Pathology of the breast

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Normal Breast

- Specialized epithelium and stroma that gives rise to both benign and malignant lesions
- Six to ten major ductal systems originate at the nipple.
- Branching of the large ducts leads to the terminal duct lobular units.
- The TDU branches into grapelike clusters of small acini to form the lobule.

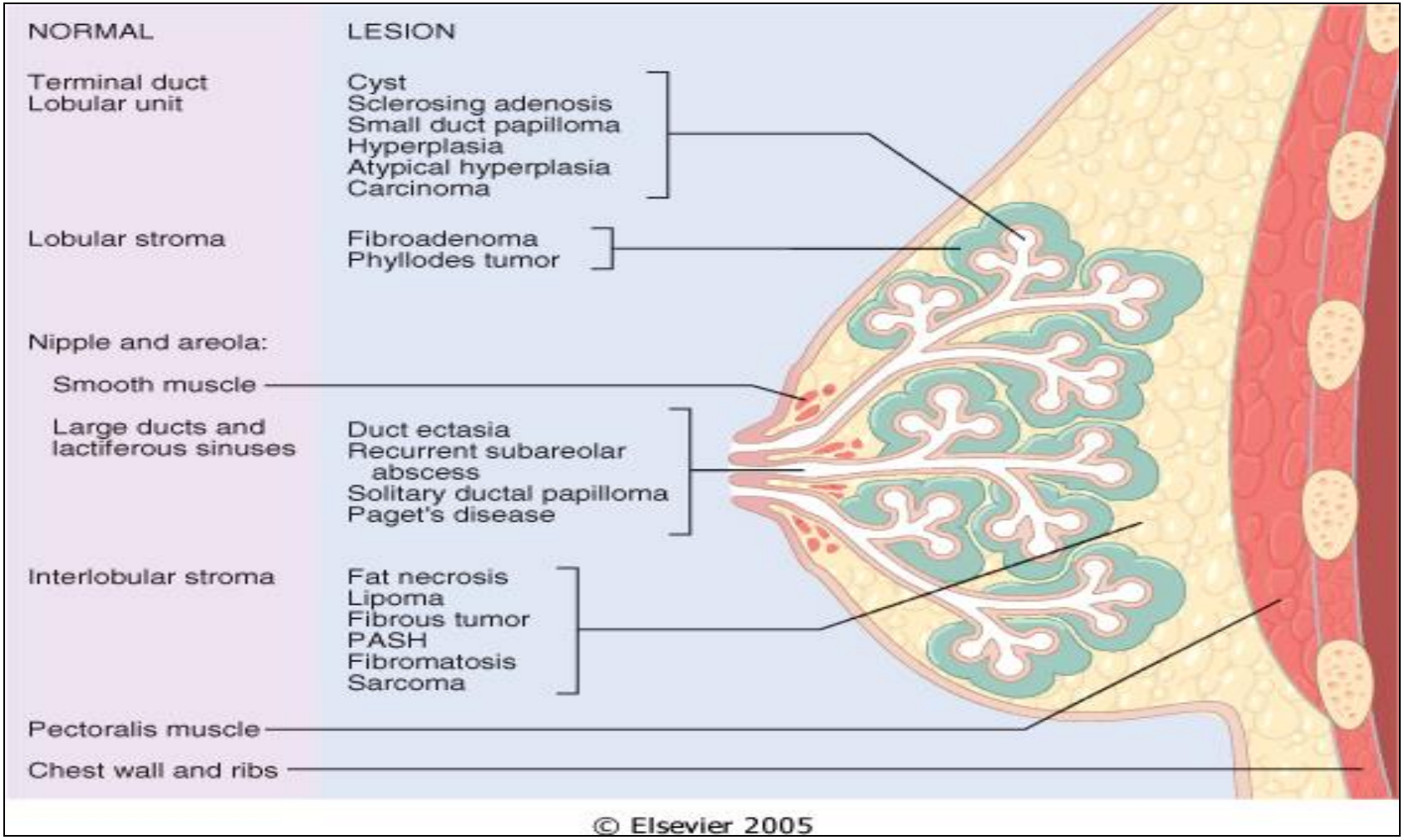
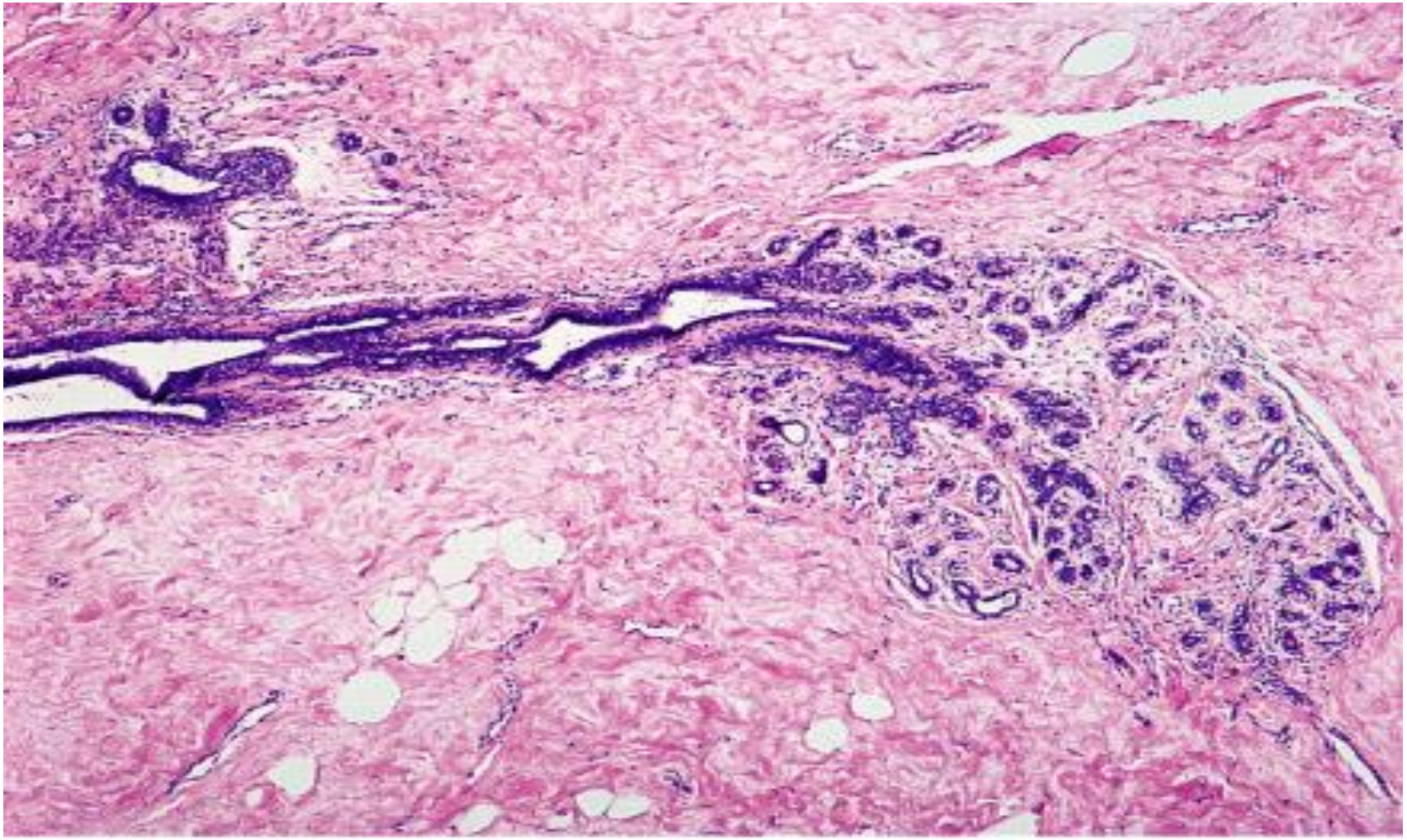


Figure 23-1 Normal breast anatomy and anatomical location of common breast lesions.



Breast
Clinical Presentation

1) Pain (mastalgia)

- the most common breast symptom and may be cyclical with menses or noncyclical.
- Diffuse cyclical pain has no pathologic significance.
- Noncyclical pain is usually associated with a focal site in the breast.
- Although the great majority of painful masses are benign, about 10% of breast cancers present with pain, and all masses need to be investigated.

2)Palpable mass

3)Nipple discharge:

- Milky discharge has not been associated with malignancy.
- Bloody or serous discharges are most commonly associated with benign lesions but, rarely, can be due to a malignancy.

Breast
Benign Epithelial Lesions

1- Non proliferative breast changes

2- Proliferative breast disease

3- Atypical hyperplasia

Non proliferative Breast Changes (Fibrocystic Changes)

- No increased risk for cancer
- Could produce palpable breast mass, mammographic densities, calcifications ,or nipple discharge.
- Cysts are the most common cause of a palpable mass and they are alarming when they are solitary, firm .
- Three patterns of morphologic changes :

1- Cyst formation

2- Fibrosis

3- Adenosis

Fibrocystic changes

- **Cysts** :small to big in size ,lined by benign epithelium with apocrine metaplasia, Semi-translucent or turbid fluid
- **Fibrosis** : contribute to the palpable firmness of the breast
- **Adenosis** : Increase in the number of acini per lobule. Normal adenosis could be seen during pregnancy

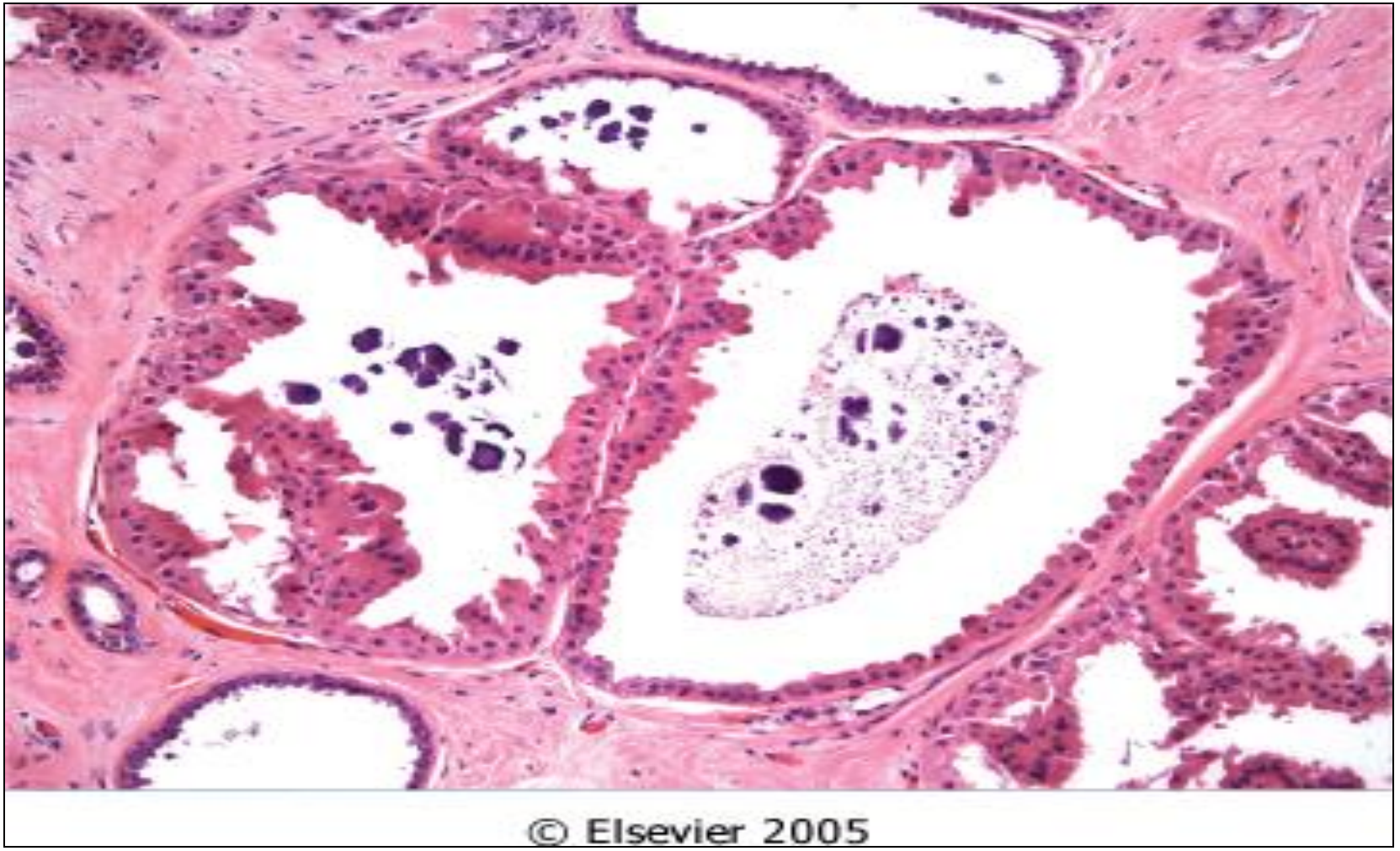


Figure 23-7 Apocrine cysts. Cells with round nuclei and abundant granular eosinophilic cytoplasm, resembling the cells of normal apocrine sweat glands, line the walls of a cluster of small cysts. Secretory debris, frequently with calcifications, is often present. Groups of cysts are common findings associated with clustered mammographic calcifications.

Benign Epithelial Lesions proliferative Disease without Atypia

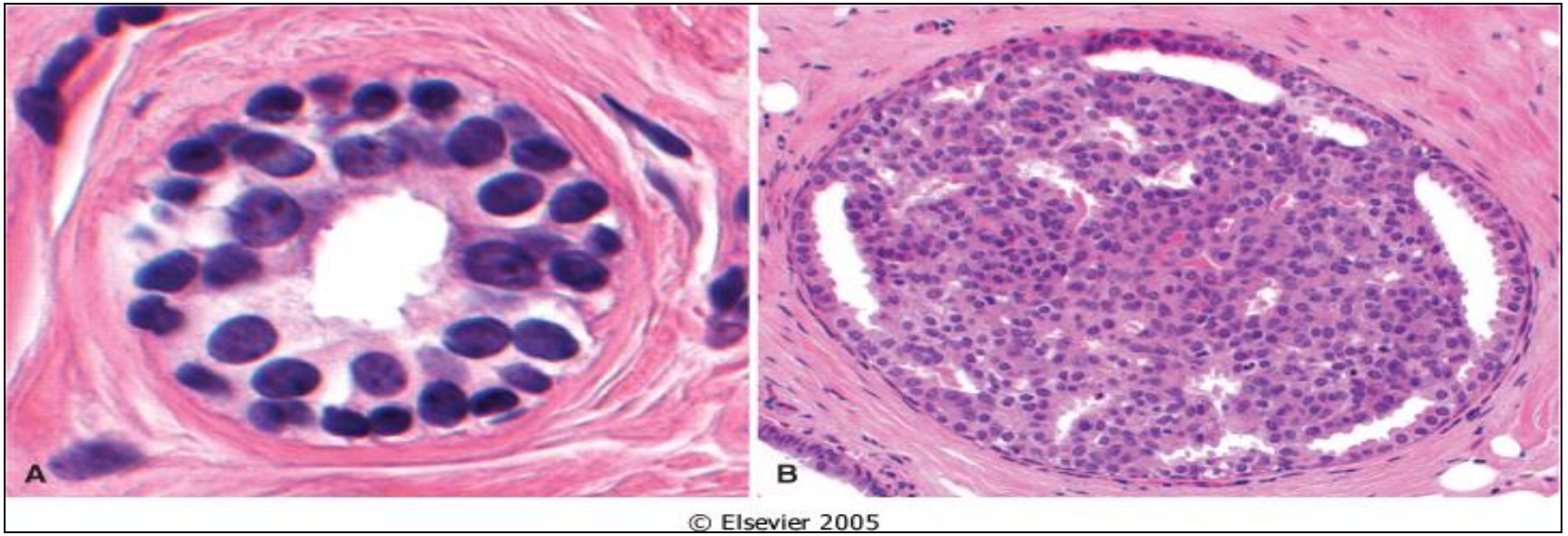
- Rarely form palpable masses
- Detected as mammographic densities.
- Incidental finding
- Large duct papilloma present in 80% as nipple discharge.
- Risk for cancer is 1.5 – 2 times normal
- Many entities included here :

1- Epithelial hyperplasia

2- Sclerosing adenosis

3- complex sclerosing lesions/radial scar

3- Papillomas



Epithelial hyperplasia: The proliferating epithelium, often including both luminal and myoepithelial cells, fills and distends the ducts and lobules.

Figure 23-8 A, Normal. A normal duct or acinus has a single basally located myoepithelial cell layer (cells with dark, compact nuclei and scant cytoplasm) and a single luminal cell layer (cells with larger open nuclei, small nucleoli, and more abundant cytoplasm). B, Epithelial hyperplasia. The lumen is filled with a heterogeneous population of cells of different morphologies, often including both luminal and myoepithelial cell types. Irregular slitlike fenestrations are prominent at the periphary.

Benign Epithelial Lesions proliferative Disease without Atypia

Sclerosing Adenosis.

- Number of acini per terminal duct is increased.
- Normal lobular arrangement is maintained.
- The acini are compressed and distorted. Myoepithelial cells are usually prominent.

On occasion histologic pattern mimics the appearance of invasive carcinoma

-Calcifications are frequently present within the lumens of the acini.

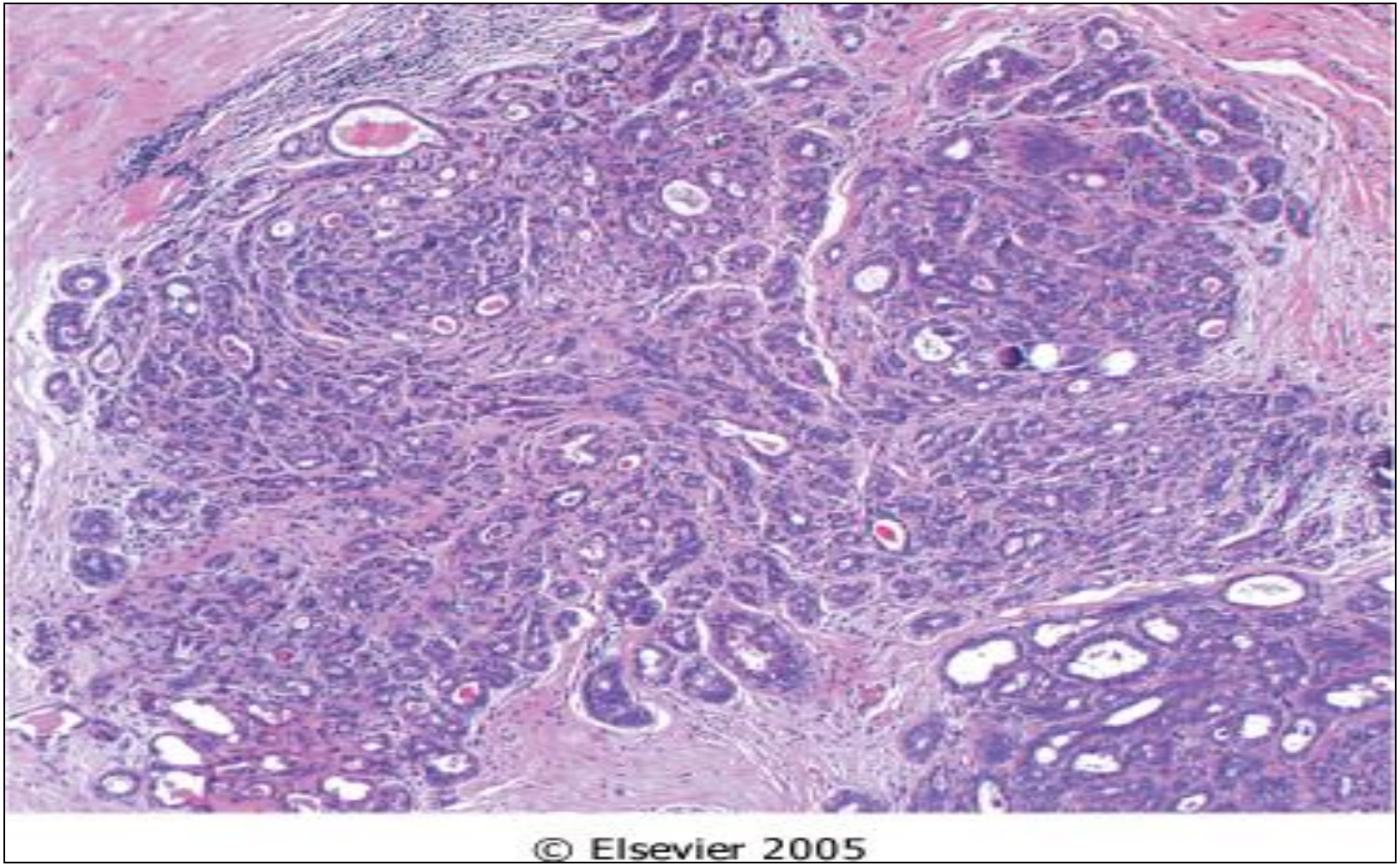


Figure 23-9 Sclerosing adenosis. The involved terminal duct lobular unit is enlarged, and the acini are compressed and distorted by the surrounding dense stroma. Calcifications are often present within the lumens. Although this lesion is frequently mistaken for an invasive carcinoma, unlike carcinomas, the acini are arranged in a swirling pattern, and the outer border is usually well circumscribed.

Benign Epithelial Lesions proliferative Disease without Atypia

Complex Sclerosing Lesion (Radial Scar).

- Radial scars are stellate lesions characterized by a central nidus of entrapped glands in a hyalinized stroma
- can resemble irregular invasive carcinomas mammographically or on gross examination.
- "scar" refers to the morphologic appearance, as these lesions are not associated with prior trauma or surgery.

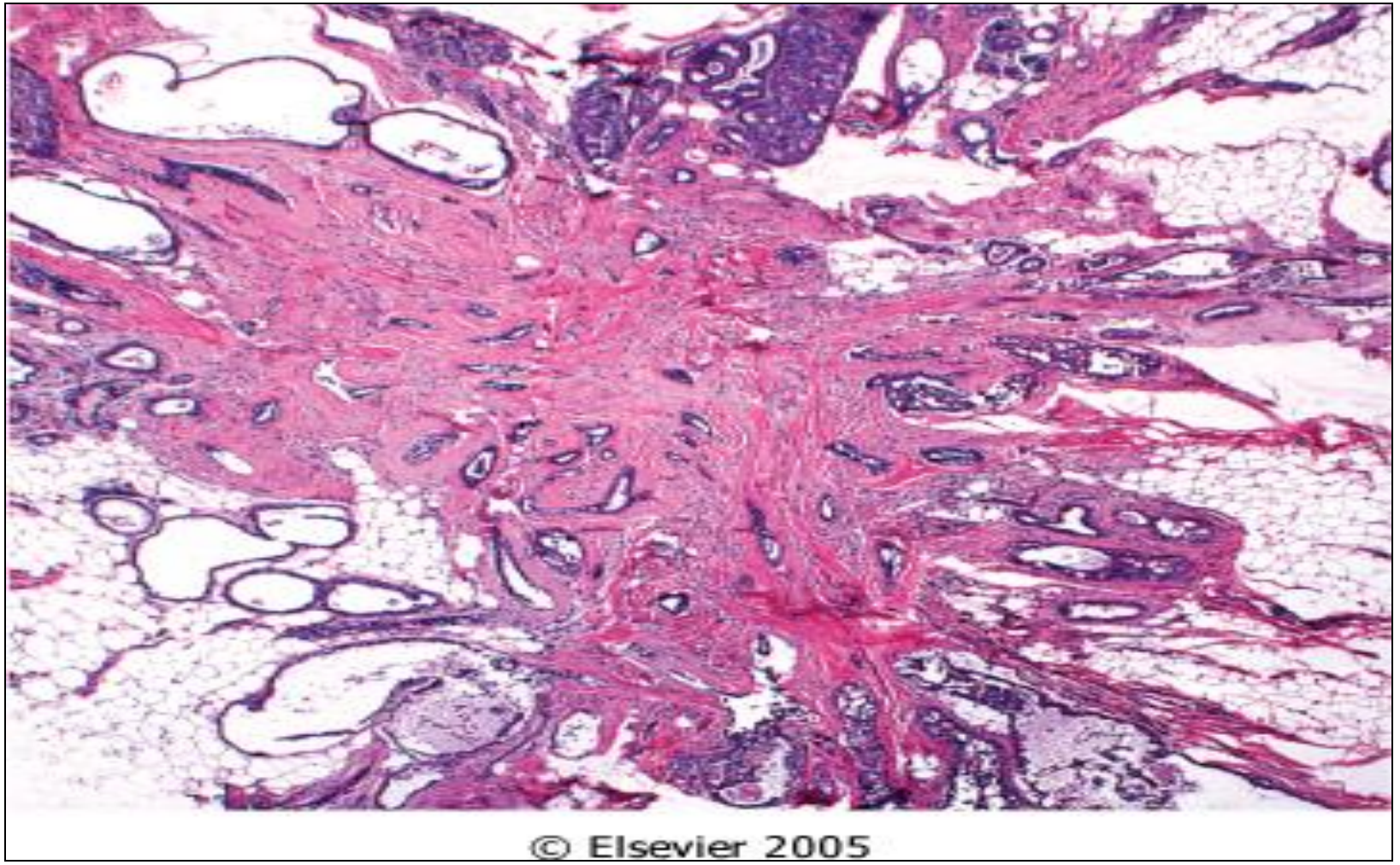


Figure 23-10 Complex sclerosing lesion (radial scar). There is a central nidus consisting of small tubules entrapped in a densely fibrotic stroma surrounded by radiating arms of epithelium with varying degrees of cyst formation and hyperplasia. These lesions typically present as an irregular mammographic density and closely mimic an invasive carcinoma.

Benign Epithelial Lesions proliferative Disease without Atypia

Papillomas

- composed of multiple branching fibrovascular cores, each having a connective tissue axis lined by luminal and myoepithelial cells.
- It occurs within a dilated duct. Epithelial hyperplasia and apocrine metaplasia are frequently present.

Figure 23-11 Intraductal papilloma. A central fibrovascular core extends from the wall of a duct. The papillae arborize within the lumen and are lined by myoepithelial and luminal cells.

Proliferative Breast Disease with Atpyia

- Risk for cancer is 4-5 times normal
- Include two entities

1 –Atypical ductal hyperplasia

2 –Atypical lobular hyperplasia

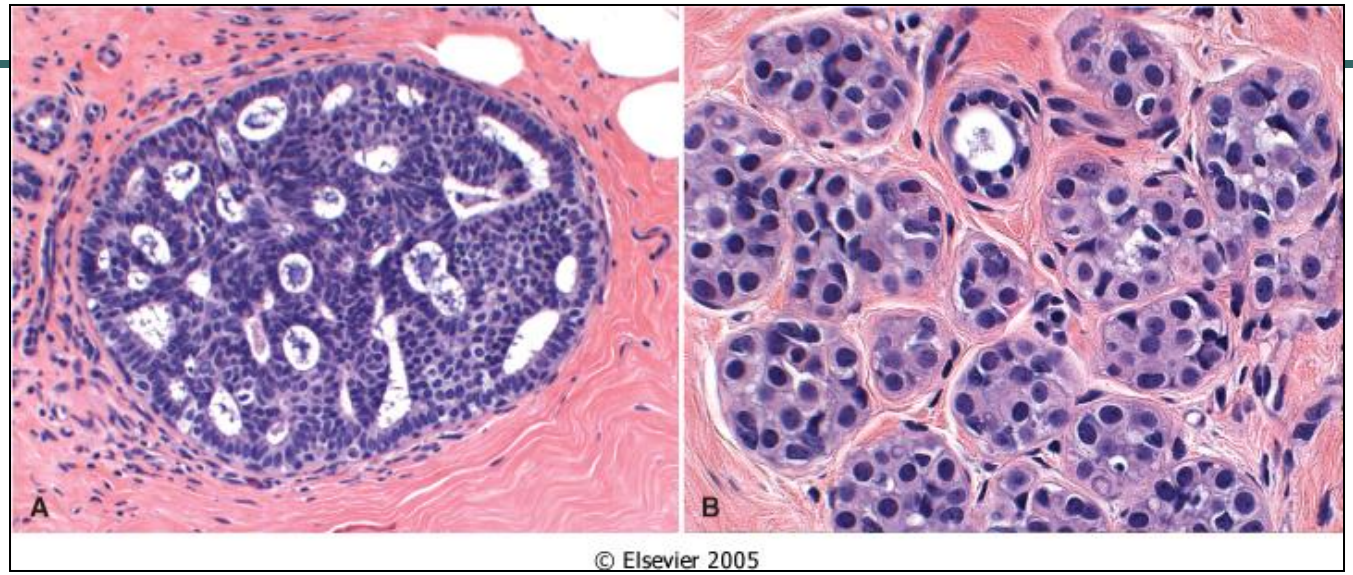


Figure 23-12 A, Atypical ductal hyperplasia. A duct is filled with a mixed population of cells consisting of oriented columnar cells at the periphery and more rounded cells within the central portion. Although some of the spaces are round and regular, the peripheral spaces are irregular and slitlike. These features are highly atypical but fall short of a diagnosis of DCIS. B, Atypical lobular hyperplasia. A population of monomorphic small, rounded, loosely cohesive cells partially fill a lobule. Some intracellular lumina can be seen. Although the cells are morphologically identical to the cells of LCIS, the extent of involvement is not sufficient for this diagnosis.

Breast cancer

Breast Carcinoma

- The most common malignancy of breast is carcinoma
- Carcinoma of the breast is the most common cancer in women
- Mammographic screening increased dramatically the detection of small invasive cancers

Breast Cancer
Risk Factors

- Age : breast cancer is rare before 25 yrs, except familial forms ,77% of cases occur in women >50 yrs of age. The average age at diagnosis is 64 years
- Age at Menarche: Menarche younger than age 11 have a 20% increased risk to that who have their menarch at 14yrs.
- First Live birth: Full term pregnancy before age 20 years has half the risk of nulliparous ,or women who have first birth after age 35.

Breast Cancer
Risk Factors

- First Degree relative with Breast Cancer . The risk increases with the number of affected first degree relatives. The majority of cancers occur in women without such history
- Breast Biopsy :Atypical hyperplasia increases the risk for breast cancer
- Race :Overall incidence of breast cancer is lower in African American women
- Estrogen Exposure: postmenopausal hormone replacement slightly increase the risk

Breast Cancer
Risk Factors

- Radiation exposure: Higher rate of breast cancer
- Carcinoma of the contralateral breast or Endometrium
- Geographic influence :Four to seven times in USA and Europe higher than those in other countries
- Diet: Fat might increase the risk
- Obesity : may play a role

Hereditary Breast Cancer

- A family history of breast cancer in a first-degree relative is reported in 13% of women with the disease
- *About 25% of familial cancers (or around 3% of all breast cancers) can be attributed to two highly penetrant autosomal-dominant genes: BRCA1 and BRCA2*

Sporadic Breast Cancer

- *The major risk factors for sporadic breast cancer are related to hormone exposure:* gender, age at menarche and menopause, reproductive history, breast-feeding, and exogenous estrogens. The majority of these cancers occur in postmenopausal women and overexpress ER.

Breast Carcinoma Classification

- Almost all are Adenocarcinoma
- Divided into In situ Carcinoma and Invasive carcinoma

Breast Carcinoma Classification ,Carcinoma in situ

Carcinoma In Situ

1- DCIS In Situ Carcinoma 80%

2- LCIS 20%

DCIS(Ductal Carcinoma In Situ)

- Rapidly increased in the past two decades
- Half of mammographically detected cancers
- Most frequently as a calcifications
- Less frequently as a density or a vaguely palpable mass or nipple discharge

Ductal carcinoma insitu

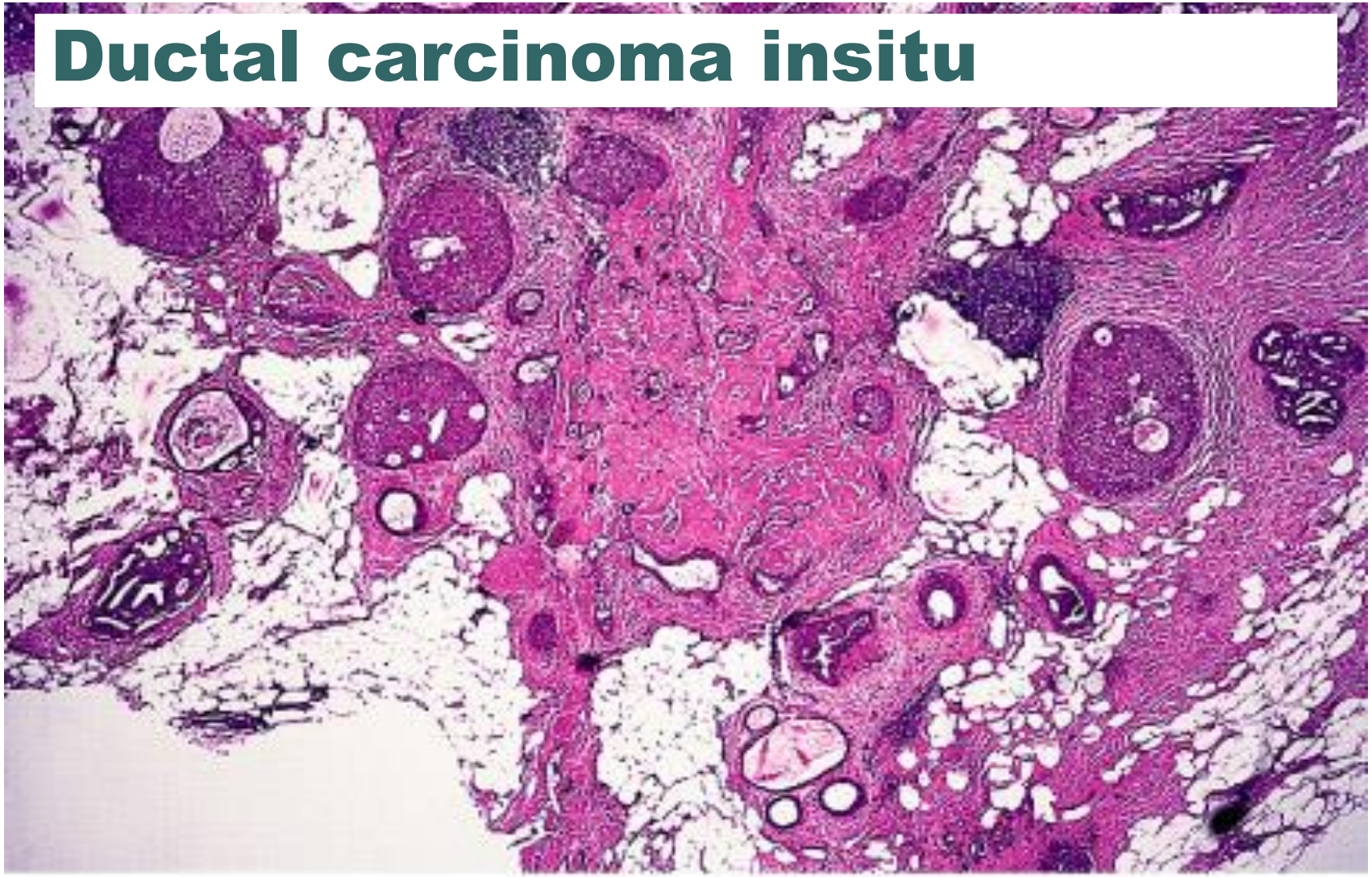
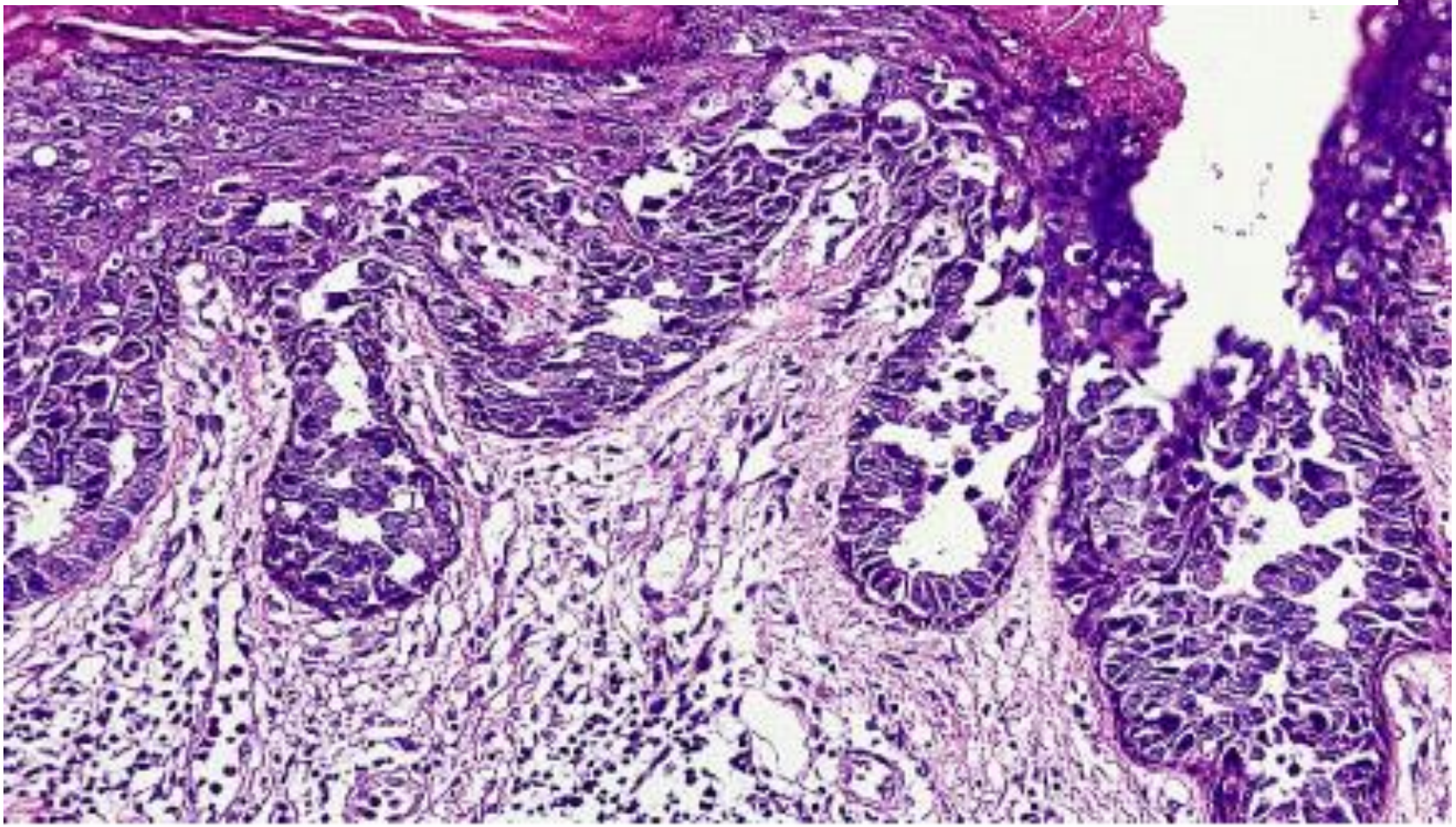


Figure 23-16 A, This mammogram reveals multiple clusters of small, irregular calcifications in a segmental distribution. Suspicious calcifications must be biopsied, as 20% to 30% will prove to be due to DCIS. B, Comedo DCIS fills several adjacent ducts (or completely replaced lobules) and is characterized by large central zones of necrosis with calcified debris. This type of DCIS is most frequently detected as radiologic calcifications. Less commonly, the surrounding desmoplastic response results in an ill-defined palpable mass or a mammographic density.

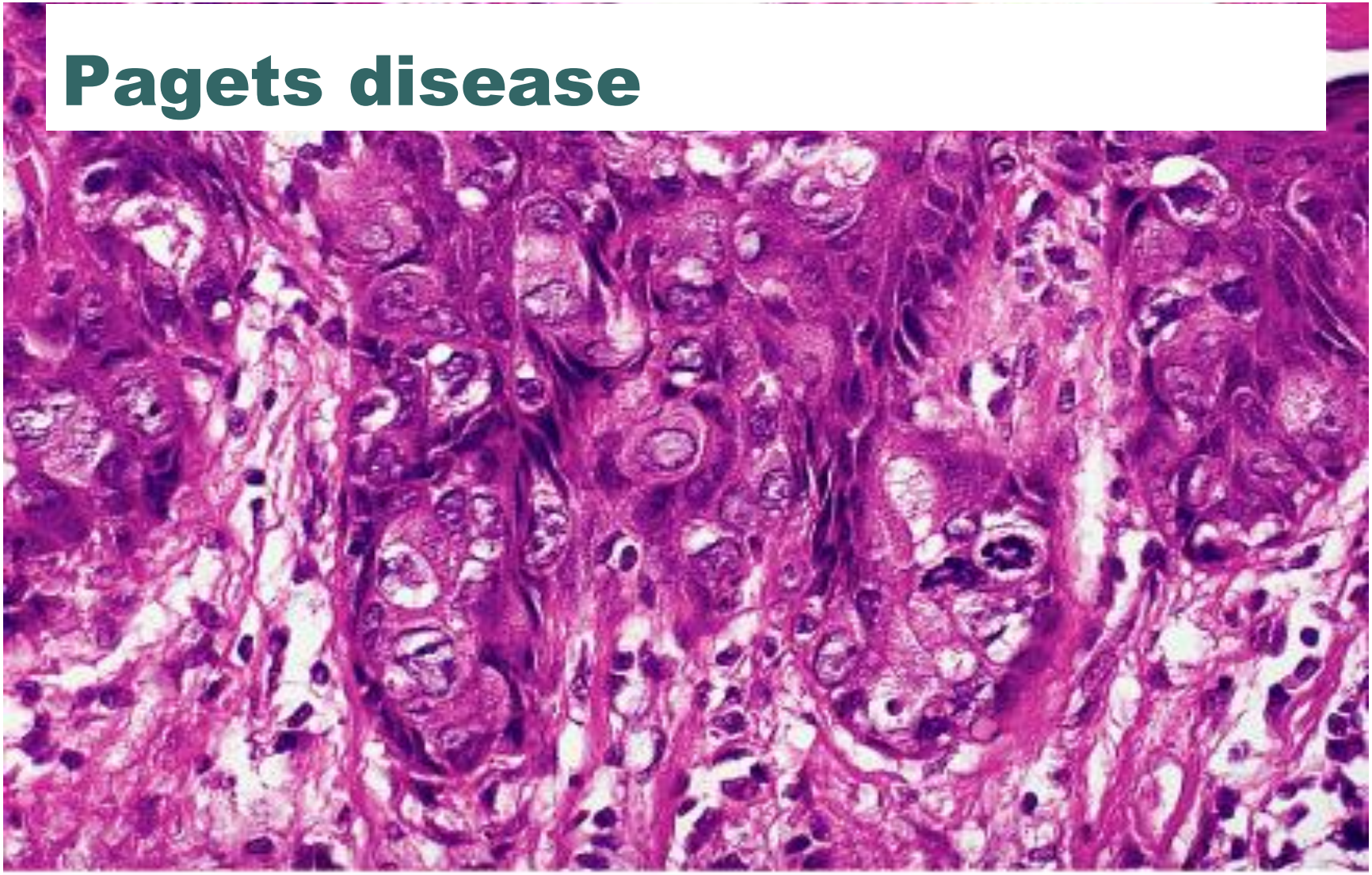
Paget's Disease

- Rare manifestation of breast cancer(1 to 2 %)
- Pruritus is common ,might be mistaken for Eczema, presents as a unilateral erythematous eruption with a scale crust.
- Malignant cells, referred to as Paget cells and are found scattered ion the epidermis.
- Paget cells extend from DCIS within the ductal system into nipple skin without crossing the basement membrane
- Palpable mass is present in 50 to 60% of women with Paget disease indicating an underlying invasive carcinoma.

Pagets disease



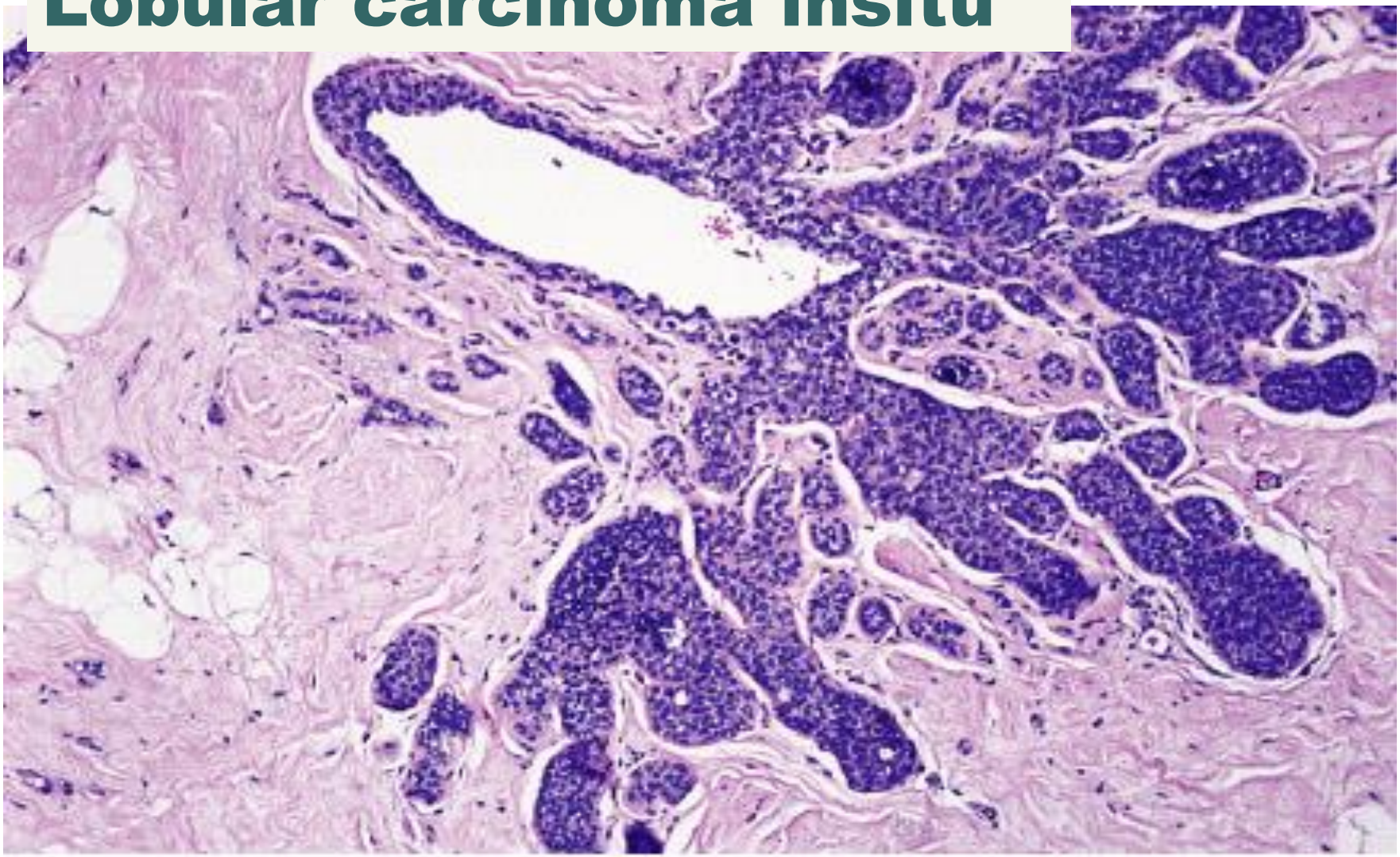
Pagets disease



LCIS -Lobular Carcinoma in Situ

- Always an incidental finding in a biopsy performed for another reason
- Infrequent (1% to 6%) of all carcinomas
- Bilateral in 20% to 40% of women when both breasts are biopsied
- LCIS is frequently multicentric and bilateral and subsequent carcinomas occur at equal frequency in both breasts

Lobular carcinoma insitu



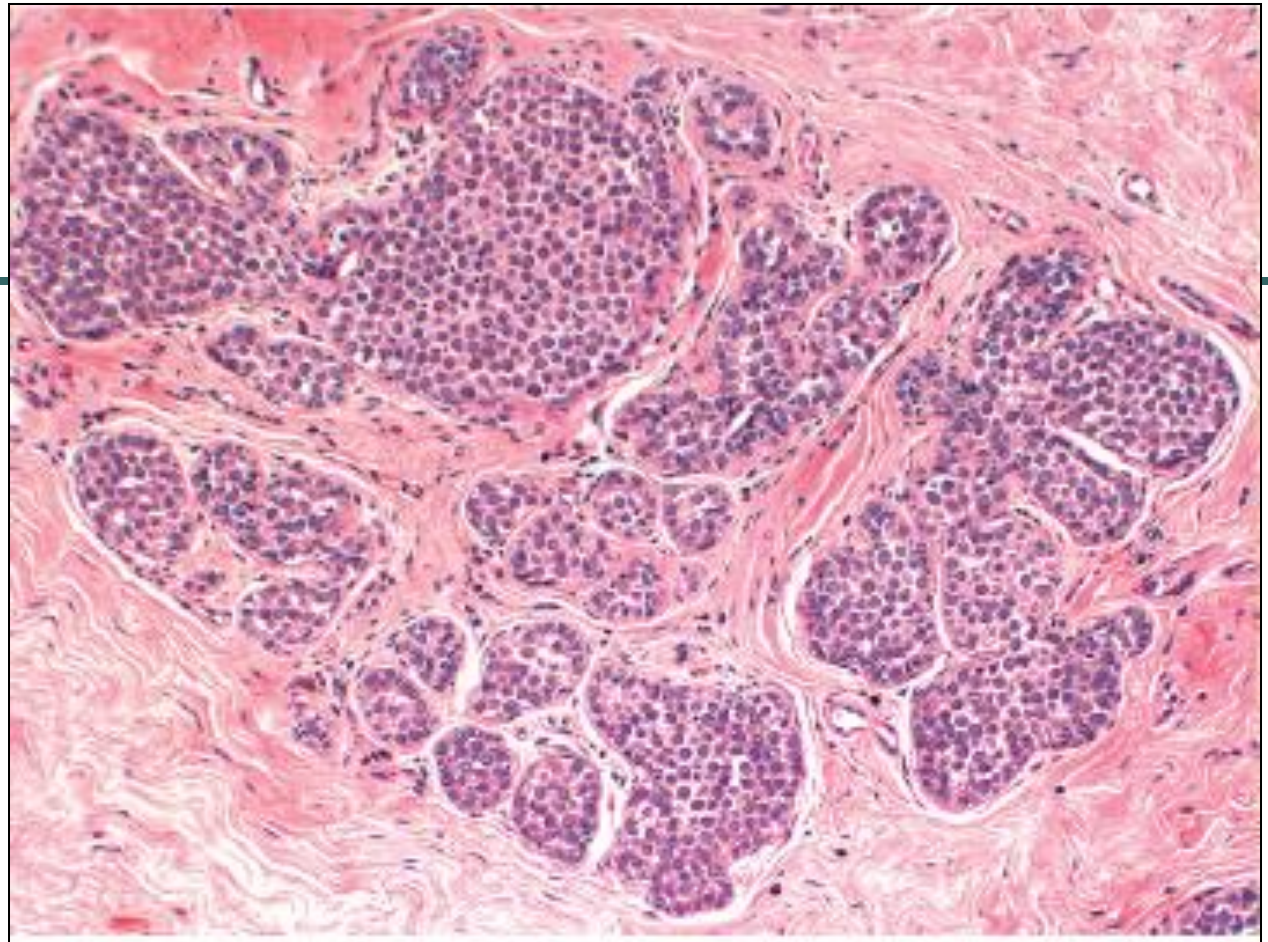


Figure 23-20 Lobular carcinoma in situ. A monomorphic population of small, rounded, loosely cohesive cells fills and expands the acini of a lobule. The underlying lobular architecture can still be recognized.

Invasive Breast Carcinoma Classification

- Invasive Carcinoma :

1- NOS Ductal 80%

2- Lobular 10%

3- tubular 6%

4-Mucinous(Colloid) 2%

5- Medullary 2%

6- Papillary 1%

7- Metaplastic Carcinoma 1%

CLINICAL FEATURES OF BREAST CANCER

- In young women or in older women not undergoing mammographic screening, invasive carcinoma almost always presents as a palpable mass. By the time a cancer becomes palpable, over half the patients will have axillary lymph node metastases .
- Larger carcinomas may be fixed to the chest wall or cause dimpling of the skin.
- Lymphatics may become so involved as to block the local area of skin drainage and cause lymphedema and thickening of the skin, a change referred to as *peau d'orange*.
- When the tumor involves the central portion of the breast, retraction of the nipple may develop.

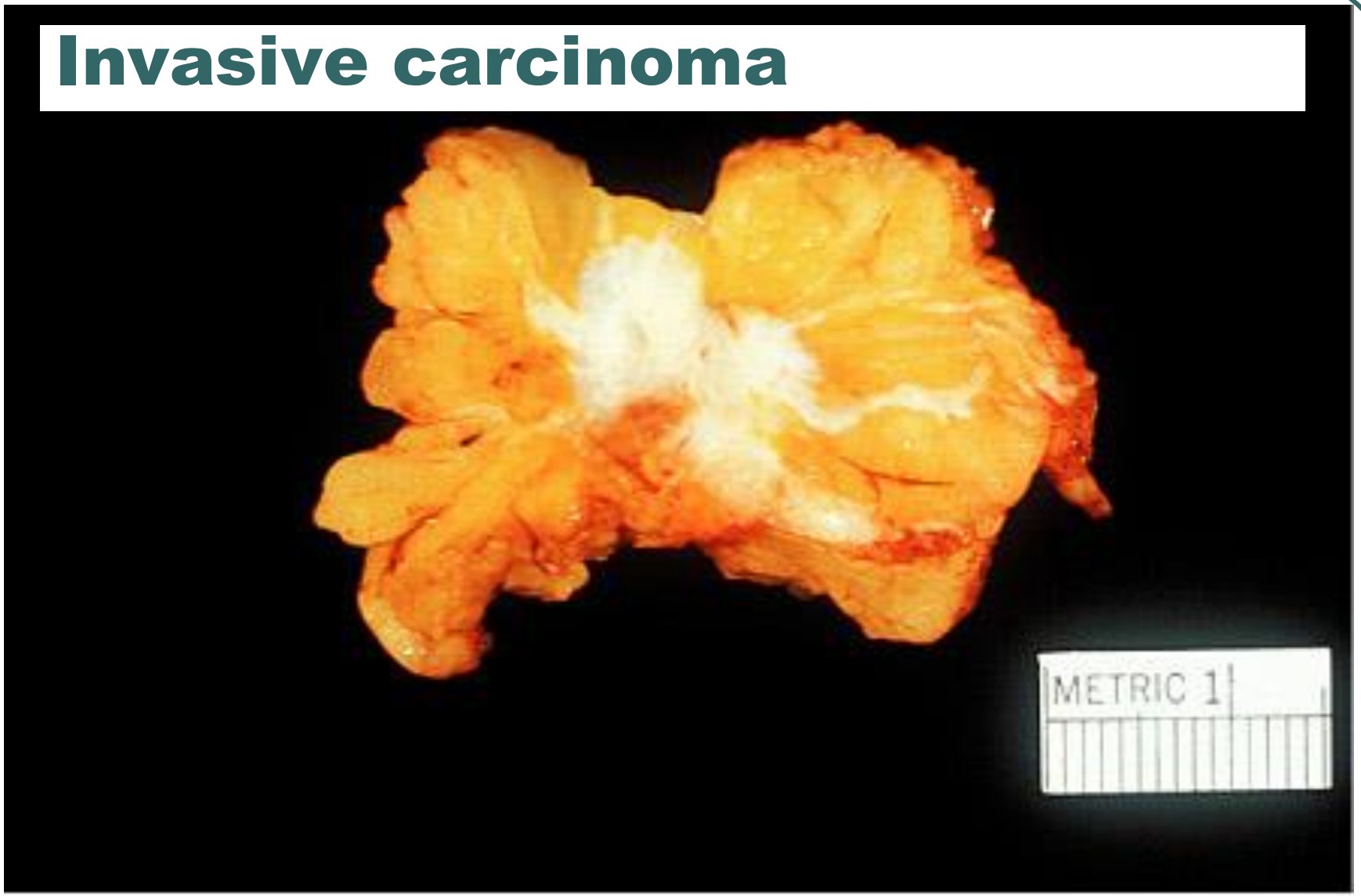
CLINICAL FEATURES OF BREAST CANCER

- In older women undergoing mammography, invasive carcinomas most commonly present as a density and are, on average, half the size of a palpable cancer. Fewer than 20% will have a nodal metastases. Invasive carcinomas presenting as mammographic calcifications without an associated density are very small in size, and metastases are unusual.

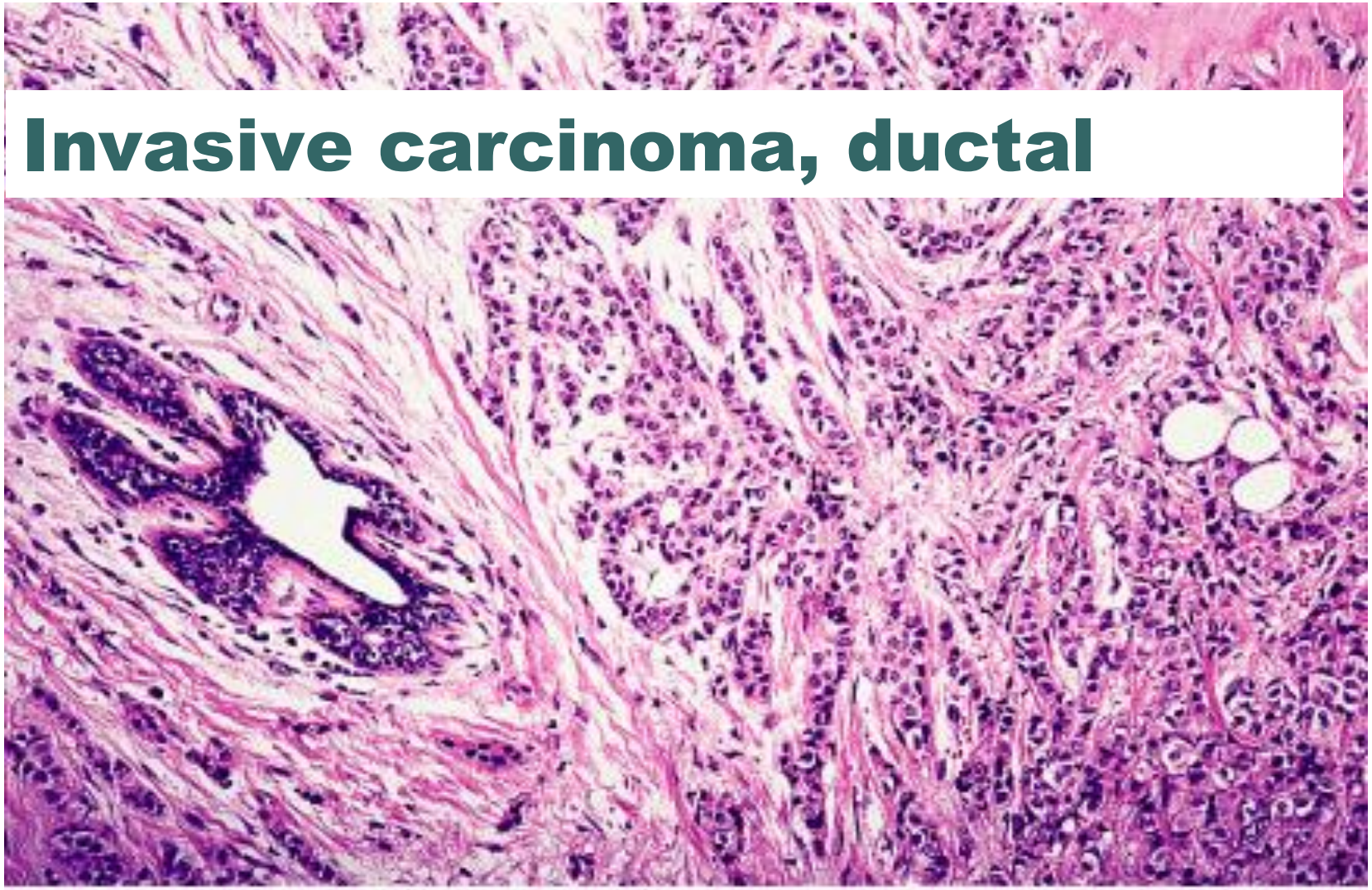
CLINICAL FEATURES OF BREAST CANCER

- The term "inflammatory carcinoma" refers to the clinical presentation of a carcinoma extensively involving dermal lymphatics, resulting in an enlarged erythematous breast. The diagnosis is made on clinical grounds and does not correlate with a specific histologic type of carcinoma

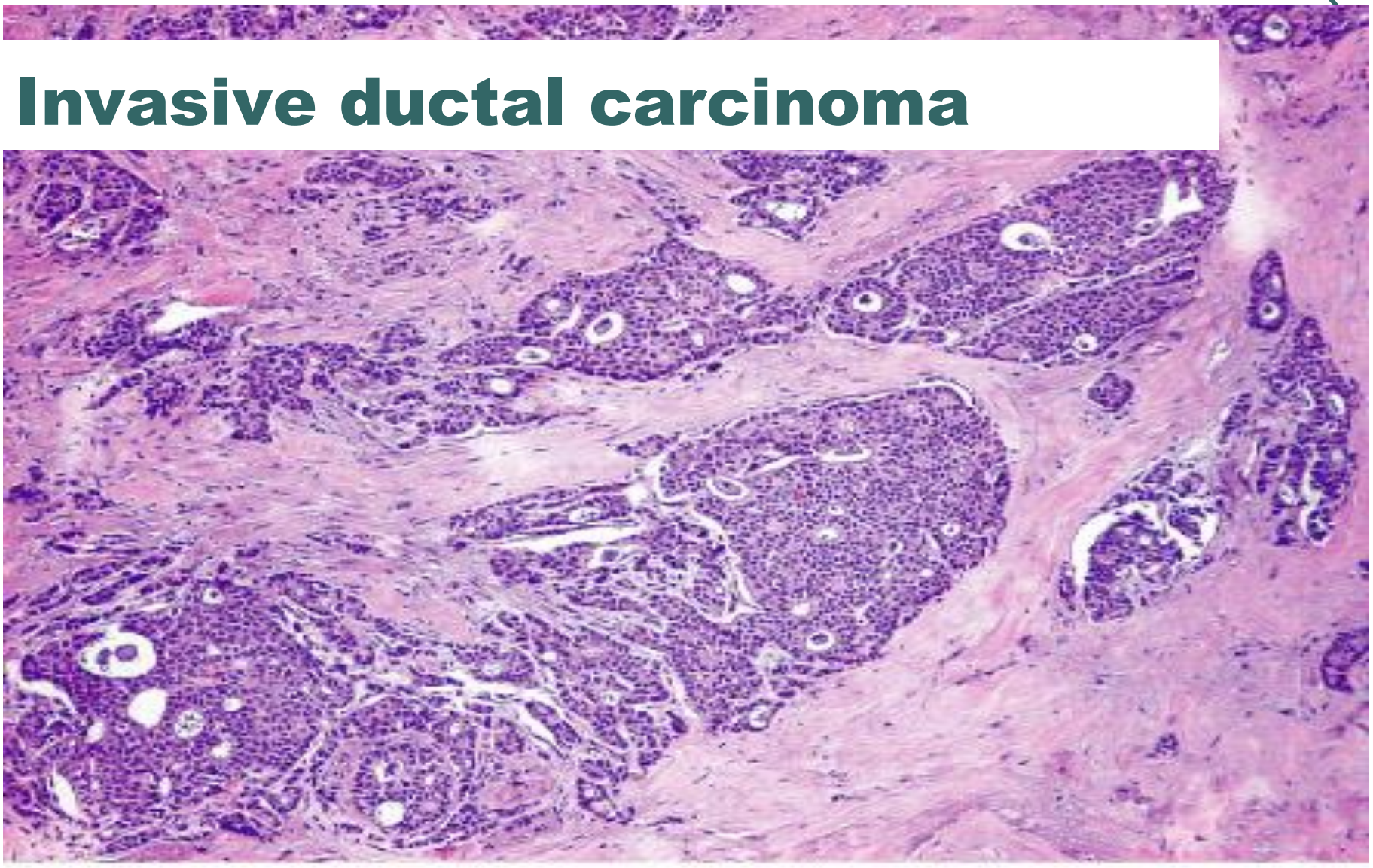
Invasive carcinoma



Invasive carcinoma, ductal



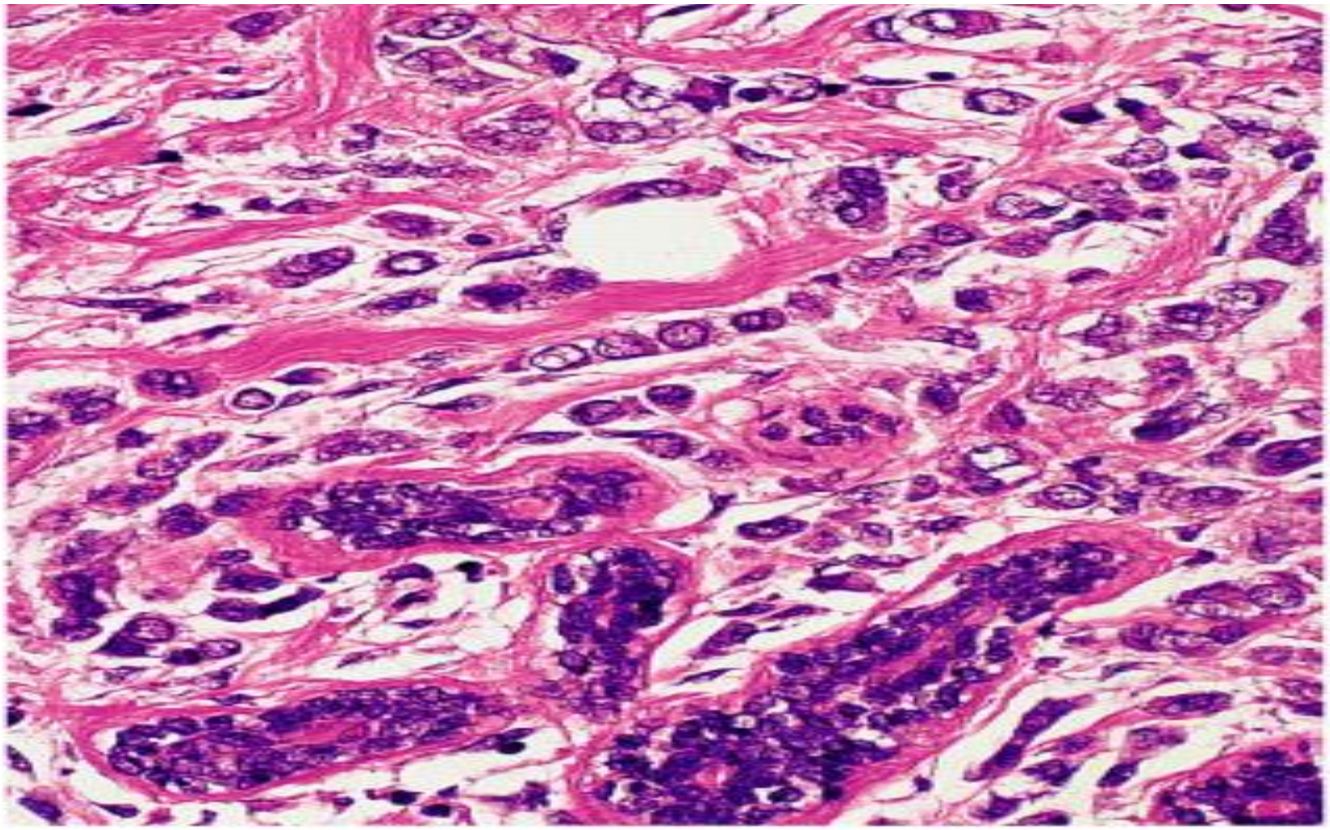
Invasive ductal carcinoma



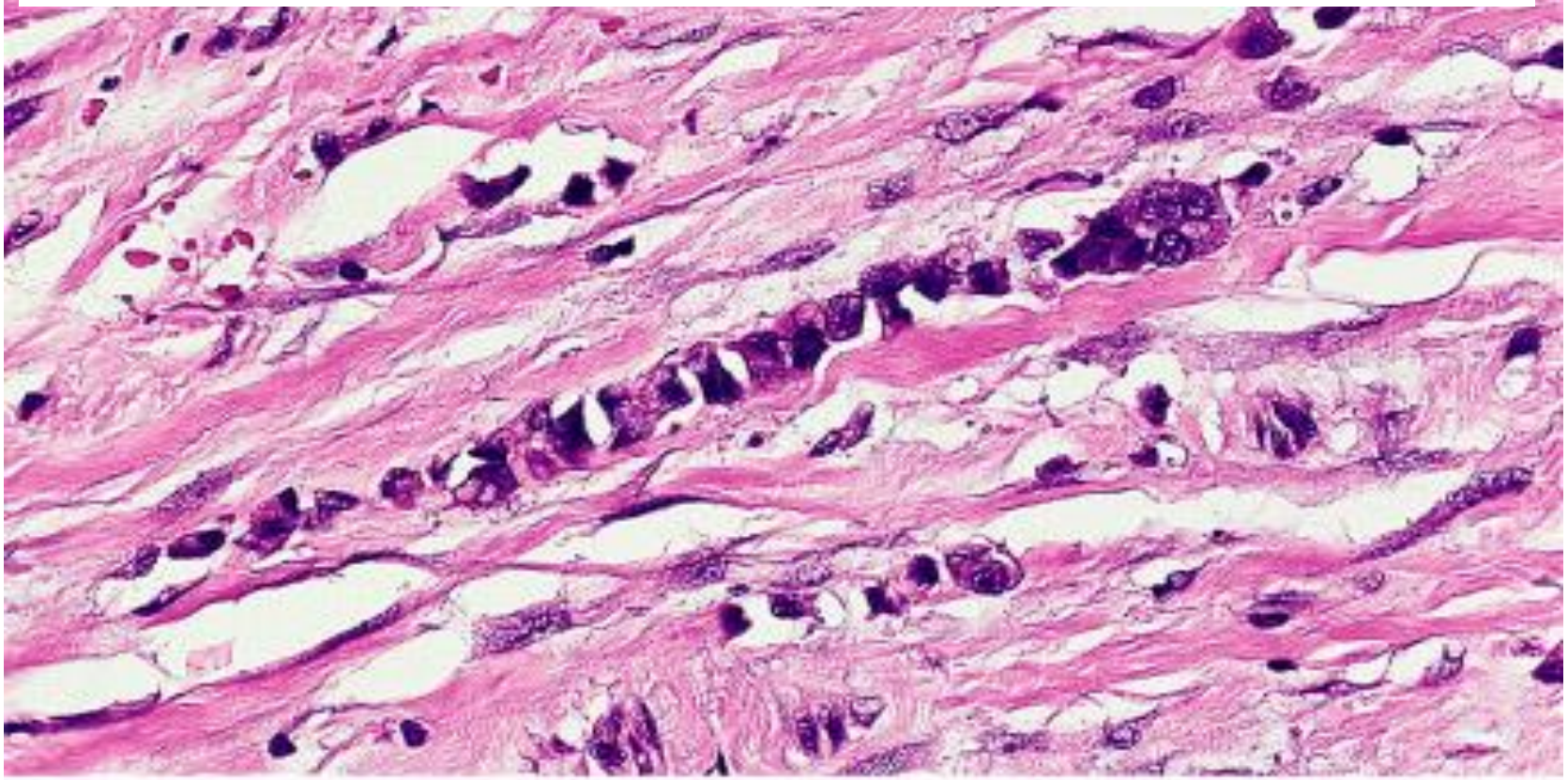
Invasive Lobular Carcinoma

- Most are firm to hard with irregular margins
- Single infiltrating cells ,often one cell width
- No tubules or papillary formation

Invasive lobular carcinoma



Invasive lobular carcinoma



Breast Carcinoma , Major Prognostic Factors

- 1- Invasive or In situ disease: By definition, in situ carcinoma is confined to the ductal system and cannot metastasize. Breast cancer deaths associated with DCIS are due to the subsequent development of invasive carcinoma or areas of invasion undetected at the time of diagnosis. The great majority of women with adequately treated DCIS will be cured. In contrast, at least half of invasive carcinomas will have metastasized locally or distantly at the time of diagnosis.

- 2- Distant metastasis: Once distant metastases are present, cure is unlikely, although long-term remissions and palliation can be achieved. Favored sites for dissemination are the lungs, bones, liver, adrenals, brain, and meninges.

- 3- Lymph node metastasis: *Axillary lymph node status is the most important prognostic factor for invasive carcinoma in the absence of distant metastases.* The clinical assessment of nodal involvement is very inaccurate, therefore, biopsy is necessary for accurate assessment.
  With no involvement, the 10-year disease-free survival rate is close to 70% to 80%; the rate falls to 35% to 40% with one to three positive nodes and 10% to 15% in the presence of more than 10 positive nodes.

Sentinel lymph nodes:

- Most breast carcinomas drain to one or two *sentinel nodes* that can be identified by radiotracer colored dye, or both.
- The sentinel node is highly predictive of the status of the remaining nodes.
- Sentinel node biopsy can spare women the increased morbidity of a complete axillary dissection.

- 4- Tumor Size: The size of the carcinoma is the second most important prognostic factor. The risk of axillary lymph node metastases does increase with the size of the carcinoma.

- 5- Locally advanced disease:Tumors invading into skin or skeletal muscle are frequently associated with concurrent or subsequent distant disease. With increased awareness of breast cancer detection, such cases have fortunately decreased in frequency and are now rare at initial presentation.

- 6- Inflammatory Carcinoma: Women presenting with the clinical appearance of breast swelling and skin thickening have a particularly poor prognosis with a 3-year survival rate of only 3% to 10%.

Breast Carcinoma , Minor Prognostic Factors

- **Histologic Subtype:** tubular, mucinous, medullary, lobular, and papillary have better prognosis.

- **Tumor Grade:** The most commonly used grading system to assess the degree of tumor differentiation (*Bloom Richardson*) combines nuclear grade, tubule formation, and mitotic rate. There are there grades and grade 1 has better prognosis then grade2.

- **Estrogen and progesterone receptors:**

50% to 85% of carcinomas express estrogen receptors, such tumors are more common in postmenopausal women, hormone positive cancers have better prognosis.

They respond well to specific drugs eg. Tamoxifen. Therefore reporting of ER/PR positivity is important when reporting breast cancer.

- *HER2/neu.* (human epidermal growth factor receptor 2 or c-*erb B2* or *neu*) is a glycoprotein overexpressed in 20% to 30% of breast carcinomas.

  Many studie shave shown that overexpression of *HER2/neu* is associated with a poor prognosis.

  In addition, ongoing studies have shown that *HER2/neu*-overexpressing tumors respond very well to hormonal or anthracycline chemotherapy regimens

  eg. Trastuzumab (Herceptin). Therfore evaluation of HER2/neu is most important when reporting breast cancer.

- **Lymphovascular invasion:** Tumor cells may be seen within vascular spaces (either lymphatics or small capillaries) surrounding tumors. This finding is strongly associated with the presence of lymph node metastases and is a poor prognostic factor in women without lymph node metastases.

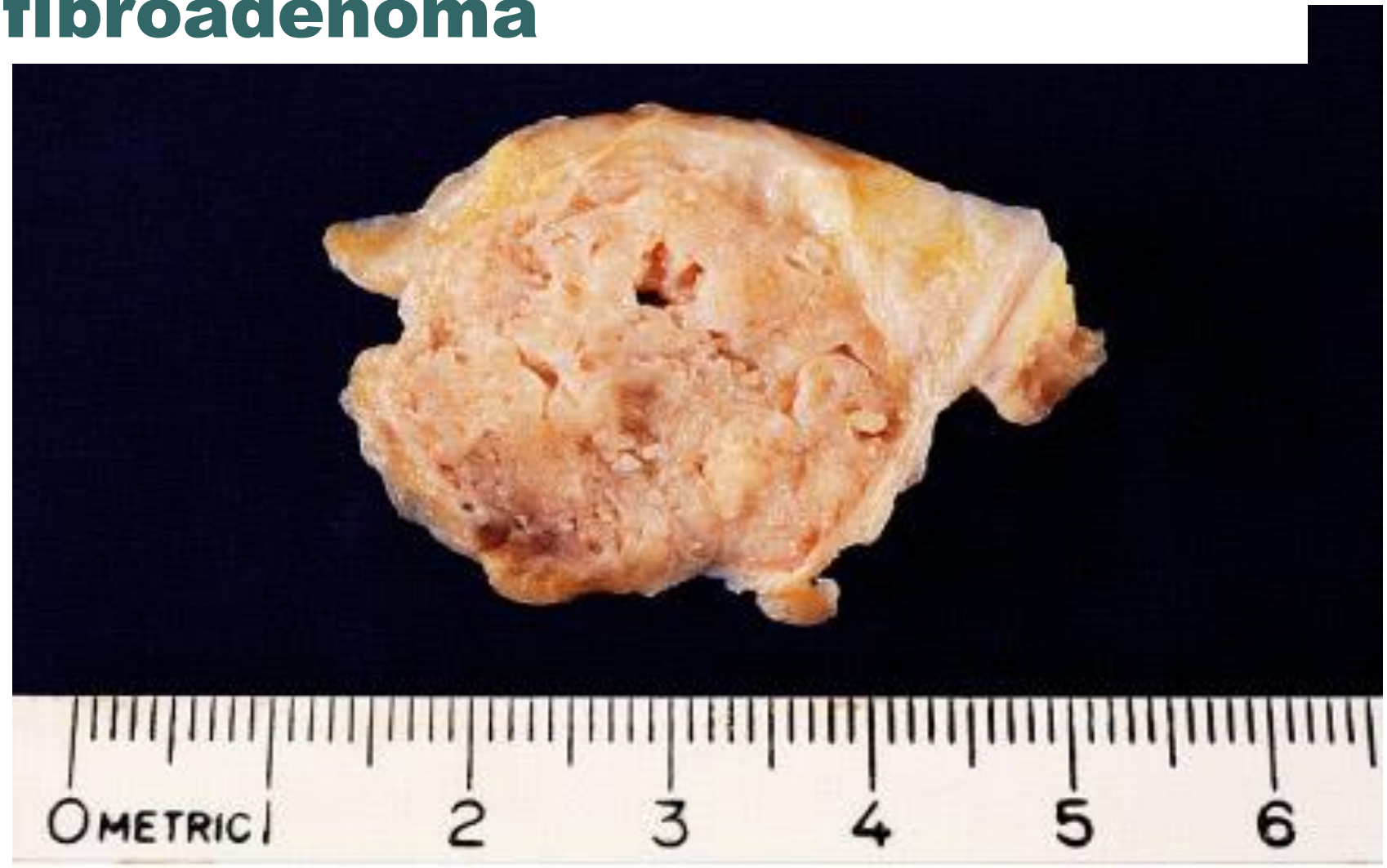
- **Proliferative rates**

Metastasis to vertebra

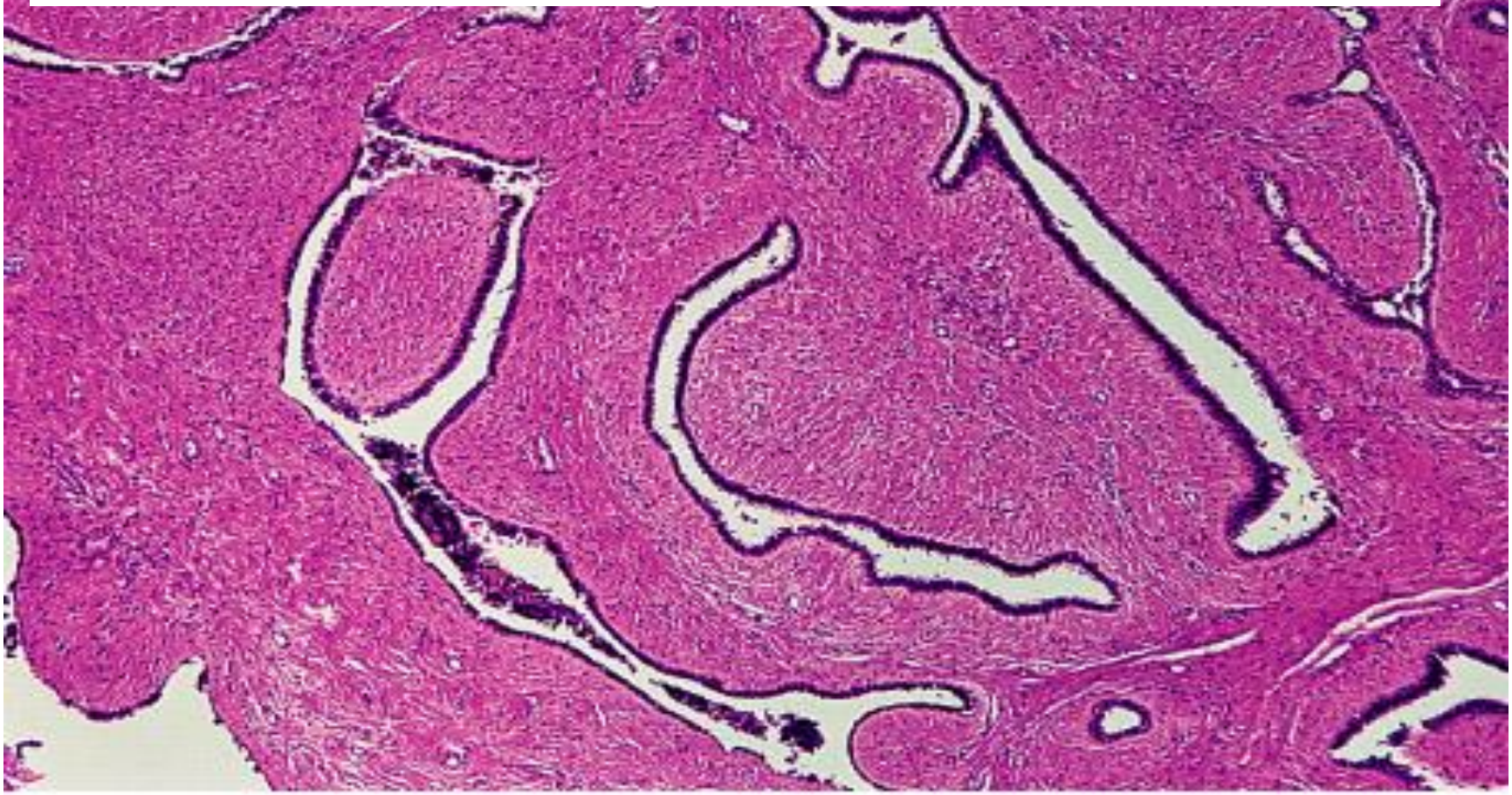
Stromal tumors -Fibroadenoma

- The most common benign tumor of the female breast
- Any age ,most common before age 30
- Usually present with a palpable mass
- Regression usually occurs after menopause
- Spherical nodules
- Sharply demarcated
- Freely movable
- Size vary
- Proliferation in both glands and stroma
- Treatment: lumpectomy (only the lump is removed)

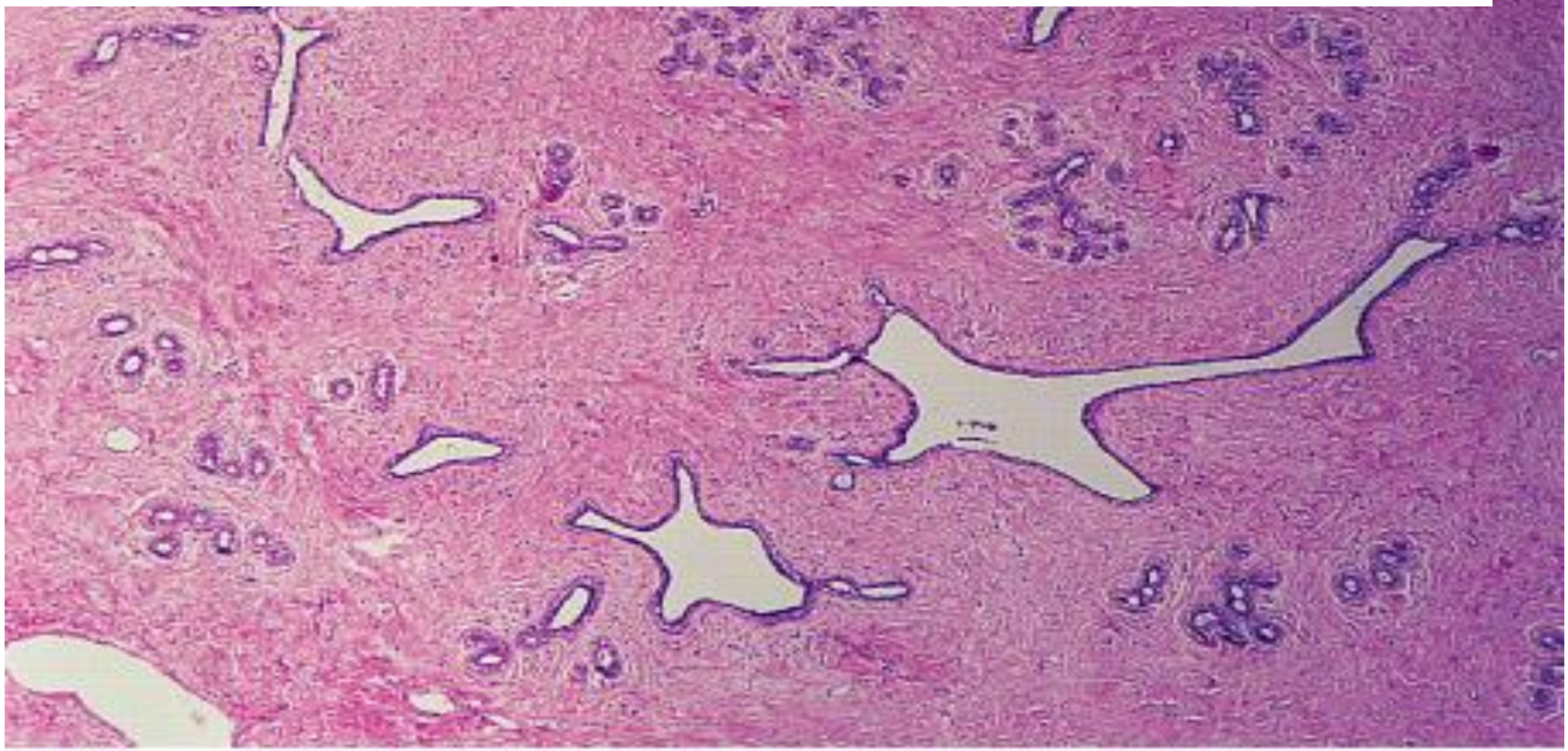
fibroadenoma



fibroadenoma



fibroadenoma



Stromal tumors- Phylloides tumor

- Phyllodes tumors, like fibroadenomas, arise from intralobular stroma. Although they can occur at any age, most present in the sixth decade, 10 to 20 years later than the average presentation of a fibroadenoma
- Most present as palpable masses
- Phyllodes tumors must be excised with wide margins to avoid the high risk of local recurrences.
- The majority are low-grade tumors that may recur locally but only rarely metastasize. Rare high-grade lesions behave aggressively, with frequent local recurrences and distant hematogenous metastases in about one third of cases.


NEVER
GIVE UP!