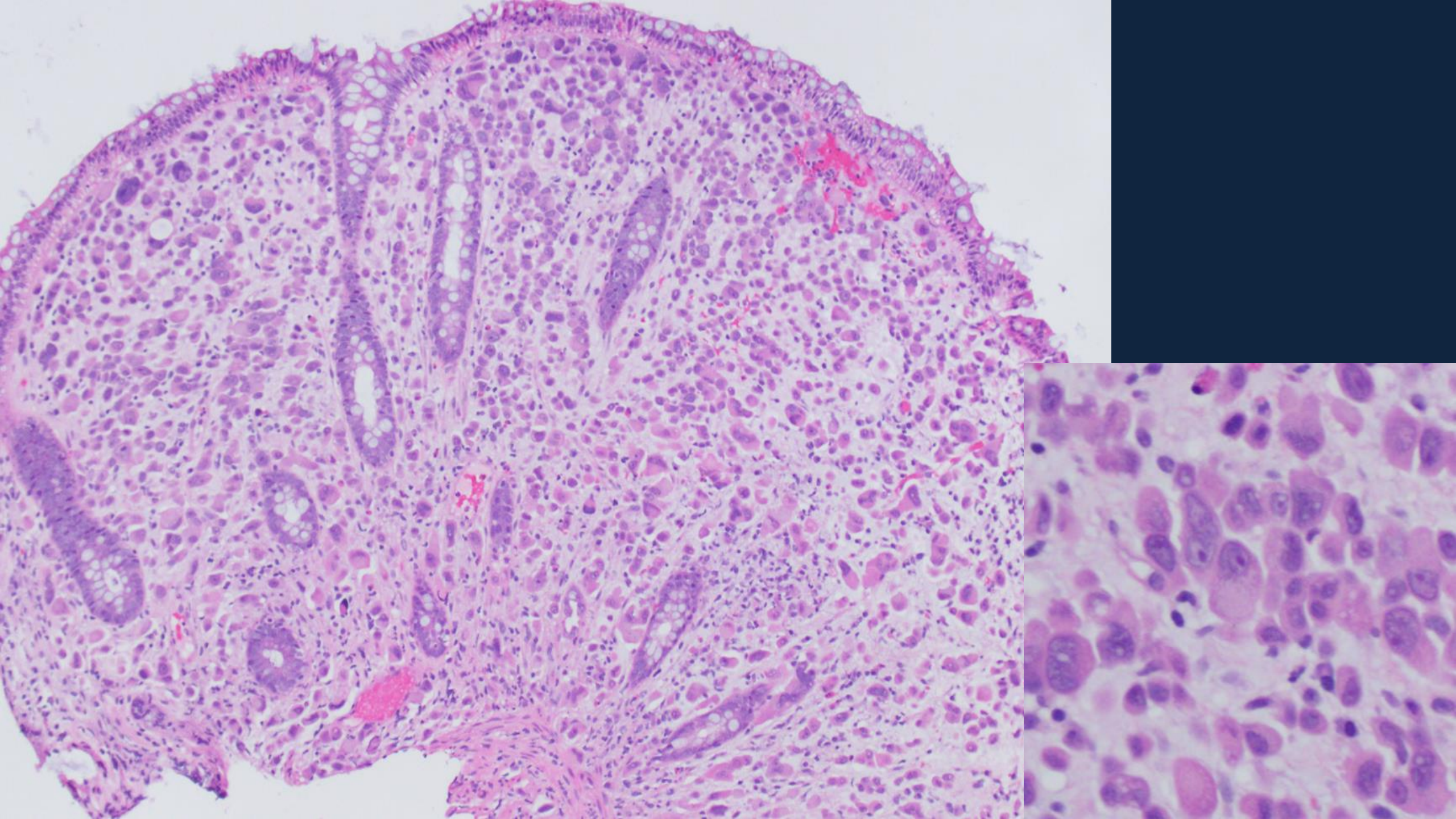
It is important for us to classify a tumor as lobular?

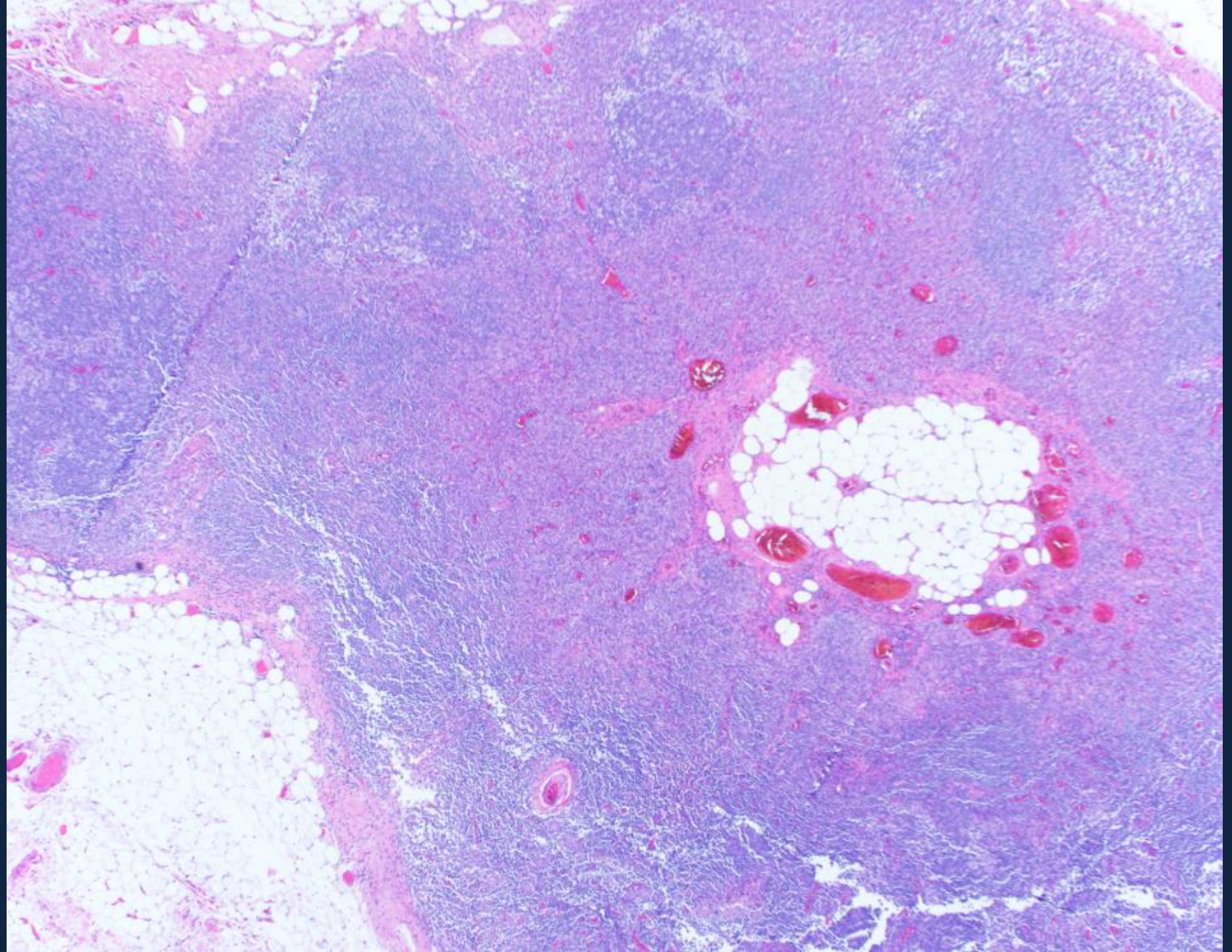
- Older age
- Better differentiated, more frequently ER-positive
- Less frequent lymphovascular invasion
- Less frequent downstaging after NAC
- Higher risk of late (>10 years) distant recurrence
- Different patterns of metastatic spread

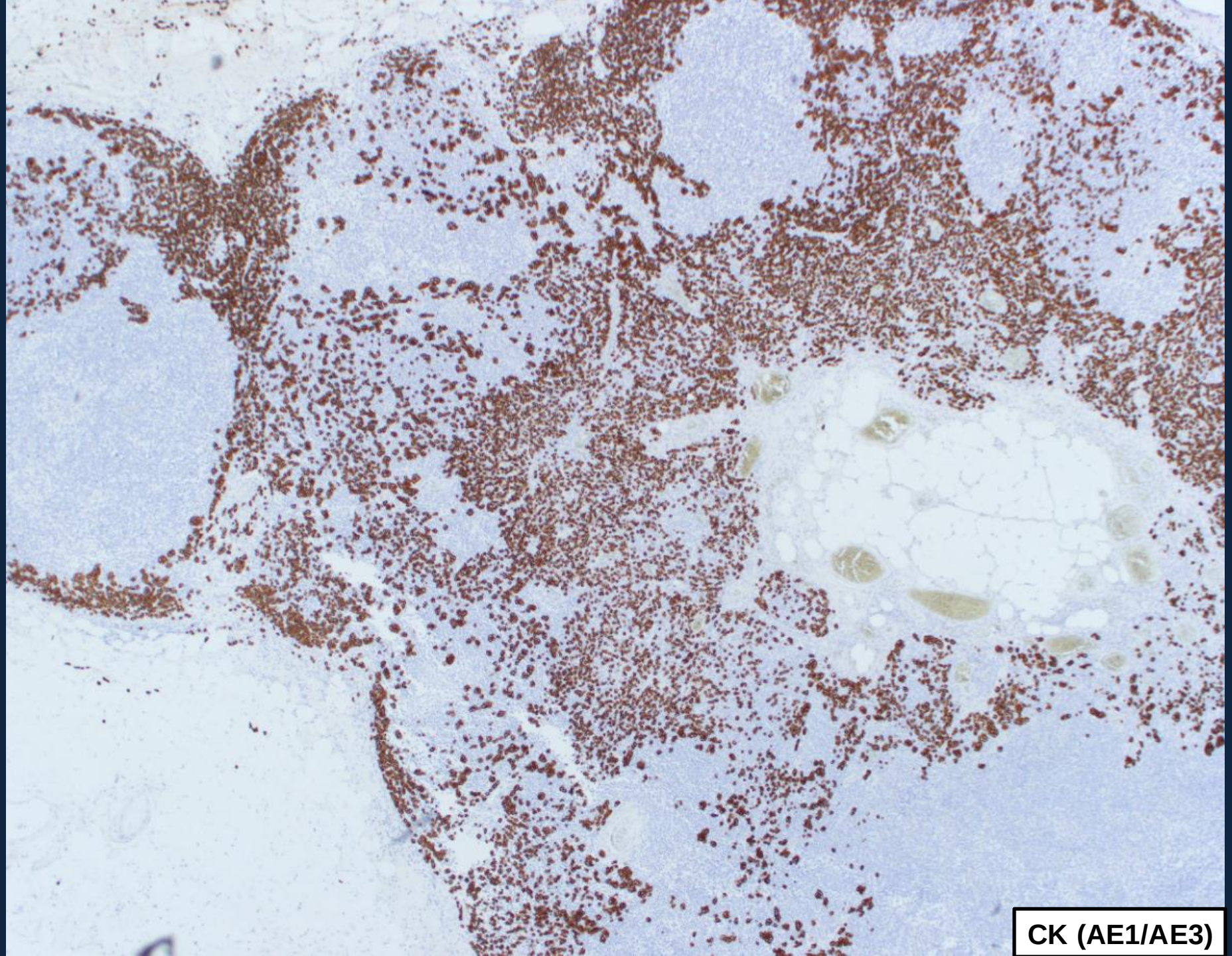
J Clin Oncol 2008;26(18):3006-14.
Eur J Cancer 2004;40(3):336-341.
Br J Cancer 2013;108(2):285-91.

Metastasis of lobular carcinoma

- Lower frequency of axillary lymph node involvement
- Higher frequency of GI tract, serosal surfaces, meninges, ovary, skin



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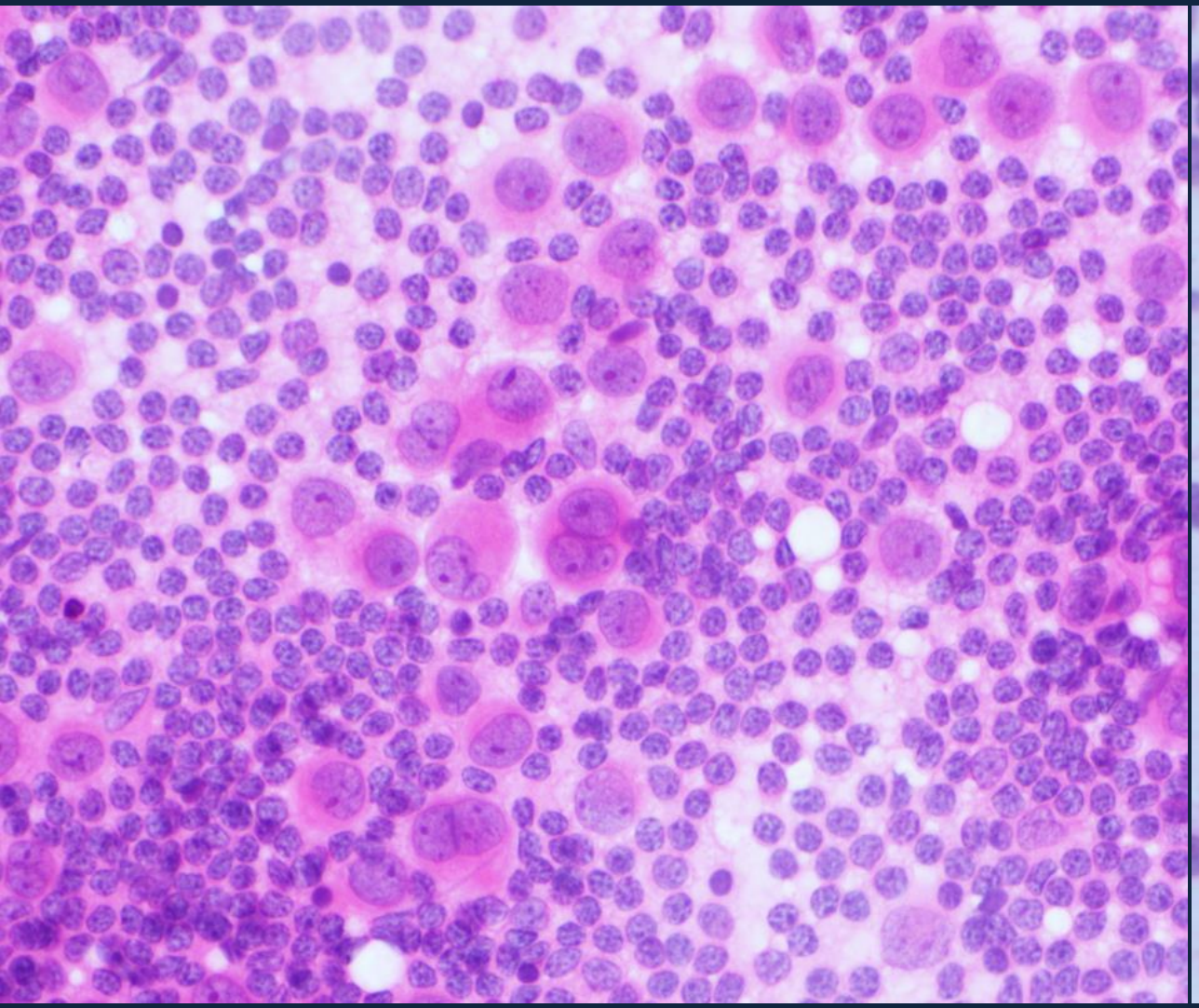
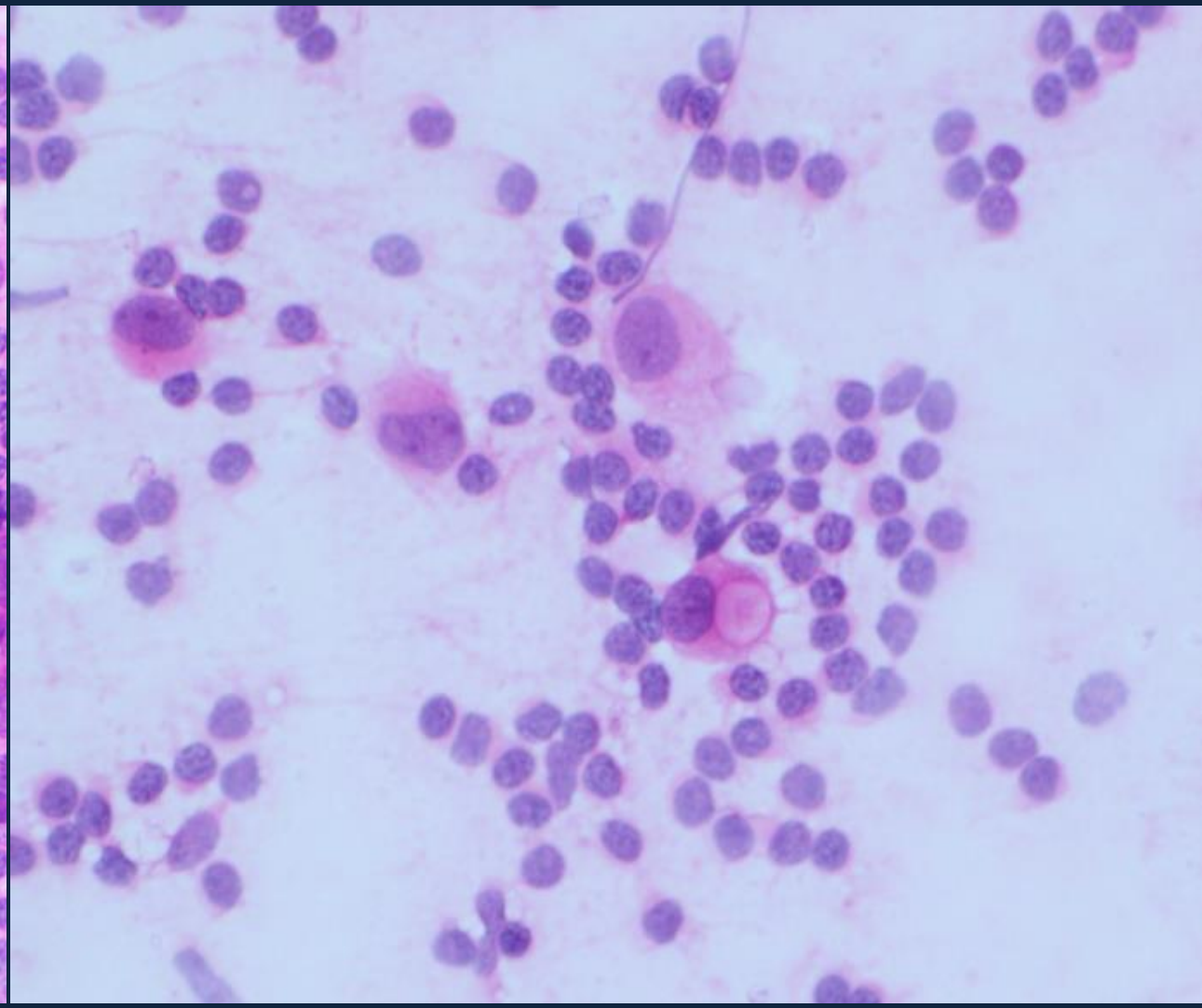




Interobserver agreement for ILC diagnosis

- Lack of standardization
- Variable E-cadherin staining and interpretation
- Variable use of other markers (p120, beta catenin)

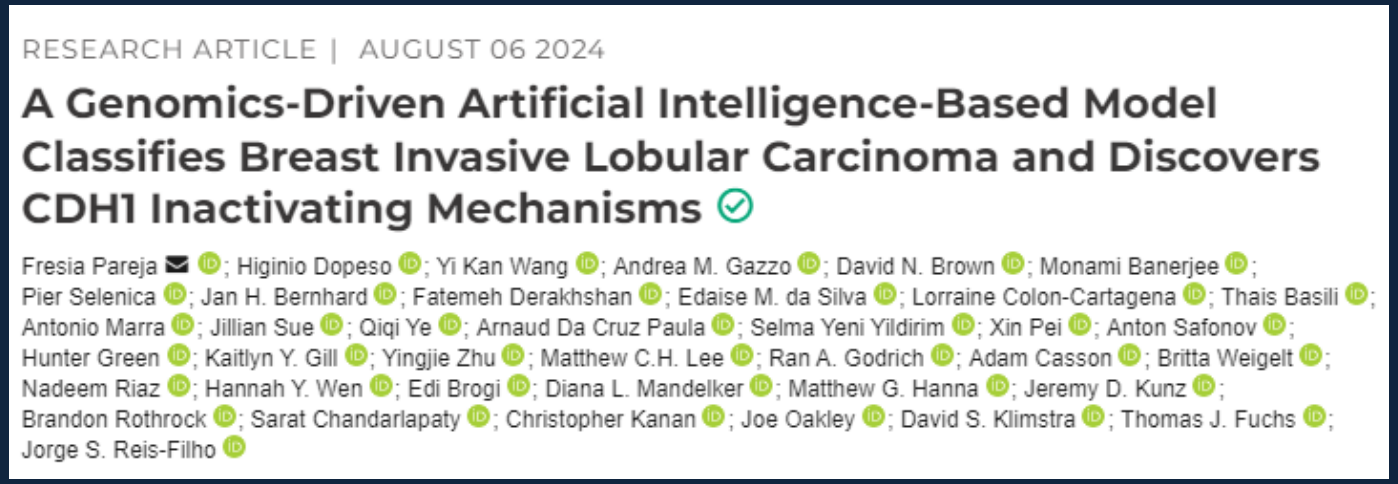
- Need better agreement to study ILC in clinical trials

Results of a worldwide survey on the currently used histopathological diagnostic criteria for invasive lobular breast cancer

Maxim De Schepper[1,27], Anne Vincent-Salomon[2,27], Matthias Christgen[3,27], Karen Van Baelen[1], François Richard[1], Hitoshi Tsuda[4], Sasagu Kurozumi[5], Maria Jose Brito[6], Gabor Cserni[7], Stuart Schnitt[8], Denis Larsimont[9], Janina Kulka[10], Pedro Luis Fernandez[11], Paula Rodríguez-Martínez[11], Ana Aula Olivar[12], Cristina Melendez[12], Mieke Van Bockstal[13], Aniko Kovacs[14], Zsuzsanna Varga[15], Jelle Wesseling[16], Rohit Bhargava[17], Pia Boström[18], Camille Franchet[19], Blessing Zambuko[20], Gustavo Matute[21], Sophie Mueller[3], Anca Berghian[22], Emad Rakha[23], Paul J. van Diest[24], Steffi Oesterreich[25], Patrick W. B. Derksen[24,28], Giuseppe Floris[26,28]✉ and Christine Desmedt[1,28]✉

- **52% use IHC (mainly E-cadherin) routinely to make a diagnosis of ILC; 3% never use IHC**
- **51% use additional IHC (β-catenin, p120-catenin) if lobular morphology but positive E-cadherin**
- **Variability in reporting histologic variants**

Mod Pathol 2022;35(12):1812-1820



RESEARCH ARTICLE | AUGUST 06 2024

A Genomics-Driven Artificial Intelligence-Based Model Classifies Breast Invasive Lobular Carcinoma and Discovers CDH1 Inactivating Mechanisms

Fresia Pareja; Higinio Dopeso; Yi Kan Wang; Andrea M. Gazzo; David N. Brown; Monami Banerjee; Pier Selenica; Jan H. Bernhard; Fatemeh Derakhshan; Edaise M. da Silva; Lorraine Colon-Cartagena; Thais Basili; Antonio Marra; Jillian Sue; Qiqi Ye; Arnaud Da Cruz Paula; Selma Yeni Yildirim; Xin Pei; Anton Safonov; Hunter Green; Kaitlyn Y. Gill; Yingjie Zhu; Matthew C.H. Lee; Ran A. Godrich; Adam Casson; Britta Weigelt; Nadeem Riaz; Hannah Y. Wen; Edi Brogi; Diana L. Mandelker; Matthew G. Hanna; Jeremy D. Kunz; Brandon Rothrock; Sarat Chandarlapaty; Christopher Kanan; Joe Oakley; David S. Klimstra; Thomas J. Fuchs; Jorge S. Reis-Filho

- **AI algorithm to classify ILC based on ground truth of tumor genomics (*CDH1* bi-allelic mutations)**

- **Detects ILCs with bi-allelic *CDH1* mutations and alternative *CDH1* inactivating alterations**

***Cancer Res* 2024 PMID: 39106449**

Invasive lobular carcinoma
Take home points…

- Heterogenous special type of invasive carcinoma
  - Morphology
  - Genomic features
  - ER/PR/HER2
  - Clinical behavior, response to treatment

Invasive lobular carcinoma
Take home points…

- Heterogenous special type of tumor
  - Morphology
  - Genomic features
  - ER/PR/HER2
  - Clinical behavior, response to treatment
- Stricter histologic classification by pathologists necessary for clinical studies
- Further study of AI-based classification models expected

Thank you for your attention!