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MEDICAL BREAST TRAINING PROGRAM

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LCIS

LOBULAR CARCINOMA IN SITU

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DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INDUSTRY

- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

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LEARNING OBJECTIVES

- Define and describe lobular carcinoma in situ (LCIS), the risk associated with LCIS, and how it differs from ductal carcinoma in situ.
- Discuss management strategies for LCIS.
- Briefly discuss risk-reduction strategies as they apply to LCIS including lifestyle recommendations and enhancing screening considerations.

CASE

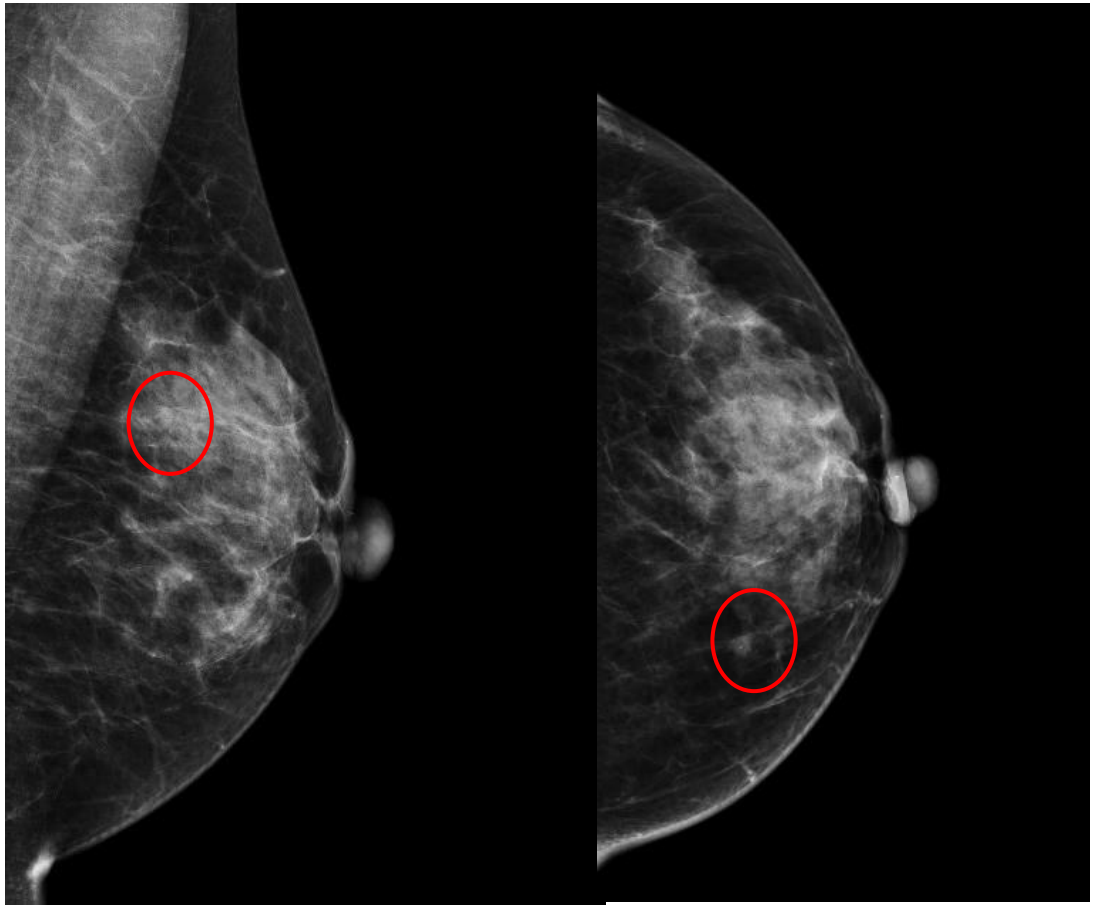
PATIENT HY

- 49 yo Ethiopian woman presenting with a screen-detected left breast imaging finding
- History of GERD, appendectomy, C-section
- No family history, menarche at age 14, DLMP 10 days ago, G1P1
- Had left breast imaging work-up for 2-week history of left breast discomfort (since resolved)
- O/E: no palpable adenopathy, visible biopsy scar left breast at 9 o’clock, no palpable findings

CASE 1

PATIENT HY

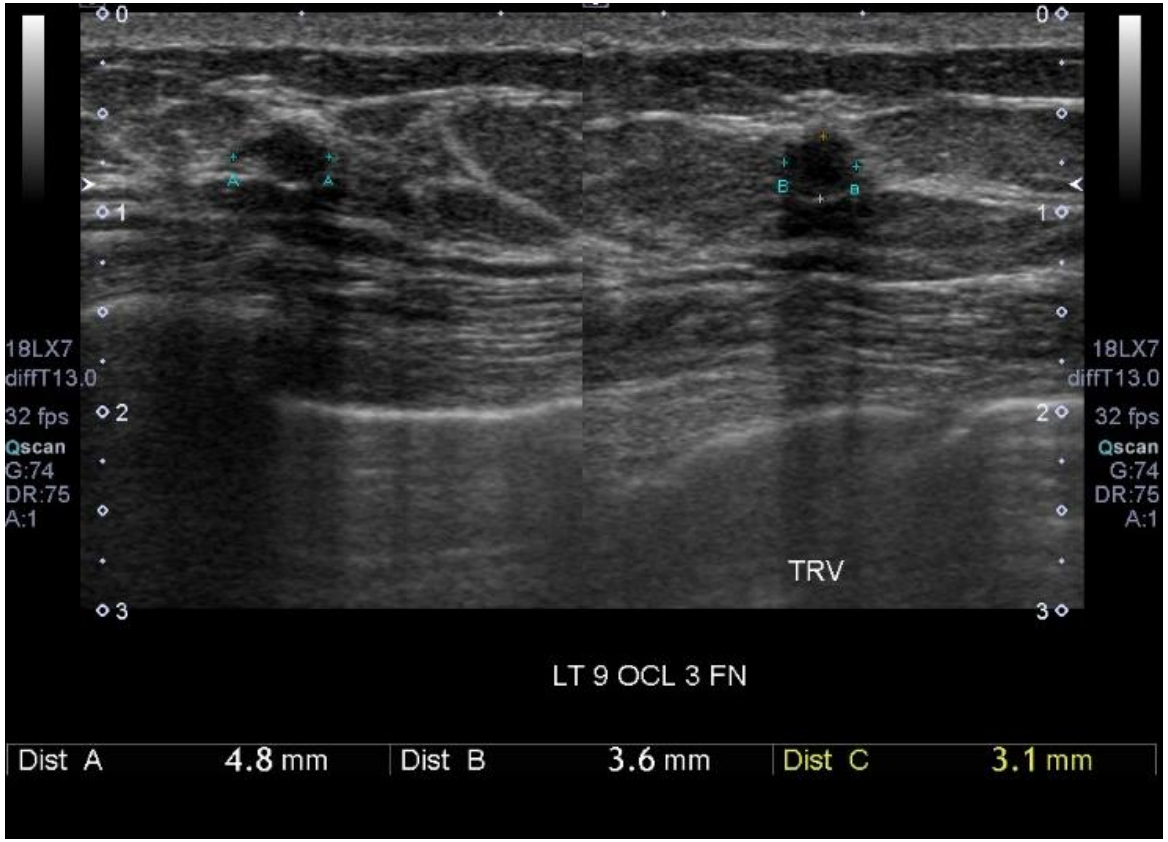
- Bilateral mammogram: heterogeneously dense breasts, within left upper inner breast is 6 mm circumscribed mass with two foci of internal calcifications



CASE 1

PATIENT HY

- Ultrasound: At 9 o’clock, 3 cm from the nipple, correlating with the mass on mammogram, there is a rounded hypoechoic mass with partially indistinct margins measuring 5 x 3 x 4 mm. No concerning lymphadenopathy within the left axilla. Core biopsy is performed.



CASE 1

PATIENT HY

- Core biopsy: lobular carcinoma in situ, classical-type
- Next step?

LCIS

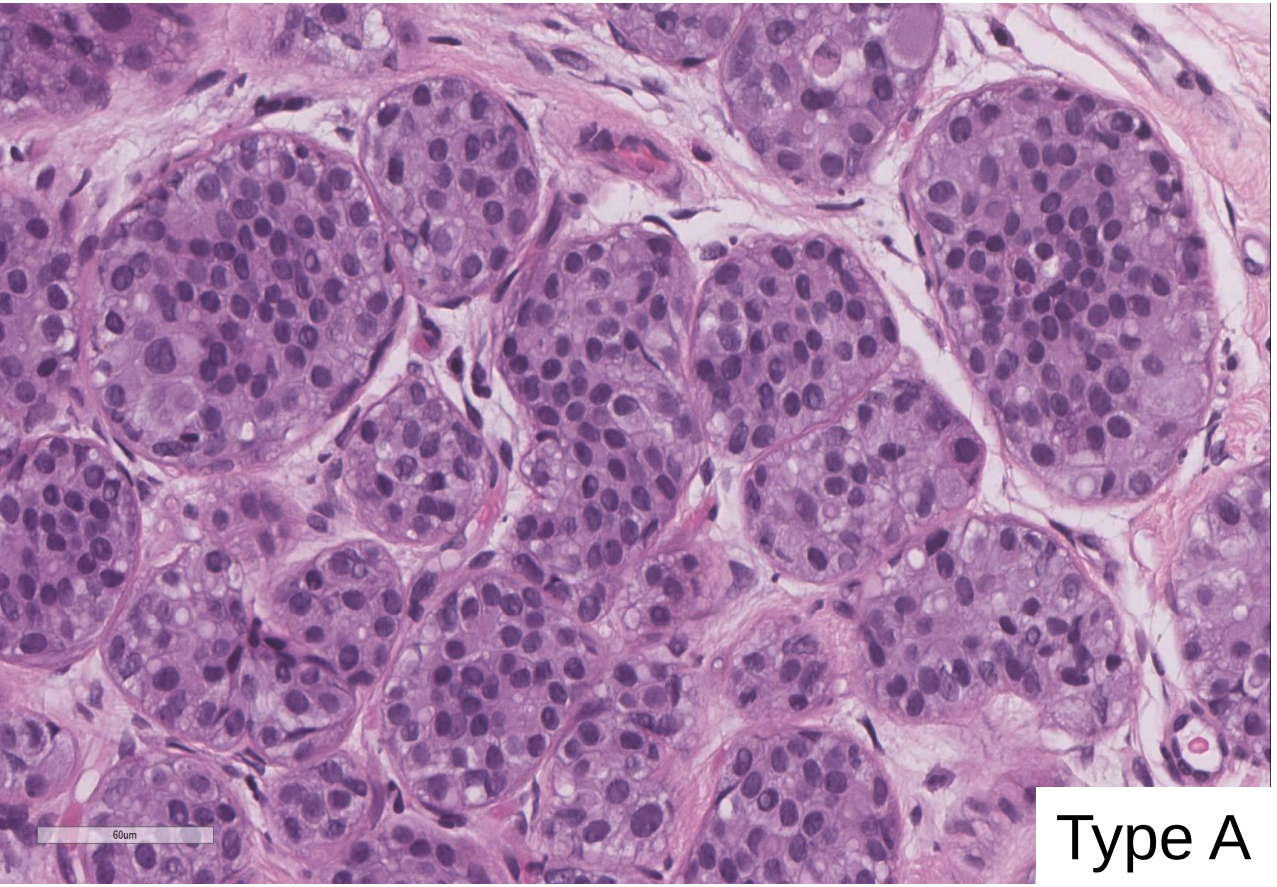
LOBULAR CARCINOMA IN SITU

- Part of the spectrum of “lobular neoplasia” = non-invasive proliferative within the breast lobule (i.e. lobular lesion)
  - Atypical Lobular Hyperplasia (ALH)
  - Lobular Carcinoma In Situ (LCIS)
- Both ALH and LCS are associated with an increased risk of breast cancer
  - LCIS greater risk
- Incidence of pure lobular neoplasia:
  - 0.5 – 4%, frequently multicentric and bilateral
  - Typically presents in younger women than does invasive lobular carcinoma (ILC)
- LCIS is NOT cancer
  - a non-obligate precursor lesion to invasive lobular carcinoma

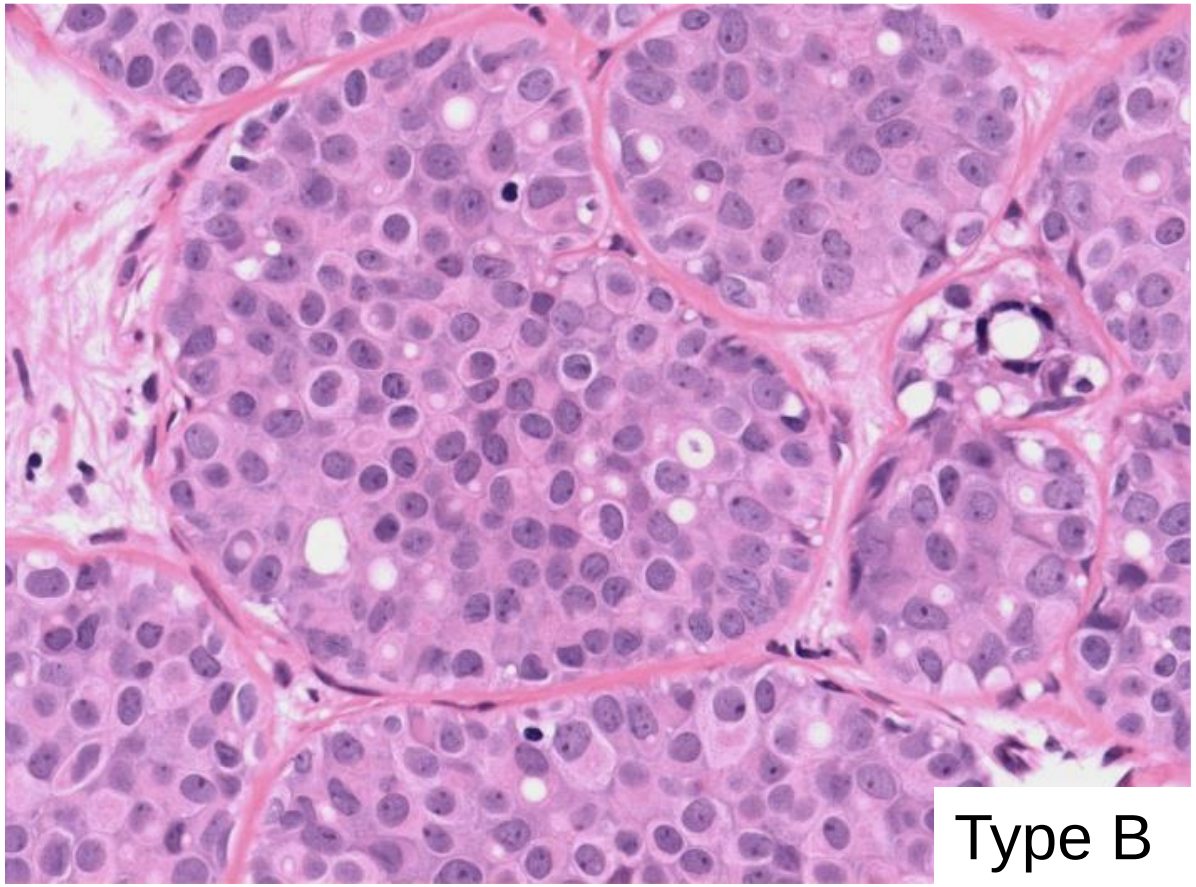
LCIS

HISTOLOGY

- Arises from the terminal ductal lobular unit, filling and expanding acini
  - Like ALH, LCIS can extend into ducts if extensive (DIAL = ductal involvement by atypical lobular cells)
- Proliferation of monomorphic cells that fill and distend the lobules (> ½ of the acini within a lobule)
  - VS ALH = only partially involves the lobule by filling up <1/2 of the acini without significant distention
  - VS DCIS = proliferation of malignant epithelial cells within the ductal system
- Classical LCIS:
  - cells are small, uniform, round and loosely cohesive, indistinct cell borders and pale cytoplasm, uniform small nuclei, evenly distributed chromatin and inconspicuous nucleoli
    - Mitotic figures and necrosis are rarely seen
    - Typically involve lobules but may grow along the basement membrane of extralobular ducts (“pagetoid” growth) and may secondarily involve benign lesions (e.g. radial scars, papillomas, fibroadenomas, etc.)



Type A



Type B

Type A (classic cellular features):

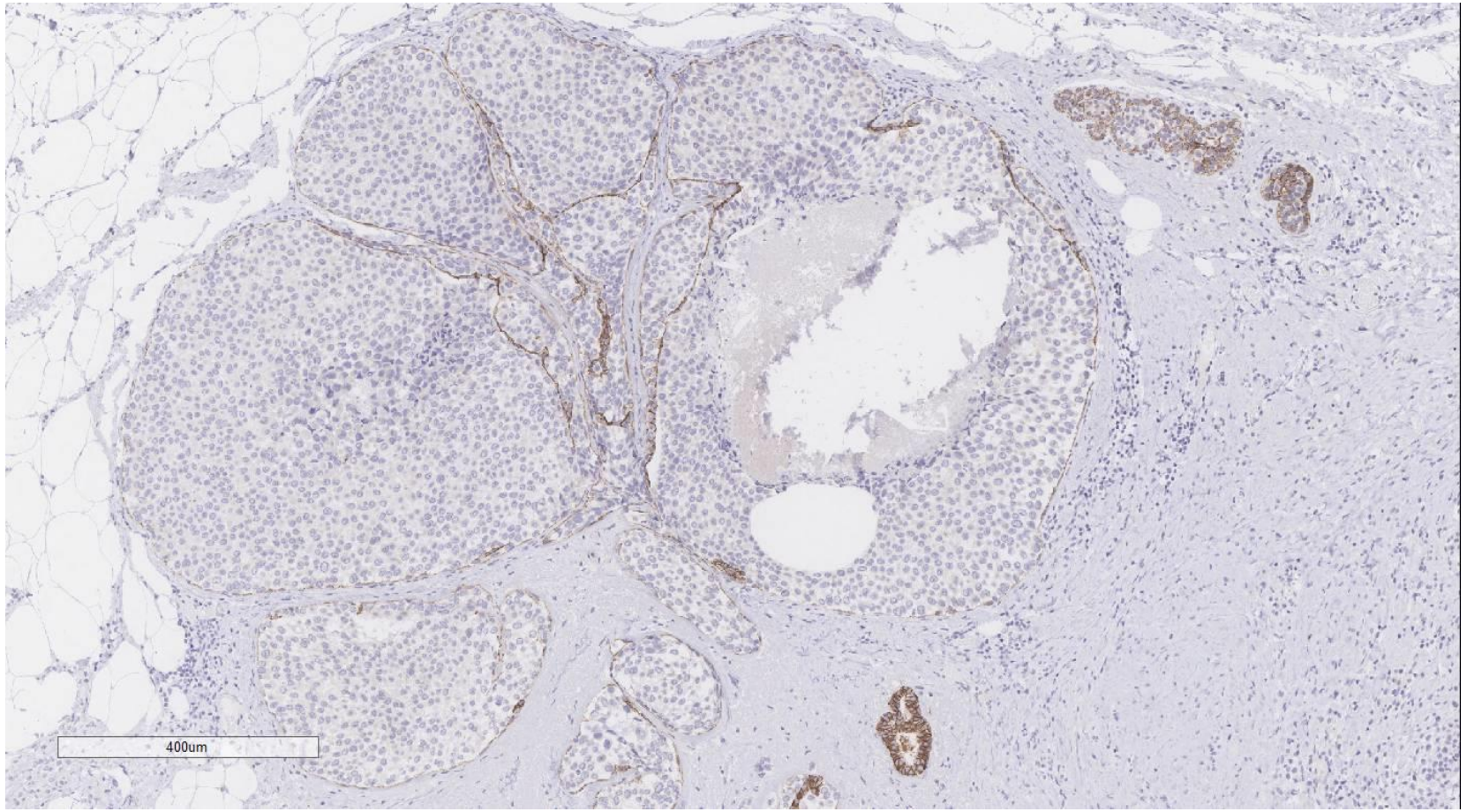
Loosely cohesive cells with scant cytoplasm and uniform, small round nuclei and homogenous chromatin, lack nucleoli

Type B

Larger atypical poorly cohesive cells with mild to moderate nuclear variability, large nuclei and prominent nucleoli, more abundant cytoplasm

Pathology Slides courtesy from Dr. Anna Marie Mulligan, MB BCH MRCPath, Staff Pathologist, University Health Network, Toronto, ON.
Associate Professor, Department of Laboratory Medicine & Pathobiology – Anatomic Pathology, University of Toronto, Toronto, ON, Canada

LOSS OF E-CADHERIN STAINING IN LOBULAR NEOPLASM



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CLASSIC LCIS

CLINICAL PRESENTATION

- Typically has no clinical signs, no signs on mammography and can’t be identified on gross pathologic examination
- Almost always an incidental finding found on a breast biopsy that is performed for another reason (i.e. mass, calcifications, area of enhancement)
- Mean age of diagnosis 44-46
- 80-90% occur in pre-menopausal women
  - Possibly hormonal influence (LCIS cells typically are strongly ER+)
  - Incidence is rising in post-menopausal women

LCIS VS DCIS

	LCIS (classical)	DCIS
Clinical Presentation	Incidental finding	Mammogram abnormality (calcifications), palpable mass, nipple discharge, Paget's disease, incidental
Location	Lobules	Ducts
Cell size	Small	Medium or large
Pattern	Solid	Comedo, cribriform, micropapillary, papillary, solid
Calcifications	Usually no	Yes or No
Focality	Often multifocal	Unifocal
Risk of future breast cancer	Lower	Higher
Location of future breast cancer	Ipsilateral or contralateral	Ipsilateral

CLASSIC LCIS

MANAGEMENT – AFTER A BREAST BIOPSY

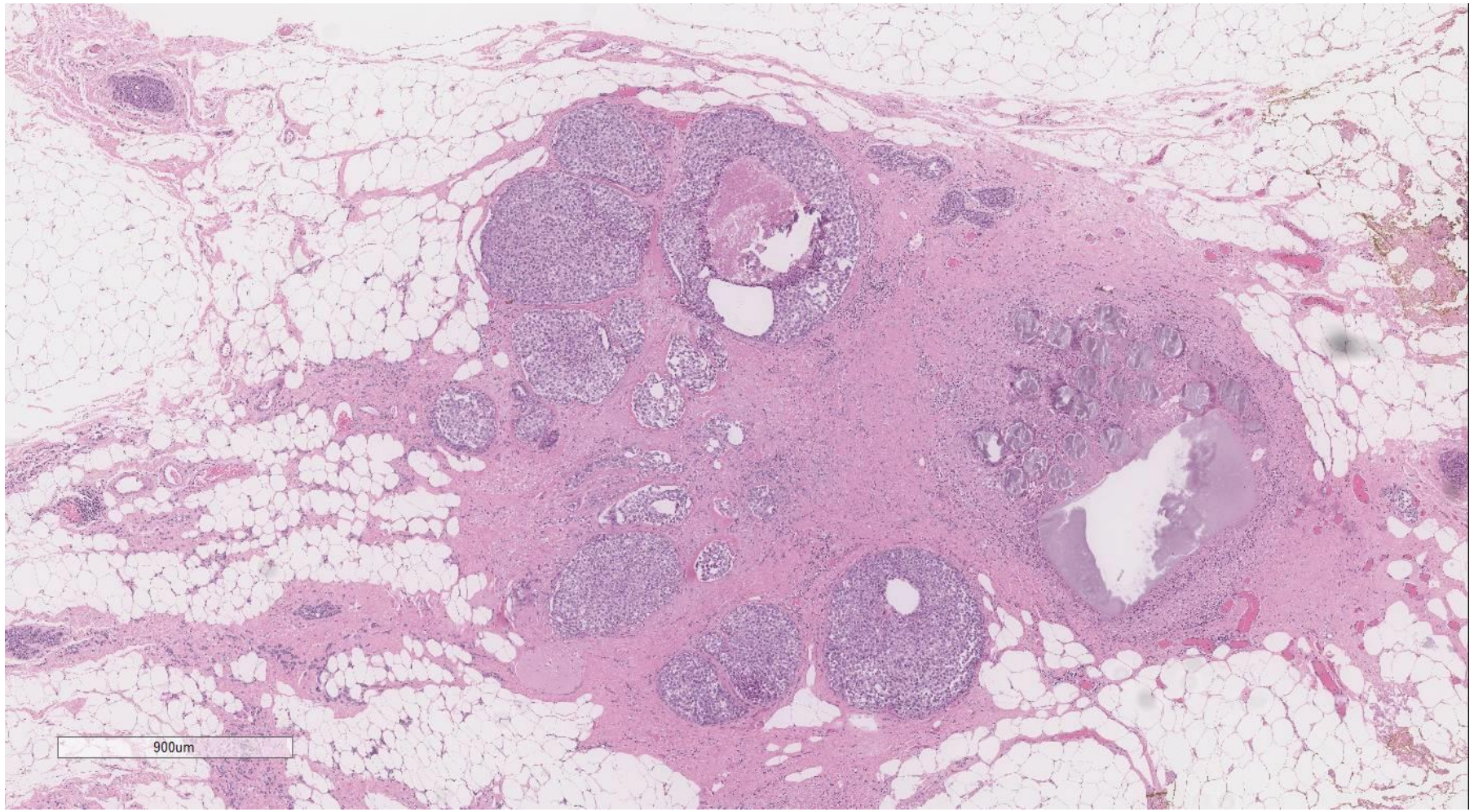
- Radiologic-pathologic concordance and no other high-risk lesions (i.e ADH, papilloma, radial scar) identified that require excision, LCIS can be observed with clinical and imaging follow-up
  - Upgrade rate <5%
  - NCCN, American Society of Breast Surgeons
- Discussing radiologic-pathologic concordance with radiologist is KEY!
  - Biopsy was often done for a mass, calcifications or enhancement
  - Often, the lesion is excised for definitive diagnosis due to discordance:
    - Targeted versus incidental lesions
    - Cases with fewer cores taken
    - Mass lesions
      - These factors are associated with risk of upgrade following surgical excision.
- If surgical pathology demonstrates classical LCIS, no further surgery is needed.
- If classical LCIS is present at the surgical margin, no re-excision is necessary.

NON-CLASSICAL LCIS

- Pleomorphic LCIS
- Florid LCIS
- LCIS with necrosis
- LCIS with signet ring features
  - Signet ring appearance to LCIS cells is due to intracytoplasmic mucin
- LCIS with apocrine features

- These lesions all tend to have high-grade cytology and variable biomarker profile.

PLEMORPHIC LCIS



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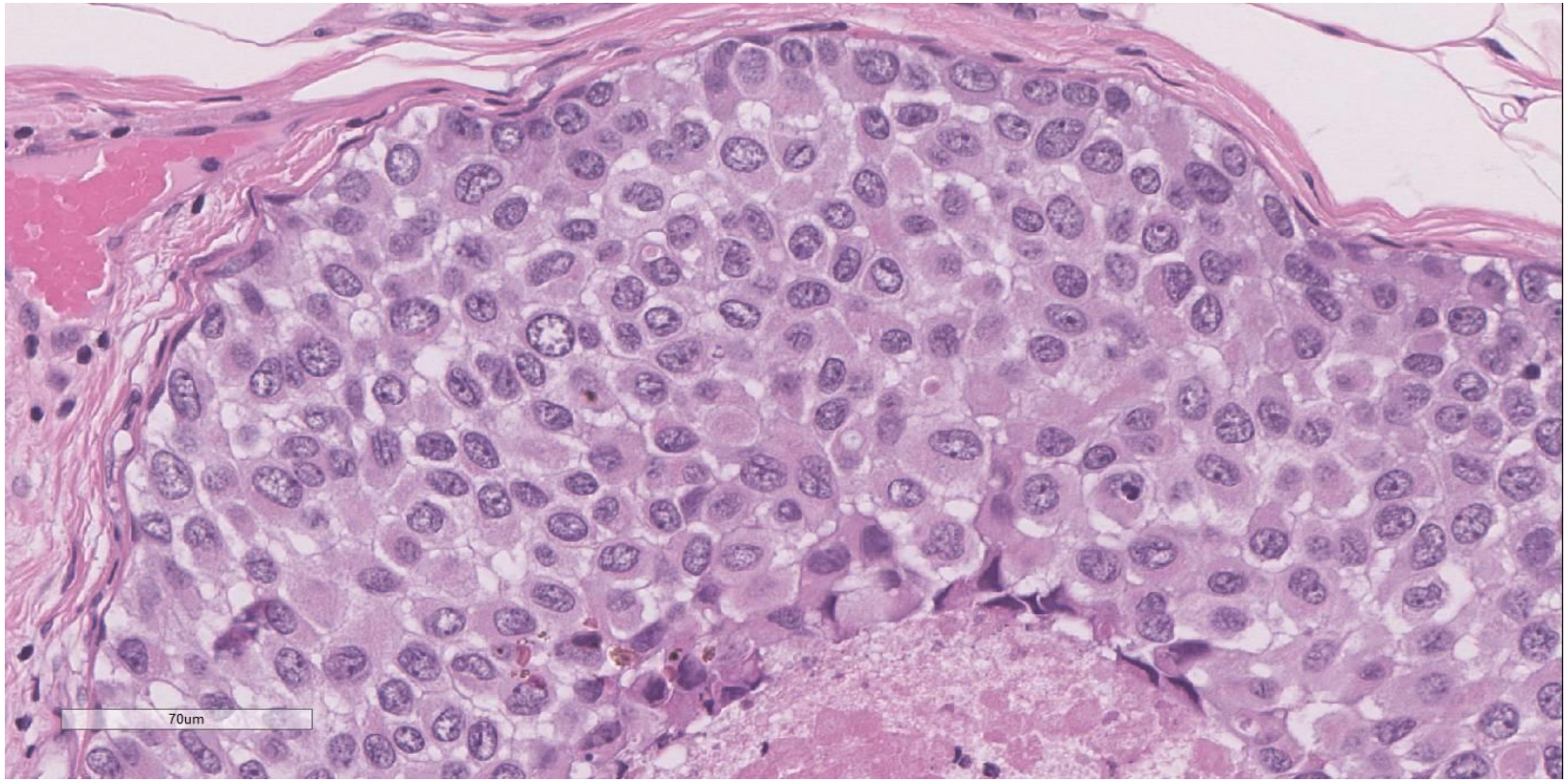
PLEMORPHIC LCIS



- Larger cells with marked nuclear pleomorphism (enlarged, eccentric nuclei), prominent nucleoli
- Similar cell dyscohesion and intracytoplasmic vacuoles as classical LCIS, may have more abundant cytoplasm than classical
- May have intracytoplastic mucin vacuoles (signet ring features)
- May have apocrine features (abundant eosinophilic cytoplasm, cytoplasmic granules, prominent nucleoli)
- Can have florid growth pattern

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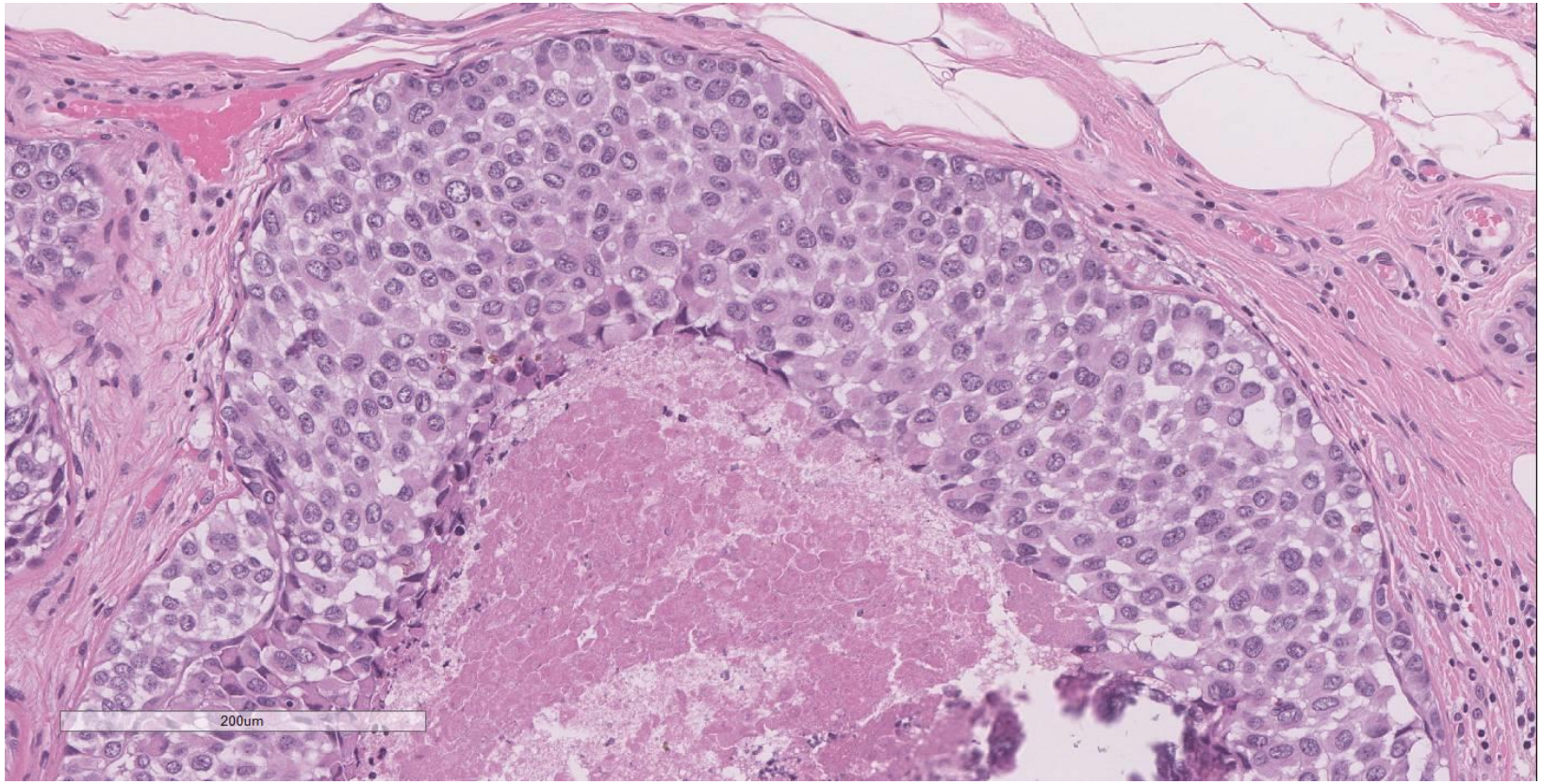
PLEMORPHIC LCIS



- Often has central necrosis and calcifications (rare with classical LCIS)
- Pleomorphic LCIS = LCIS with high-grade cytologic features (can mimic DCIS), can be associated with invasive pleomorphic lobular carcinoma

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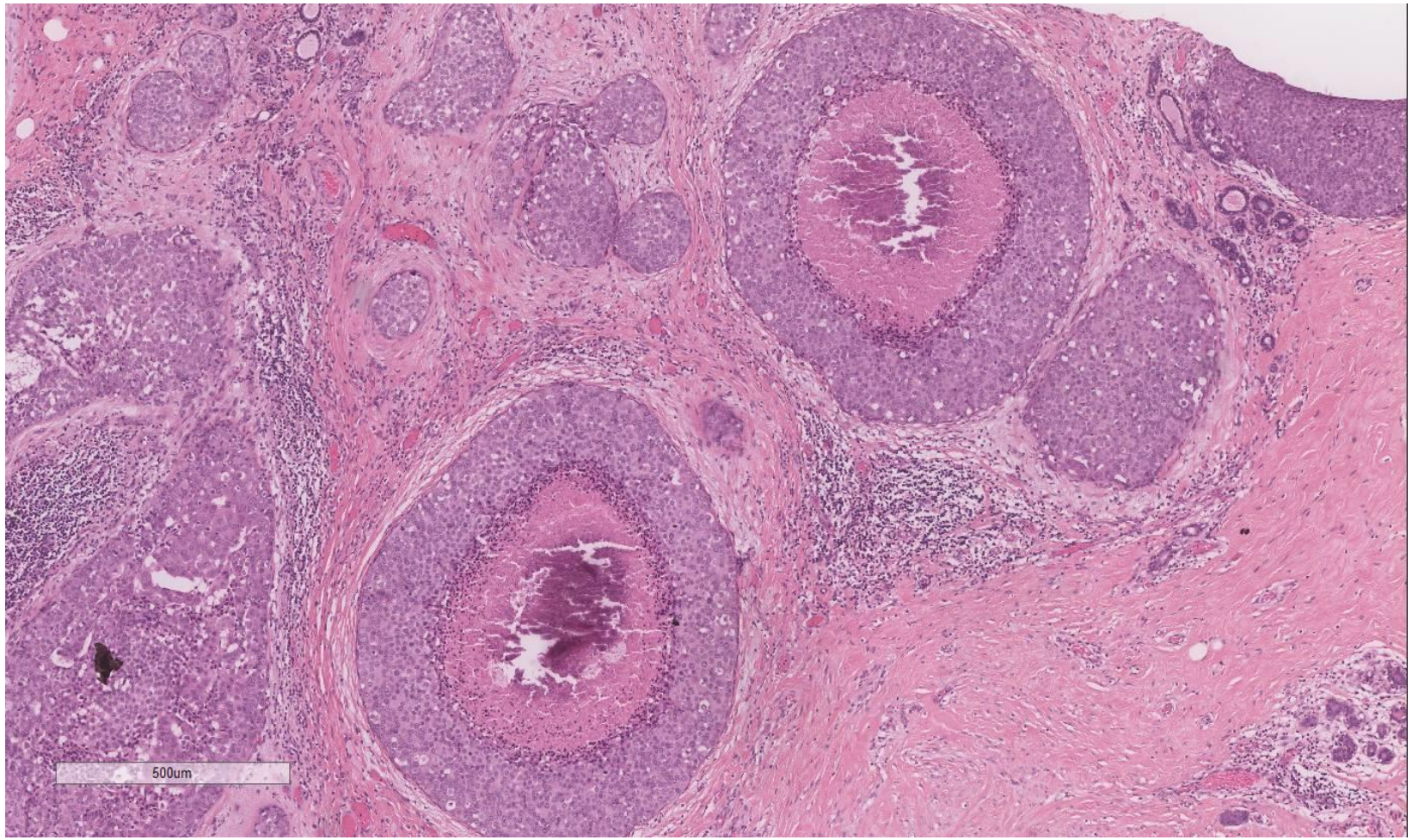
FLORID LCIS (LCIS WITH COMEDONECROSIS)



- Marked distension of involved lobules and ducts (typically be cells of classic LCIS of low to intermediate grade) to the point that it becomes mass-forming
- Often there is central necrosis or comedonecrosis within the involved spaces, which may calcify
- Thus, florid LCIS may present as an image-detected mass or as microcalcifications
- Florid LCIS = describes an architectural growth pattern where LCIS causes marked expansion of ducts and lobules

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	Classical LCIS	Florid LCIS	Pleomorphic LCIS
Age (years)	Premenopausal, 40-50	Postmenopausal, 50-60	
Imaging	No findings, occasionally punctate calcifications	Calcifications (similar to DCIS) or mass	
Histology	Loosely cohesive cells fill and distend lobules; pagetoid growth in ducts; occasional calcifications; no/rare mitoses, no necrosis, Type A (small low-grade cytology) and B (intermediate-grade)	Marked ductal expansion by loosely cohesive cells, common necrosis and calcifications Type A (small low-grade cytology) and B (intermediate-grade)	Lobular and ductal expansion by loosely cohesive cells, common necrosis and calcifications, frequent mitoses Cytology: high-grade, nuclear enlargement, pleomorphism Apocrine features: eosinophilic cytoplasm, granules, nucleoli
Biomarker	> 95% ER+/PR+, HER2-	Most ER+ and PR+ Rare HER2 +	Most are ER+ & PR+ (45-50%) but decreased expression compared with classical LCIS, may be negative (particularly apocrine type) 13% HER2 positivity (more common in apocrine type – 31%)

NON-CLASSICAL LCIS

- Pleomorphic LCIS, Florid LCIS, LCIS with necrosis, LCIS with signet ring features, LCIS with apocrine features

- These lesions should be treated similar to DCIS - complete surgical excision.
- There are no data on the optimal width of negative margin or the benefit of radiation for pleomorphic or florid LCIS, although treatment principles are extrapolated from management of DCIS.
- If present at surgical margin, resect to a negative margin.

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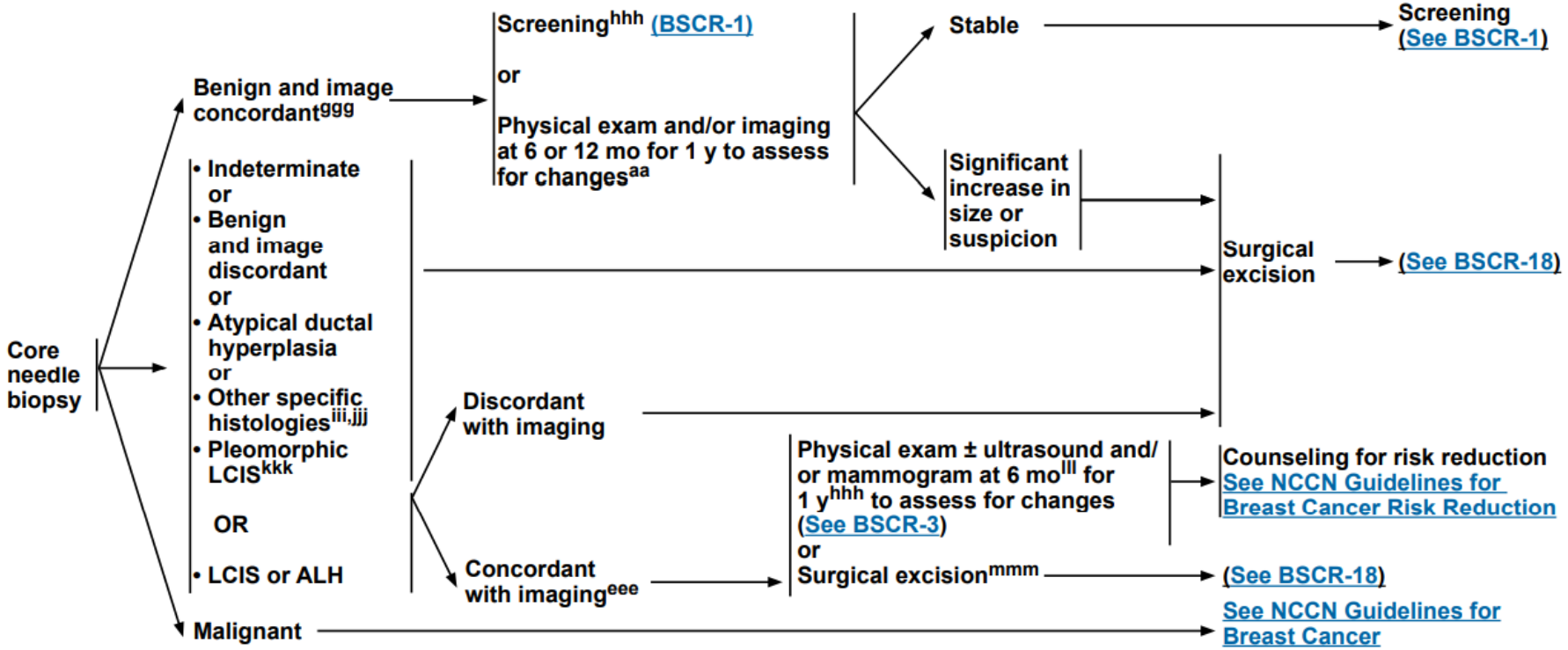
Breast Cancer Screening and Diagnosis

FOLLOW-UP EVALUATION AFTER CORE NEEDLE BIOPSY



[aa]There may be variability on the follow-up interval of physical exam based on the level of suspicion.

[ggg]Pathology matches imaging findings.

[hhh]While most would return to annual screening, there is the option of physical exam with or without further imaging for individuals under 40 y of age.

[iii]Select patients may be suitable for monitoring in lieu of surgical excision (eg, ADH, LCIS, ALH, flat epithelial atypia [FEA], papillomas without atypia, fibroepithelial lesions favoring fibroadenoma, radial scars adequately sampled or incidental).

[jjj]Other histologies that may require additional tissue: mucin-producing lesions, potential phyllodes tumor, papillary lesions, radial scar, or histologies of concern

[kkk]Clinicians may consider complete excision with negative margins for pleomorphic LCIS. However, outcomes data regarding treatment of individuals with pleomorphic LCIS are lacking, due in part to a paucity of histologic categorization of variants of LCIS.

[lll]Initiation of high-risk MRI screening may obviate the need for 6-month mammogram/ultrasound.

[mmm]Multifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy may be associated with increased risk for invasive cancer on surgical excision. (Rendi MH, et al. Ann Surg Oncol 2012;19:914-921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21861212).

CASE

PATIENT HY

- 47 yo Ethiopian woman referred for a screen-detected breast imaging abnormality
- History of GERD, appendectomy and C-section
- No family history, menarche at age 14, DLMP 10 days ago, G1P1
- Had left breast imaging work-up for 2-week history of left breast discomfort (since resolved)
- O/E: no palpable adenopathy, biopsy scar Left breast 9 OC, 3 cm from the nipple, no palpable findings
- Bilateral mammogram: heterogeneously dense breasts, within left upper inner breast is 6 mm circumscribed mass with two foci of internal calcifications
- Ultrasound: At 9 o'clock, 3 cm from the nipple, correlating with the mass on mammogram, there is a rounded hypoechoic mass with partially indistinct margins measuring 5 x 3 x 4 mm. No concerning lymphadenopathy within the left axilla. Core biopsy is performed.
- Core biopsy: lobular carcinoma in situ, classical-type
- Next step?

CASE

PATIENT HY

- Discussed at Breast Imaging Rounds
- Radiologic-pathologic discordance
- Image-guided lumpectomy
- Pathology: radial scar with classical LCIS

SURVEILLANCE AFTER LCIS

NCCN GUIDELINES

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Breast Cancer Screening and Diagnosis

NCCN Guidelines Index
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Discussion

SCREENING OR SYMPTOM CATEGORY[a]	SCREENING/FOLLOW-UP
Increased Risk:	
5-year risk of invasive breast cancer ≥1.7% in individuals ≥35 y (per Gail Model)[i] →	• Clinical encounter[b,c,d,e,k] every 6–12 mo ‣ to begin when identified as being at increased risk by Gail Model • Annual screening[b] mammogram,[m] consider tomosynthesis[o] ‣ to begin when identified as being at increased risk by Gail Model • Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction) • Breast awareness[l]
OR	
Lobular neoplasia (LCIS/ALH) or ADH[r] and ≥20% lifetime risk →	• Clinical encounter[b,c,d,e,k] every 6–12 mo ‣ To begin at diagnosis of lobular neoplasia (LCIS/ALH) or ADH • Annual screening[b] mammogram,[m] consider tomosynthesis[o] ‣ To begin at diagnosis of lobular neoplasia (LCIS/ALH) or ADH but not prior to age 30 y • Consider annual breast MRI[b,p] ‣ To begin at diagnosis of lobular neoplasia (LCIS/ALH) or ADH but not prior to age 25 y ‣ Consider contrast-enhanced mammography[b] or whole breast ultrasound[b] for those who qualify for but cannot undergo MRI • Consider risk reduction strategies (See NCCN Guidelines for Breast Cancer Risk Reduction) • Breast awareness[l]

[a]For individuals with a prior history of breast cancer, please refer to the NCCN Guidelines for Breast Cancer - Surveillance Section.
[b]See Breast Screening Considerations (BSCR-A).
[c]Medicare and insurers allow the individual direct access to scheduling for screening mammography.
[d]At minimum medical and family history should be obtained and clinical encounter should encompass ongoing risk assessment, risk reduction counseling, and preferably a clinical

[k]Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical encounter is to maximize earliest detection of breast cancers and assure ongoing risk assessment.
[l]Individuals should be familiar with their breasts and promptly report changes to their health care provider.
[m]See Mammographic Evaluation (BSCR-20).
[o]Tomosynthesis can decrease call back rates and improve cancer detection but has not

- MRI not supported if LCIS alone without <20-25% lifetime risk of breast cancer.

LCIS & INVASIVE BREAST CANCER

MANAGEMENT OF POSITIVE LCIS MARGINS

- LCIS is found to be associated with 5% of invasive carcinomas
  - LCIS is not a contra-indication to breast-conserving therapy.
- Classical LCIS: no need to obtain negative margins around the LCIS as long as the margins around the invasive carcinoma is negative
- Non-classical LCIS (pleomorphic & florid LCIS): consider achieving negative margins around pleomorphic and florid LCIS if is present at the surgical margin

MARGIN STATUS RECOMMENDATIONS AFTER BCS FOR INVASIVE CANCERS AND DCIS

Invasive Breast Cancer

- **For invasive breast cancers that have a component of DCIS, regardless of the extent of DCIS, the negative margin definition of "no ink on tumor" should be based on the invasive margin guideline. In this setting, "no ink on tumor" is recommended for either DCIS or invasive cancer cells, primarily because the natural history, treatment, and outcomes of these lesions are more similar to invasive cancer than DCIS. For specifically challenging cases, clinical judgment and discussion with the patient should precede routine re-excision.**
- **These margin recommendations cannot be applied directly to patients undergoing APBI,[1] where data regarding local recurrence are more limited. Furthermore, individualized clinical judgment should be utilized on a case-by-case basis, using postoperative mammography to identify residual calcifications and clinical-pathologic factors such as quantitative extent of disease near margin, presence of extensive intraductal component (EIC),[3] young age, or multiple close margins to assist in identifying patients who may have an increased risk of IBTR and therefore may be selected to benefit from re-excision.**
- **For patients with invasive breast cancer after BCS, with microscopically focally positive margins (in the absence of an EIC),[3] the use of a higher radiation boost dose to the tumor bed may be considered, since generally a boost to the tumor bed is recommended for patients at higher risk of recurrence. See BINV-I.**

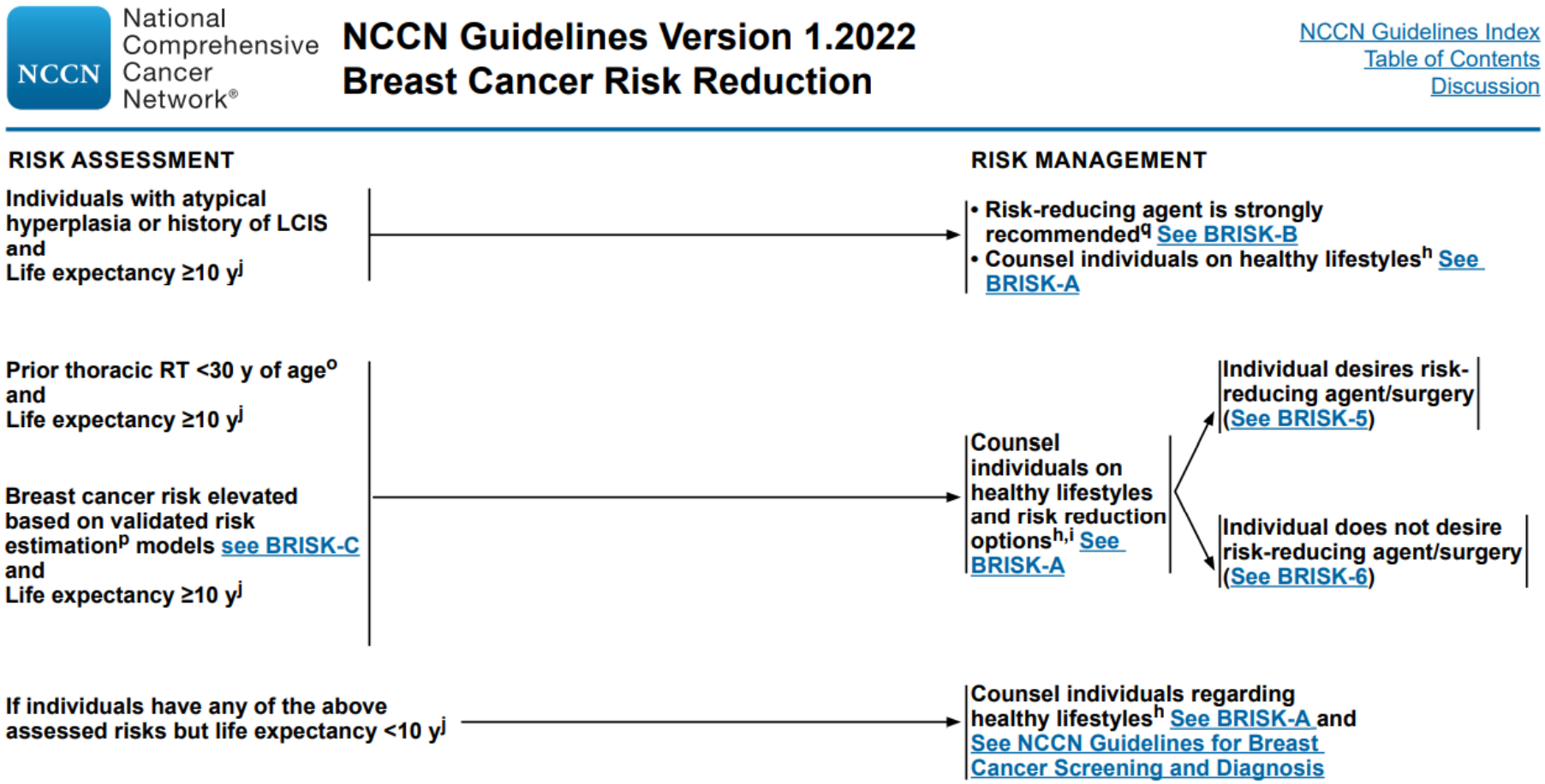
	No ink on tumor	2-mm margin	No margin necessary
Invasive breast cancer	X		
Invasive breast cancer + DCIS	X		
Invasive breast cancer + extensive DCIS	X		
Pure DCIS		X	
DCIS with microinvasion		X	
Pure LCIS* at surgical margin			X
Atypia at surgical margin			X

*For pleomorphic LCIS, the optimal width of margins is not known.

LCIS & FUTURE RISK OF BREAST CANCER

- 7-11 fold higher relative risk of developing an invasive breast cancer
- Absolute risk: ~1% per year, life-long risk
- Risk is conferred to both breasts
- Increased risk for IDC, ILC and DCIS
- Included in the IBS/Tyrer-Cuzick model but overestimates the risk of future breast cancer for women with LCIS

LCIS & RISK REDUCTION STRATEGIES



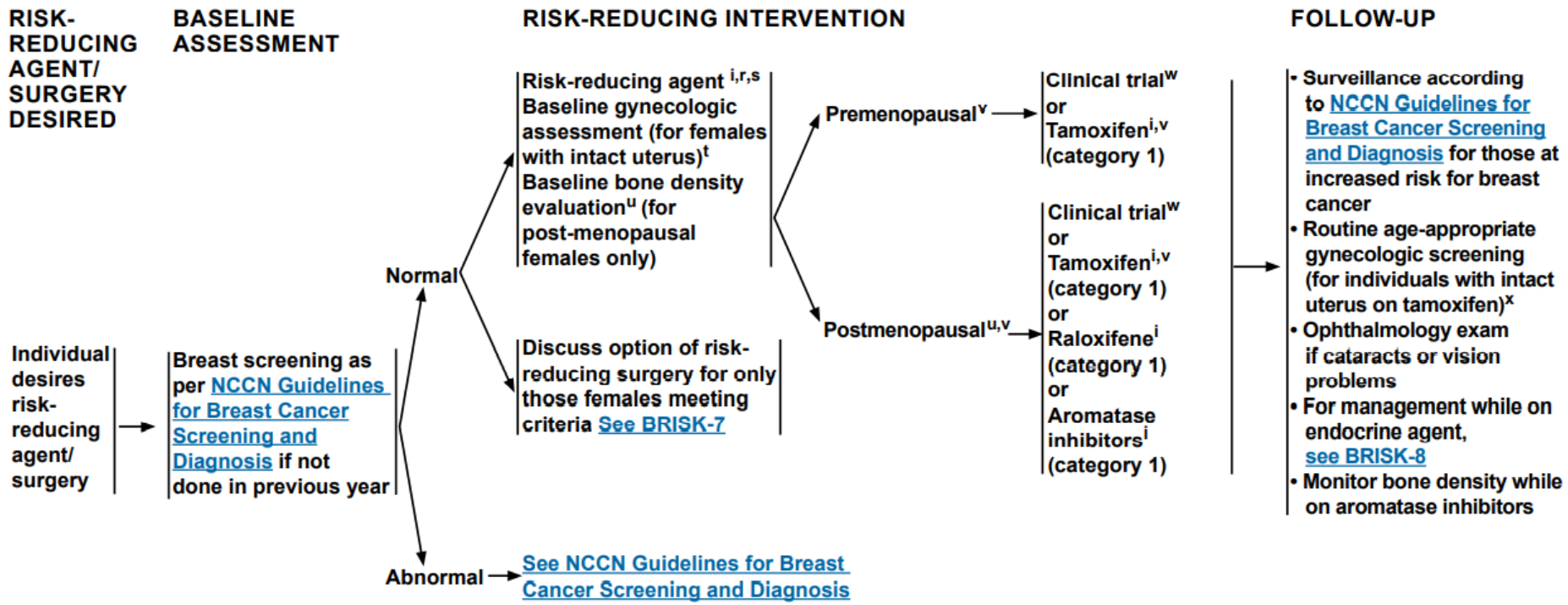
LCIS & RISK REDUCTION STRATEGIES

- Healthy lifestyle for breast cancer risk reduction
  - Consider breast cancer risks associated with combined estrogen/ progesterone agents ≥3–5 year's duration of use.
  - Alcoholic drinks increase the risk for breast cancer and are best avoided; patients who choose to drink alcohol should limit their consumption to no more than one drink equivalent per day.
  - Exercise[1]
    - Be active daily; avoid being sedentary. Take part in 150–300 minutes of moderate-intensity physical activity per week; exceeding the upper limit is optimal.
  - Weight control
    - Evidence suggests that maintaining a healthy body weight (20–25 BMI) helps reduce breast cancer risk.

LCIS & RISK REDUCTION STRATEGIES

CHEMOPREVENTION

- Endocrine therapy as chemoprevention reduces the risk of developing an invasive breast cancer by 50%.
- However, it has not been shown to improve survival.



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