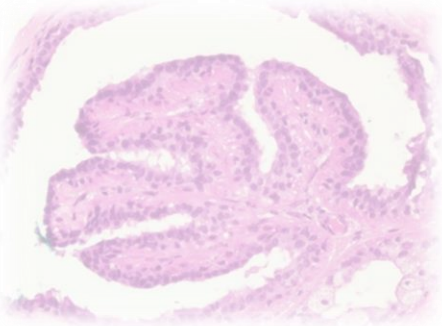
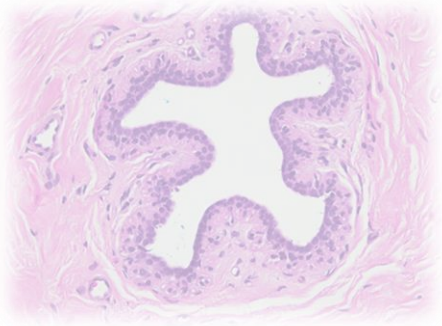
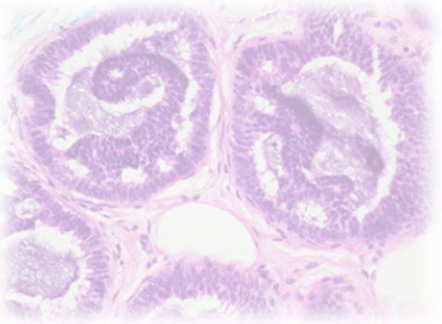
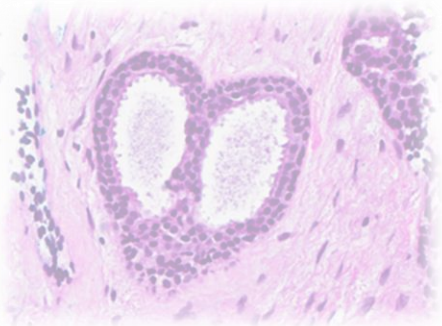
Breast Pathology Course 2019









Case 26

39 year old Chinese female.
Right skin sparing mastectomy.

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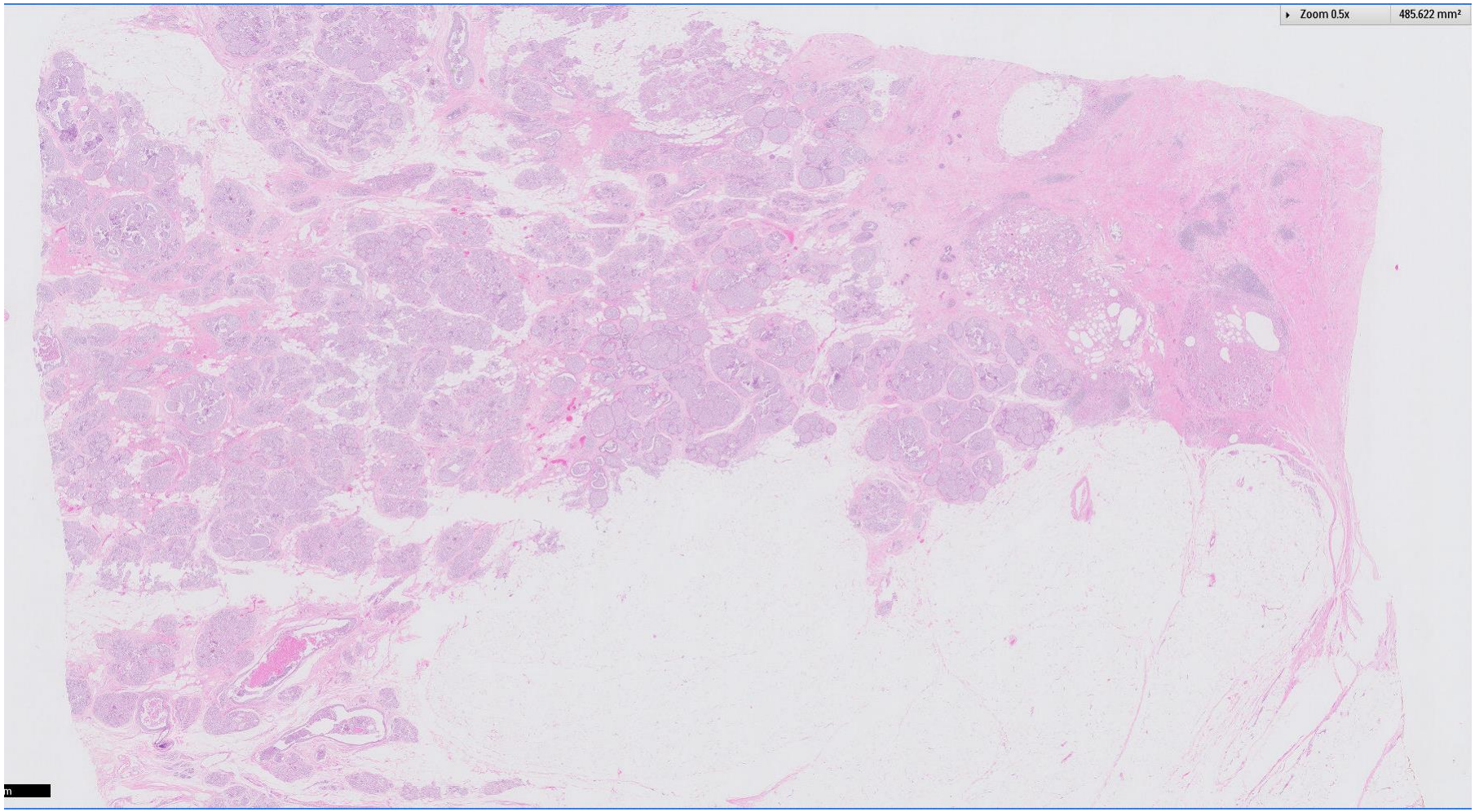

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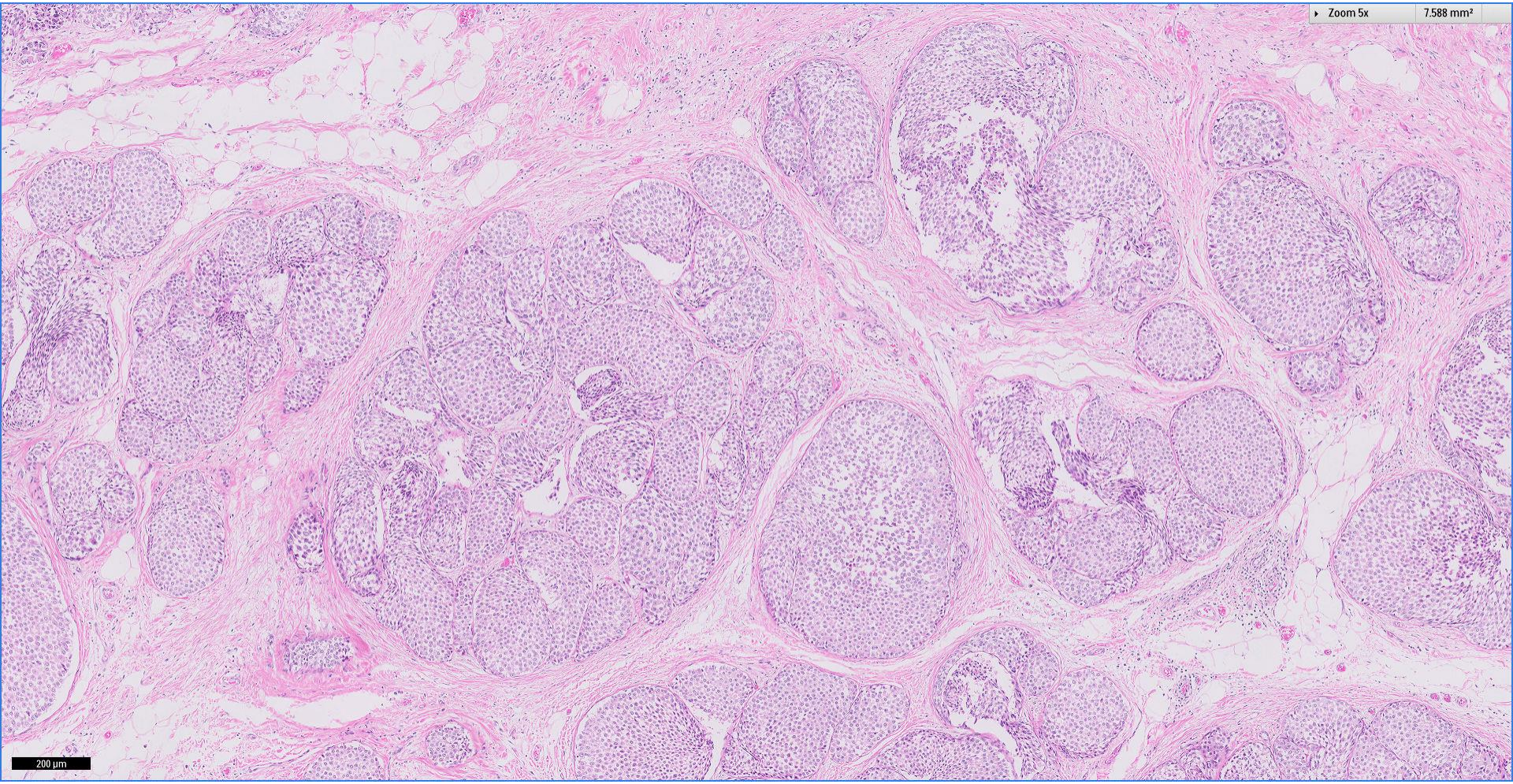

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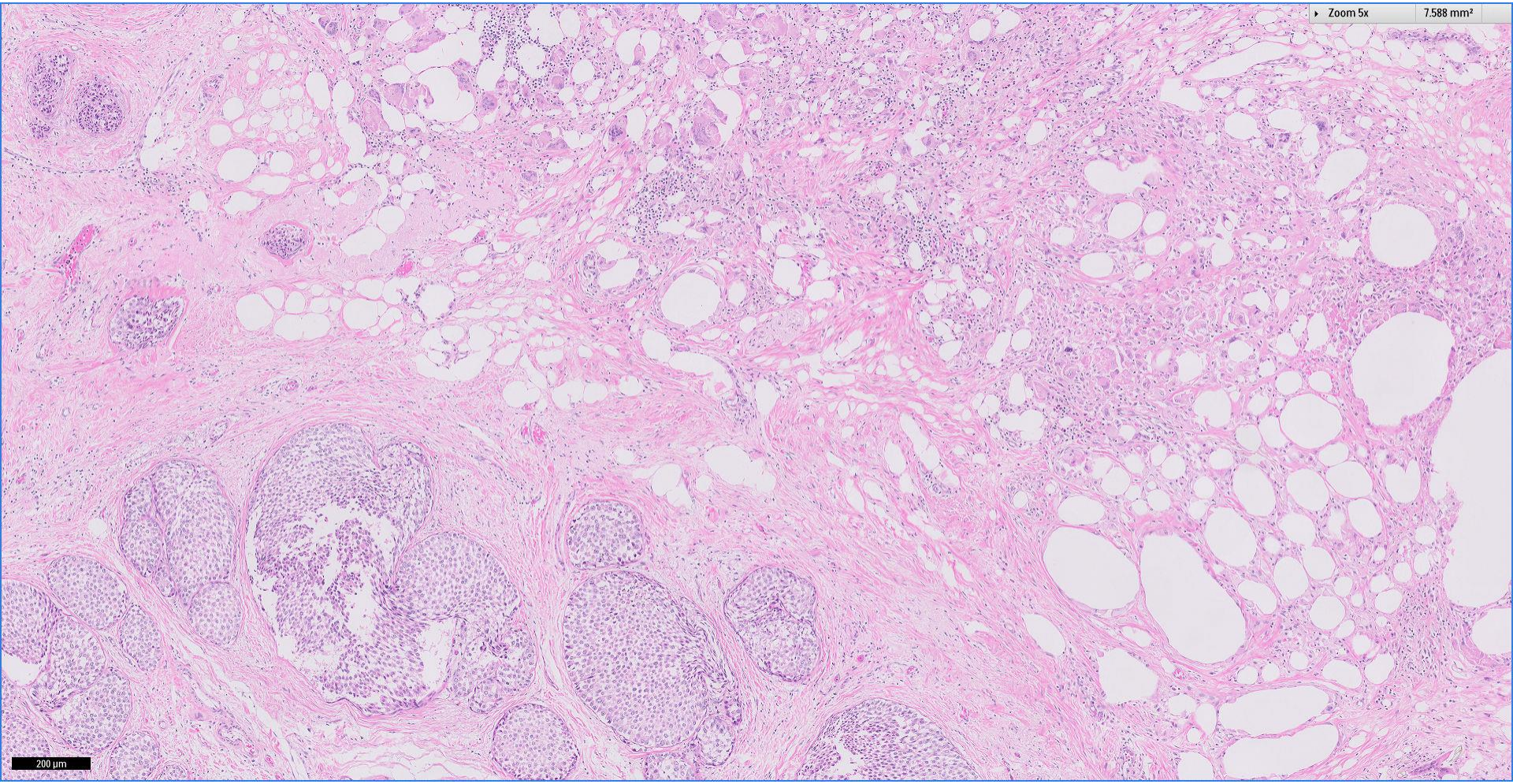

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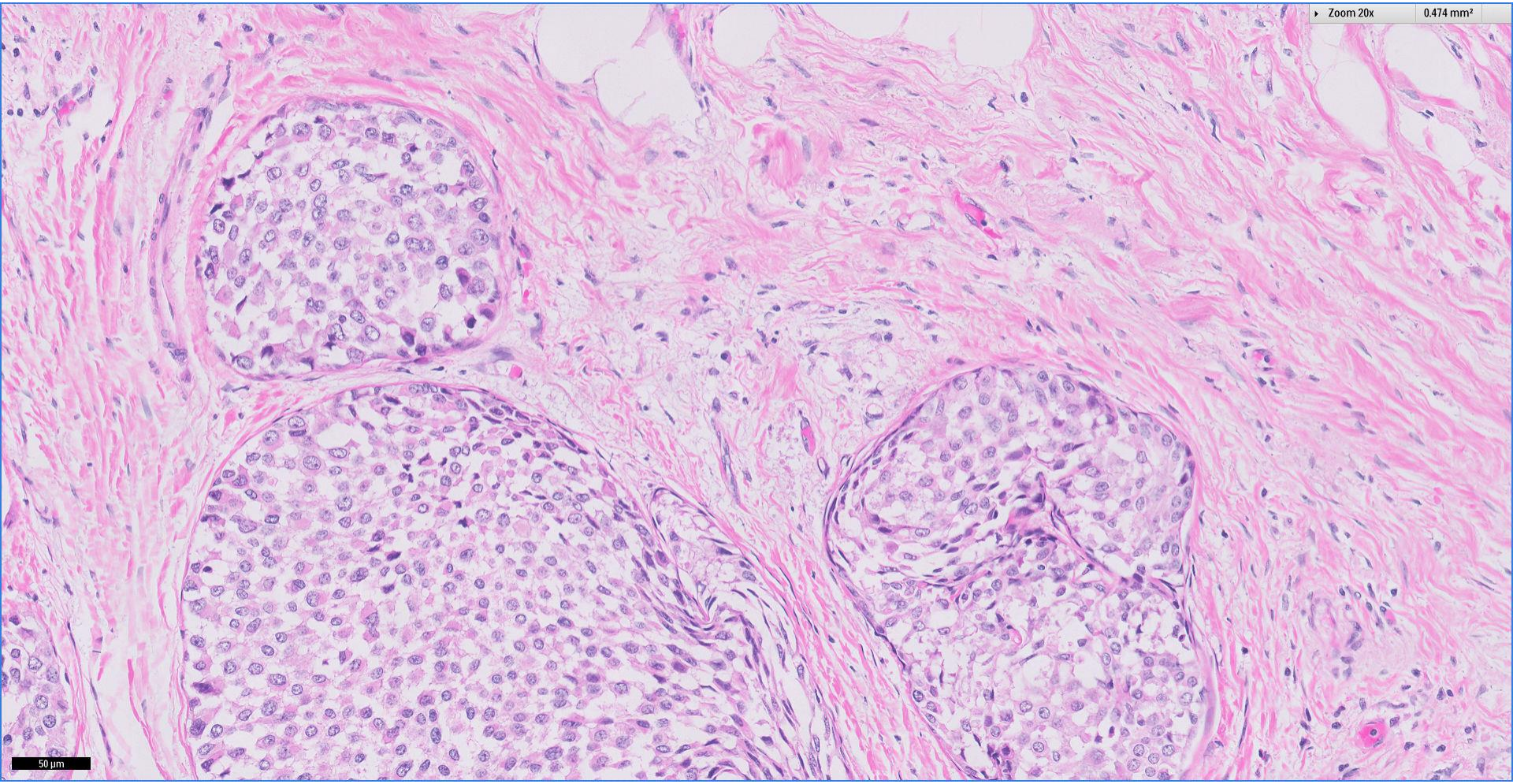

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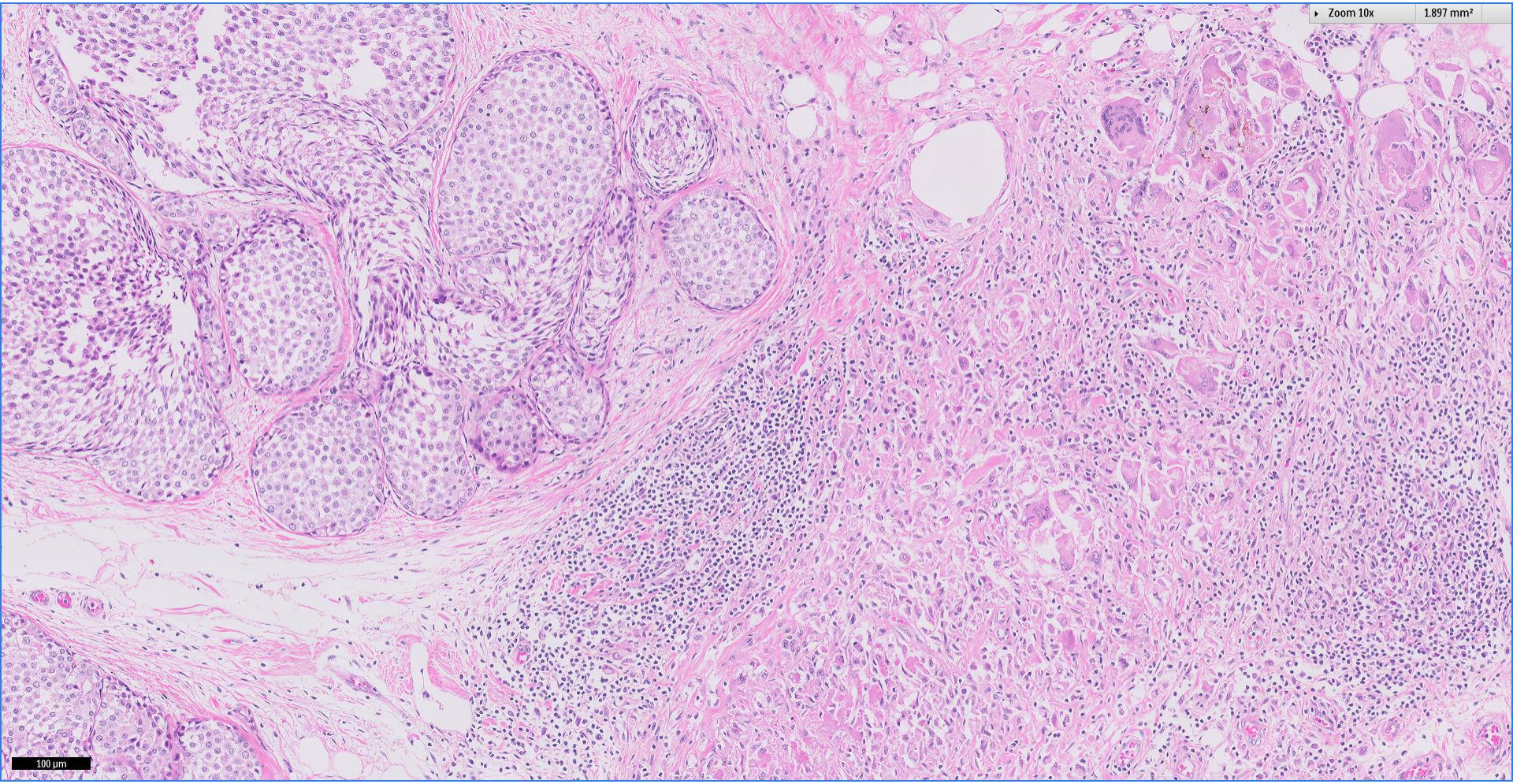

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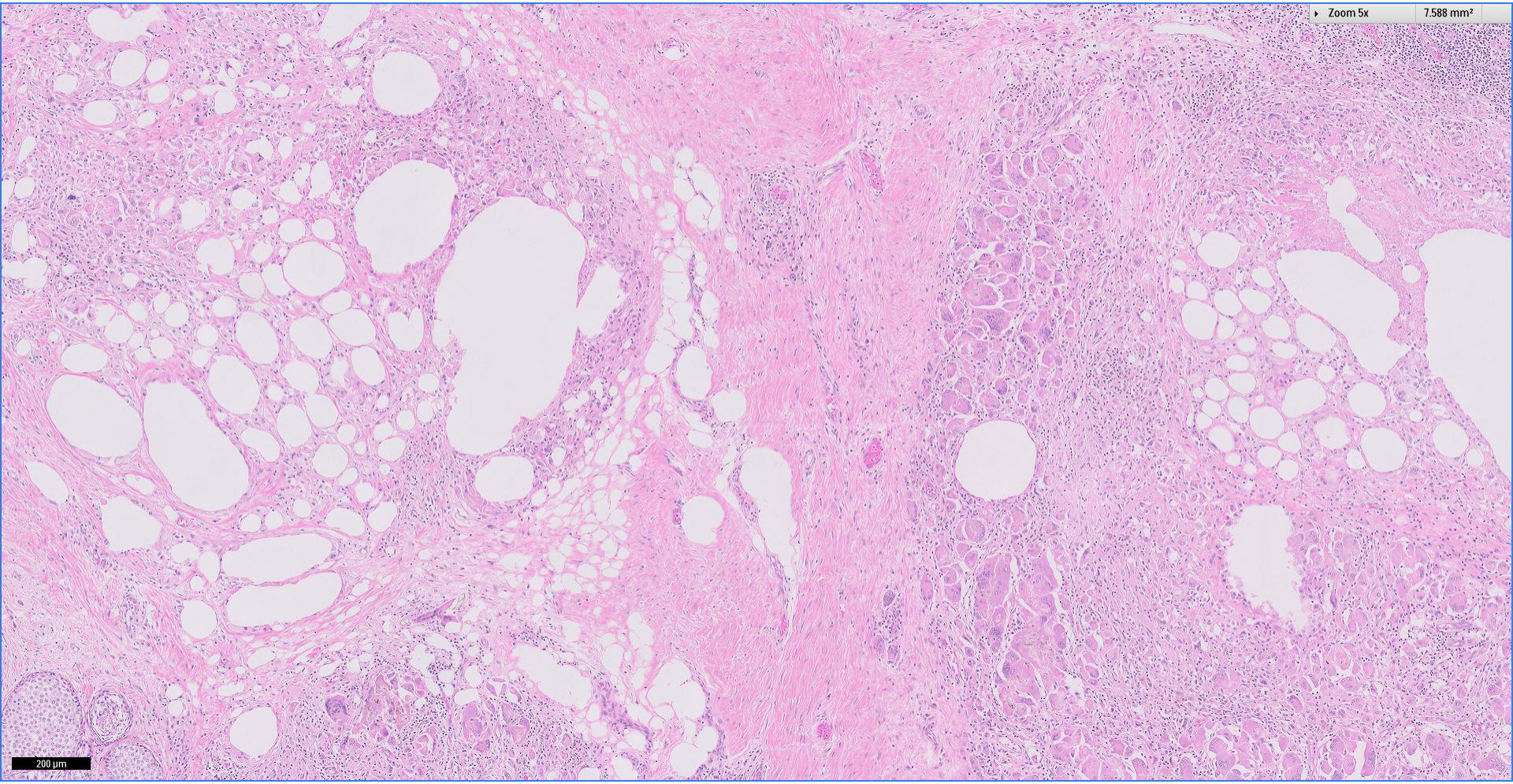

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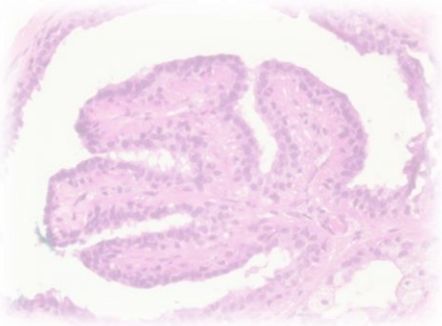
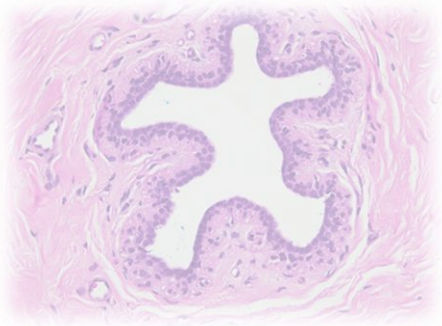
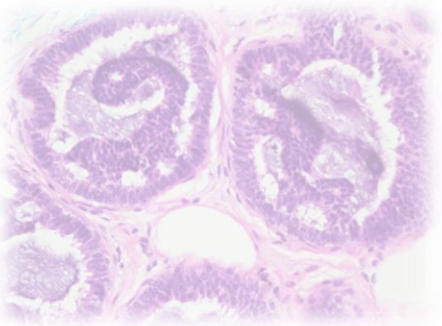
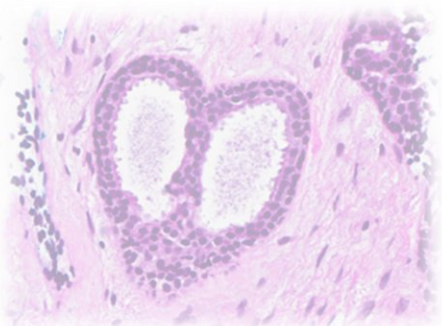
Diagnosis, case 26

- Right breast, skin sparing mastectomy:

  Extensive lobular carcinoma in situ, 15.5cm.

  Four benign sentinel lymph nodes.

Lobular neoplasia

- Refers to the entire spectrum of atypical epithelial lesions originating in the terminal duct lobular unit and characterized by a proliferation of generally small, non-cohesive monomorphic cells, with or without pagetoid involvement of terminal ducts.
- “Atypical lobular hyperplasia” and “lobular carcinoma in situ (LCIS)” are widely used to describe the variable extent of involvement of individual lobular units.

Lobular carcinoma in situ

- Non-invasive neoplastic proliferation of dyscohesive cells, originating in the terminal duct lobular units (TDLUs), with or without pagetoid involvement of terminal ducts.
- More than half of the acini in a TDLU are filled and expanded by the neoplastic cells.

Lobular carcinoma in situ

- **Subtypes ~**
  - Classic lobular carcinoma in situ
  - Pleomorphic lobular carcinoma in situ
  - **Florid lobular carcinoma in situ**
- **Localisation ~**
  - LCIS is multicentric in the ipsilateral breast in 80% of patients and bilateral in 30–67%.
  - Pleomorphic LCIS and florid LCIS noted to be unifocal and continuous in distribution, often colocalized with invasive lobular carcinoma (ILC) in the background of multicentric classic LCIS.

Lobular carcinoma in situ

- **Clinical features ~**
  - No specific clinical features.
  - Usually an incidental microscopic finding in breast biopsies performed for other indications.
  - Rare cases (< 2%) of classic LCIS can be targeted for biopsy due to associated imaging abnormalities, including grouped amorphous or granular calcifications on mammography or heterogeneous non–mass-like enhancement with persistent enhancement kinetics on MRI.
  - In contrast, **pleomorphic LCIS and florid LCIS are usually associated with microcalcifications and detected on screening mammography**.

Lobular carcinoma in situ

- **Epidemiology ~**
  - LCIS is found in 0.5–3.6% of otherwise benign breast biopsies and 0.04–1.2% of reduction mammoplasty specimens.
  - Epidemiological studies have demonstrated that the incidence rates of LCIS increased rapidly after the introduction of mammography (1978–1998) and declined sharply between 2001 and 2004, most likely due to decreased use of menopausal hormone replacement therapy.
  - Classic LCIS is predominantly diagnosed in premenopausal women (mean age: ~50 years).
  - **Pleomorphic LCIS and florid LCIS are diagnosed primarily in postmenopausal women (mean age: ~60 years)**.

Lobular carcinoma in situ

- **Etiology ~**
  - Many risk factors for LCIS are similar to those established for ductal carcinoma in situ (DCIS) and invasive breast carcinoma.
  - Population-based studies have reported an increased risk of LCIS associated with a family history of breast cancer, a previous benign breast biopsy, nulliparity, older age at first full-term birth, older age at menopause, and high mammographic density.
  - In postmenopausal women, hormone replacement therapy increases the risk of LCIS.
  - *CDH1* (the gene encoding the cell adhesion protein E-cadherin), localized at 16q22.1, plays an important role in the pathogenesis of lobular lesions.
  - Germline mutations in *CDH1*, which are highly penetrant, are associated with an increased risk of hereditary diffuse gastric cancer (HDGC) and an increased risk of lobular carcinoma, including bilateral LCIS, with or without ILC.
  - Of the known germline SNPs that are associated with an increased risk of ER-positive breast cancer, several have also shown an association with ILC and specifically also with LCIS.

Lobular carcinoma in situ

- **Pathogenesis ~**
  - *CDH1* inactivation, which leads to loss or impaired function of E-cadherin, is an early event and hallmark of lobular lesions.
  - E-cadherin mediates cell–cell adhesion and plays a key role in the maintenance of lobular architecture. It can also inhibit the growth and invasion of breast cancer cells.
  - Defective E-cadherin results in loss of cell–cell adhesion, increased cell proliferation, and altered organization of the lobules, giving rise to the characteristic appearance of lobular neoplasia.
  - *CDH1* mutation is identified in 81% of LCIS cases.
  - Most of the mutations seen in LCIS have been found to be associated with an age-related mutation signature, consistent with mutation signatures observed in ILC and ER-positive invasive carcinoma of no special type (NST).

Lobular carcinoma in situ

- **Pathogenesis ~**
  - Molecular analysis has demonstrated that LCIS is a clonal neoplastic proliferation and a non-obligate precursor lesion to invasive carcinoma.
  - Studies using comparative genomic hybridization and array comparative genomic hybridization have indicated that classic LCIS, pleomorphic LCIS, and florid LCIS all harbour recurrent chromosomal gain at 1q and loss at 16q, a pattern typical of the low-grade breast neoplasia pathway .
  - **Pleomorphic LCIS and florid LCIS exhibit greater genomic instability than classic LCIS**, with increased copy-number alterations and gene amplifications, suggesting that these morphological subtypes are genetically more advanced lesions than classic LCIS.
  - Studies comparing LCIS and synchronous ILC highlight shared copy-number aberrations, indicating that LCIS is a non-obligate precursor to ILC.

Lobular carcinoma in situ

- **Pathogenesis ~**
  - Massively parallel sequencing studies have revealed that LCIS can be clonally related to ILC and occasionally to DCIS present in the same quadrant.
  - LCIS is believed to be a genetically advanced lesion, harbouring a repertoire of copy-number alterations and somatic genetic mutations similar to that of ILCs, with the exception that *TP53* and *PTEN* mutations were found to be remarkably rare.
  - The most frequently mutated genes in LCIS are *CDH1* (mutated in as many as 81% of cases), *PIK3CA* (41%), and *CBFB* (12%).
  - Mutation (and amplification) of *ERBB2 (HER2)* is a frequent molecular alteration in pleomorphic ILC and pleomorphic LCIS.
  - A recent microarray gene expression profiling study demonstrated that classic LCIS is heterogeneous at the transcriptomic level and identified potential candidate precursor genes for invasion, whose biological and clinical significance warrants further exploration.

Lobular carcinoma in situ

- **Macroscopic appearance** ~
  - No grossly visible lesion.
- **Histopathology** ~
  - Pleomorphic LCIS is composed of larger cells with marked nuclear pleomorphism, which are > 4 times the size of a lymphocyte / equivalent to the cells of high-grade DCIS, with or without apocrine features.
  - In **florid LCIS**, the **LCIS cells show the cytological features of classic LCIS, but there is marked distention of TDLUs or ducts, creating a confluent mass-like architecture**.
  - **Florid LCIS should have at least one of two architectural features:**
    - **little to no intervening stroma between markedly distended acini of involved TDLUs.**
    - **size cut-off point at which an expanded acinus or duct fills an area equivalent to ~40–50 cells in diameter.**
  - LCIS lesions that are borderline between classic LCIS composed of type B cells and pleomorphic LCIS should be categorized as classic LCIS composed of type B cells.
  - SimIlarly, lesions with cytological features of classic LCIS that show distension of the acini borderline between classic LCIS and florid LCIS should be designated as classic LCIS, even when LCIS is extensive

Lobular carcinoma in situ

- Pleomorphic LCIS and florid LCIS often demonstrate comedonecrosis and calcifications.
- Due to the high prevalence (as high as 87%) of associated invasive carcinoma in these morphological subtypes, with the majority (84–100%) being ILC, detection of these lesions should prompt a careful search for subtle invasion in adjacent breast tissue.
- Signet-ring cells may be seen in any morphological subtype.
- Several other terms have been used in clinical practice for these subtypes, including “non-classic LCIS” and “variant LCIS without further clarification”.
- The WHO Classification of Tumours Editorial Board does not recommend these terms, due to lack of sufficient specificity to guide patient management.

Lobular carcinoma in situ

- Loss of membranous E-cadherin expression is the characteristic immunohistochemical feature for all forms of LCIS.
- In approximately 15% of invasive lobular lesions, the neoplastic cells have conserved but aberrant E-cadherin expression, and this is recapitulated in LCIS.
- Fragmented membranous and/or cytoplasmic aberrant staining should not be used to make a diagnosis of DCIS.
- LCIS cells exhibit strong, diffuse cytoplasmic staining for p120-catenin and loss of expression of membrane β-catenin.
- Distinction between LCIS and DCIS cannot rely solely on these immunohistochemical markers, which should be interpreted in conjunction with detailed morphological evaluation.

Lobular carcinoma in situ

- Classic and florid subtypes of LCIS are typically diffusely and strongly positive for ER, have a low Ki-67 proliferation index, and rarely show ERBB2 (HER2) overexpression or gene amplification, or *TP53* mutation.
- The pleomorphic subtype is more likely to be ER-negative (especially apocrine pleomorphic LCIS), may be AR-positive, may demonstrate HER2 overexpression and gene amplification or TP53 mutation, and has a moderate to high Ki-67 proliferation index.
- Approximately 10% of pleomorphic cases are triple-negative.

Lobular carcinoma in situ

- **Cytology ~**

FNA of LCIS shows loosely cohesive groups of small, uniform cells with occasional intracytoplasmic lumina, eccentric regular nuclei, and minimal nuclear atypia.

However, > 50% of aspirates from LCIS have been determined to be benign or non-diagnostic.

There are no reliable cytological criteria for distinguishing between LCIS and ILC .

Lobular carcinoma in situ

Diagnostic molecular pathology ~

- Not clinically relevant

Essential and desirable diagnostic criteria ~

Classic LCIS ~

- Essential: small dyscohesive cells with uniform hyperchromatic

nuclei (type A) to slightly larger vesicular nuclei with mild variability (type B), filling and expanding more than half of the acini in a TDLU.

- Desirable: loss of E-cadherin membrane staining.

Pleomorphic LCIS ~

- Essential: large dyscohesive cells with marked nuclear pleomorphism, > 4 times the size of a lymphocyte / equivalent to the cells of high-grade DCIS, with or without apocrine features.
- Desirable: loss of E-cadherin membrane staining.

Florid LCIS ~

- Essential: classic LCIS creating a confluent mass-like architecture; little to no intervening stroma between markedly distended acini of involved TDLUs, and/or a size cut-off point at which an expanded acinus or duct fills an area equivalent to ~40–50 cells in diameter.
- Desirable: loss of E-cadherin membrane staining.

Lobular carcinoma in situ

Staging ~

According to the 8th editions of the Union for International Cancer Control (UICC) TNM classification and the American Joint Committee on Cancer (AJCC) cancer staging manual, LCIS is no longer staged as Tis.

Pleomorphic LCIS is not included in the pTis classification.

Prognosis and prediction ~

LCIS is both a risk factor for and a non-obligate precursor ofinvasive breast carcinoma.

The relative risk of subsequent breast cancer in patients with classic LCIS is 8–10 times the risk in the general population.

The absolute risk of breast cancer is in the range of 1–2% per year, with a cumulative long-term rate of > 20% at 20 years and a lifetime risk of 30–40%.

The risk is bilateral and the invasive carcinoma can be either lobular or ductal. However, ipsilateral cancers predominate, with an over-representation of ILC; LCIS is therefore also considered a non-obligate precursor lesion, albeit with a low risk of progression to invasive cancer.

Lobular carcinoma in situ

- Current management for classic LCIS includes active surveillance and risk-reduction strategies for both breasts.
- The American Society of Clinical Oncology (ASCO) guidelines include recommendations for antiestrogen therapy as chemoprevention to reduce breast cancer risk in women with LCIS.
- The management of classic LCIS diagnosed on core needle biopsy has been controversial due to the wide range of reported upgrade rates (0–60%) to carcinoma (including invasive carcinoma and DCIS) on excision.
- In these studies, the upgrade rates are higher when radiological–pathological correlation is not addressed or when LCIS represents the radiological target, and the rates are even higher (as high as 66%) in cases with biopsy for mass lesions and those with imaging–histological discordance.
- However, recent studies with concordant imaging findings have reported very low (~1–4%) excisional upgrade rates of incidental classic LCIS (and atypical lobular hyperplasia) to carcinoma.
- Therefore, patients with incidental classic LCIS on core biopsy showing concordant imaging–histological findings can be spared surgical excision.
- There is no indication that excision of classic LCIS to negative margins is useful, and it is not necessary to assess or report the status of excision margins for classic LCIS, even in the setting of coexistent pleomorphic LCIS, florid LCIS, and/or ILC.

Lobular carcinoma in situ

- Information about the natural history of pleomorphic LCIS and florid LCIS is extremely limited, and the optimal treatment for patients with these excised morphological LCIS subtypes remains unclear – including whether to achieve negative margins and whether there is any potential benefit of adjuvant radiation.
- The reported recurrence rates of pleomorphic LCIS treated with conservative surgery with or without antiestrogen therapy vary from 0% to as high as 57%, and the recurrent lesions may be pleomorphic LCIS, DCIS, ILC, or invasive ductal carcinoma.
- It is unclear whether positive margin status affects the likelihood of recurrence, but results from these studies generally support the practical utility of surgical excision to negative margins for pleomorphic LCIS if possible.
- **It is recommended that margin status be reported for pleomorphic LCIS and florid LCIS to help inform further management decisions**.
- Approximately 25–60% of cases with pleomorphic LCIS and florid LCIS on core biopsy are upgraded to carcinoma on excision.
- Although there are limitations to the data derived from such studies, the **WHO Classification of Tumours Editorial Board recommends excision for pleomorphic LCIS and florid LCIS diagnosed on core needle biopsy.**

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Thank You

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