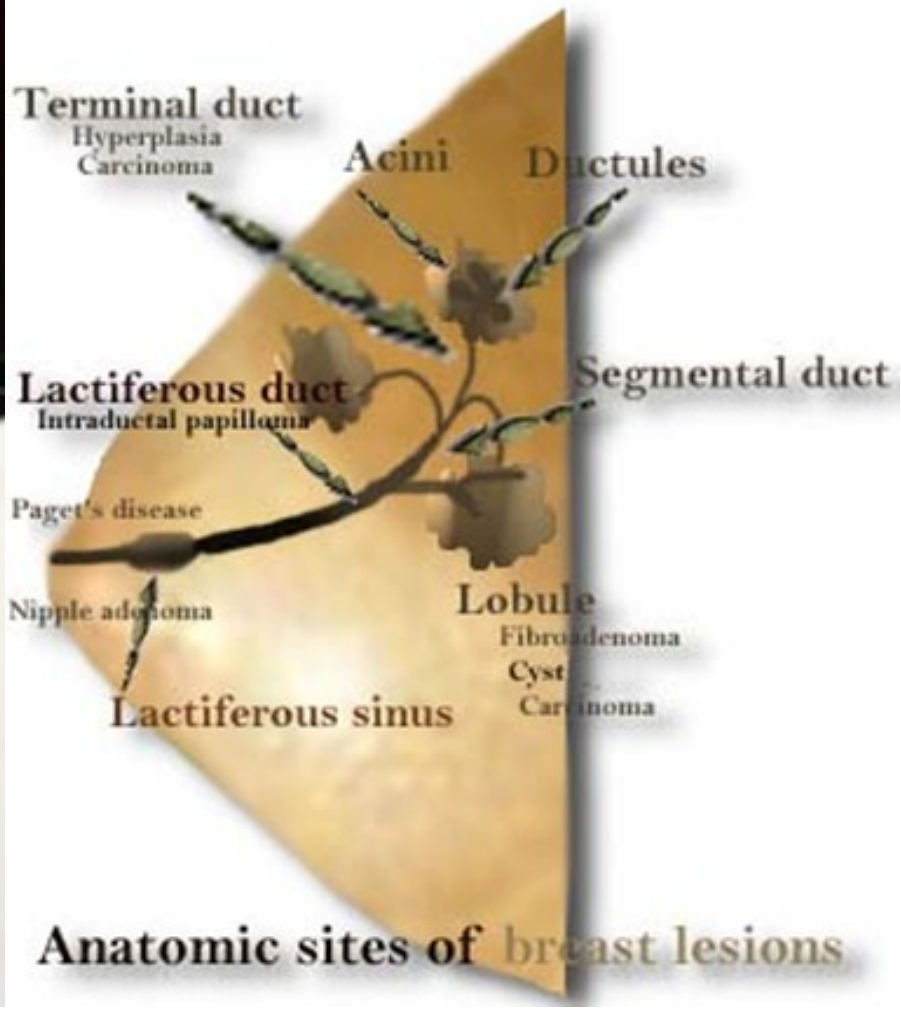
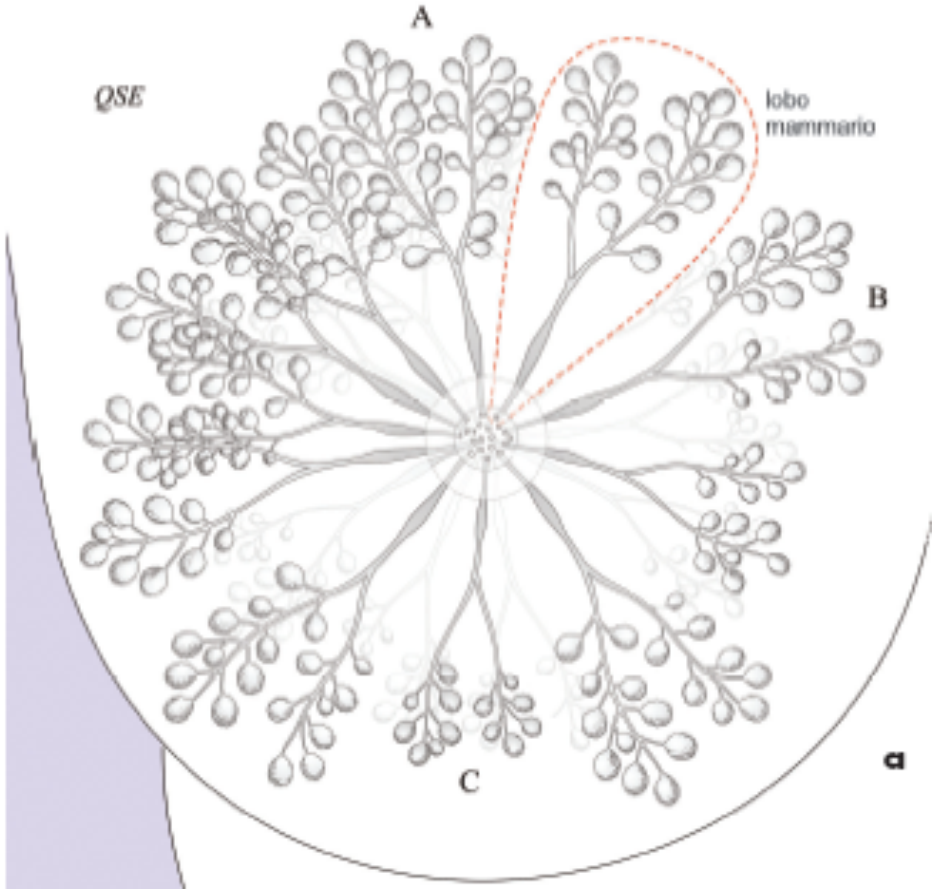
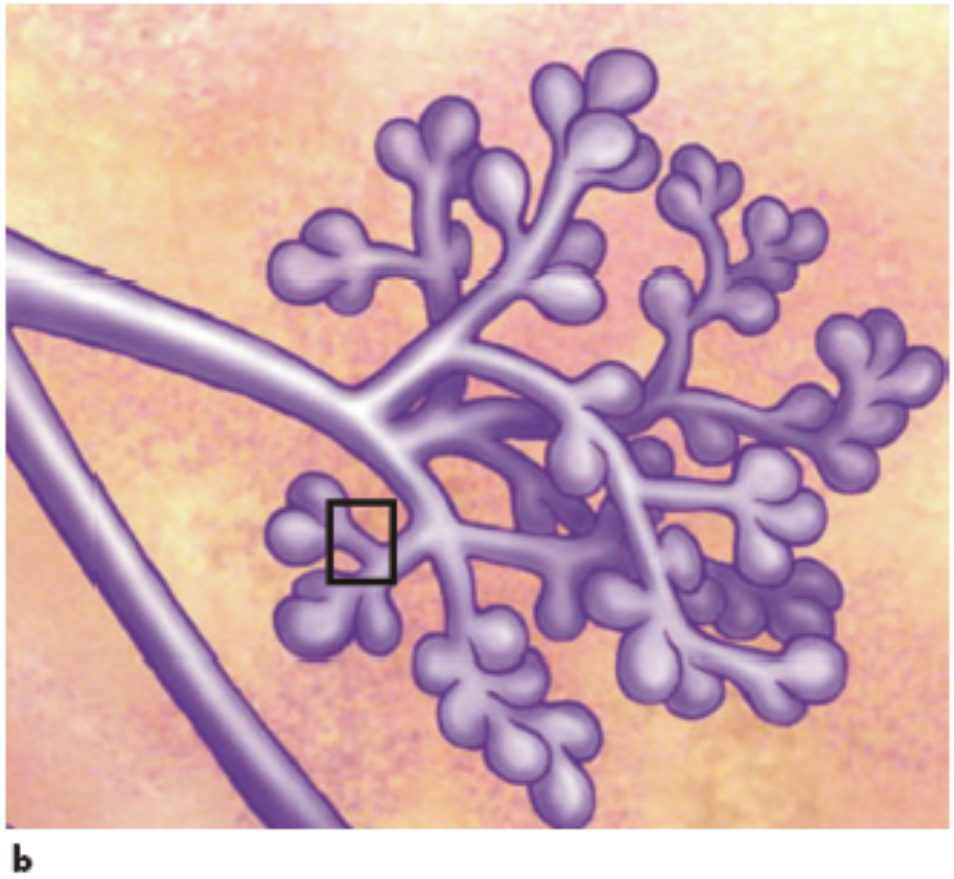
Breast Pathology

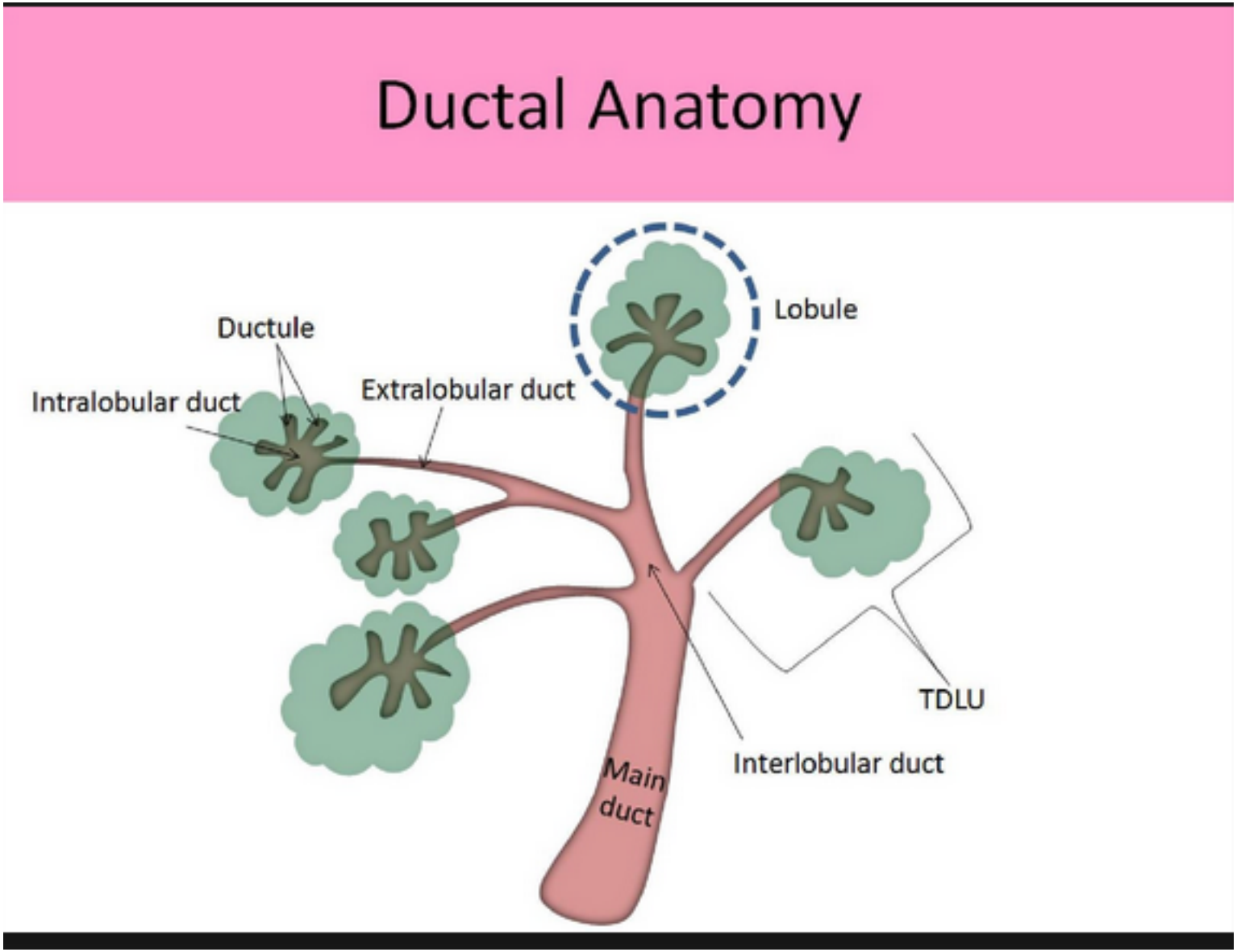


Terminal ductulo-lobular unit (TDLU)





Terminal ductulo-lobular unit (TDLU)



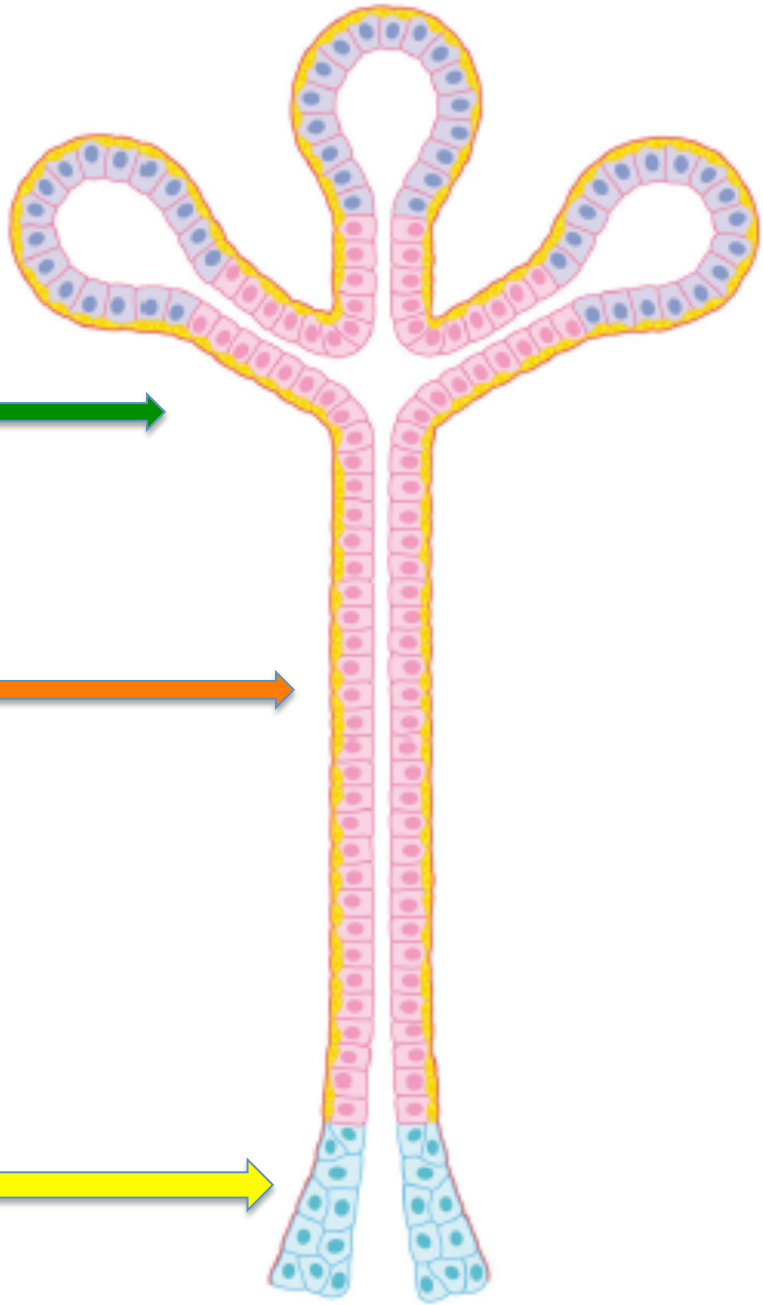
Epithelial cells: CK 19 +, CK7+, CK8/18+
Myoepithelial cells: calponin+, p63, CK14+, CK5+

Lobules (acini)

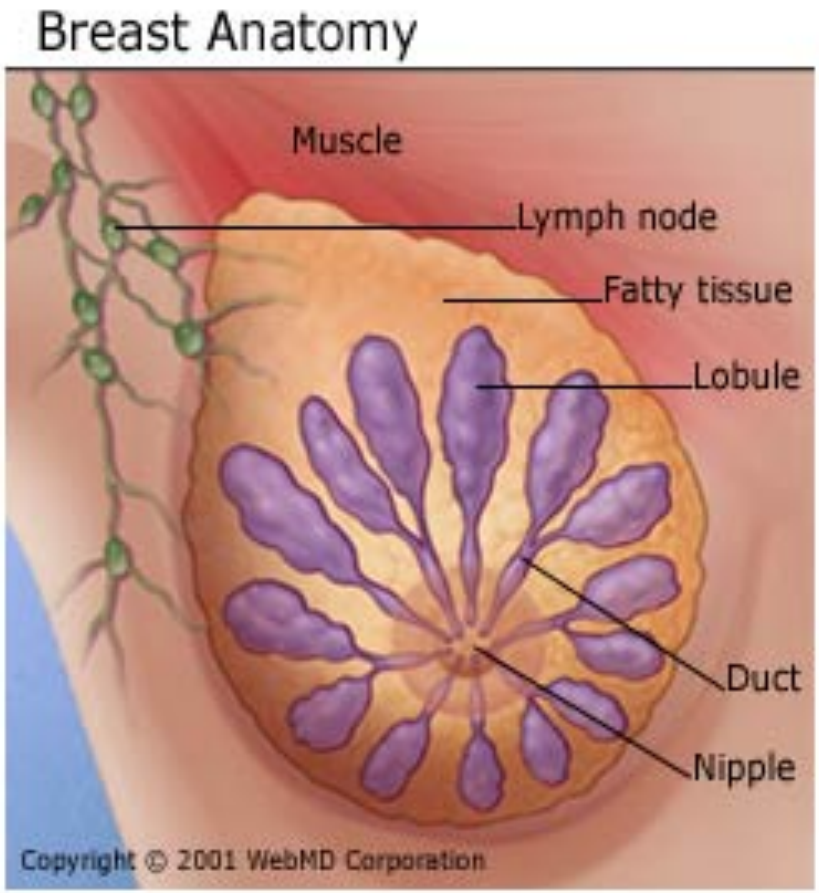
Terminal ducts

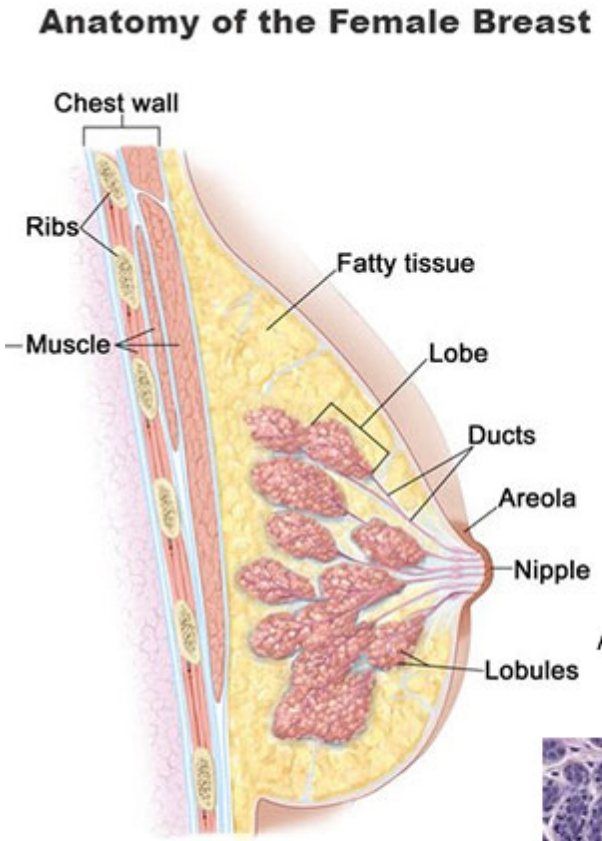
Interlobular ducts

Collecting (galactophores)ducts

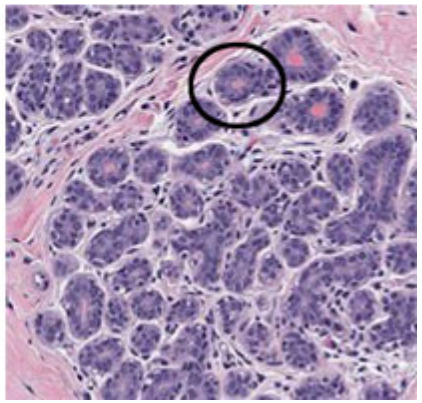


Normal breast



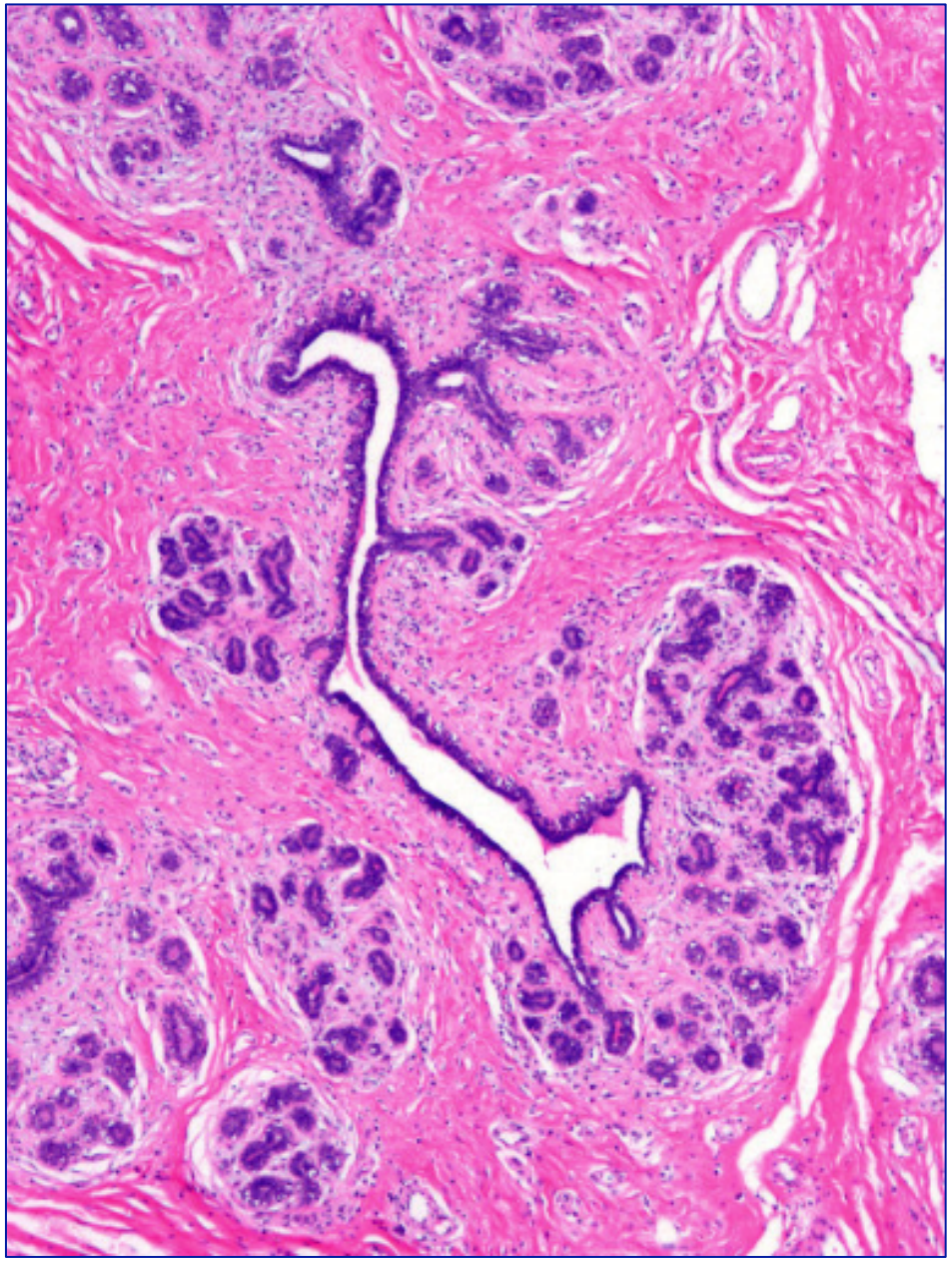


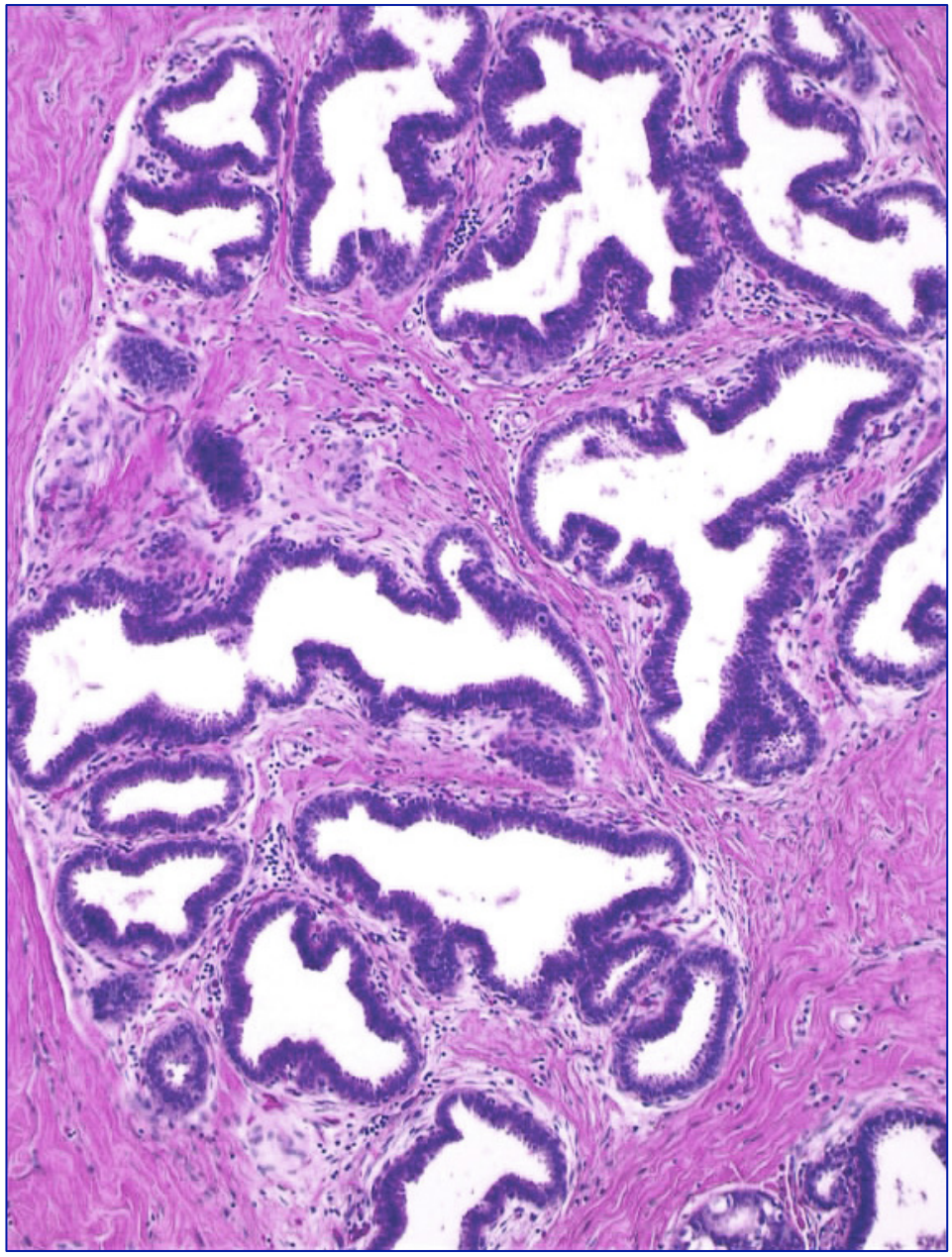
An acinus (circled in black) is an epithelial substructure found in lobules.



Courtesy of the Susan G. Komen Tissue Bank at the IU Simon Cancer Center (www.virtualtissuebank.iu.edu)

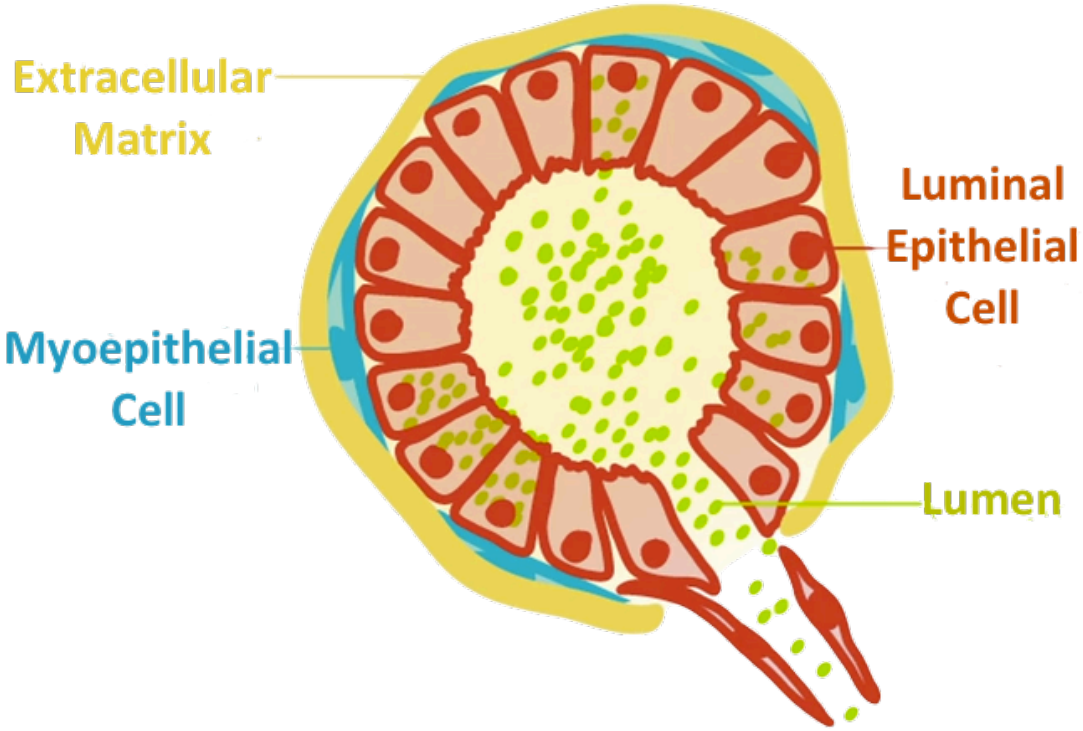
Normal breast

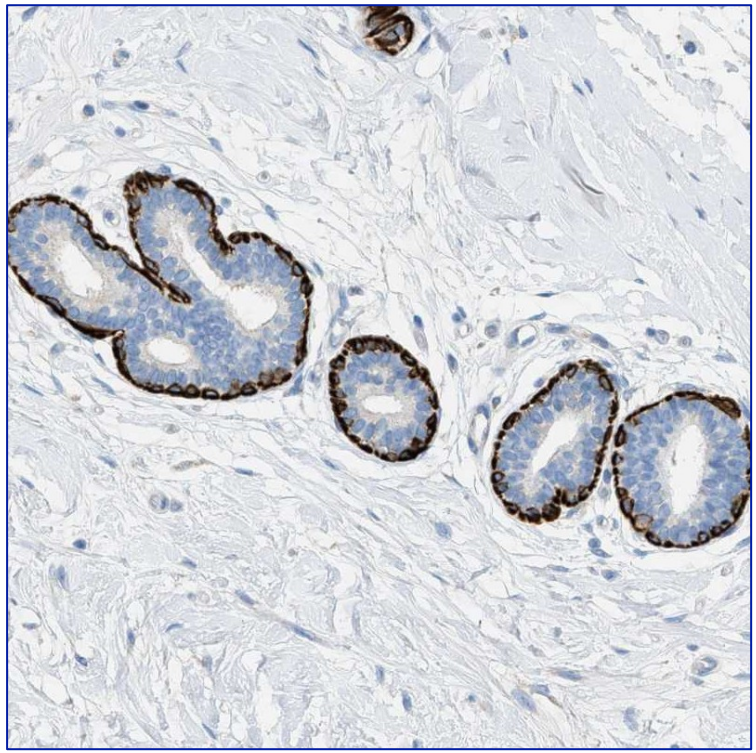




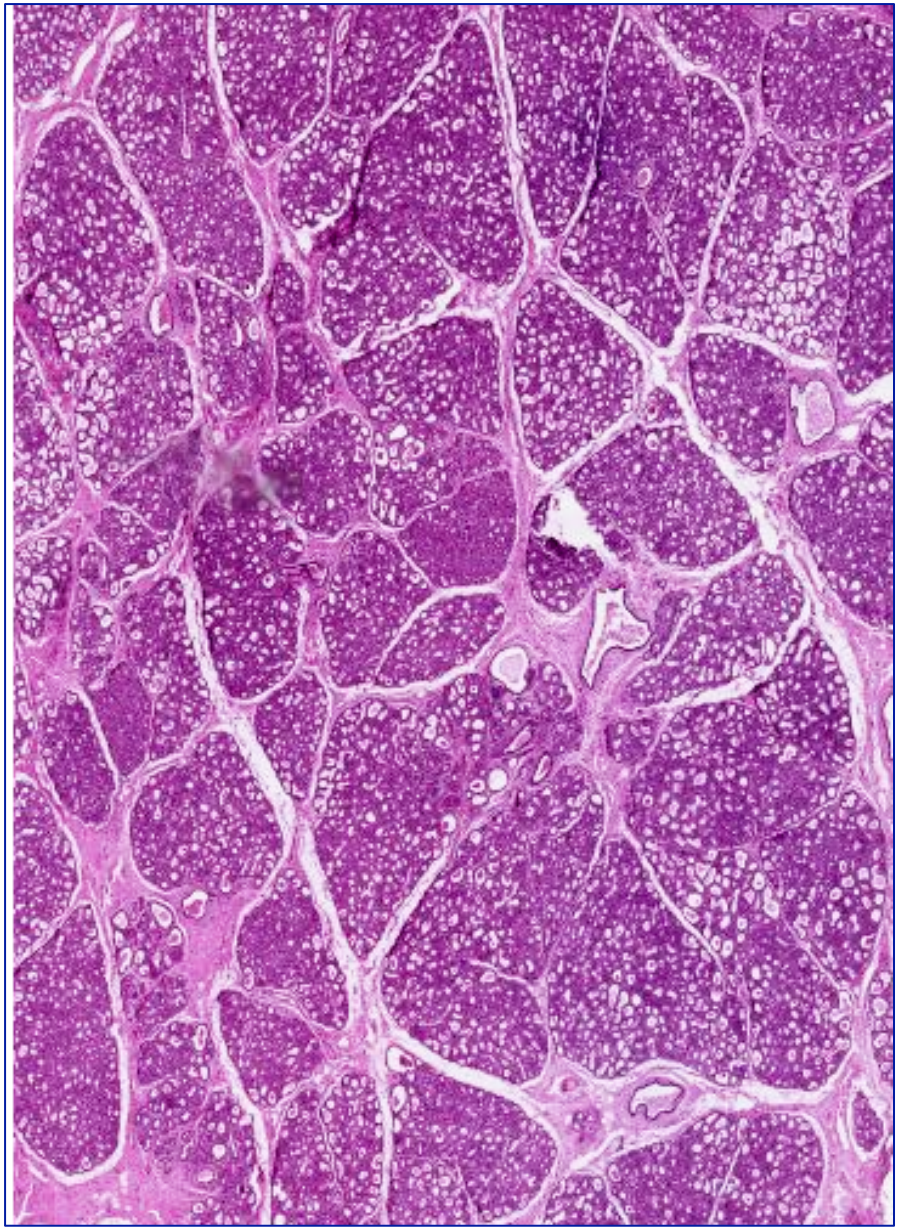
Normal breast

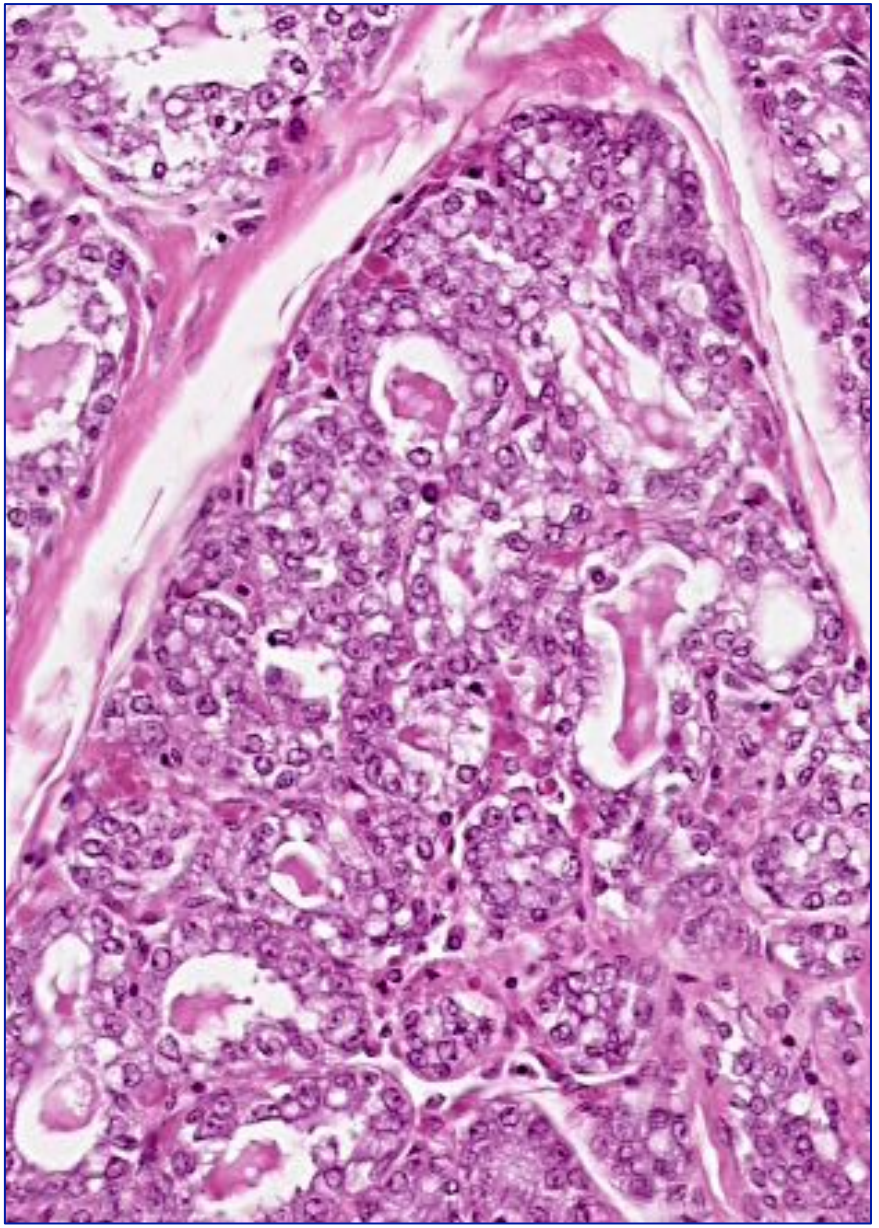
Normal breast – myoepithelial cells





Normal breast – lactation changes





Breast pathology

- Very frequent
- Fertile women (35-55 ys.)
- Neoplastic and non-neoplastic
- Increasingly detected by screening
- Increasingly curable
- Interdisciplinary approach needed

Breast pathology

- Inflammatory (mastitis)
  - → Relatively rare
  - → Young women
  - → Post-gravidic / breast-feeding
  - → Post-traumatic
  - → Symptomatic (tension, pain, red discoloration)

Breast pathology

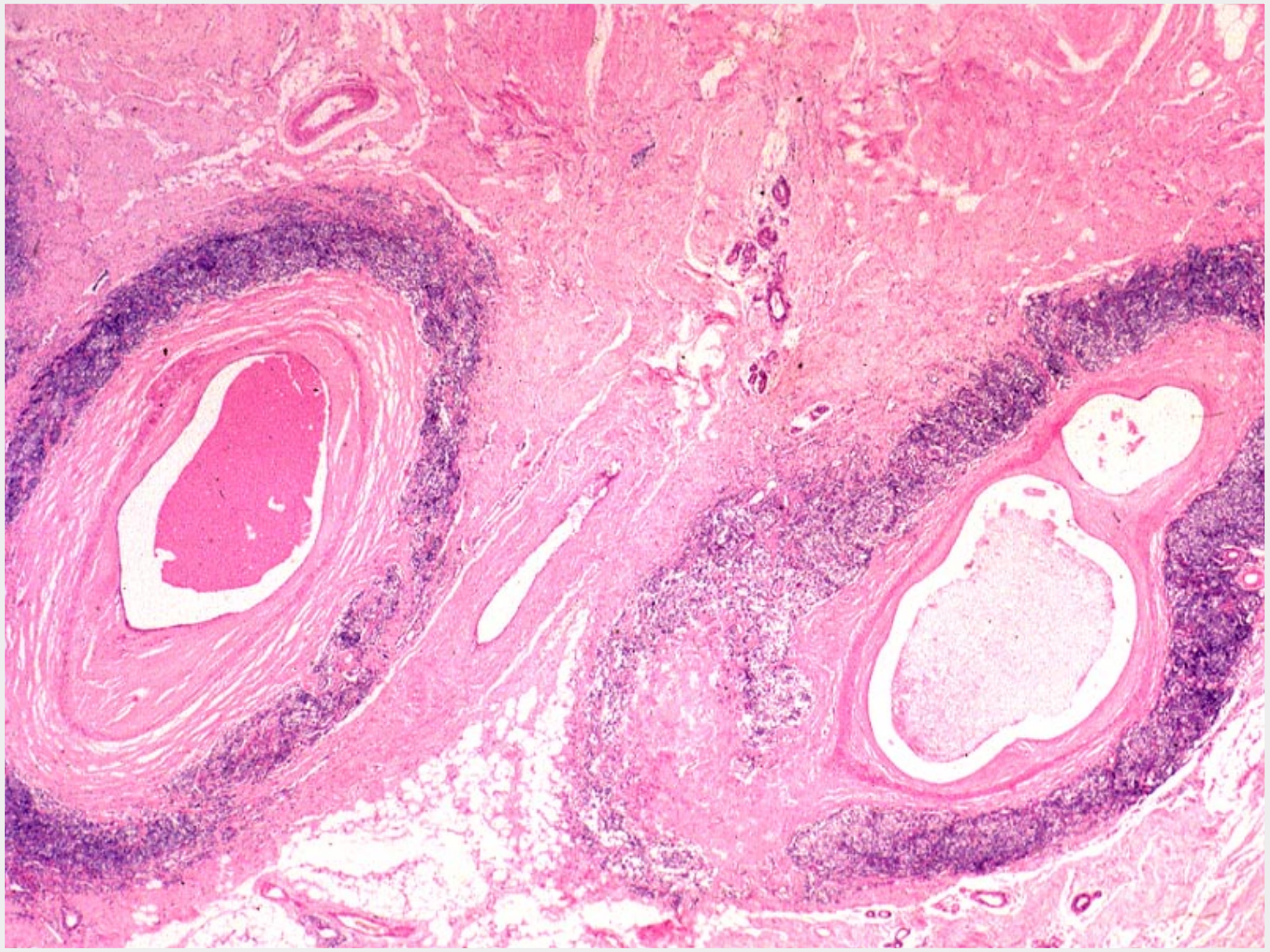
- Mastitis
  - → Acute, non-specific (mucous-purulent)
    - Nipple ulceration, fissuration
    - Ascending, canalicular
    - Abscess formation
    - Peri- and/or intra-ductal exudate
    - Possible fibrotic evolution

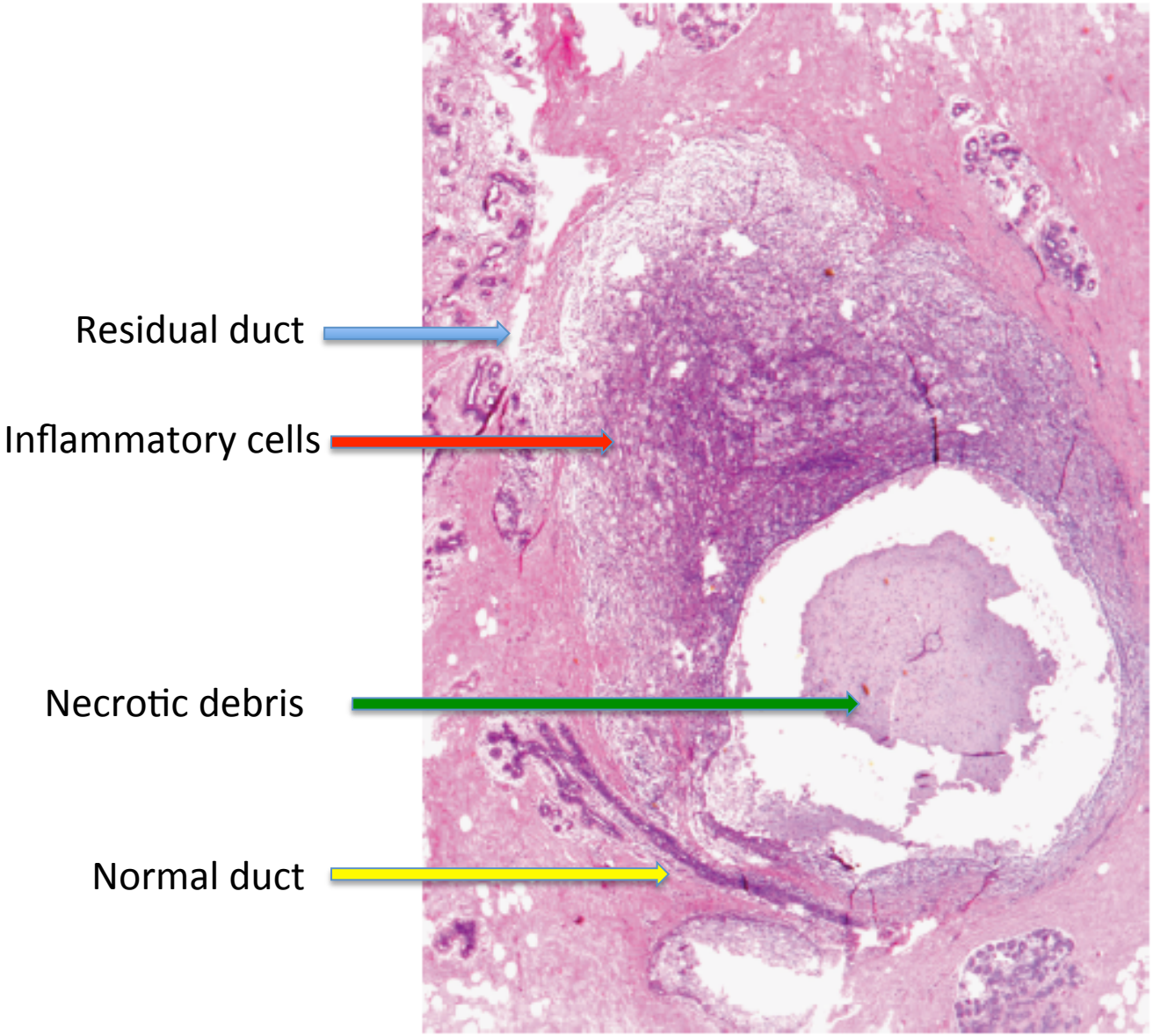
PERIDUCTAL MASTITIS

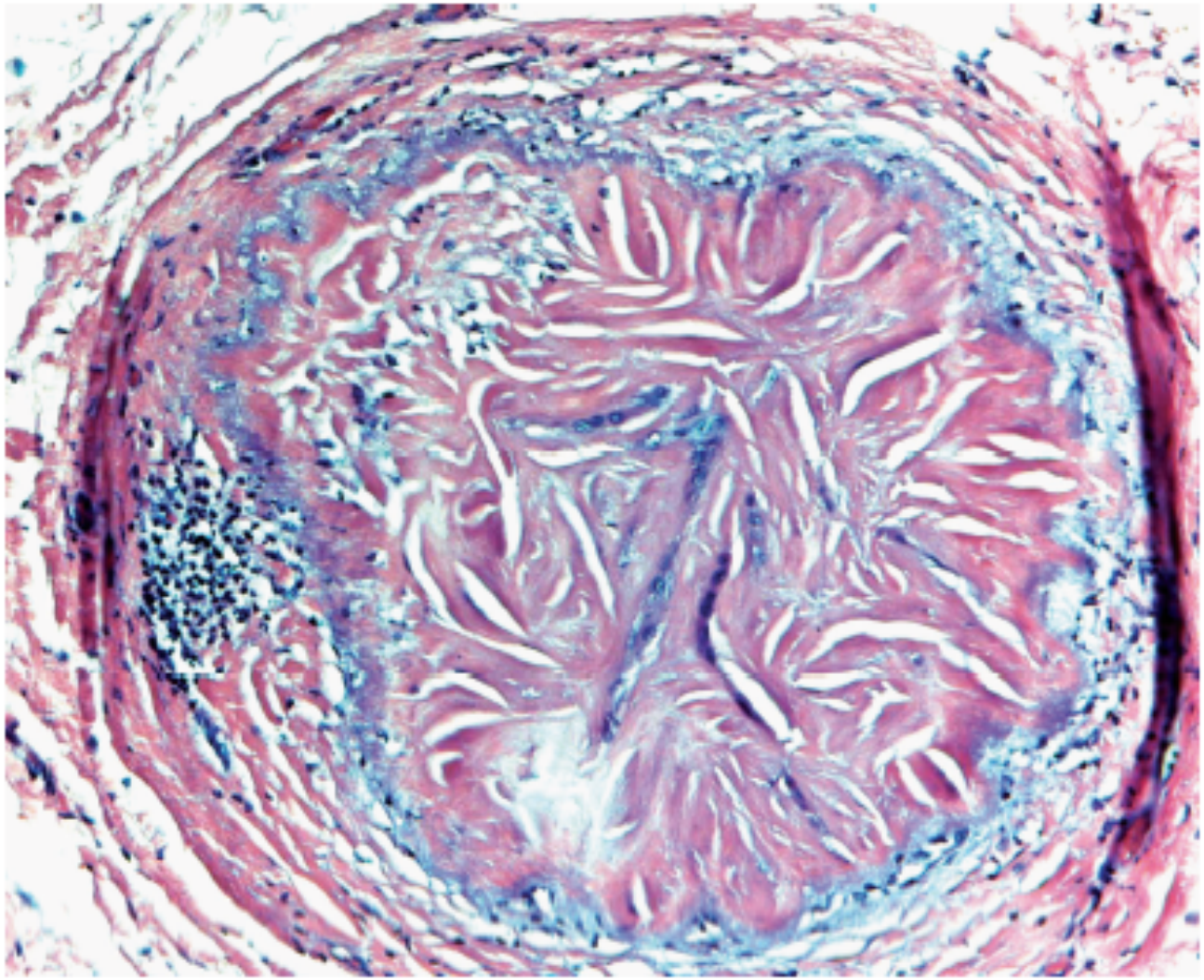
Extralobular ducts lesion:

- Variably sized cysts
- Cubic-flat epithelial lining
- No apocrine metaplasia
- Foamy macrophages and amorphous debris
- Periductal inflammation
- Calcifications
- Fibrosis

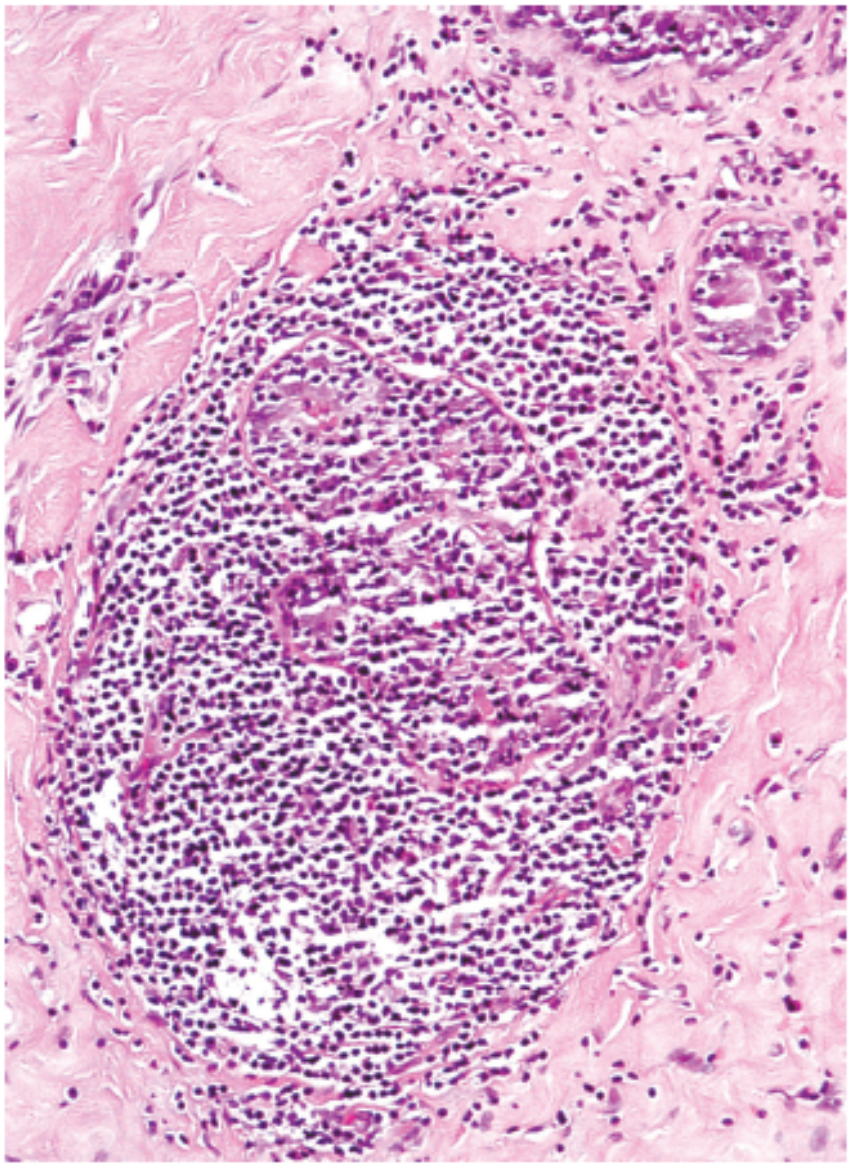
Histiocytes
Plasmacells
Giant cells




Residual duct
Inflammatory cells
Necrotic debris
Normal duct



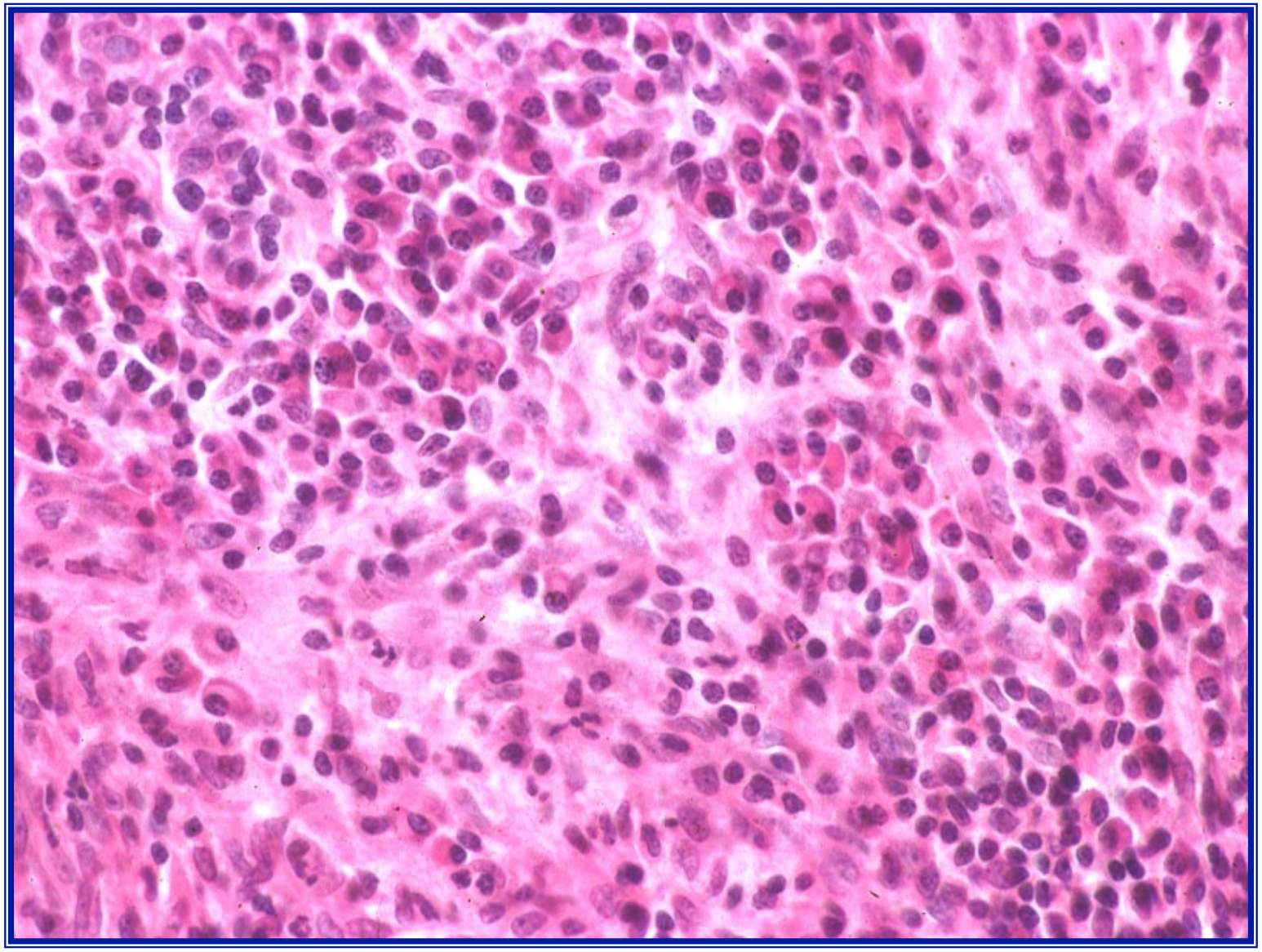
Obliterative mastisis: completely obstructed duct with fibrous plaque



Lobular inflammatory infiltration (lymphocytes)

Breast pathology

- Mastitis
  - → Plasma cell mastitis
    - Monolateral
    - Perimenopausal
    - Sub-acute / chronic
    - Periductal plasma cell infiltration
    - Ductal epithelial proliferation



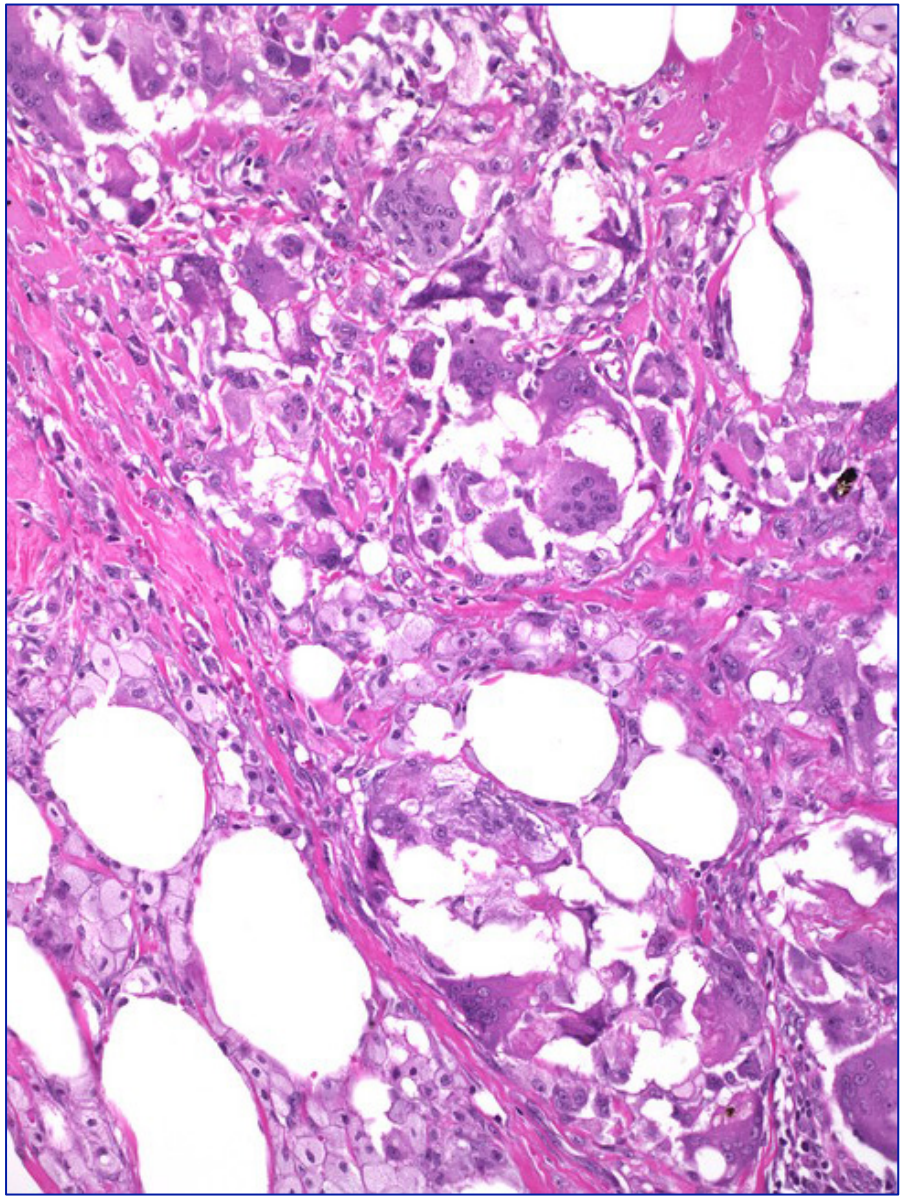
Breast pathology

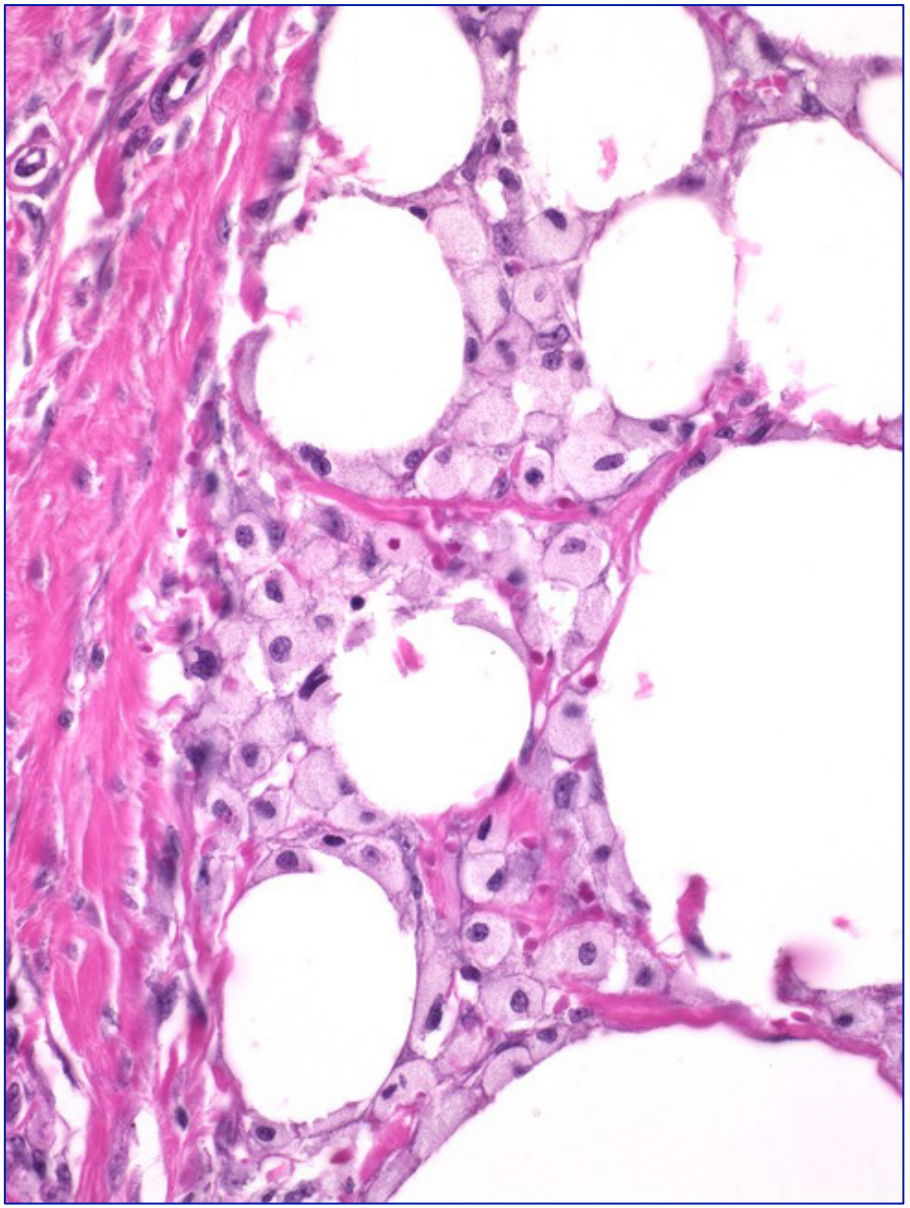
- Mastitis
  - → Tuberculous mastitis
    - Yaoung women, pregnant
    - During secondary (post-primary) TB
    - Miliar, nodular, cold abscess, galactophoritis
    - Caseating granulomas
    - Reactive axillary lymphadenitis

Breast pathology

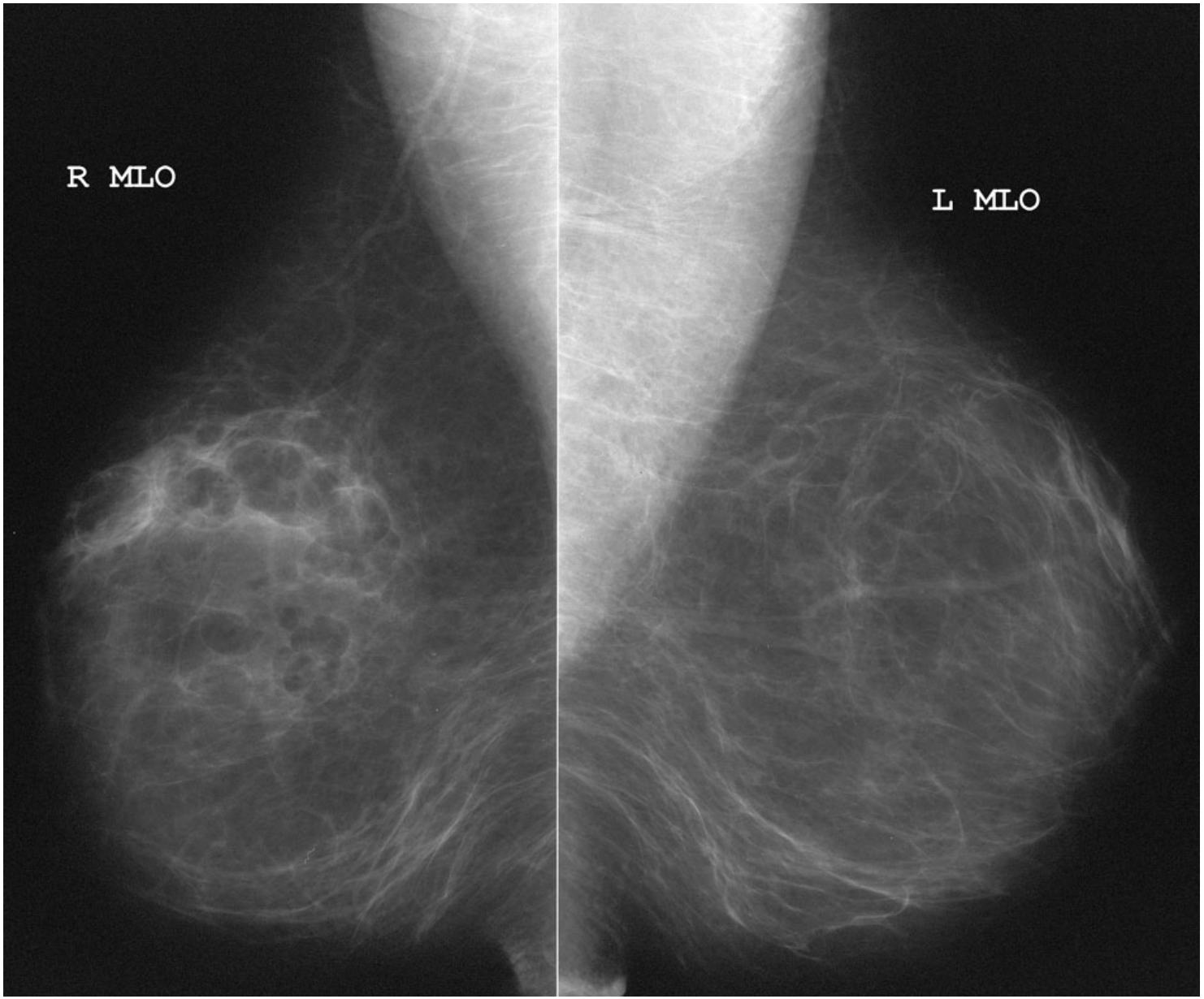
- Mastitis
  - → Liponecrosis & lipogranulomatosis
    - Mature/older women
    - Post-traumatic o post-operatory
    - Sub-acute, chronic
    - Areolar or sub-areolar
    - Fibrous, poorly demarcated plaque
    - Foamy macrophages, foreign body giant cells

Liponecrosis/granulomatosis





Liponecrosis/granulomatosis



Breast pathology

- Breast neoplasms
  - → Real increase in west countries
  - → Favoured by reduced breast-feeding
  - → Increasingly detected by screening
  - → Associated with hyper-oestrogenism
  - → Rare in hereditary conditions (BRCA1-BRCA2)

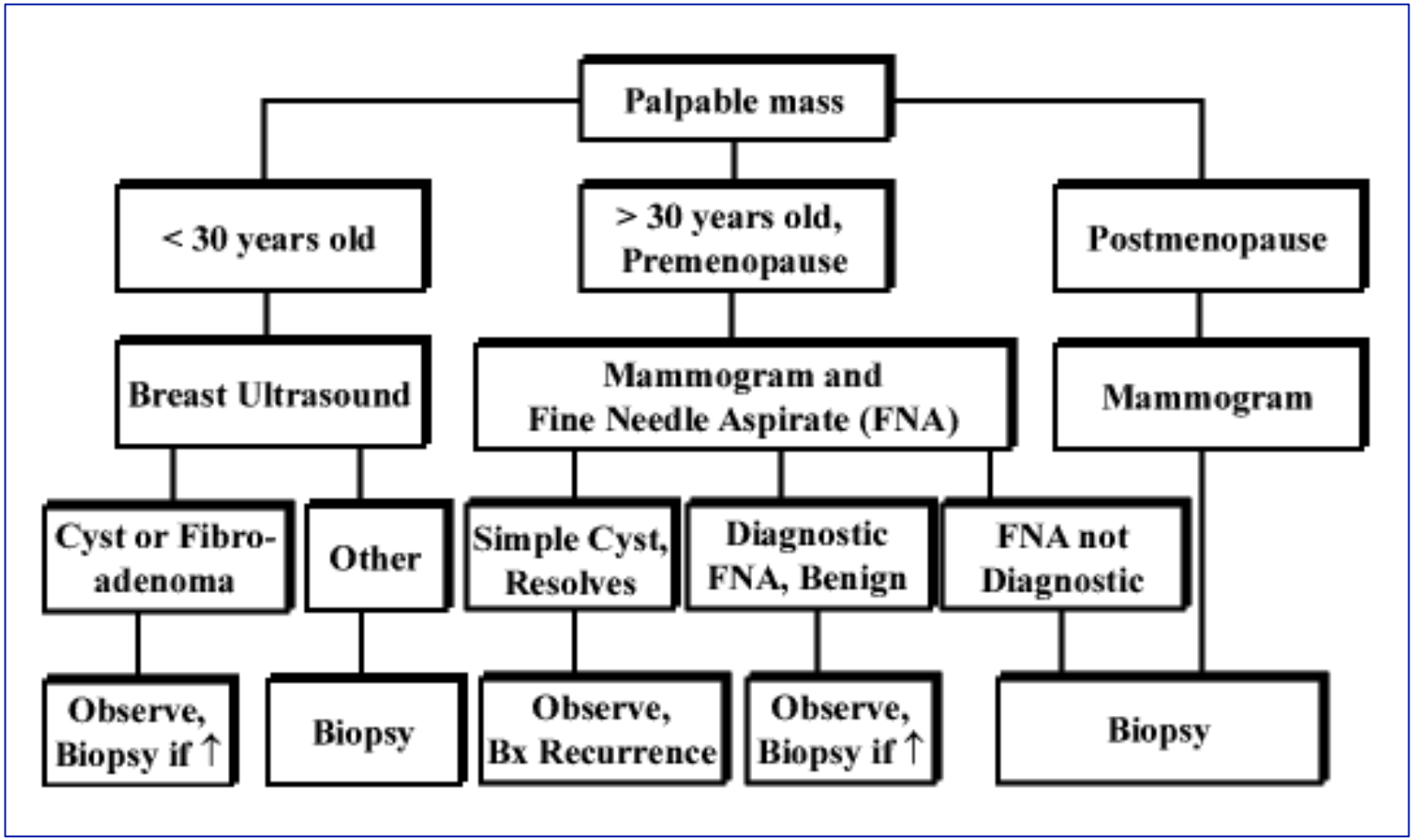
Breast neoplasms

- Breast tumour diagnosis
  - → Clinical-radio-pathologic correlations
  - → Sub-centimetric lesions identified
  - → Non-nodular lesions
    - Micro-calcifications
    - Parenchymal "*distorsions*"
  - → Usually asymptomatic

Breast neoplasms

- Screening
  - → Suggested between 25-30 ys. (earlier with familiarity)
  - → Age-related
    - Visit
    - U.S. (younger than 40 ys.)
    - Mammography (older than 40 ys.)
  - → Annual/biennal (in healthy women)

Breast neoplasms

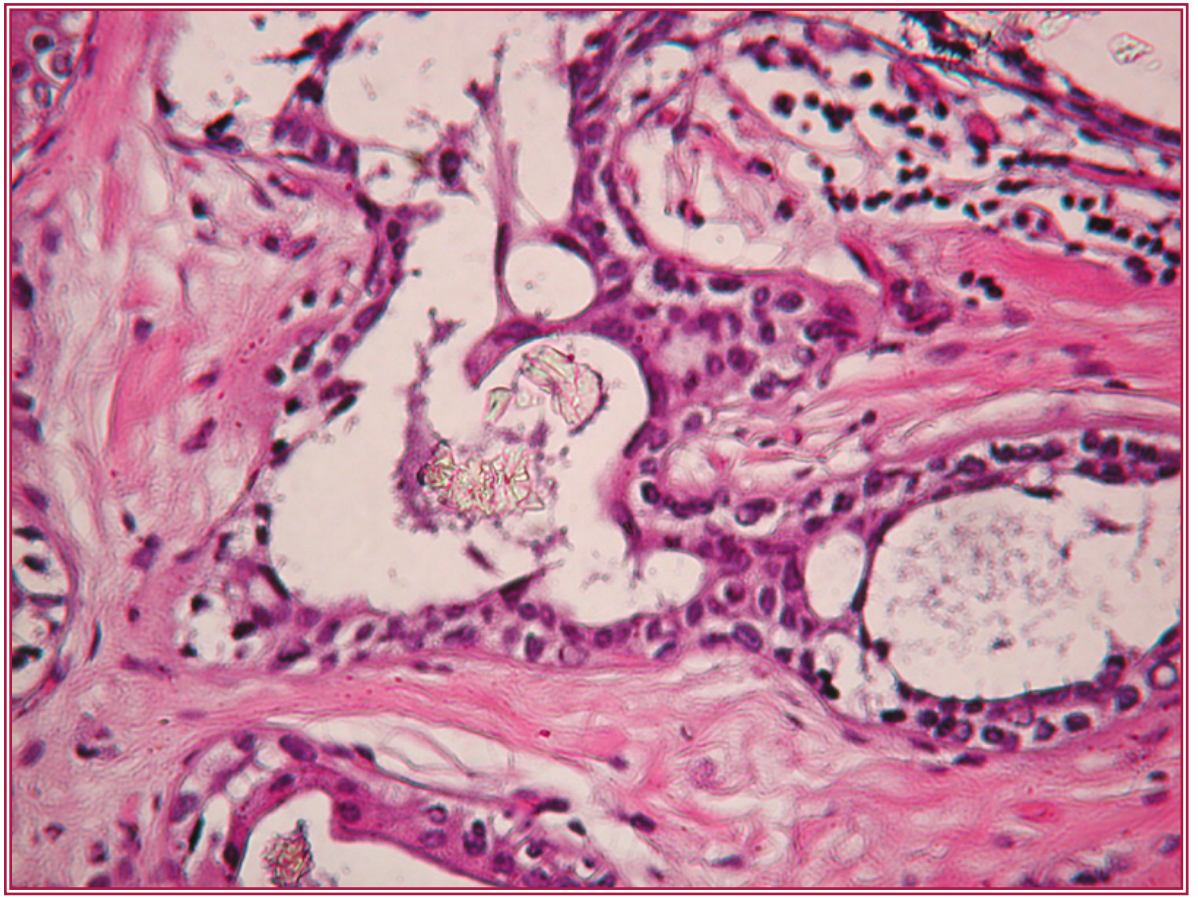


Breast neoplasms

- Screening
  - → Mini-invasive sampling
    - Fine-needle aspiration biopsy (≥ 1 cm nodules)
    - Tru-cut (Parenchymaldistorsions, neo-adjuvant tx)
    - Mammotome (microcalcifications)

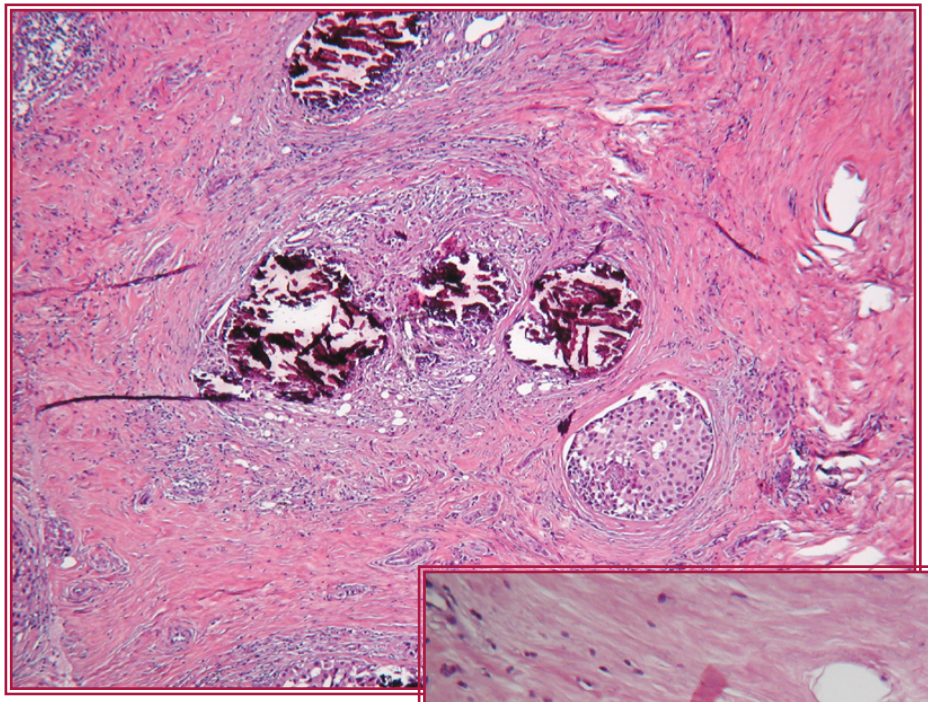
TYPE 1 MICROCALCIFICATIONS

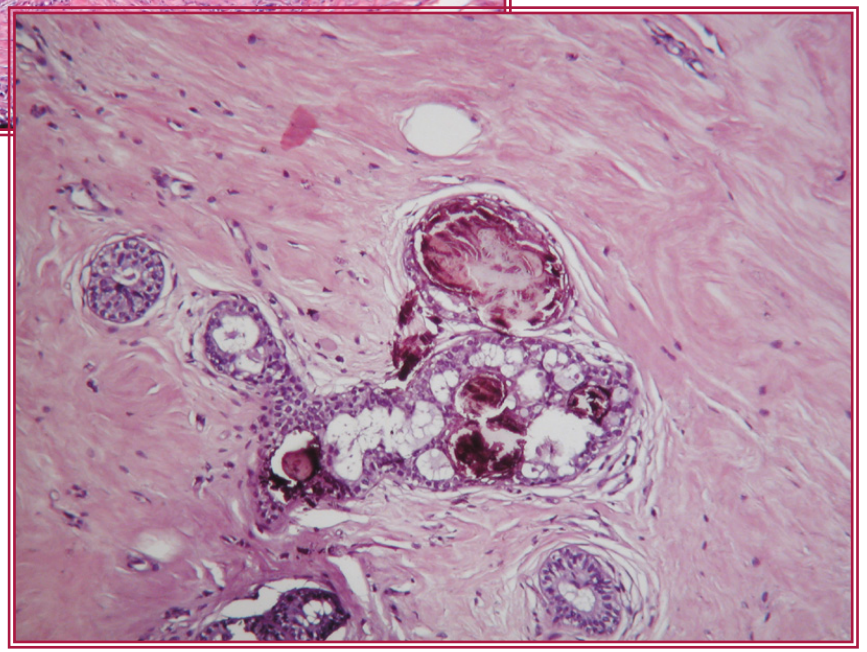
Calcium oxalate, non-tingible, bi-rifrangent under polarized light, associated with benign lesions



TYPE 2 MICROCALCIFICATIONS

Calcium phosphate, basophilic, non birifrangent





Associated with both benign and malignant lesions

Clinico-pathological correlations

SOLID NODULES

- Fibroadenoma
- Phyllodes tumour
- Adenoma
  - Tubular
  - Ductal (niplle)
  - Lactating
  - Pleomorphic
- Adenosis tumour

CYSTIC NODULES

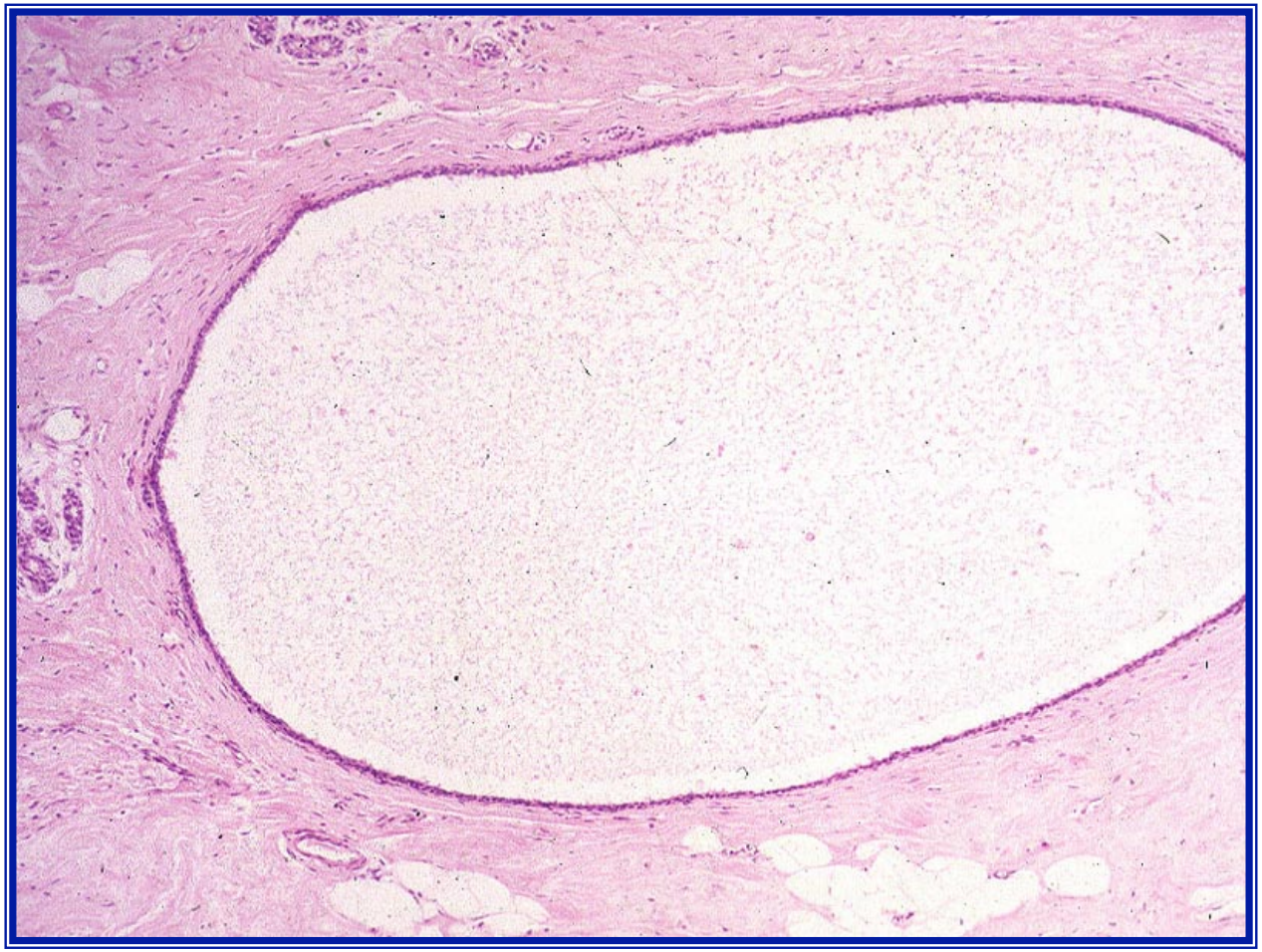
- Solitary cyst
- Duct ectasia
- Intraductal papilloma
- Fibrocystic disease

NON DEMARCATED LESIONS

- Fibroadenomatous hyperplasia
- Sclerosing lobular hyperplasia

SOLITARY CYST

Diameter> 10mm
Flat epithelial lining
Apocrine changes, scattered papillary projections



Fibrocystic disease

Very frequent, young women

- Dense breasts
- Bilateral
- Cysts and parenchymal distorsions
- Cyclic modifications (peri-menstrual)
- Painful tension (mastodinia)

Unrelated to breast cancer!

Fibrocystic disease

Non-proliferative changes

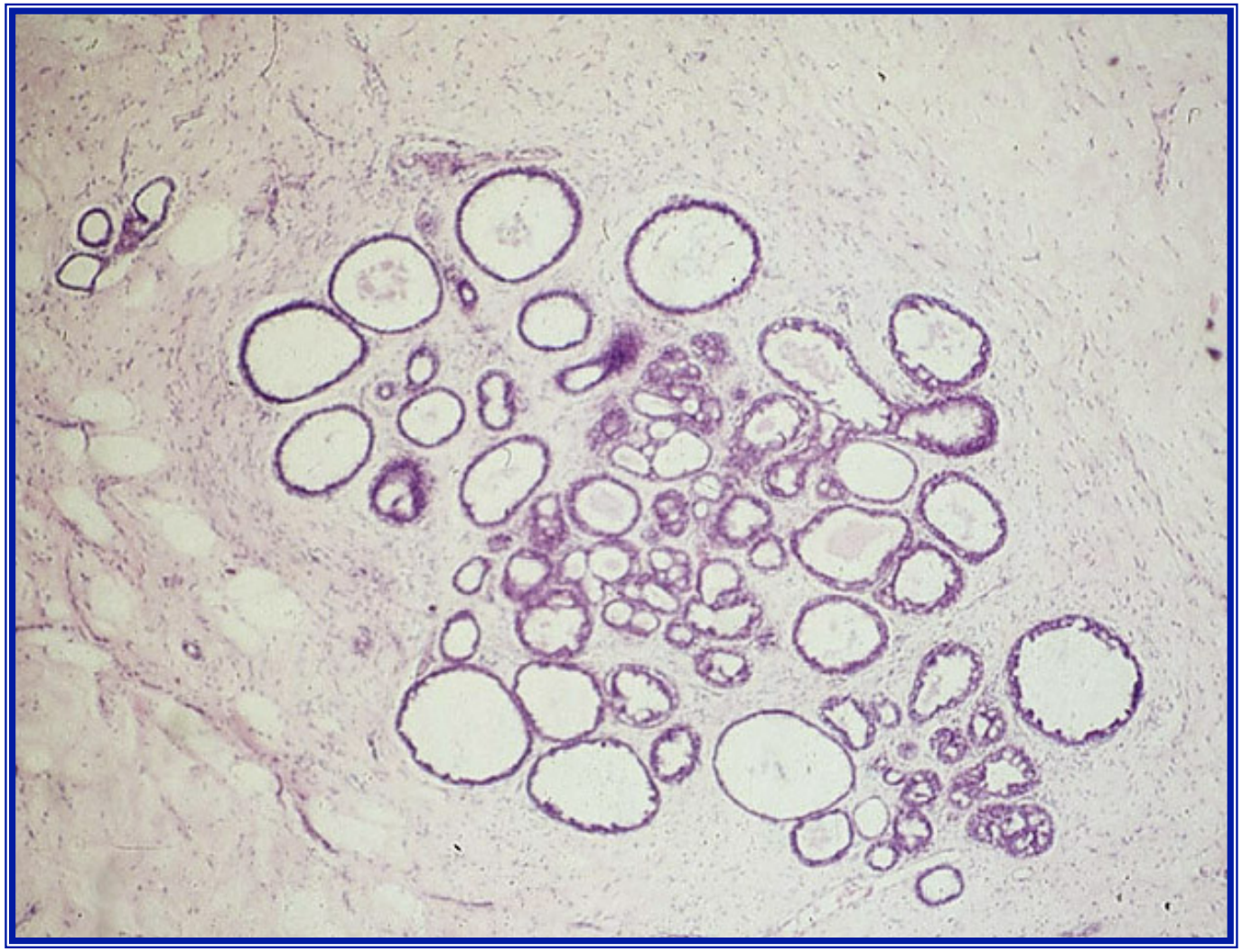
- Inflammation
- Fibrosis
- Duct ectasia/cysts
- Apocrine changes

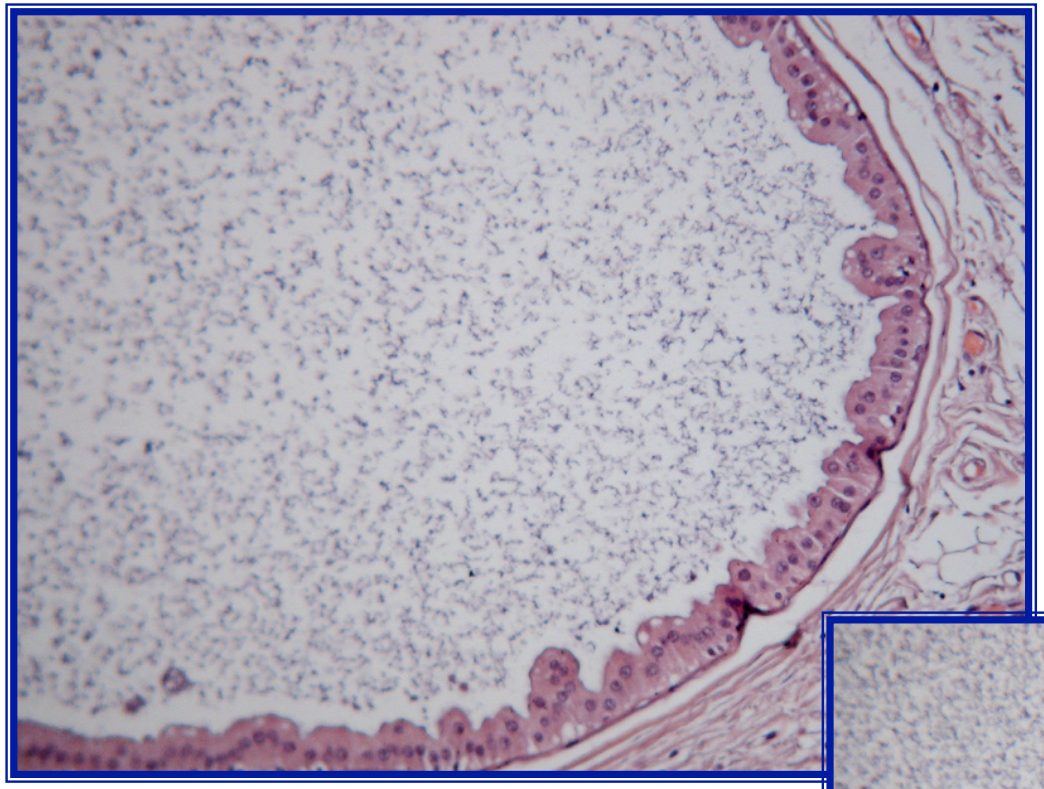
Proliferative changes

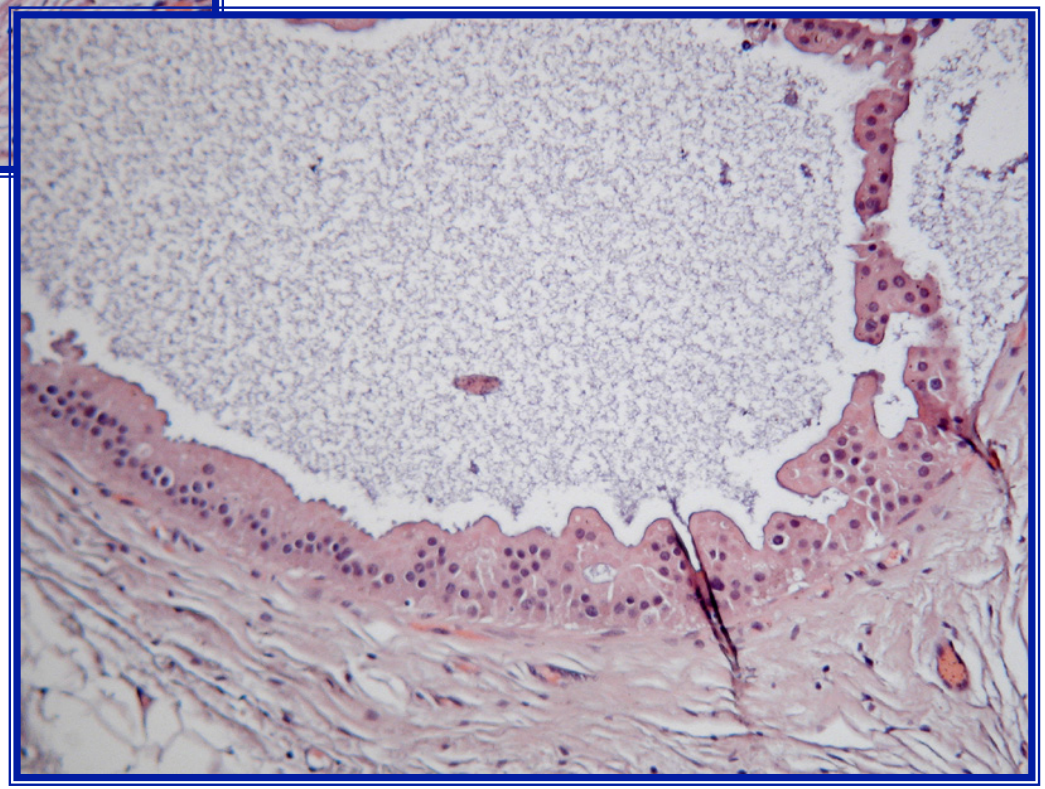
- Adenosis (acinar/lobular proliferation)
- Epitheliosis (ductal epithelial proliferation)
- Papillomatosis (intra-ductal projections)

Fibrocystic disease

Early lobular changes, progressive dilation, cyst formation, apocrine changes



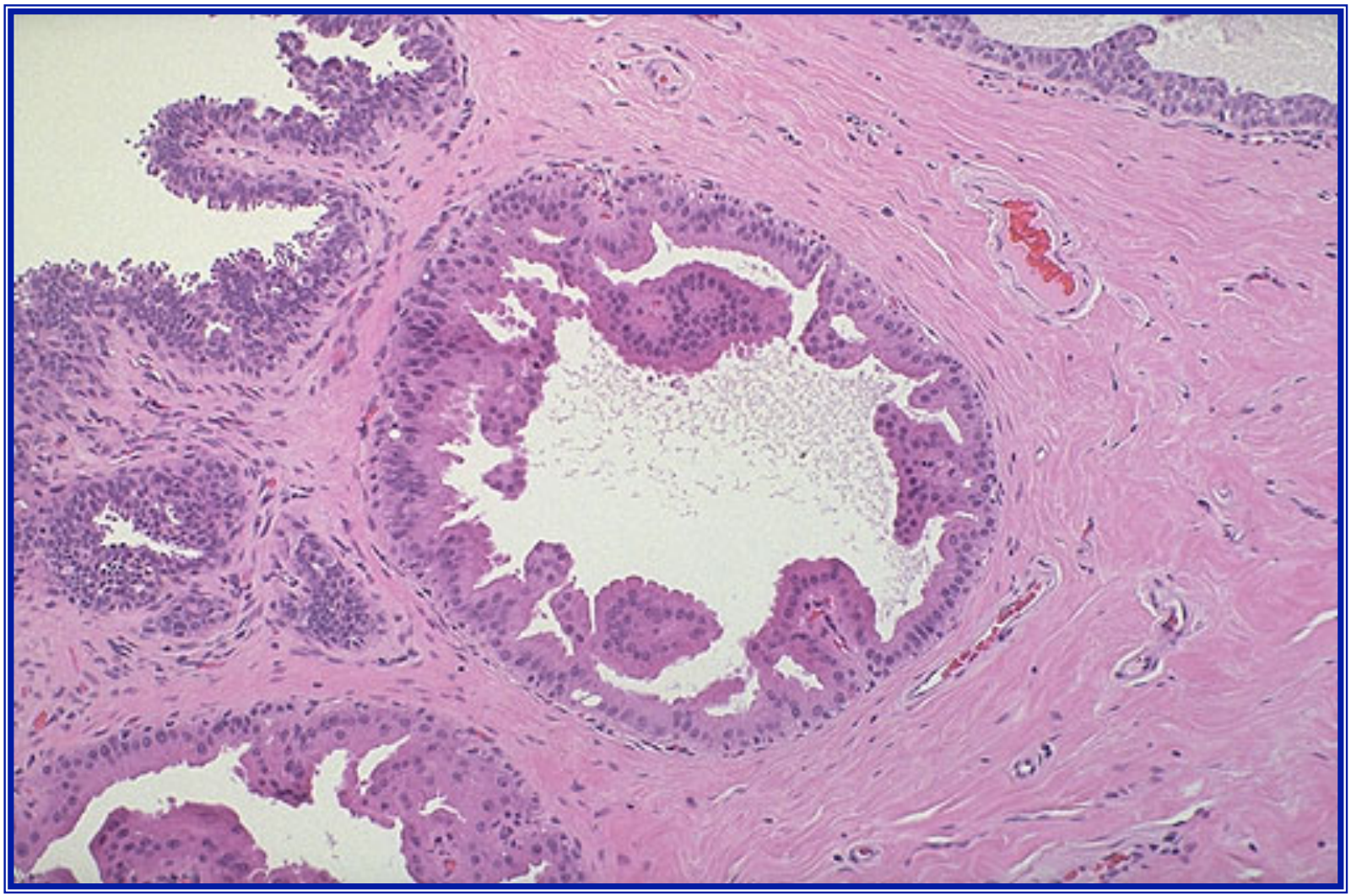




Apocrine changes

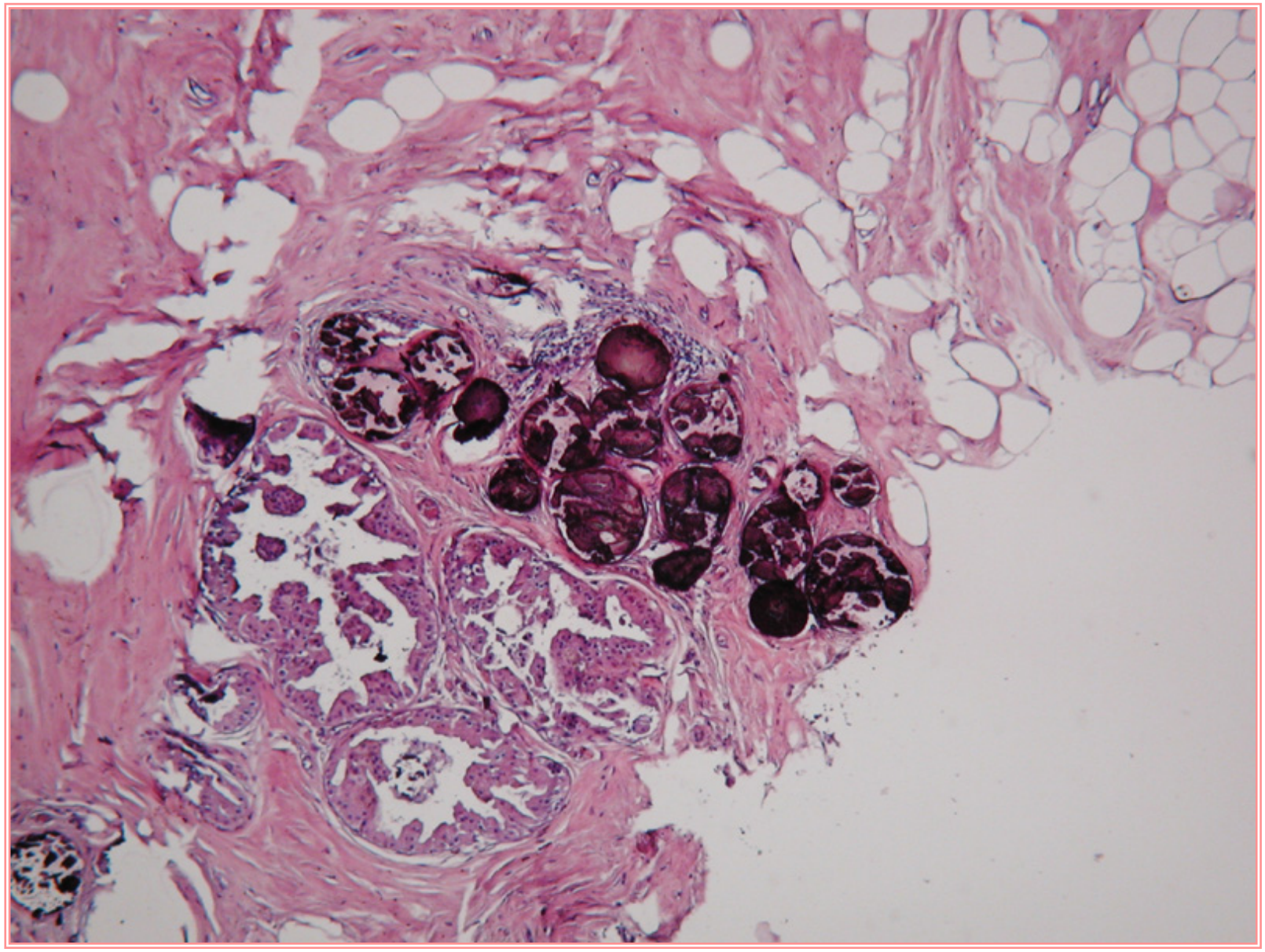
Fibrocystic disease

Papillary projections



Fibrocystic disease

Microcalcifications



Fibrocystic disease

Hyperplastic changes

Adenosis (increased acini within ductules)

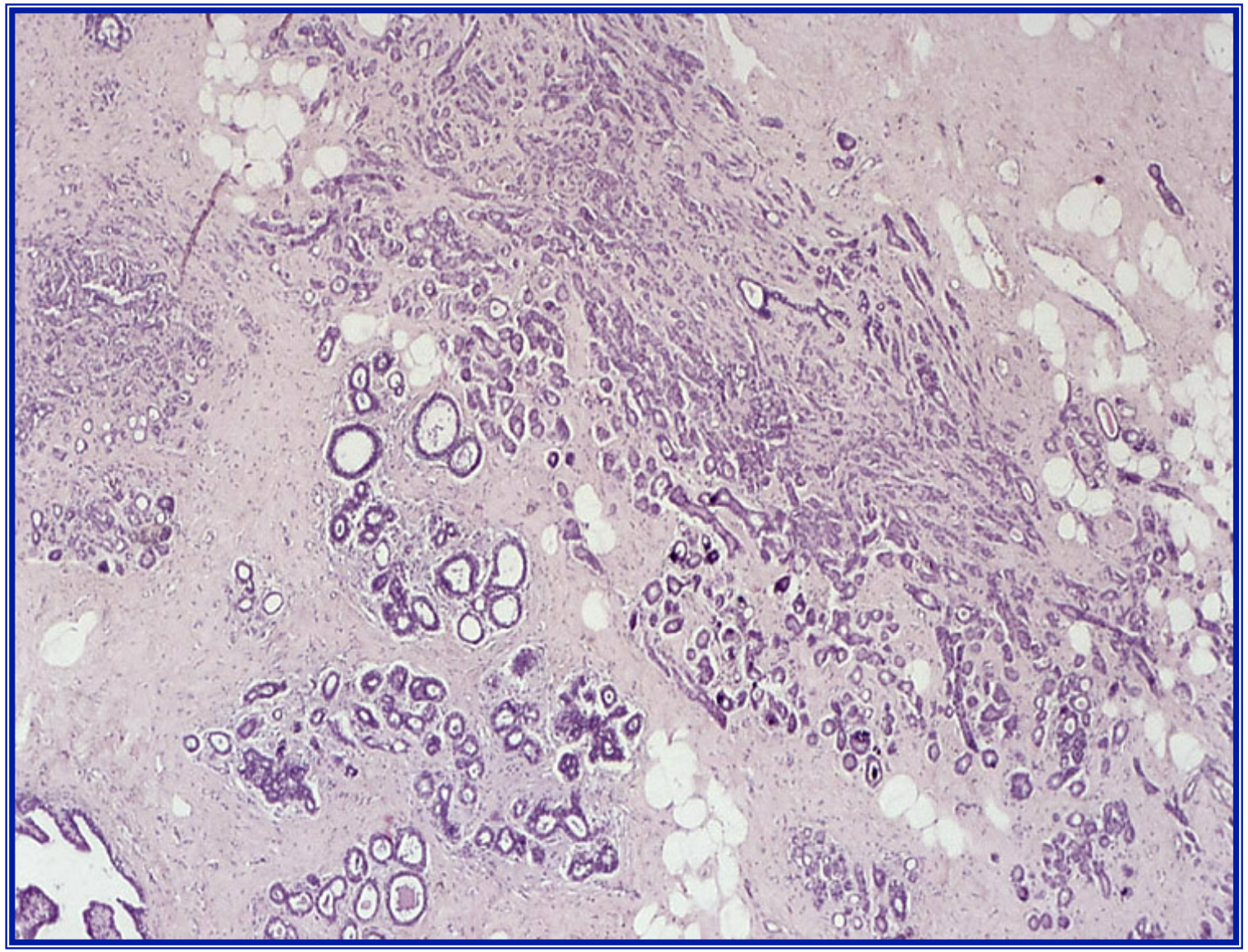
- Florid
- Sclerosing
- Blunt duct
- Microglandular
- Pseudo-tumoral (adenosis tumour)
  - Ductular proliferation
  - Epithelial + myoepithelial cells (not in microglandular)
  - Virtual or cystic lumina
  - Possible evolution in radial scar

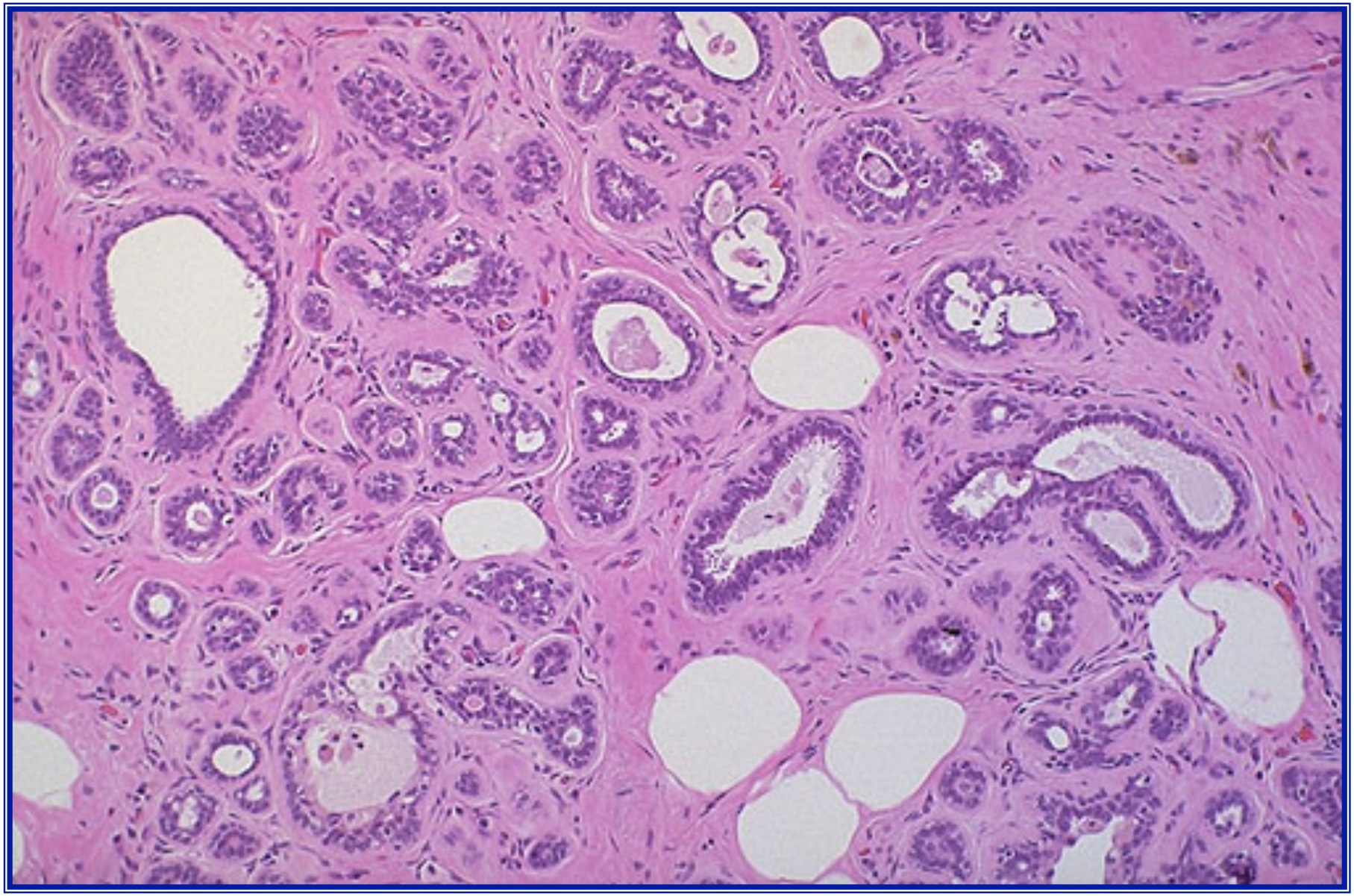
ADENOSIS

Increased number of acini with lobular expansion

Sclerosing adenosis

- Architectural distorsion
- Acinar distension
- Increased collagen stroma
- Central sclerotic focus
- Myoepithelial hyperplasia
- Pseudoinfiltration
- Microcalcifications
- Apocrine metaplasia
- No cytologic atypia

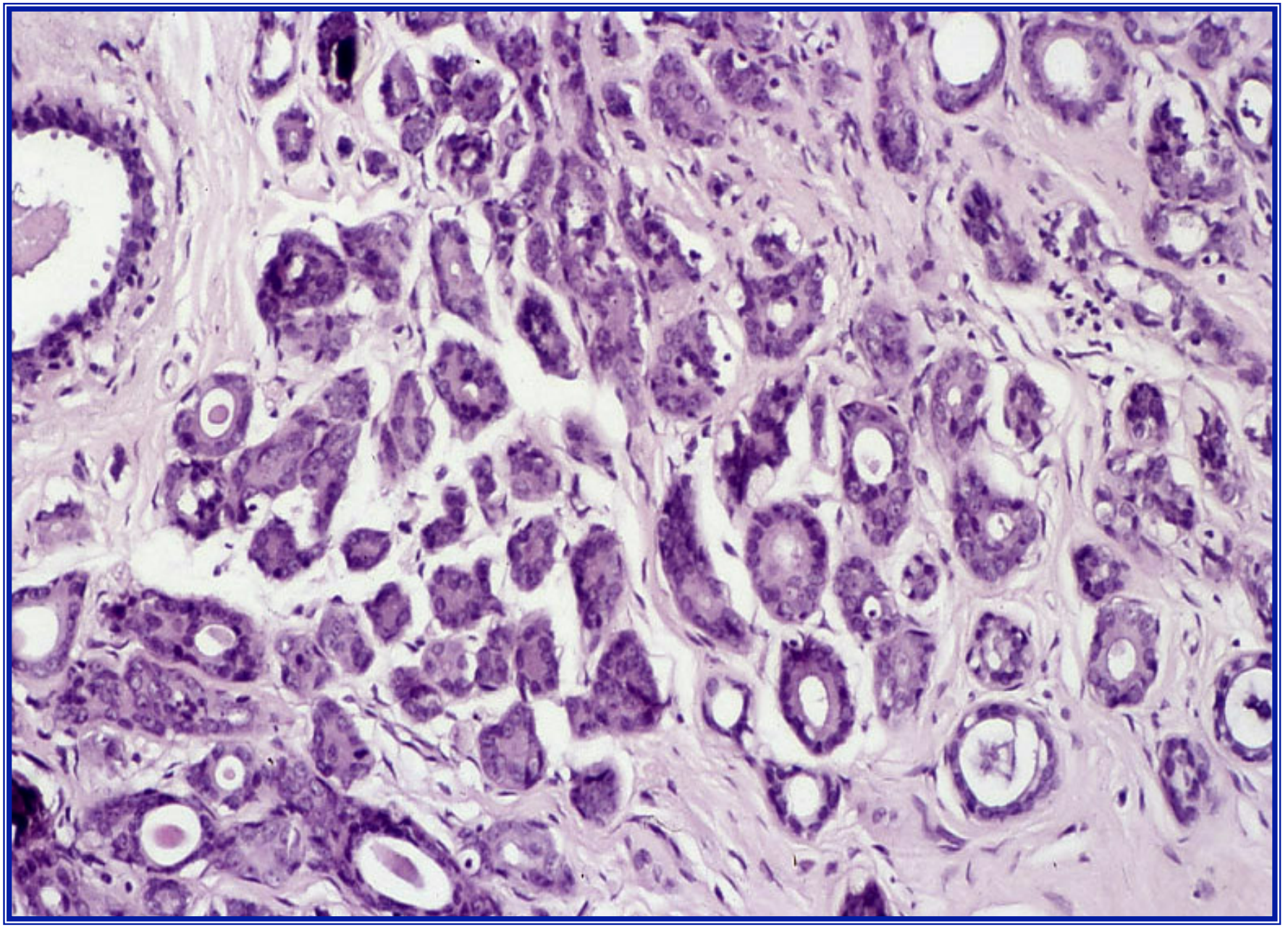


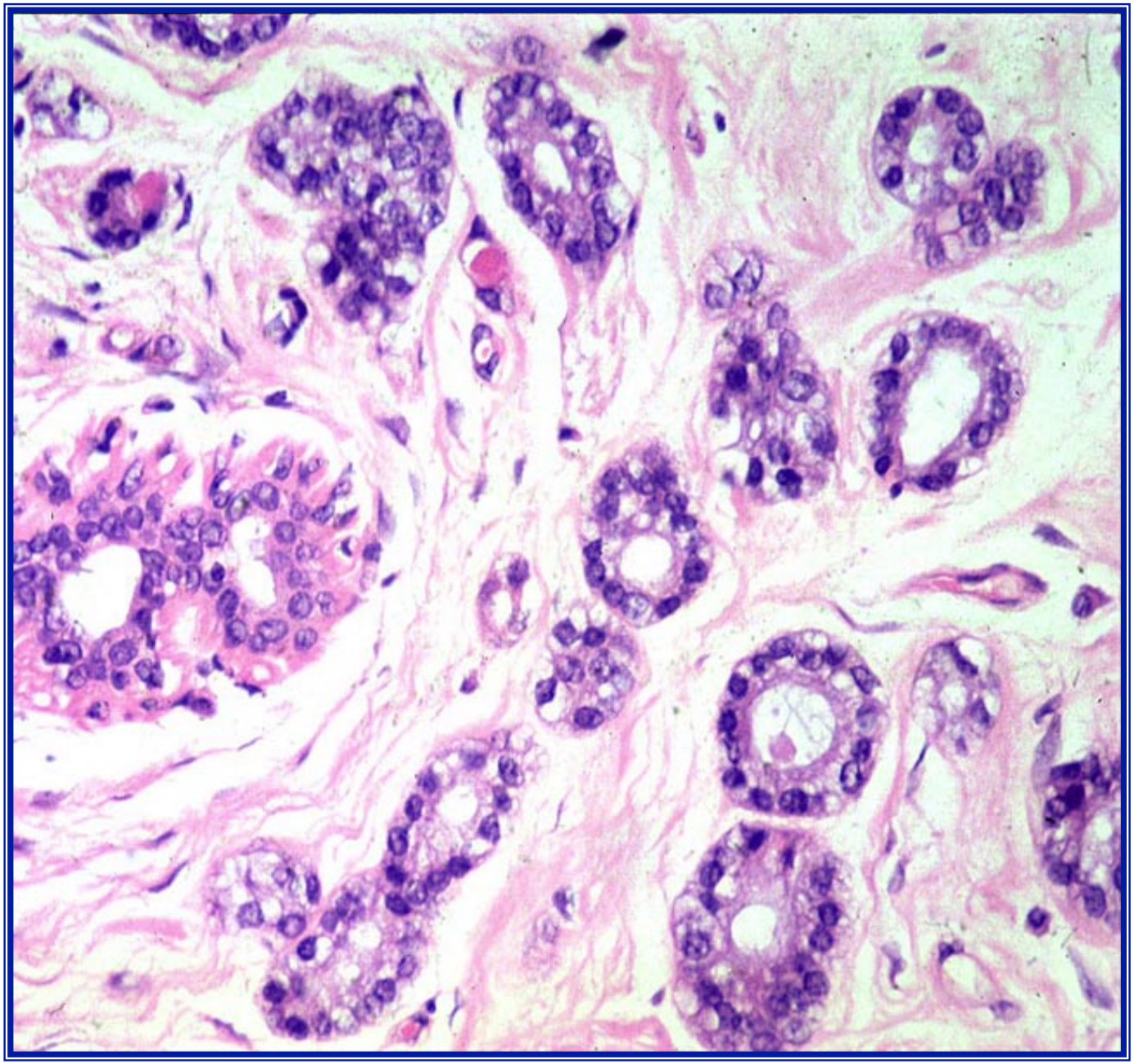


MICROGLANDULAR ADENOSIS

No lobular growth pattern

- Glandular structures with monolayered epithelium
- Pseudoinfiltrative growth in fat tissue
- No myoepithelial cells
- Endoluminal secretion
- Rare atypia or mitosis
- Clear cells

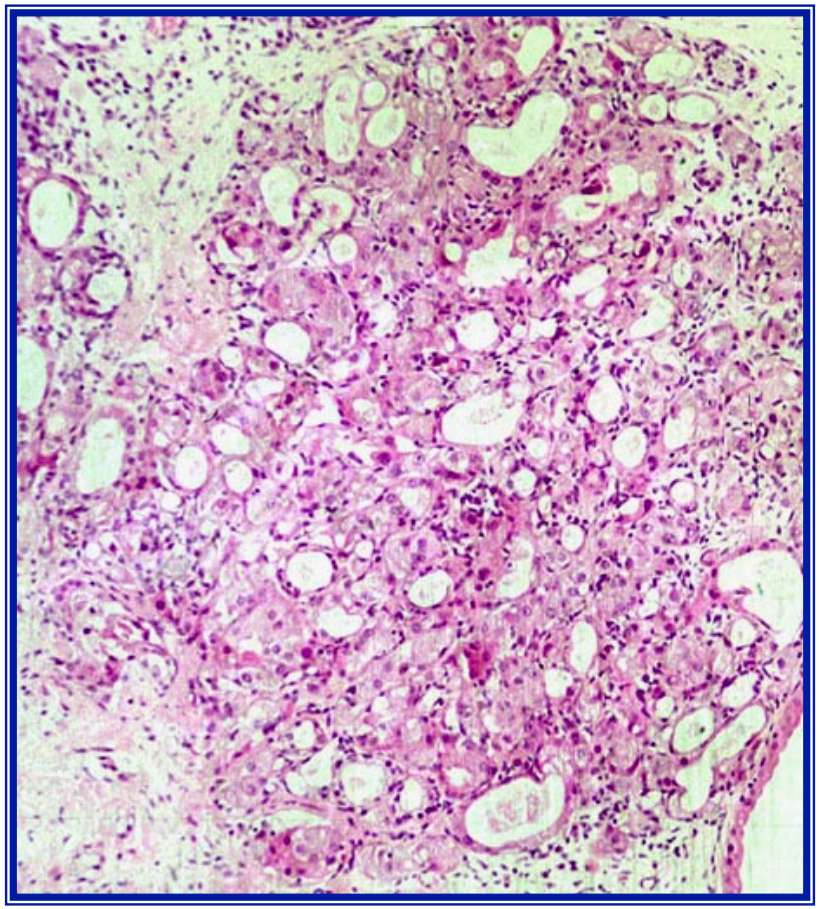


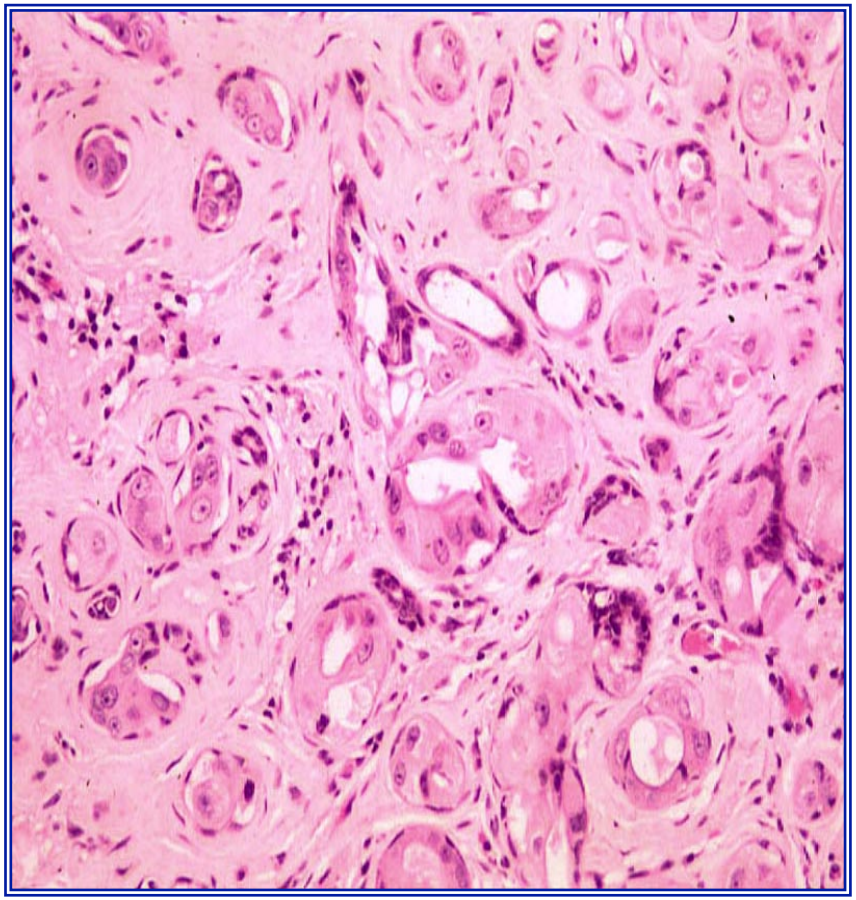


APOCRINE ADENOSIS

Apocrine cell change without cystic dilation

GCDFP + (Gross cystic Disease Fluid Protein)



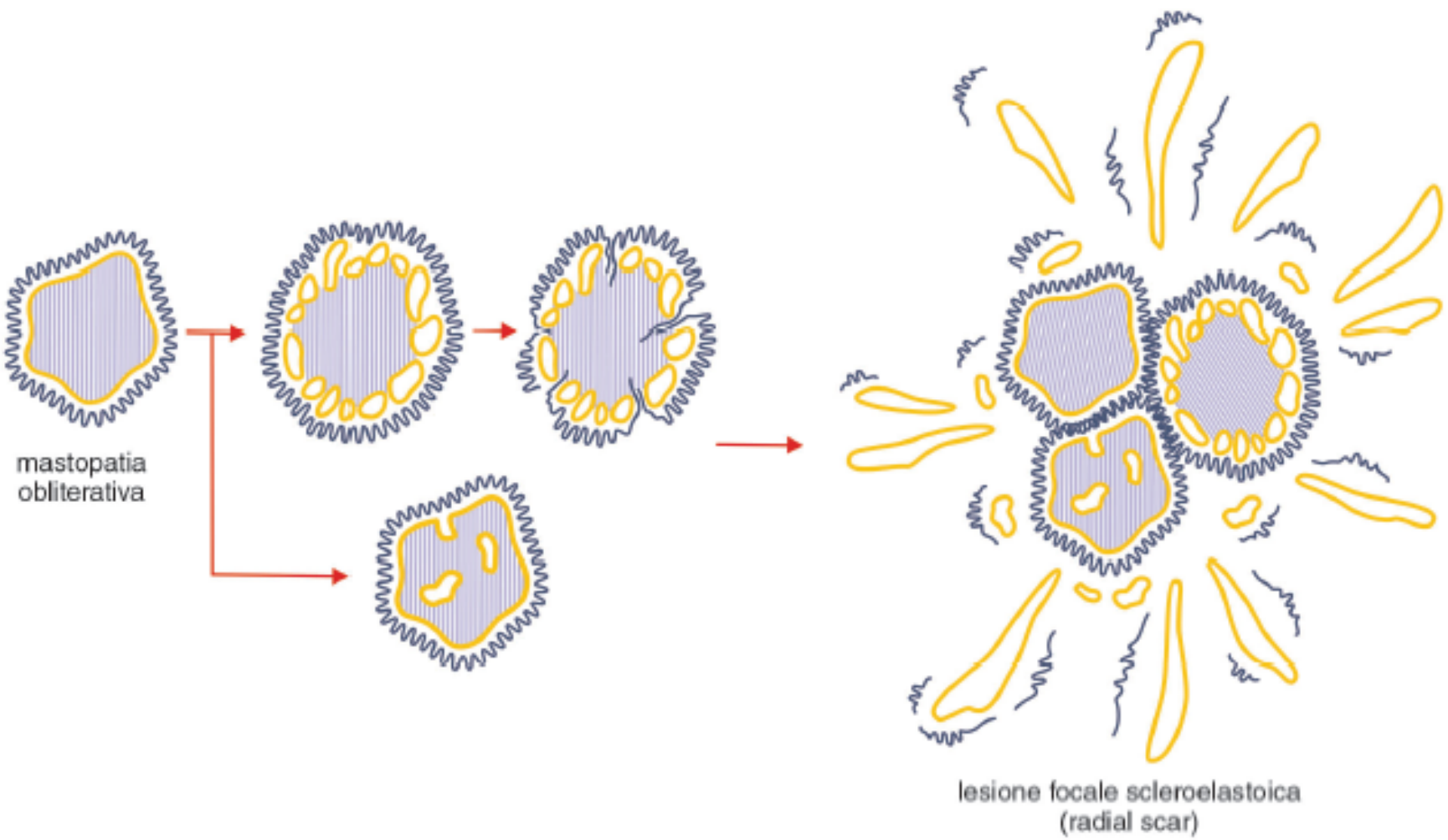


Radial (sclero-elastosic) scar

Small ducto-lobular structures, radiating from central fibrotic core:

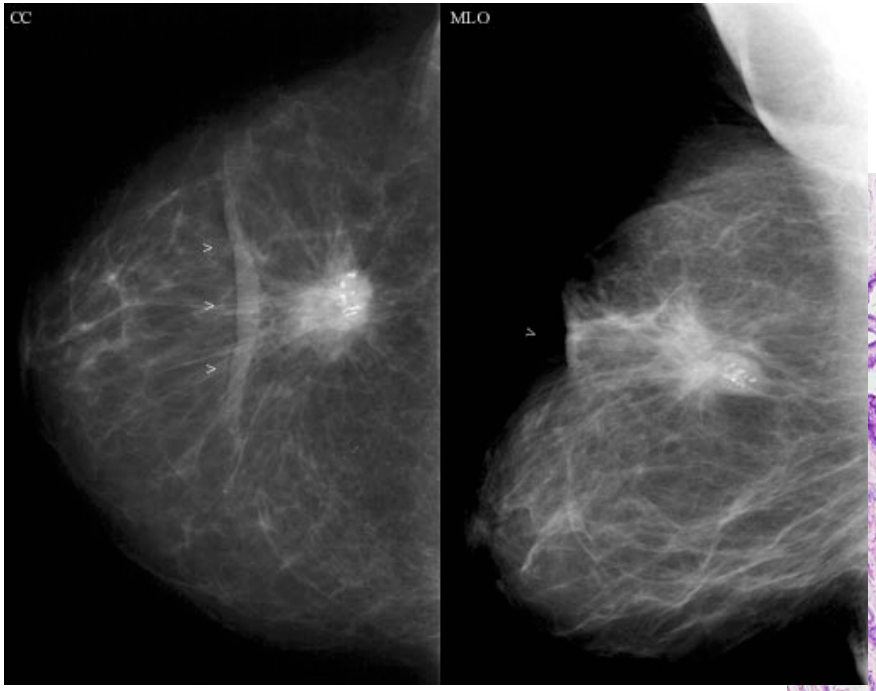
- Circumscribed nodular lesion
- Starry configuration
- < 10mm
- Elongated central tubules
- Epiteliosis & adenosis
- Myoepithelial cells
- Microcalcifications

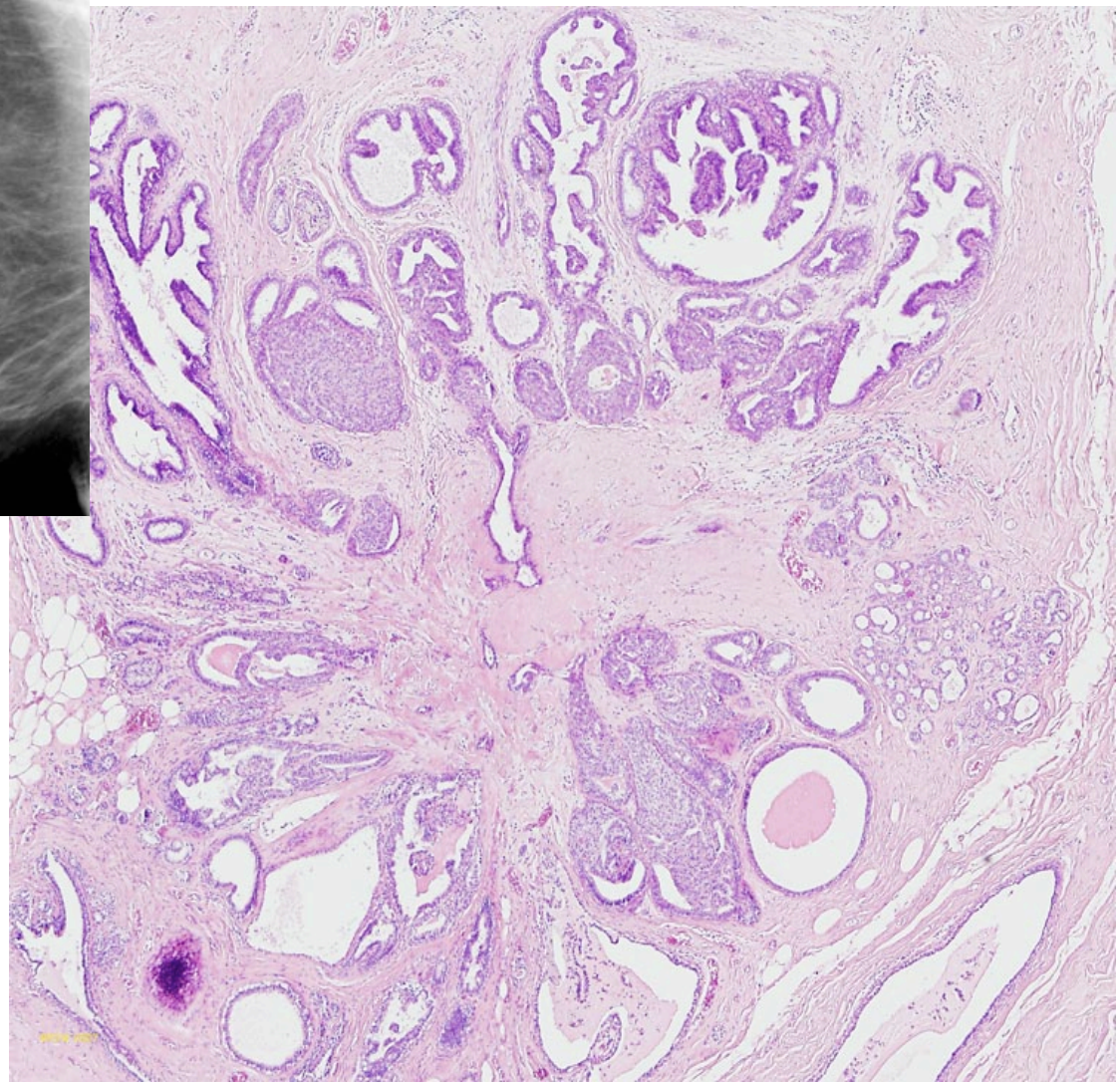
Radial (sclero-elastosic) scar

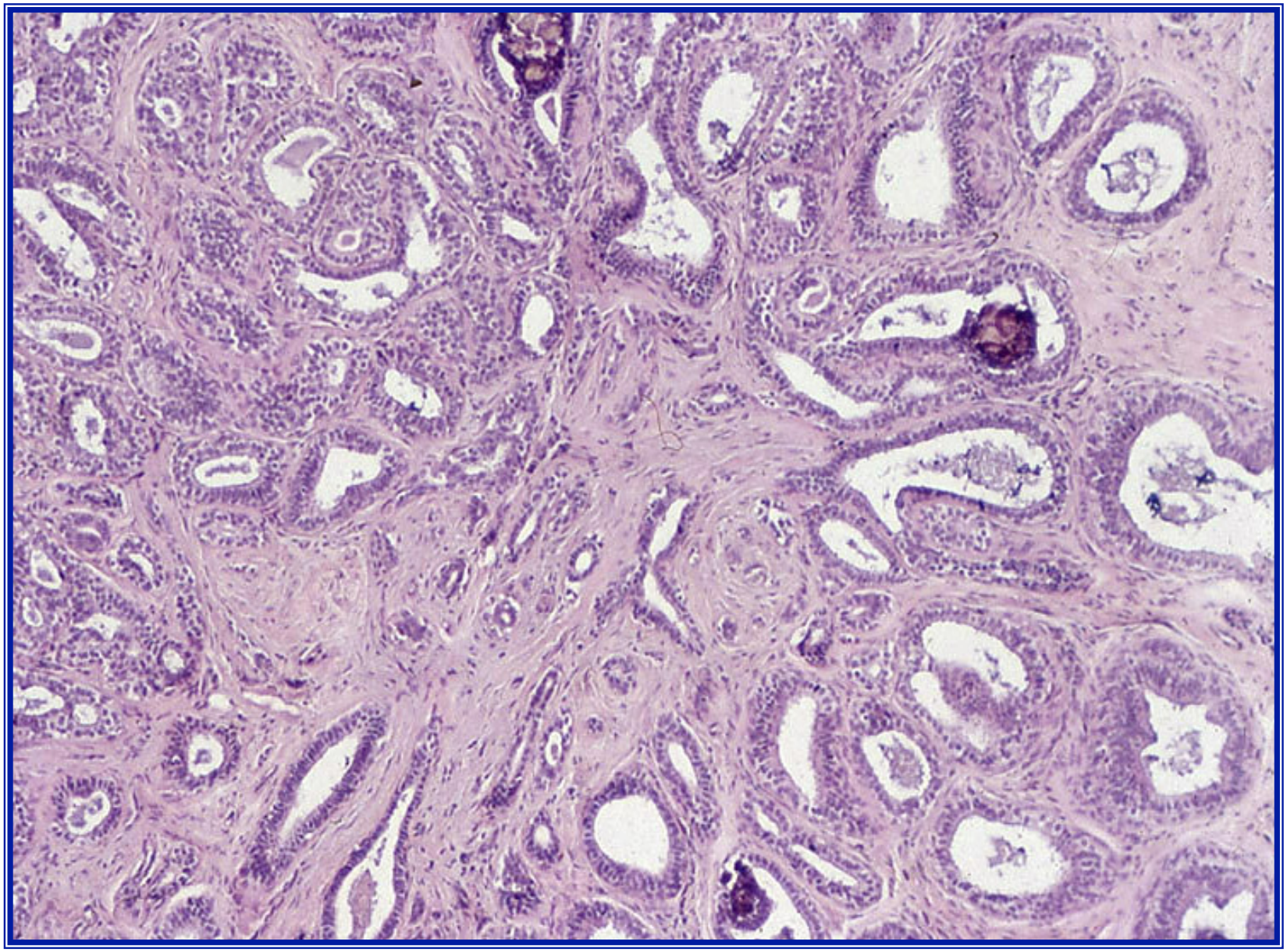


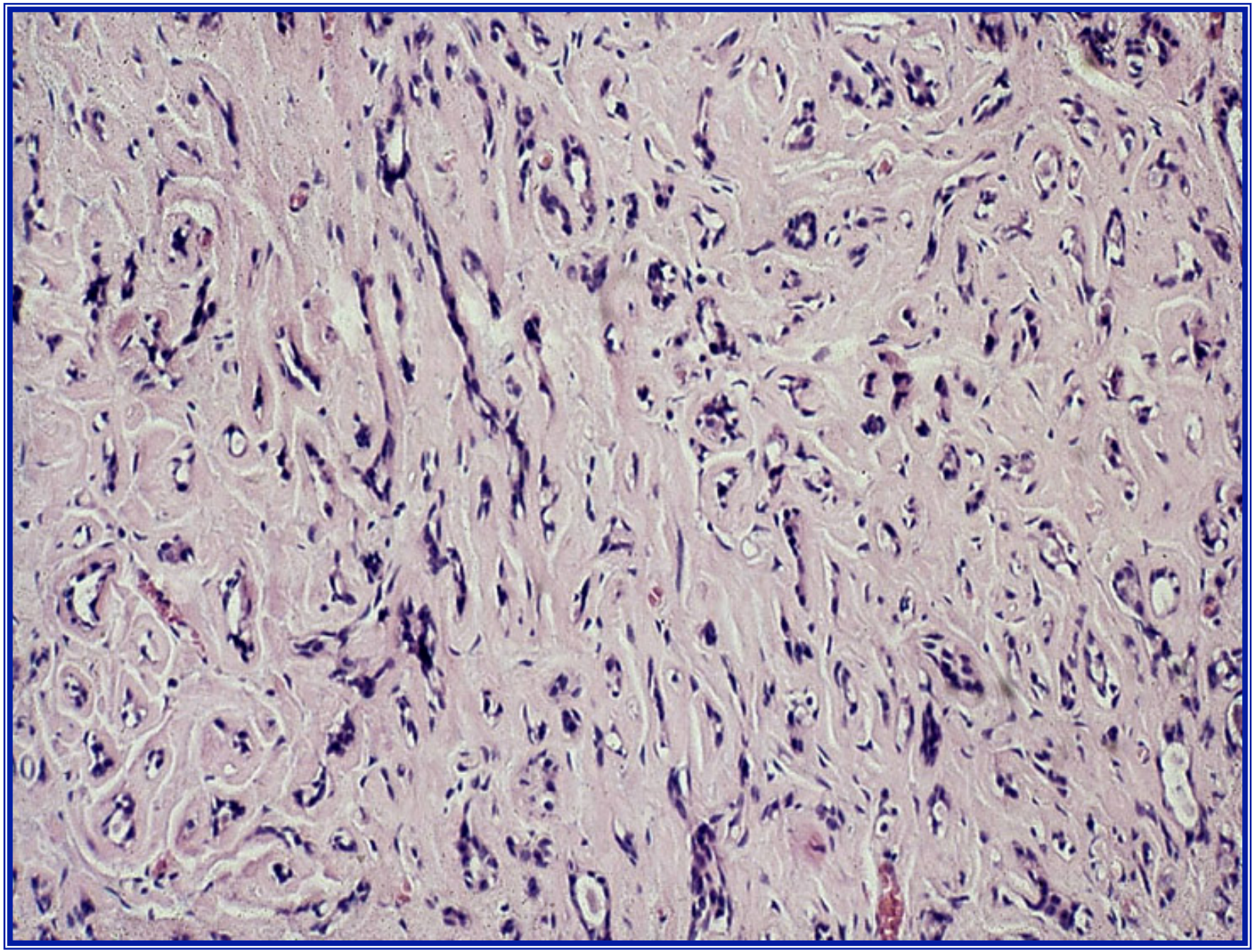
The lesion seem to develop from peripheral tubular proliferation around obstructed ducts

Radial (sclero-elastosic) scar









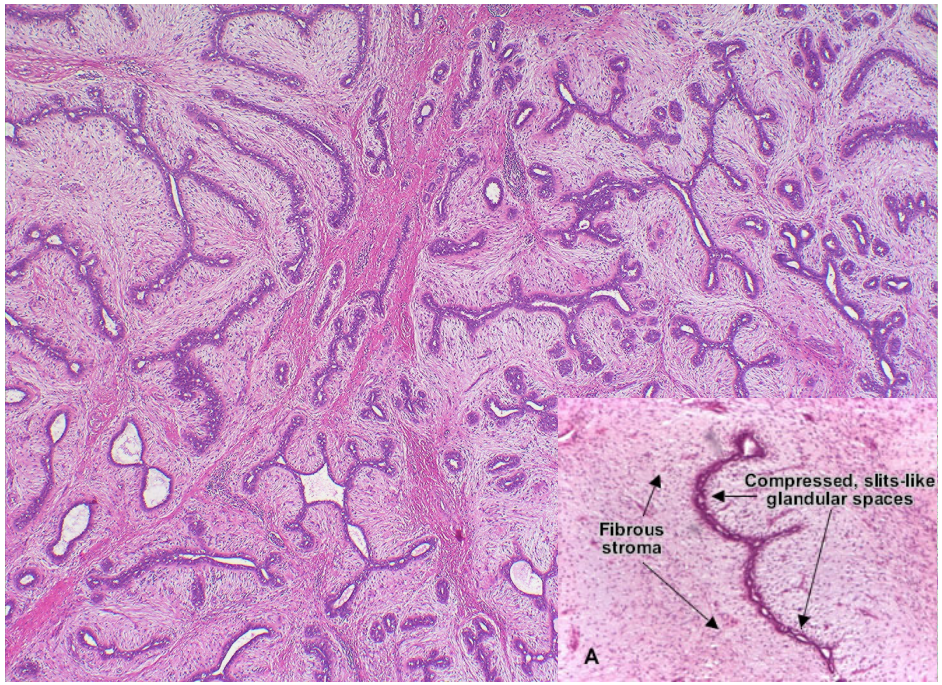
FIBROADENOMA

- Young women (15-25)
- Well-demarcated nodule/s
- Monolaterale, 20% bilateral
- ≤3 cm
- Fibro-elastic consistency
- Calcifications (pop-corn like)

FIBROADENOMA

Fibrous connective tissue

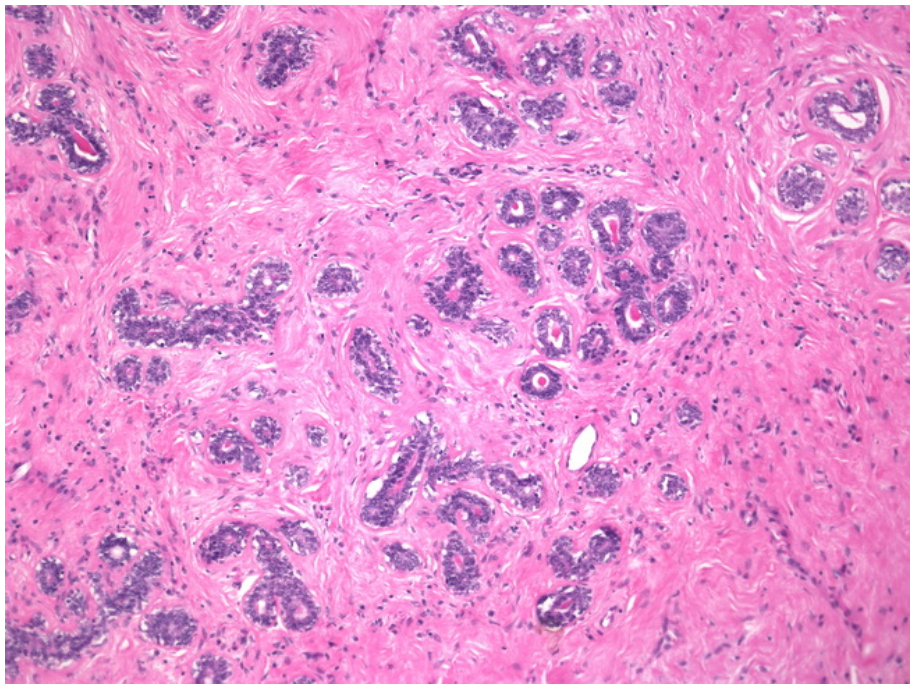
Intracanalicular



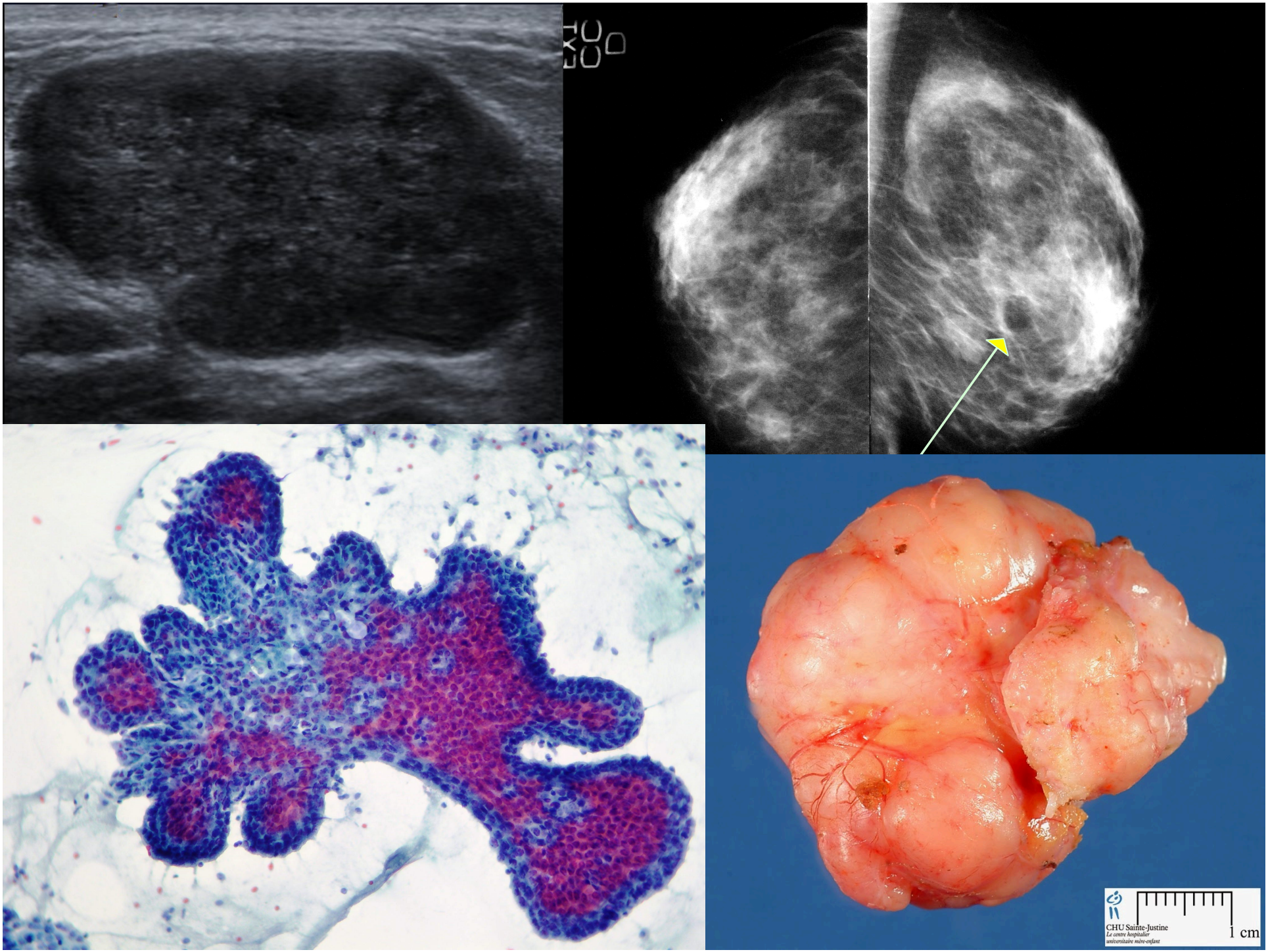
Focal fibrous proliferation compressing the enclosed glandular structures

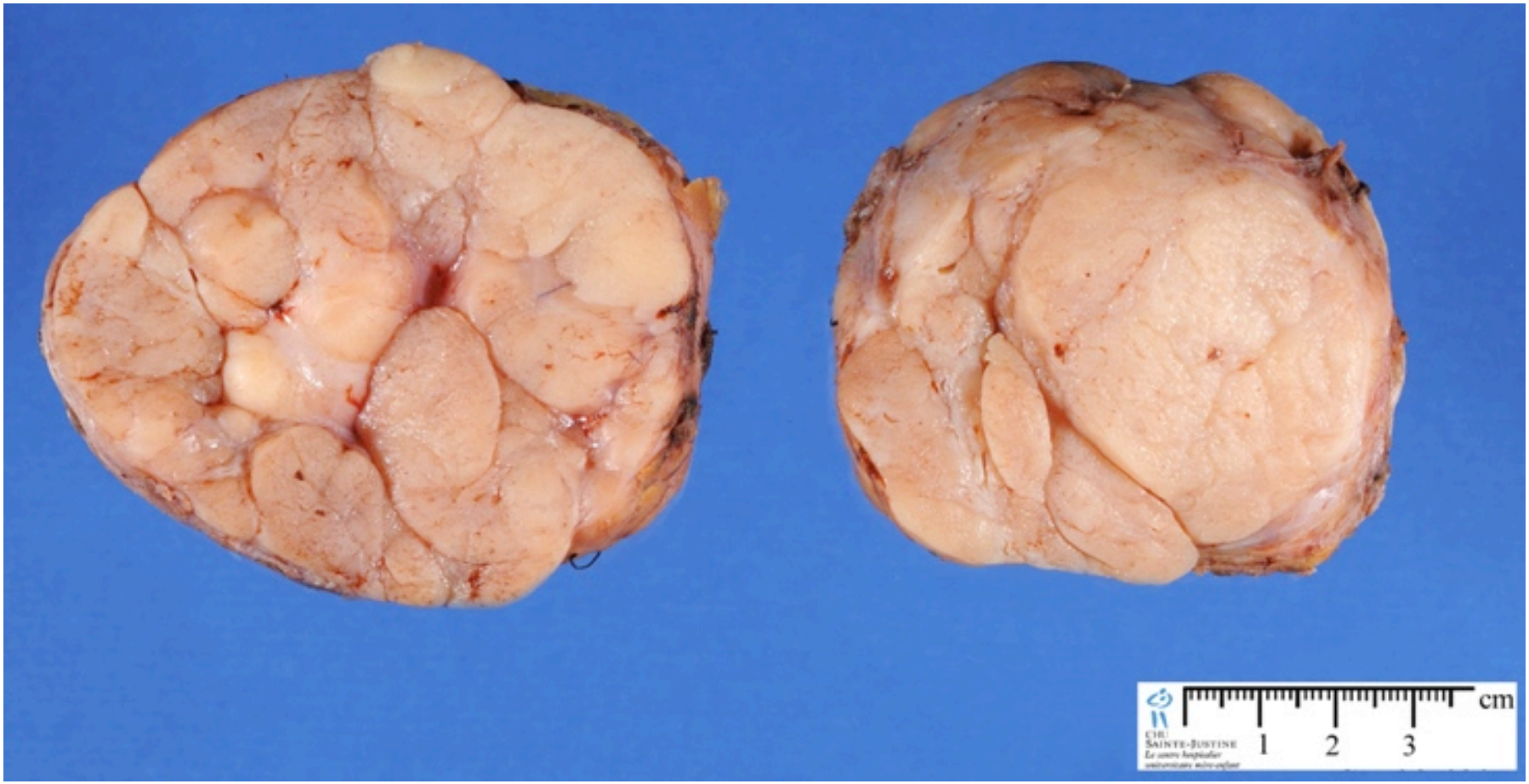
Glandular structures

Pericanicular



Ductular proliferation with preserved rounded profile, and concentric fibrous stroma


CHU Sainte-Justine
Le centre hospitalier
universitaire mère-enfant
1 cm


CHU
SAINTE-JUSTINE
1
2
3
cm

FIBROADENOMA

Epithelial tissue:

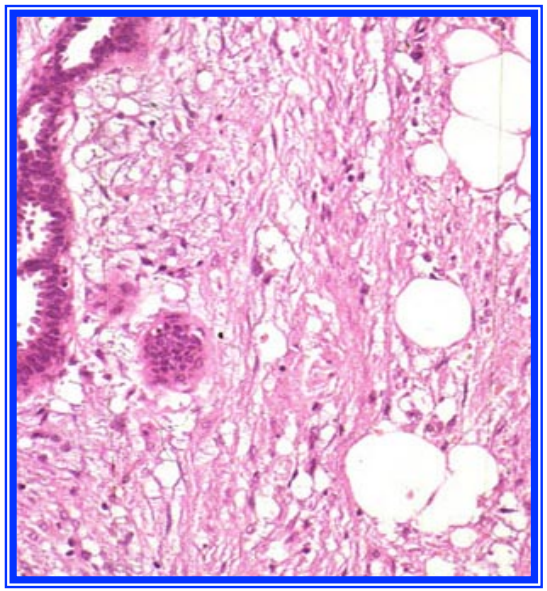
- **Double layered (epithelium & myoephitelium)**
- **Adenosis & epiteliosis**
- **In older lesions** →
  - Hyalinization
  - Calcification
  - Ossification
  - Chondroid metaplasia
  - Epithelial atrophy

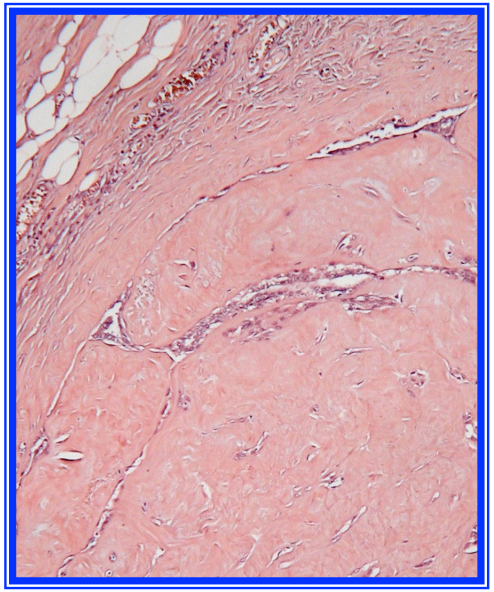
Caveat!
No risk of progression
Atypical hyperplasia & carcinoma in situ may coexist

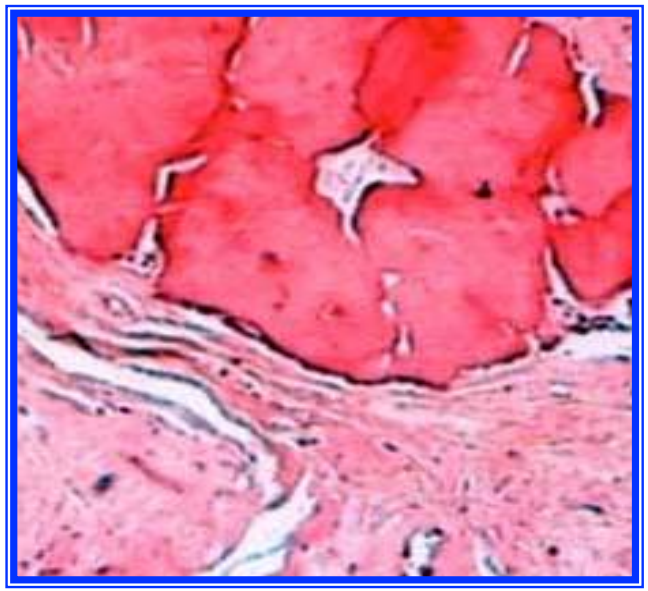
FIBROADENOMA

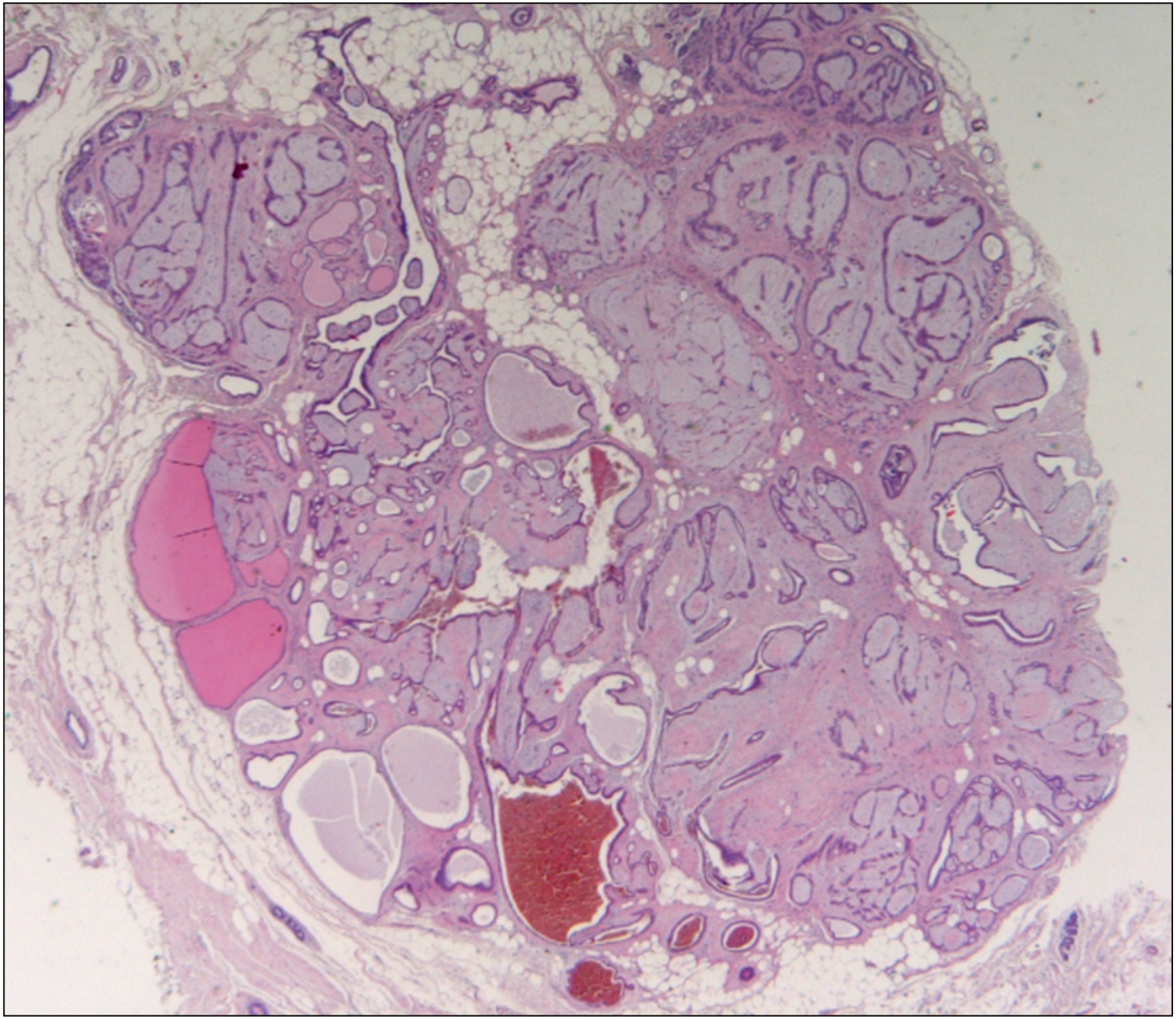
Connective tissue metaplasia

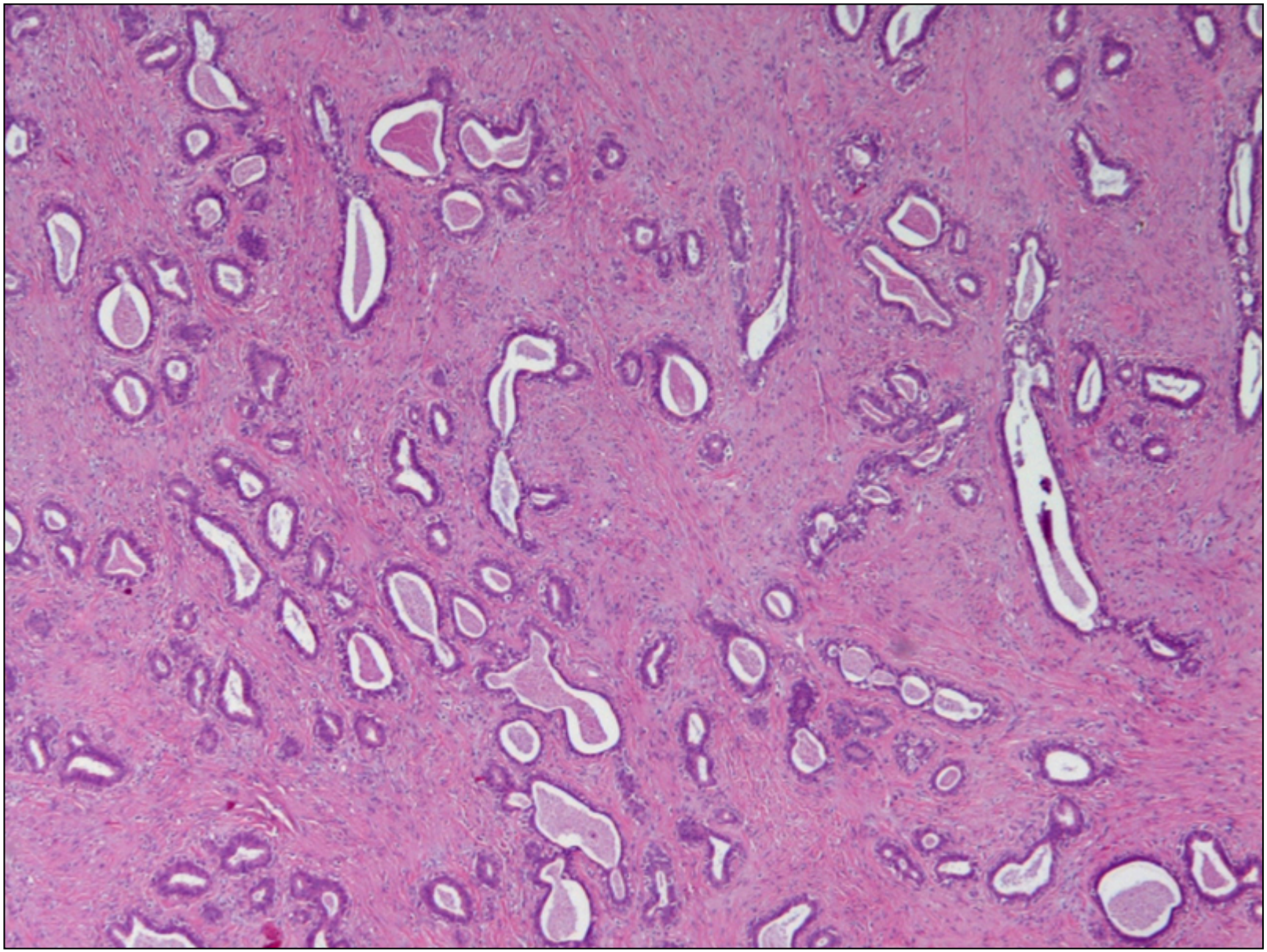
- Fibrous
- Adipose
- Smooth muscle
- Bone

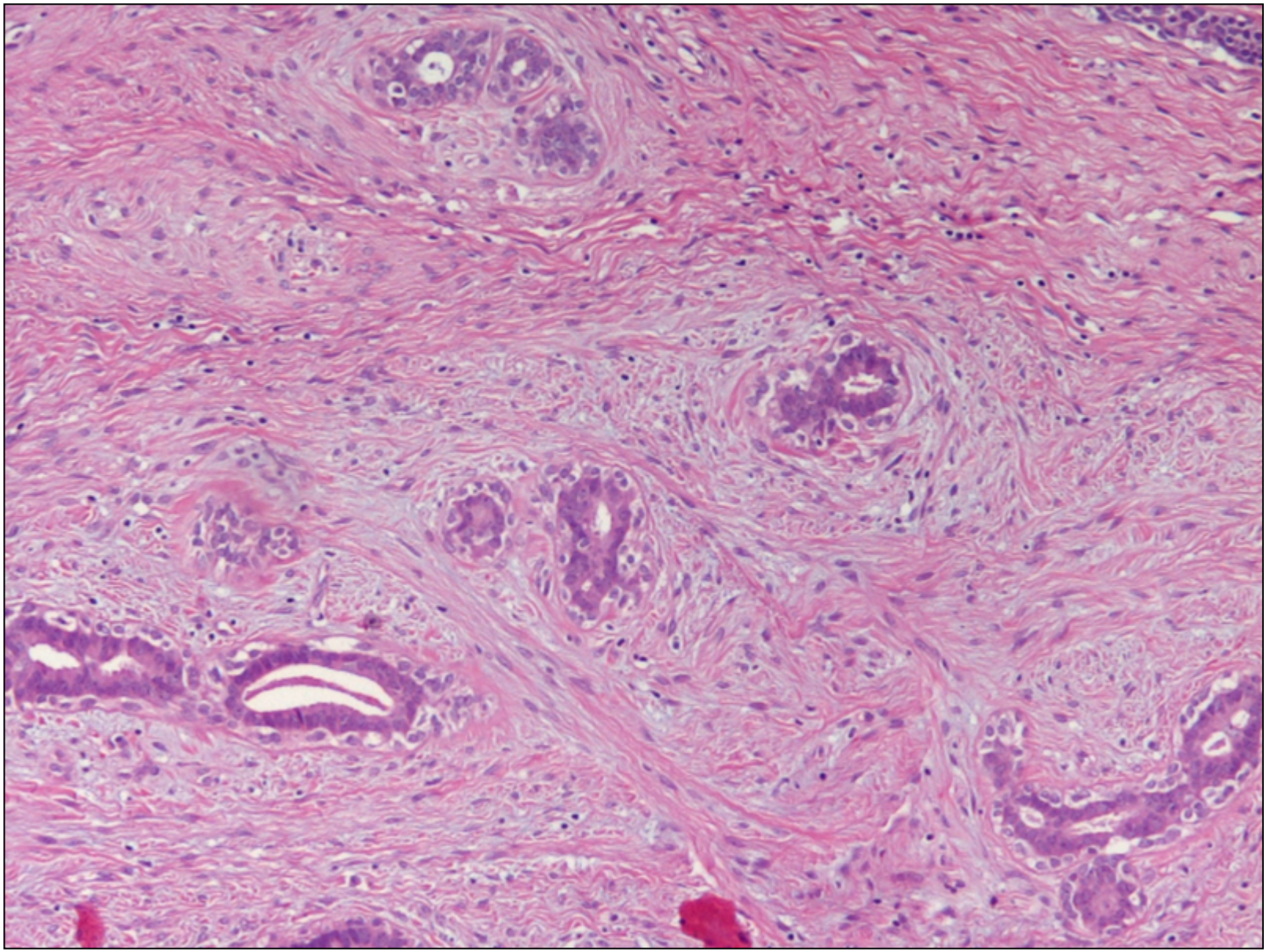










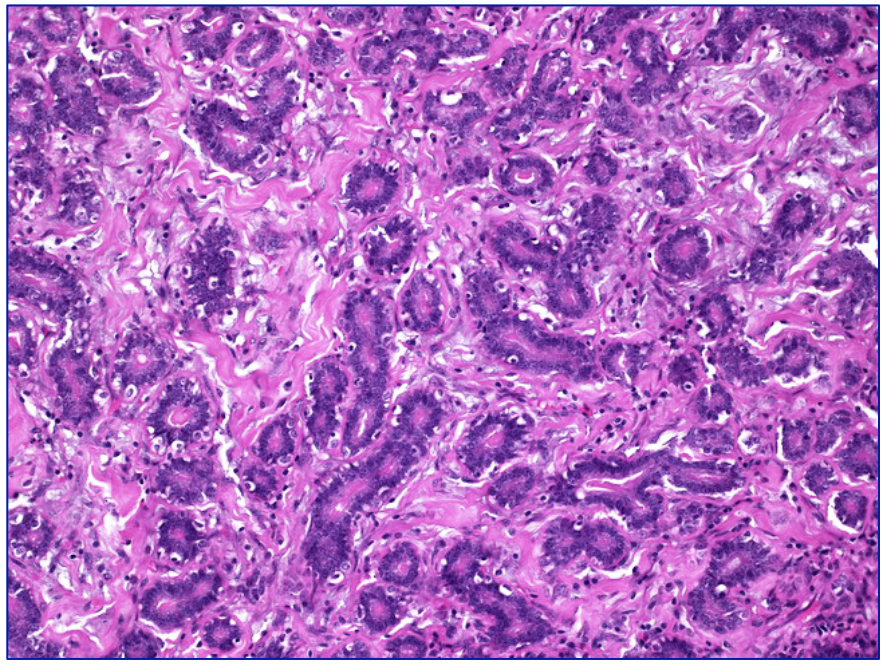


JUVENILE FIBROADENOMA

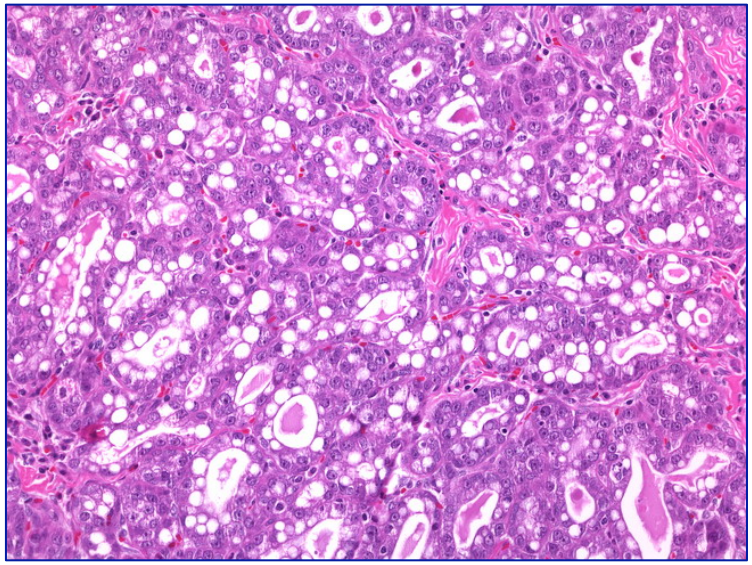
- Very young patients (<20 ys)
- Larger size (>3 cm)
- Mostly pericanalicular
- Hypercellular myxoid stroma

TUBULAR ADENOMA

- Continuum with fibroadenoma
- Less frequent
- Fibro-elastic
- ≤4 cm
- Balanced fibro-epithelial proliferation
- Compact tubules with myoepithelial cells
- Eosinophilic secretion
- Mitotically active

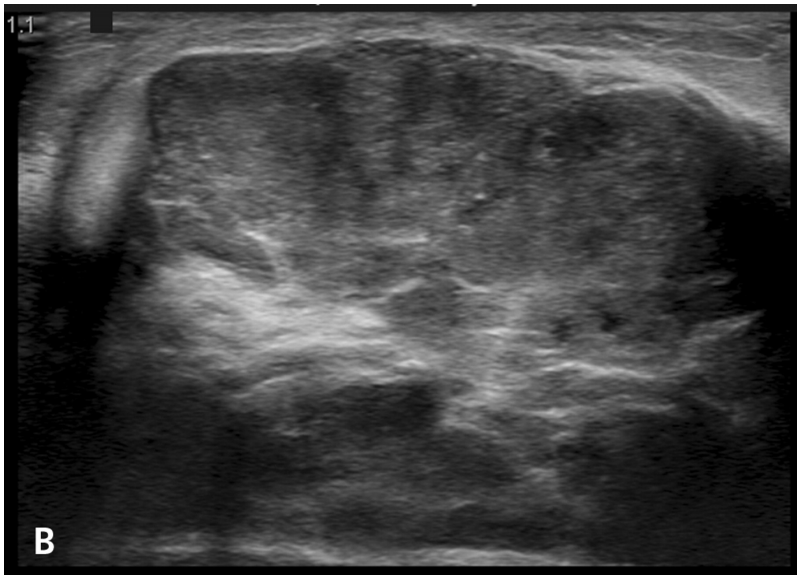


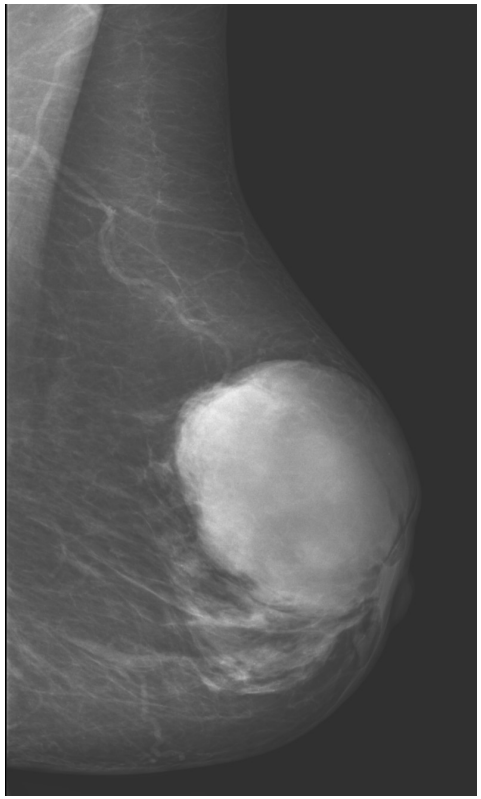
- Extensive apocrine metaplasia
  Apocrine Adenoma
- Extensive secretory component
  Lactating Adenoma

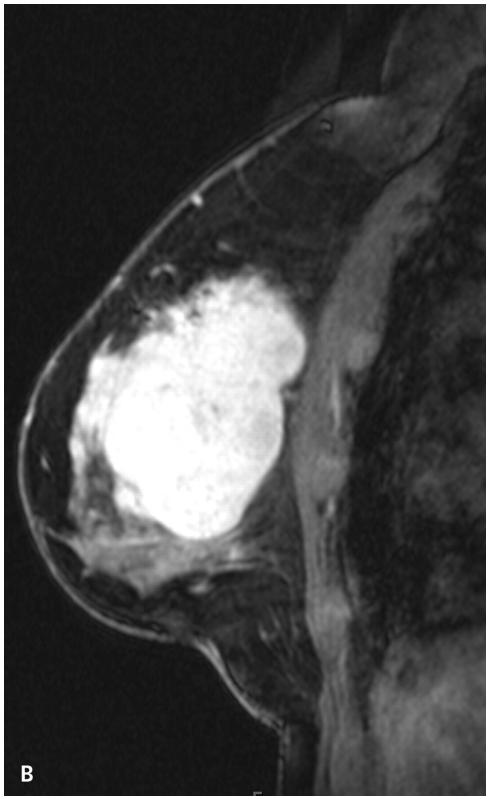


PHYLLODES TUMOUR

- Rapidly growing, well-demarcated nodule
- Larger size (≥5 cm)
- Older age (>35 ys)
- More aggressive behaviour, depending on Grade

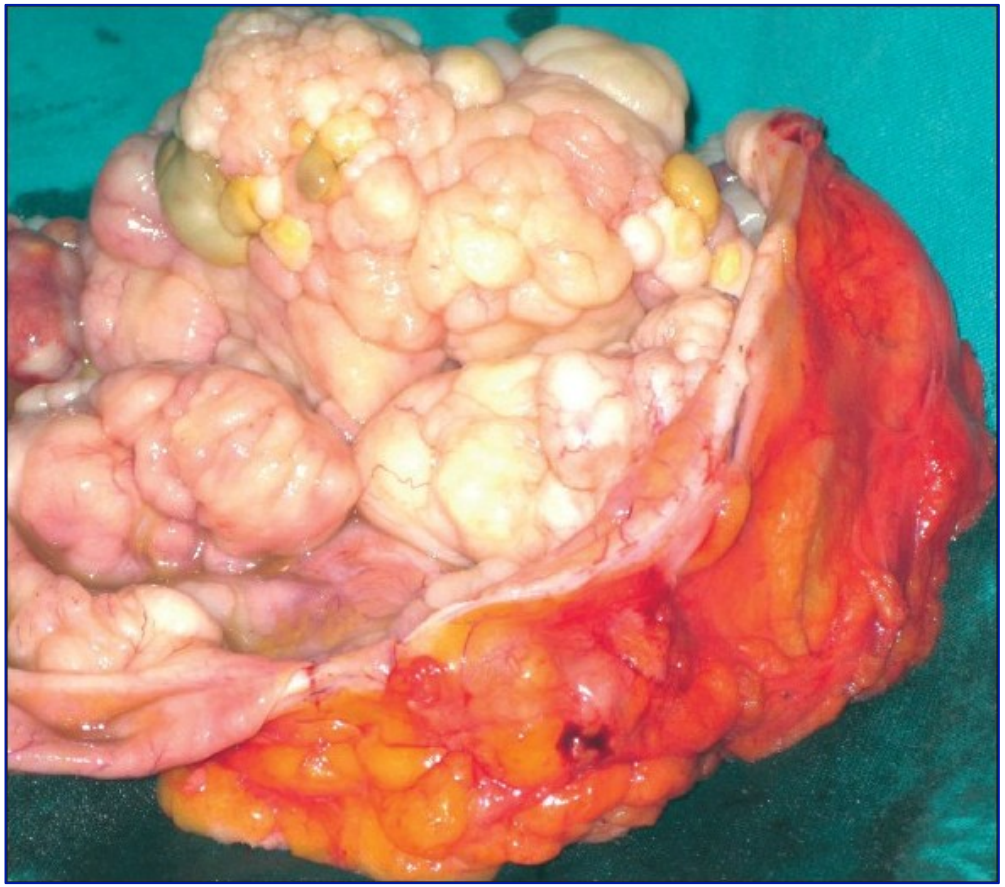




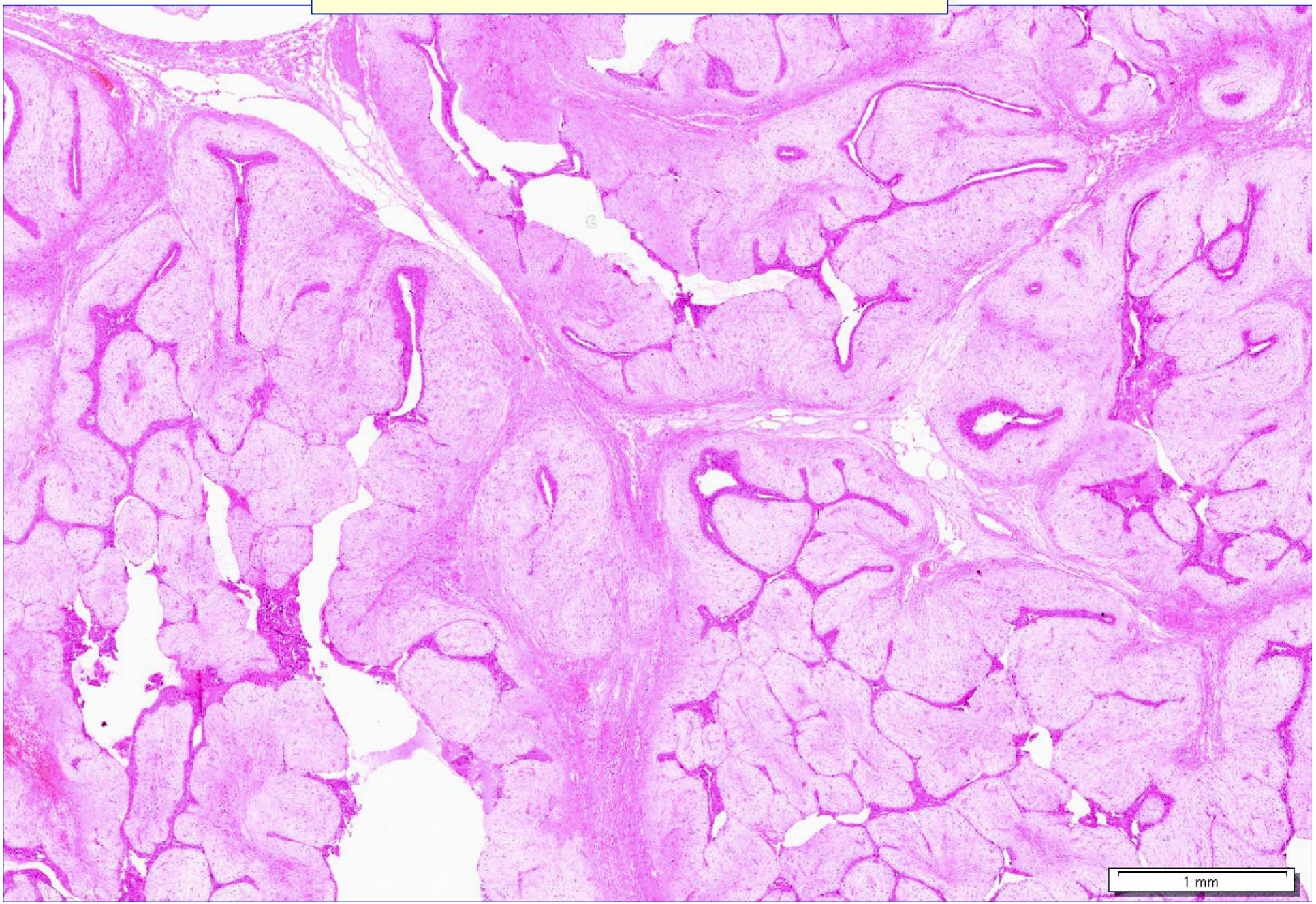


PHYLLODES TUMOUR

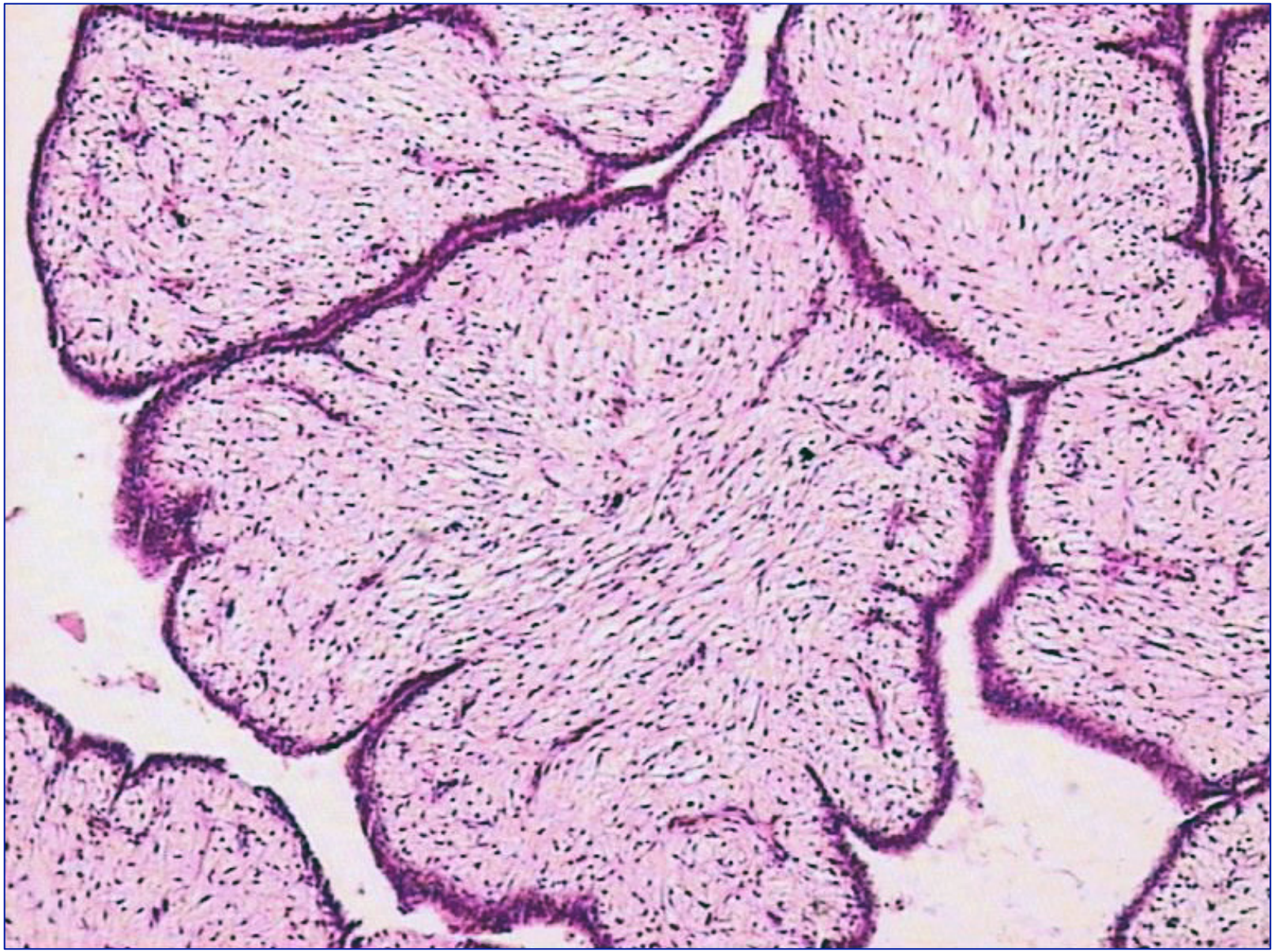
- Bossolated surface
- Fleshy appearance
- Possibly infiltrative margins



PHYLLODES TUMOUR



PHYLLODES TUMOUR (BENIGN 60%)

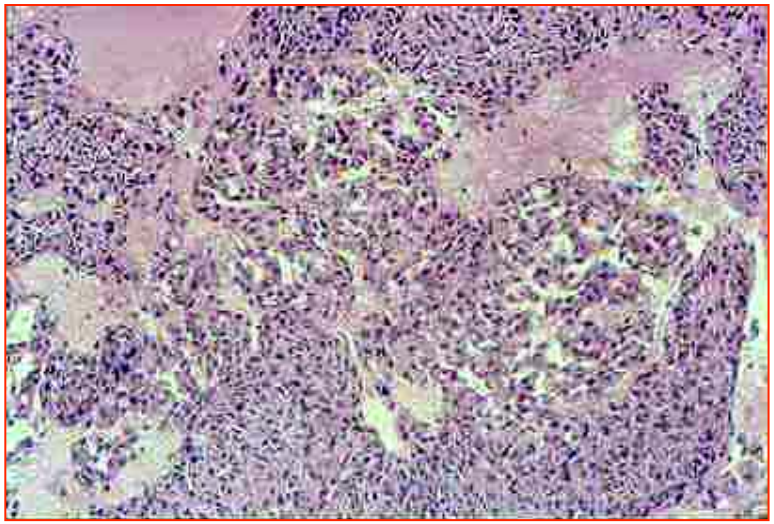


PHYLLODES TUMOUR

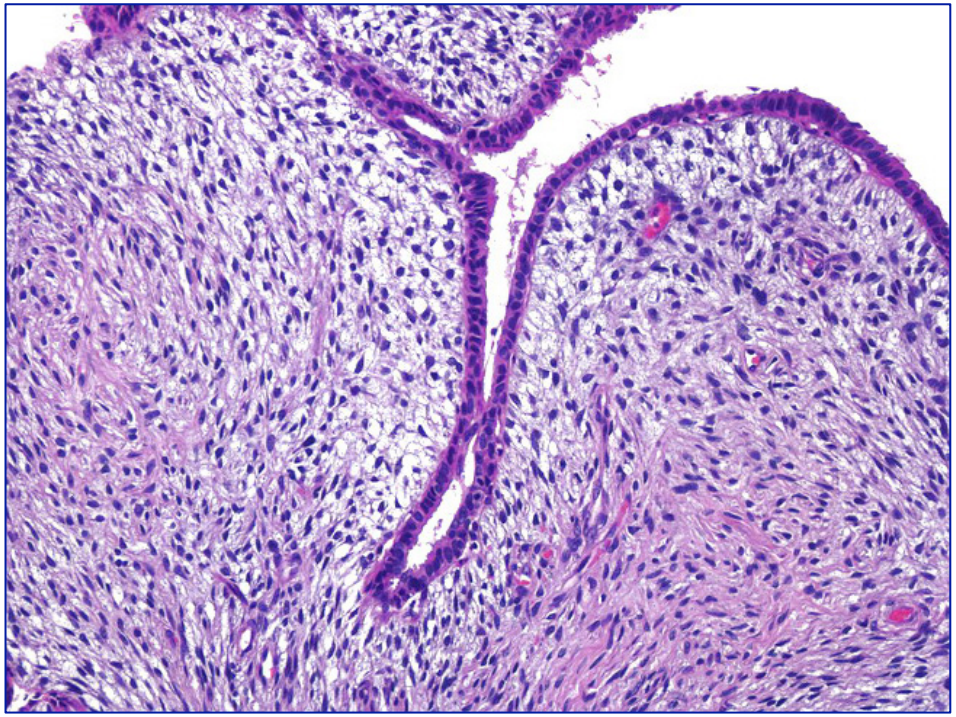
LOW GRADE MALIGNANT 20%

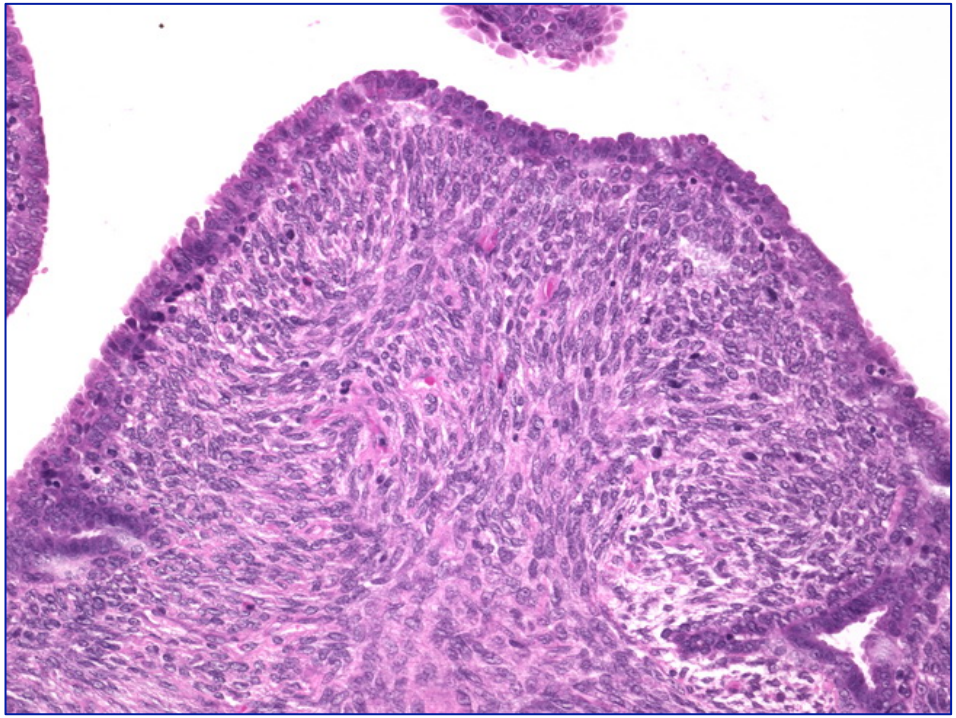
Increased stromal cellularity
Rare mitotic figures
No cytologic atypia
Increased recurrence rate

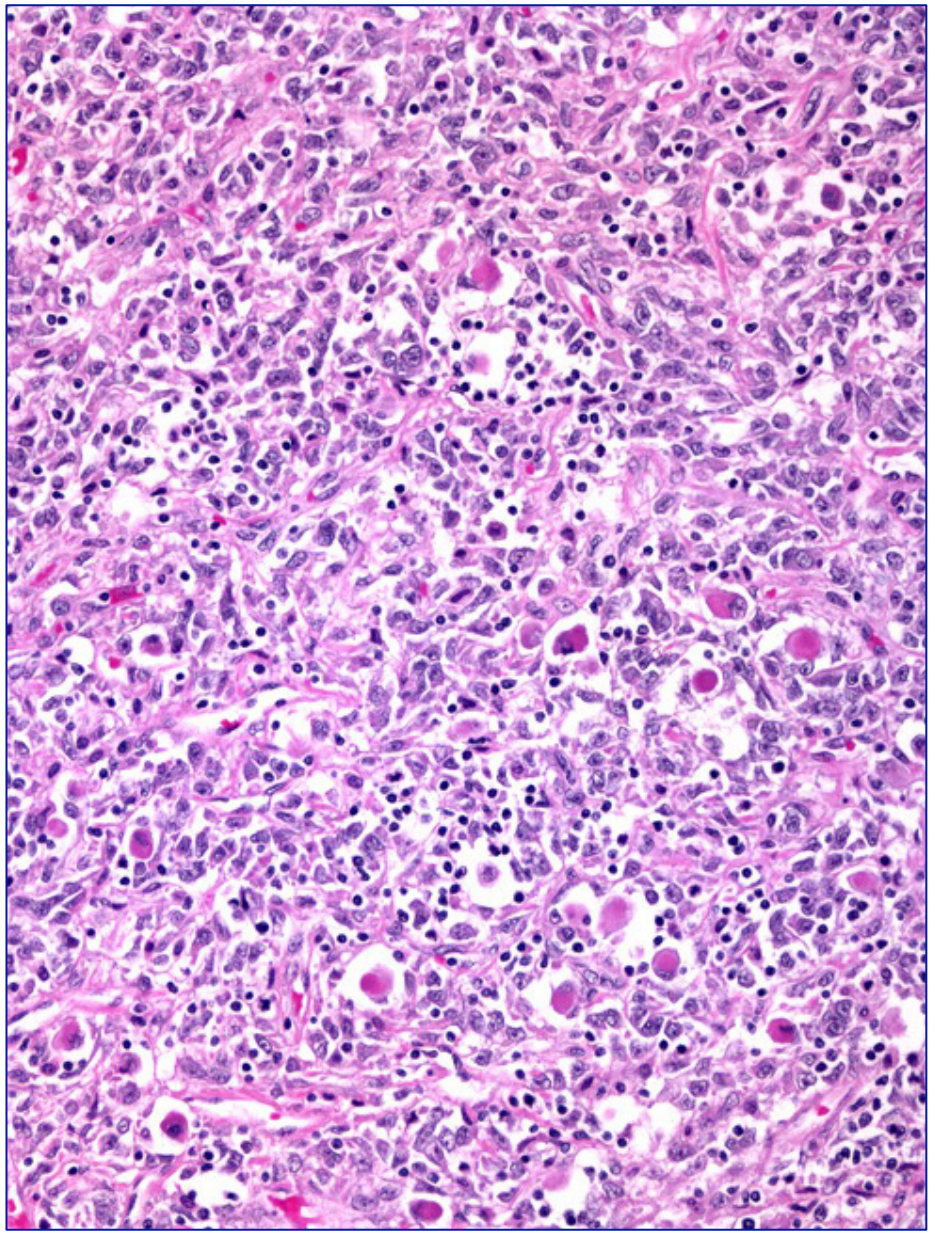
HIGH GRADE MALIGNANT 20%



Sarcomatous stroma
Nuclear pleomorphism
Mitotically active (10/10HPF)
Heterologous differentiation
Frequent recurrences
Rare distant metastases

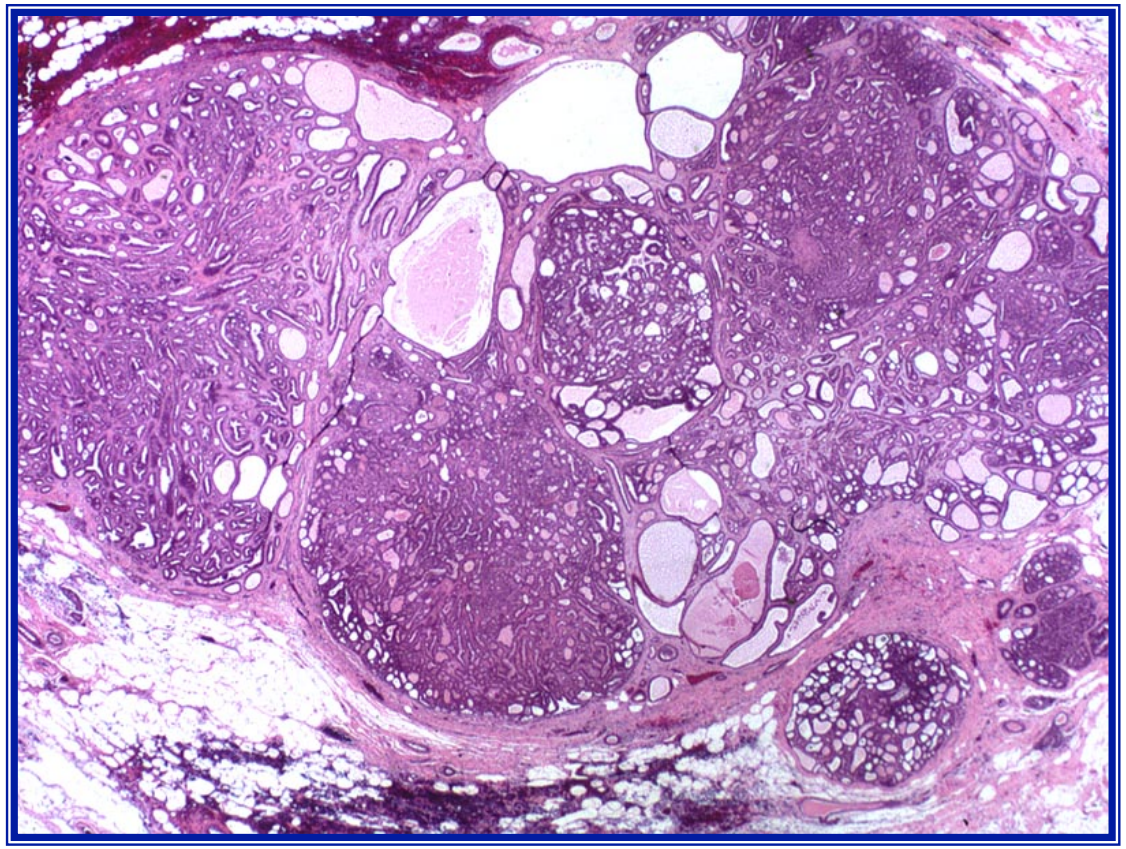






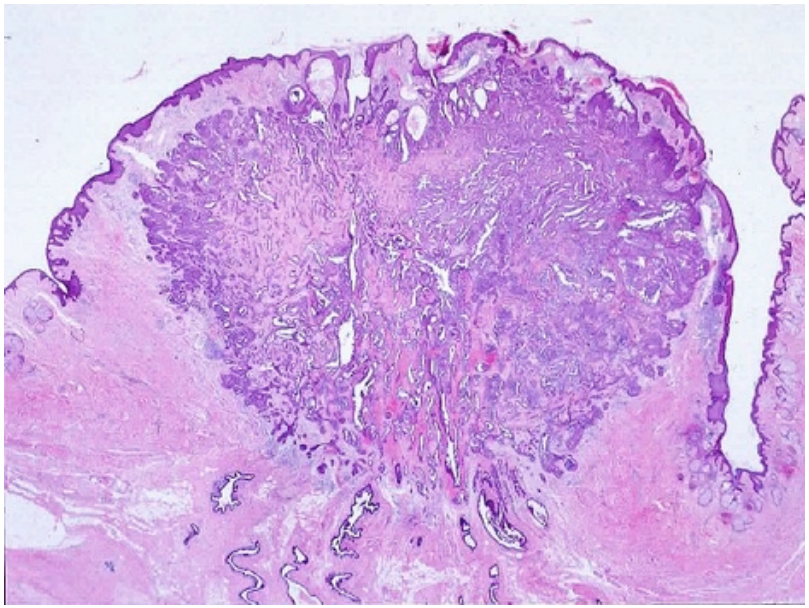
DUCTAL ADENOMA

Glandular proliferation with adenomatous and papillary growth patterns
May develop marked fibrotic proliferation, simulating a radial scar

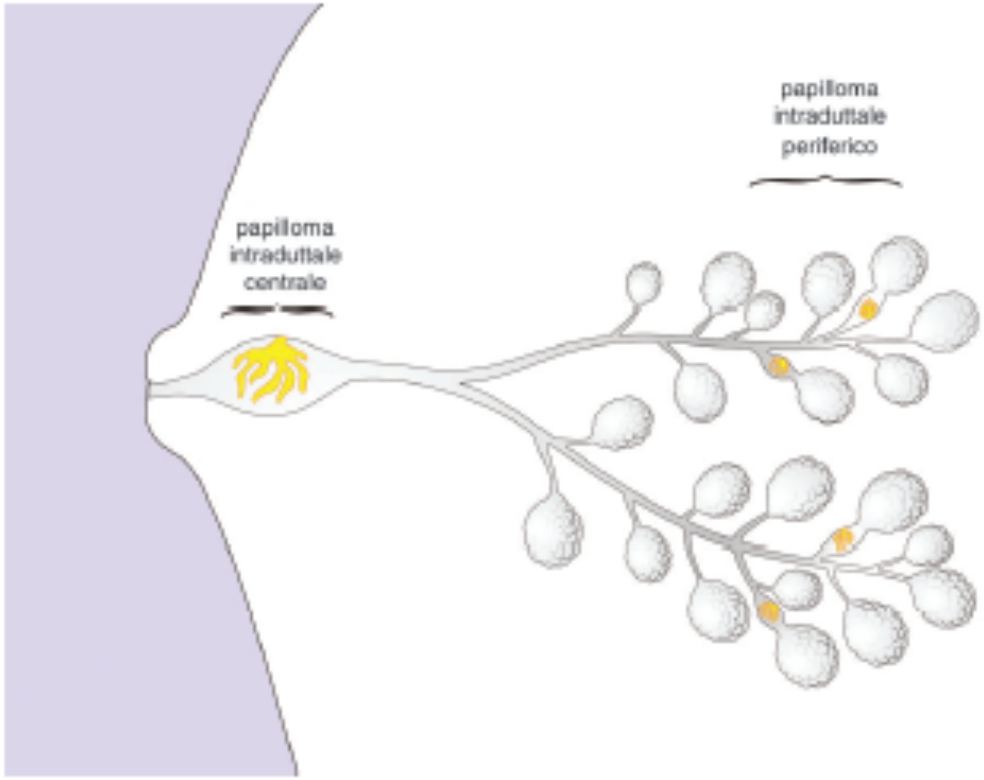


NIPPLE ADENOMA

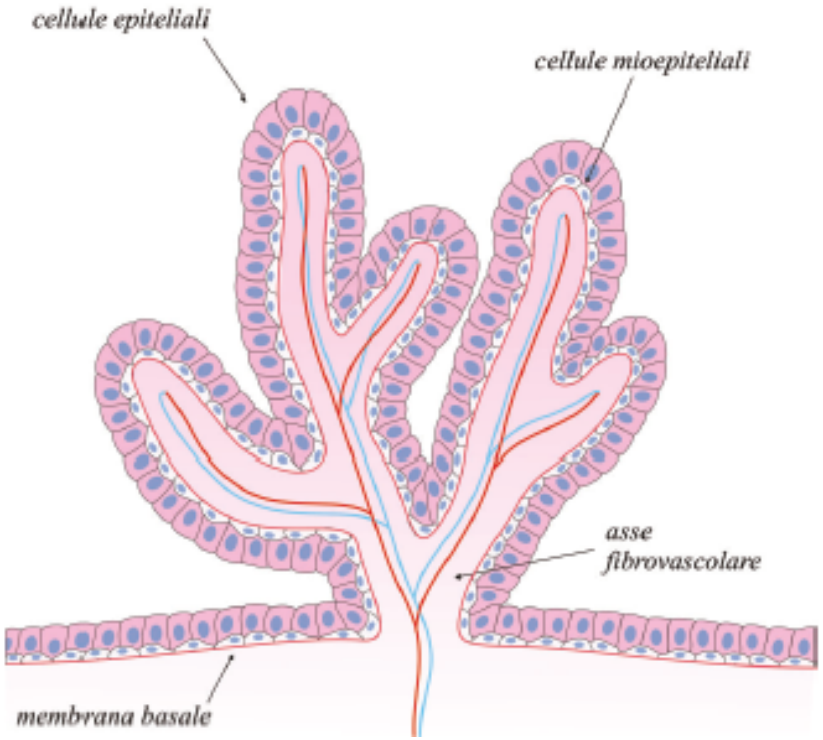
- Rare
- 40-50 ys.
- Blood discharge
- Nipple enlargement
- Skin erosion
- Simulates Paget's disease



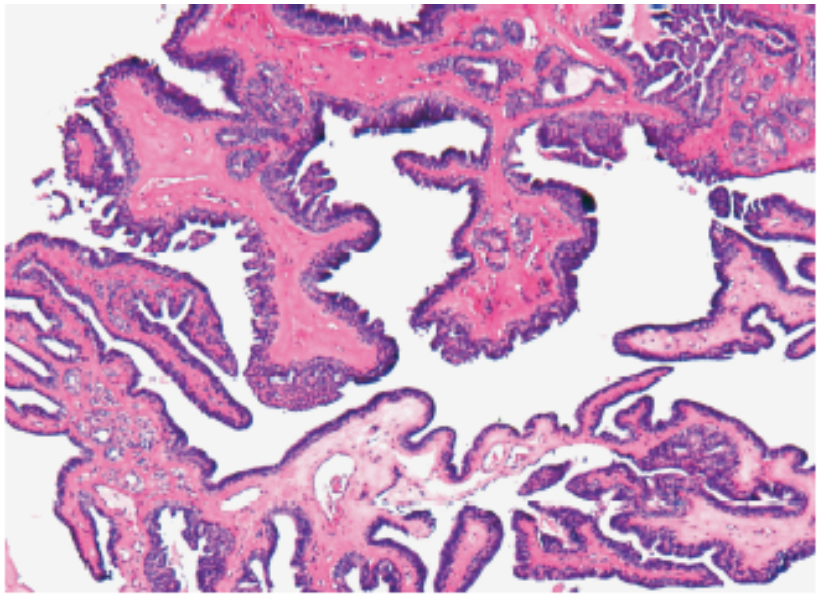
INTRADUCTAL PAPILLOMA



a



b



c

INTRADUCTAL PAPILLOMA

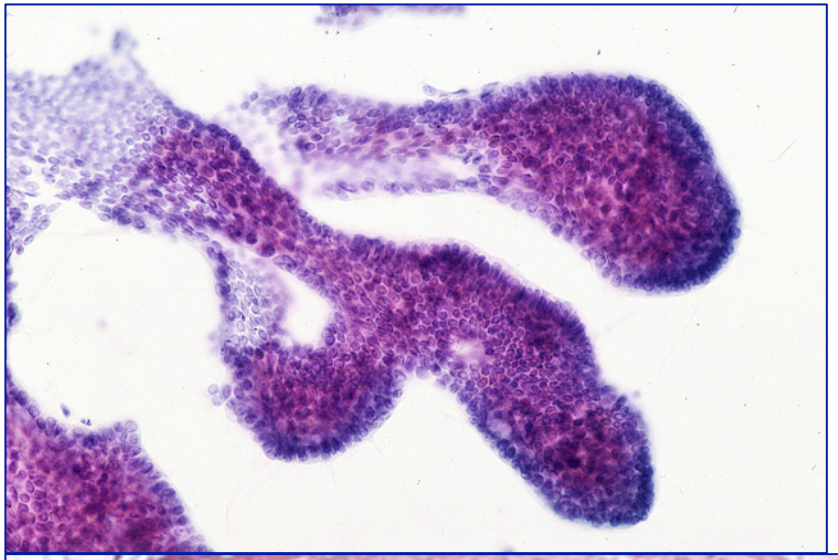
SOLITARY: central, larger, lactipherous ducts
MULTIPLE: peripheral, smaller, TDLU

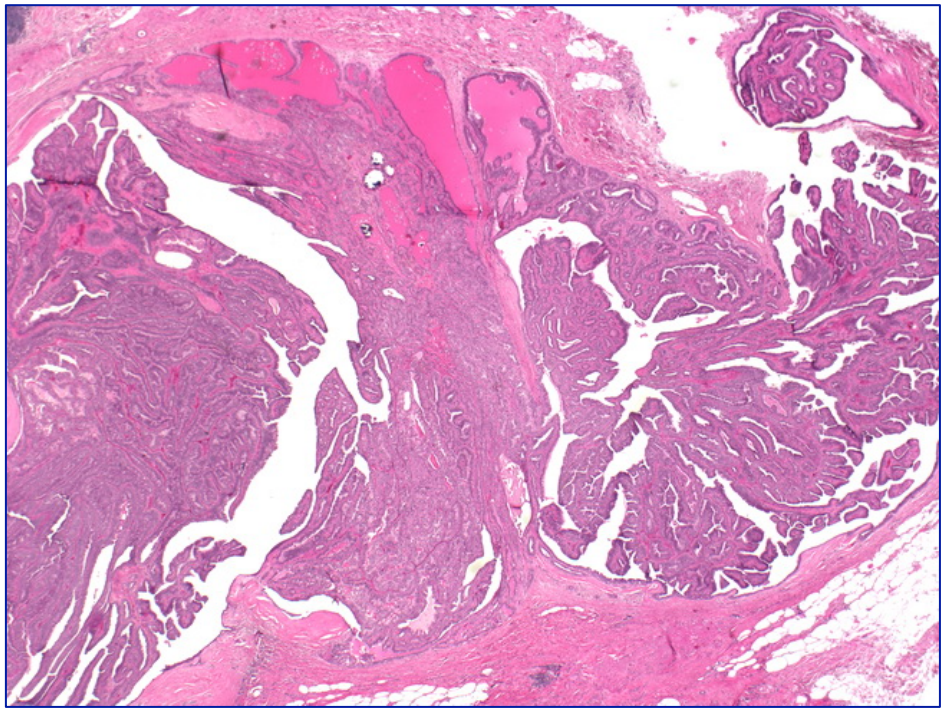
Branching fibrovascular core
Epithelial & myoepithelial cells
Apocrine or squamous metaplasia
Periductal fibrosis
Pseudo-infiltrative margins
Epithelial hyperplasia ± atypia

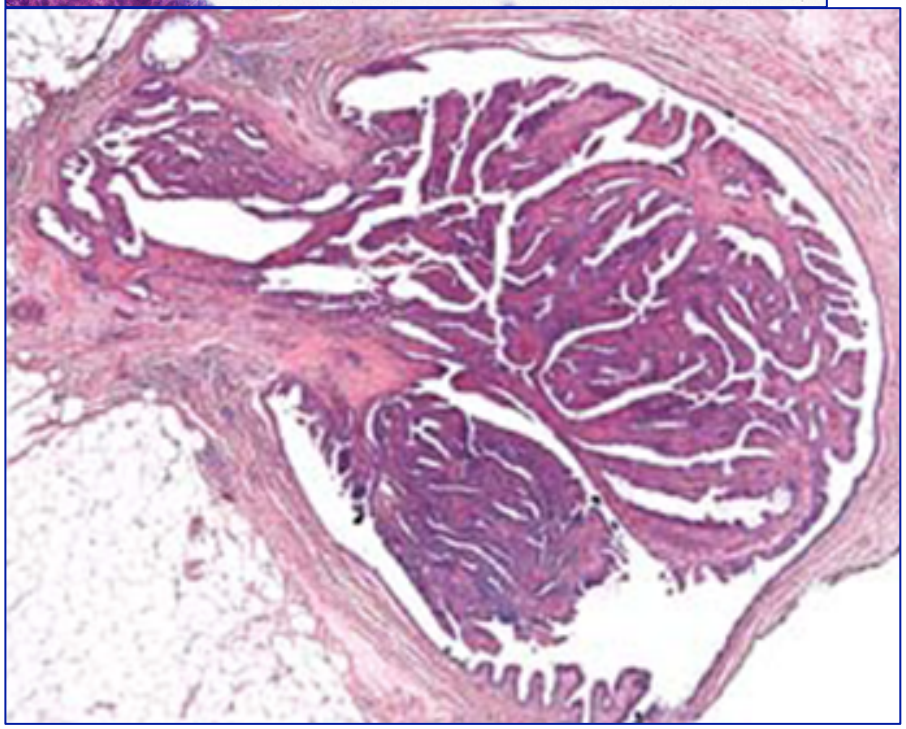
May progress into papillary carcinoma (decades)

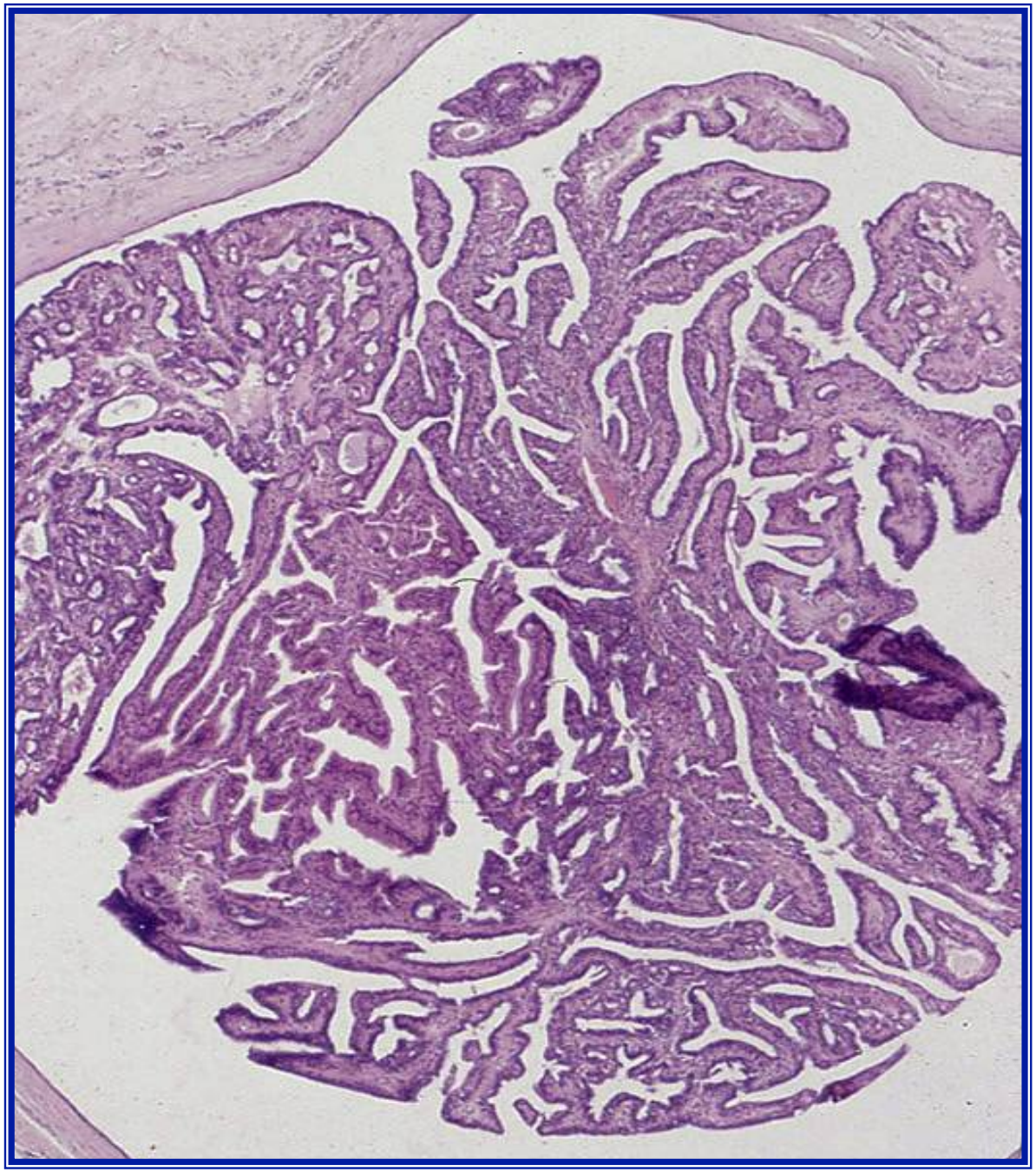
INTRADUCTAL PAPILLOMA

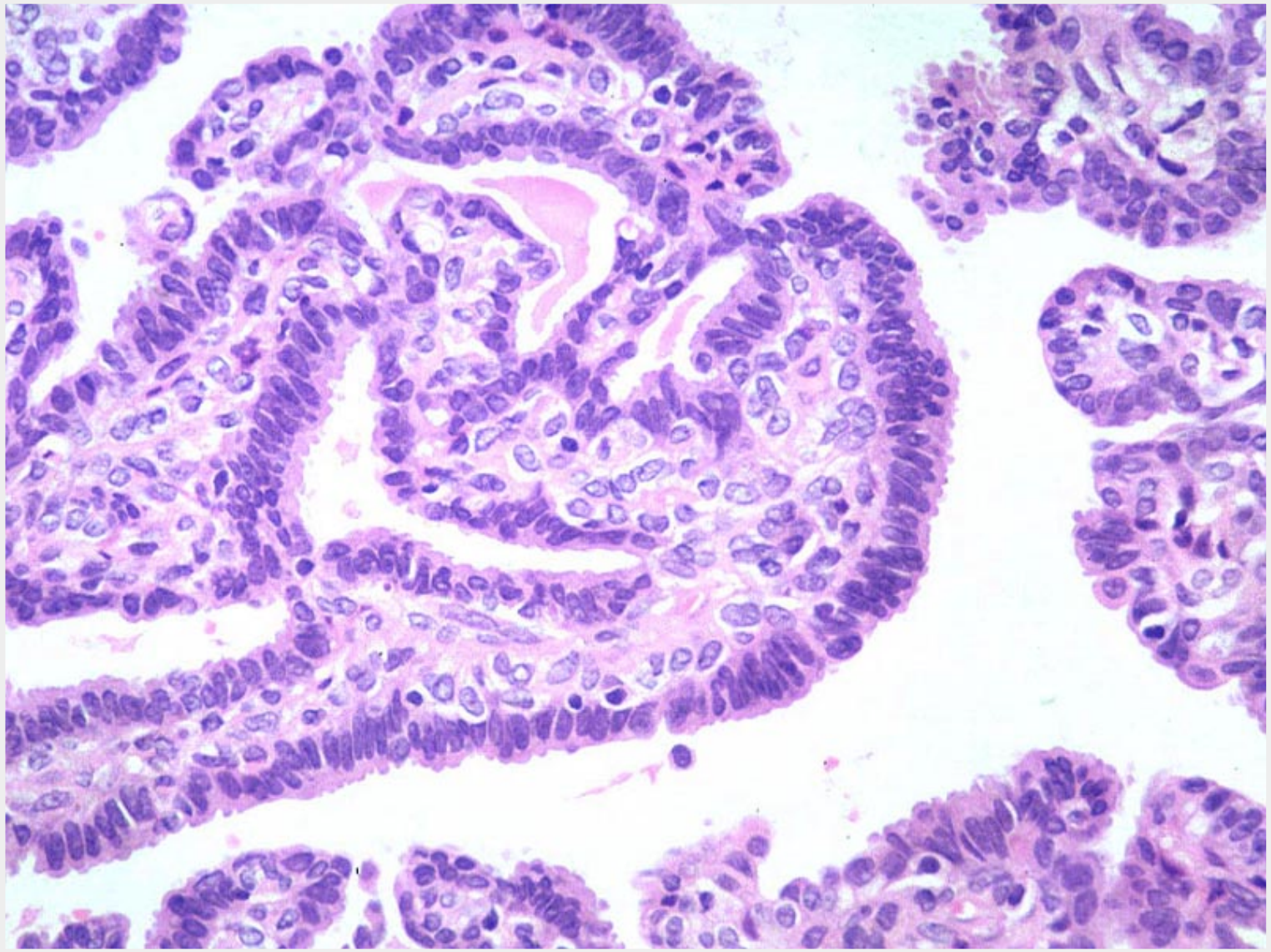
Benign Intraductal Papilloma

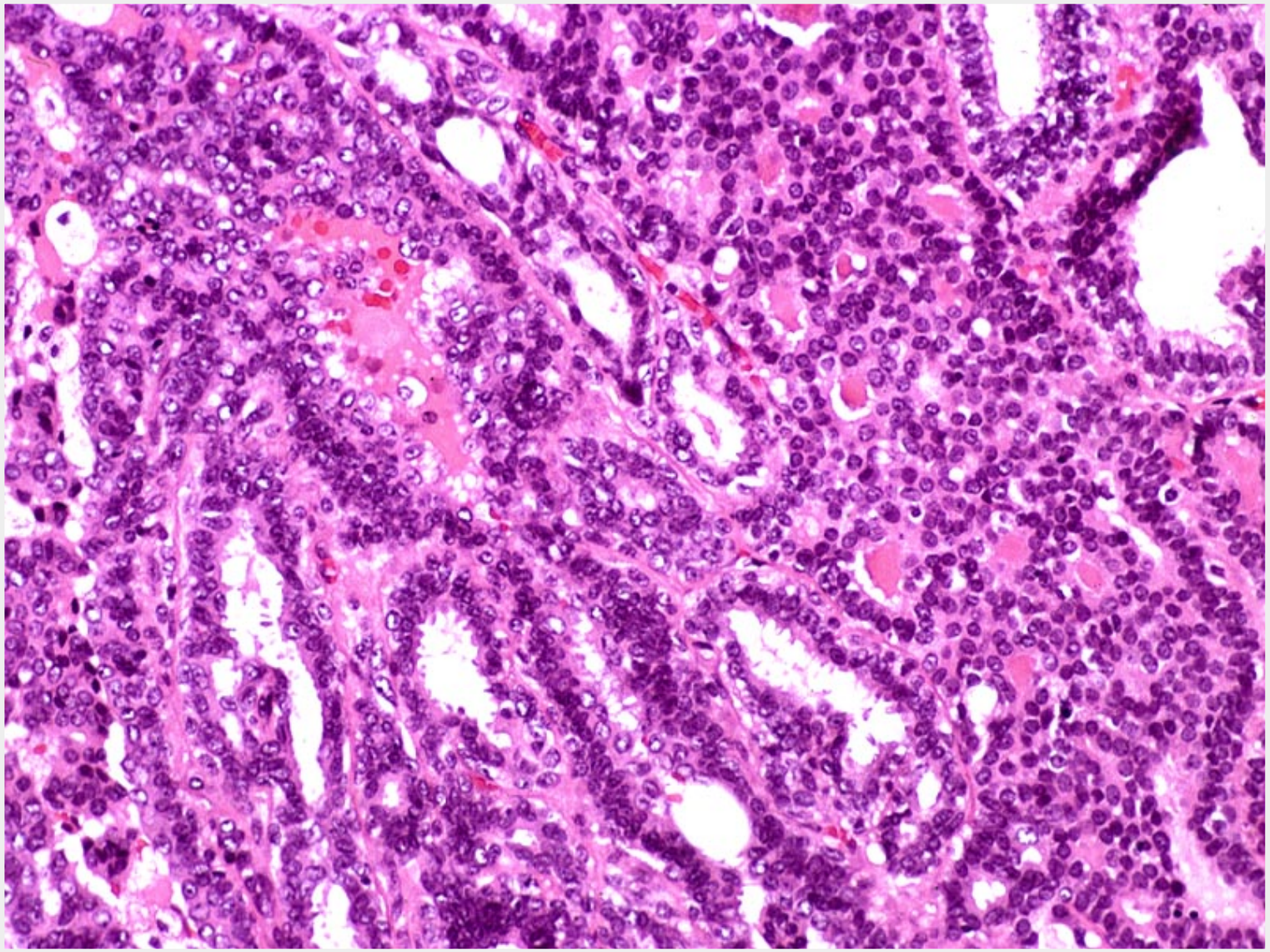


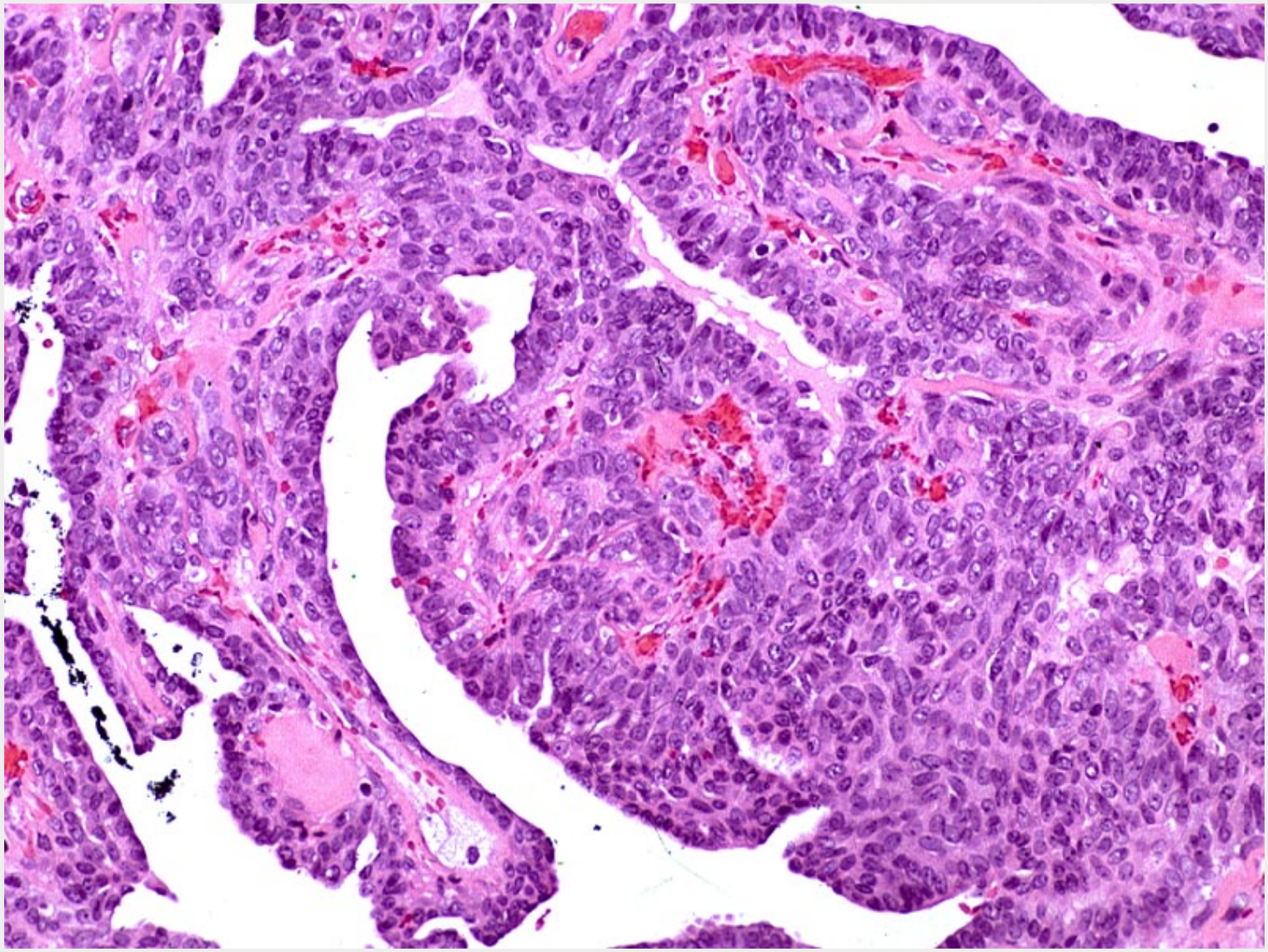




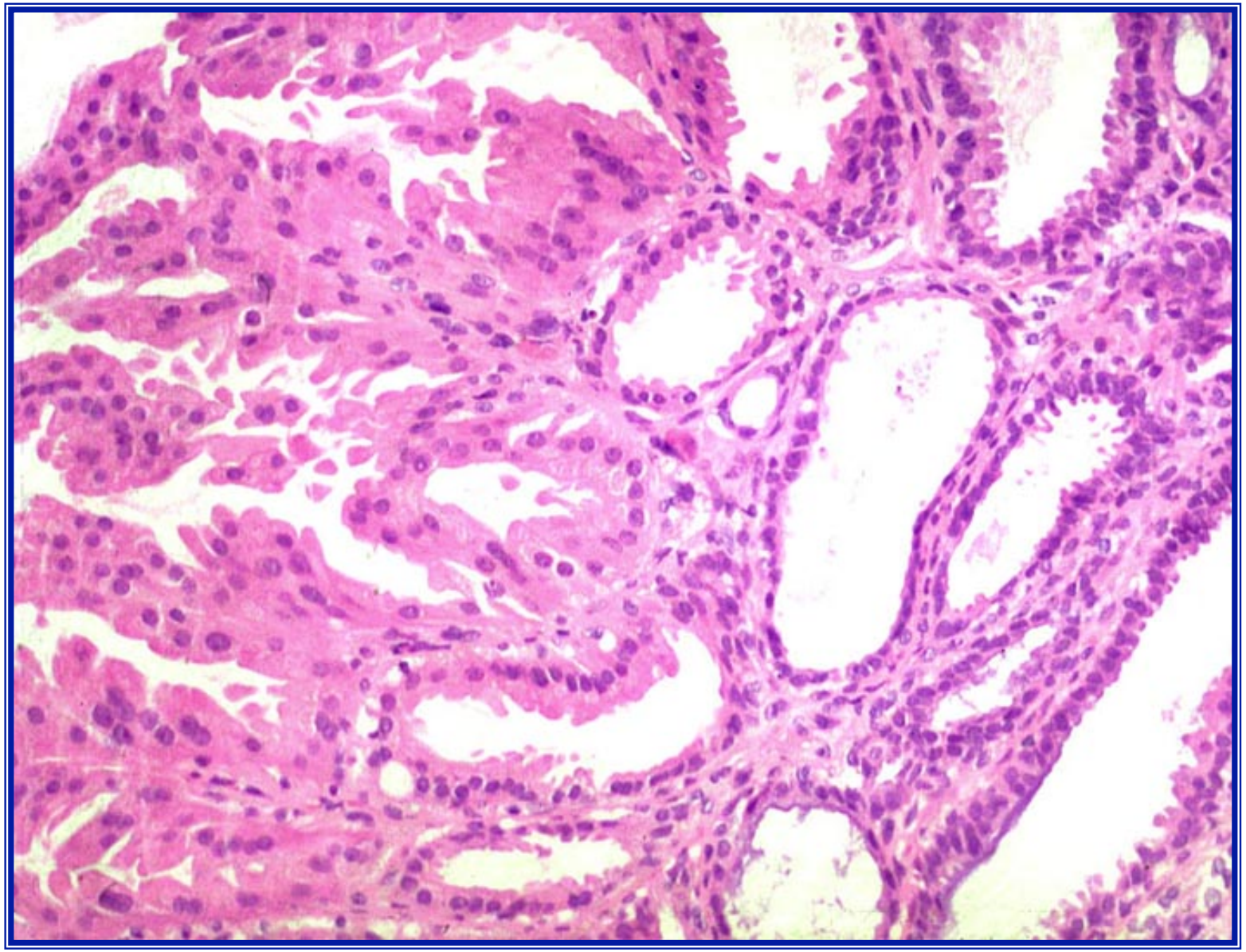


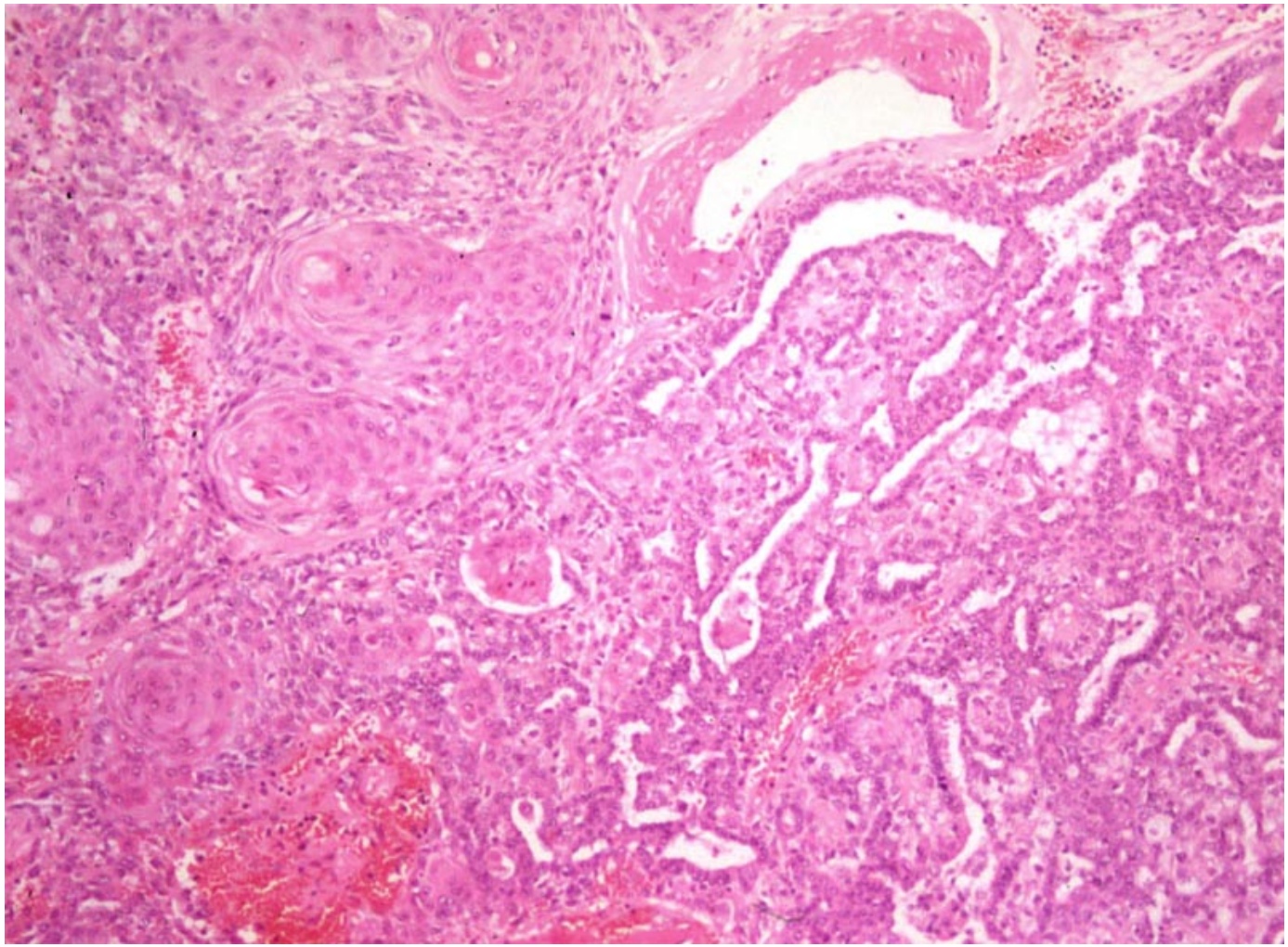






Ductal papilloma: apocrine metaplasia





Metaplasia squamosa

HYPERPLASIA

Epithelial intra-luminal proliferation

Isolated or in association with benign (fibroadenoma, fibrocystic disease, etc.) or malignant (invasive carcinoma) lesions

- **DUCTAL**: Interlobular ducts
- **LOBULAR**: TDLU

HYPERPLASIA

- **USUAL**: Increased cell number with no nuclear/architectural alterations
- **ATYPICAL**: Bland nuclear/architectural alterations
  - Columnar cell alterations
  - Atypical cystic nodules
  - Clinging (in situ) carcinoma
- **CARCINOMA IN SITU**: Frank nuclear/architectural alterations
  - Within the basal lamina
  - 3-tiered grading system

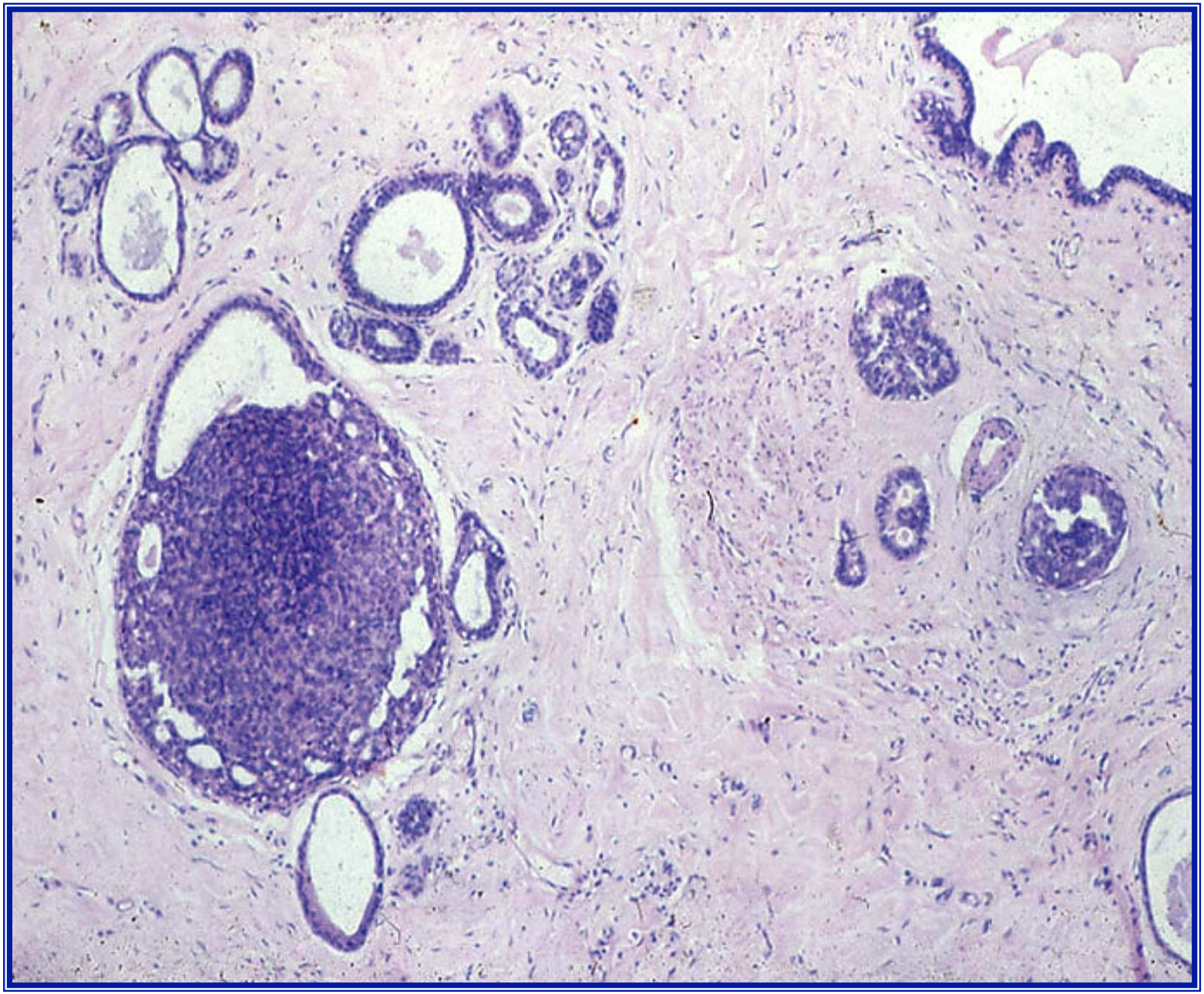
USUAL HYPERPLASIA

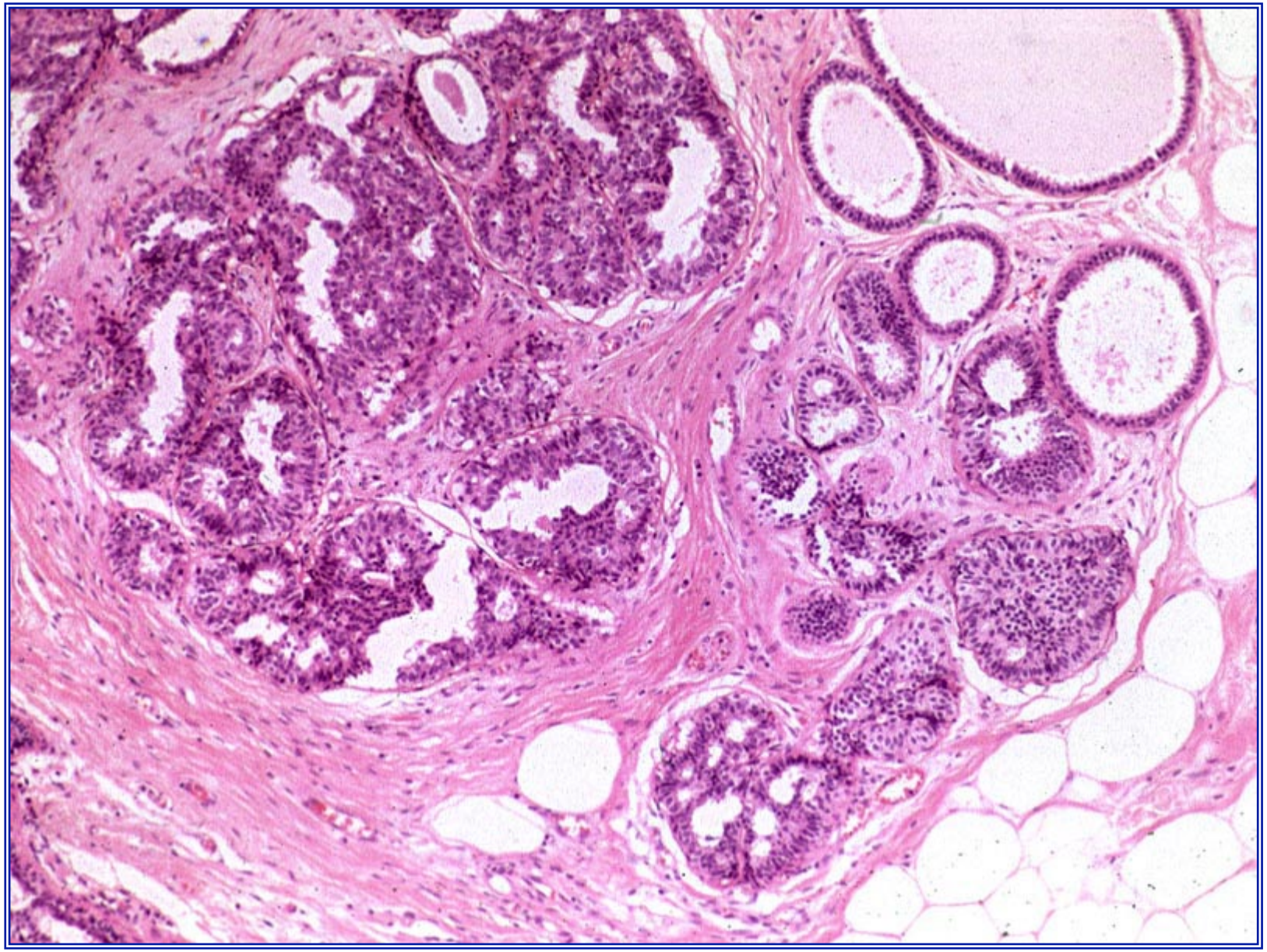
DUCTAL

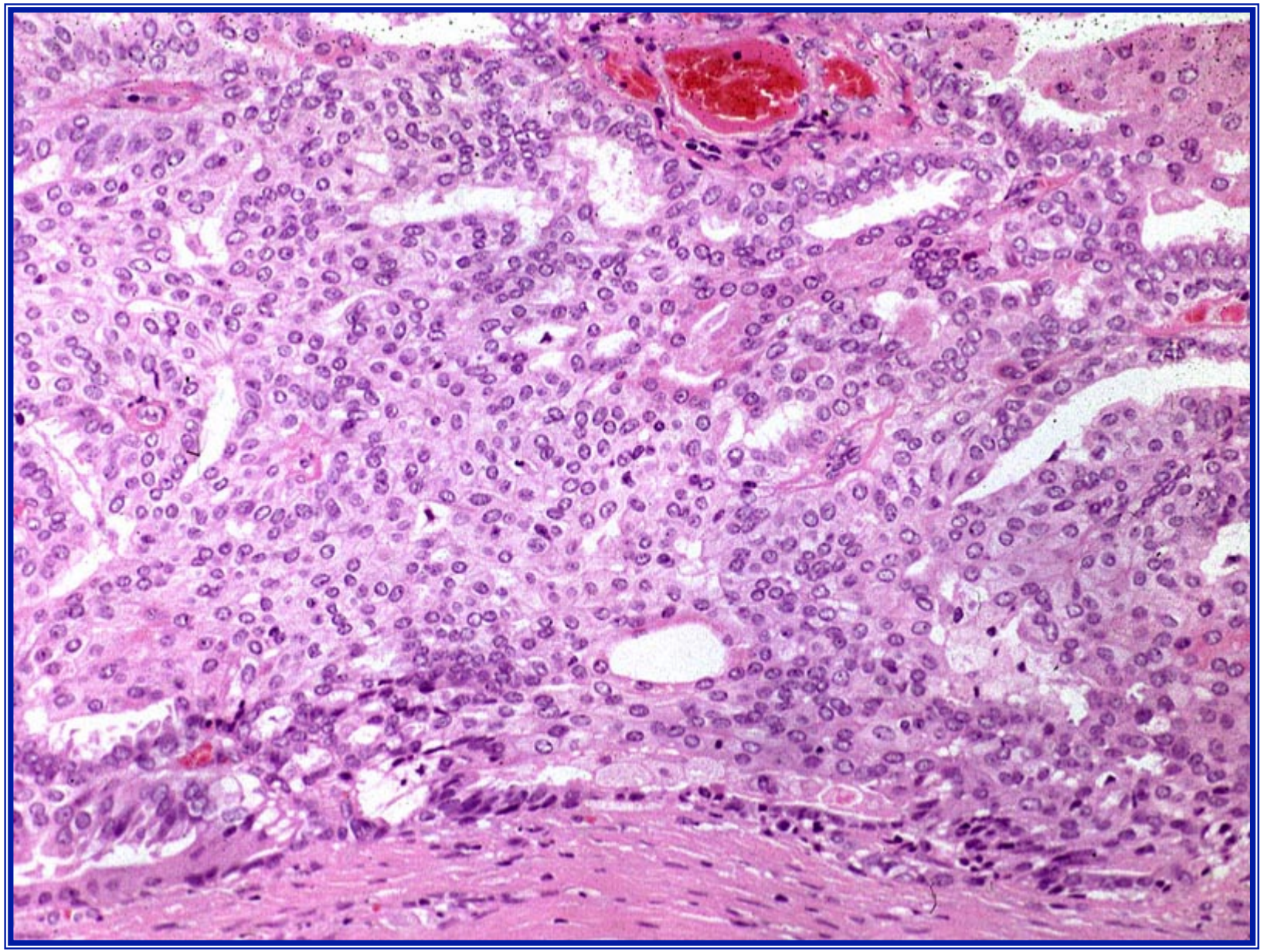
- Predominantly epithelial cells
- Elongated cells
- Nuclear streaming
- Normochromic , angulated/spindle nuclei
- Bland chromocenters
- Plump myoepithelial cells
- Polymorphic fenestrations
- Rare mitosis, no necrosis

LOBULAR

- Partial obliteration of acinar lumina
- No more than 4 cell layers
- Myoepithelial cells recognizable







ATYPICAL DUCTAL HYPERPLASIA / CARCINOMA IN SITU

- Increasingly detected by screening
- Morphologically heterogeneous lesions
- Poor inter-observer reproducibility (ADH vs. low grade DCIS)
- Different risk for progression towards invasive carcinoma
- Risk of over-treatment
- Distinct molecular alterations (LOH)
- Psychologic impact of “carcinoma”

ADH / DCIS

Cytological features

- Monotonous and uniform cells
- Increased N/C ratio
- Rosette-like formations
- Rounding and “standing” nuclei
- Nuclear hyperchromasia
- Mitosis & necrosis rare

Architectural features

- Limited extension (≤ 2mm)
- Scattered ductal structures
- Bridging
- Cribriform, micro-papillary

The D.I.N. (Ductal Intra-epithelial Neoplasia) concept

- Standardized diagnostic criteria
- Increased inter-observer agreement
- Progressively increasing risk
- Avoiding the term “carcinoma”
- Closer to other **Grading** systems

DIN 1-2-3

Traditional terminology	DIN terminology
Usual ductal hyperplasia	Usual ductal hyperplasia (UDH)
Flat epithelial atypia	DIN Grade 1a
Atypical ductal hyperplasia (ADH)	DIN Grade 1b
Ductal carcinoma in situ (DCIS) low grade	DIN Grade 1c
Ductal carcinoma in situ (DCIS) intermediate grade	DIN Grade 2
Ductal carcinoma in situ (DCIS) high grade	DIN Grade 3

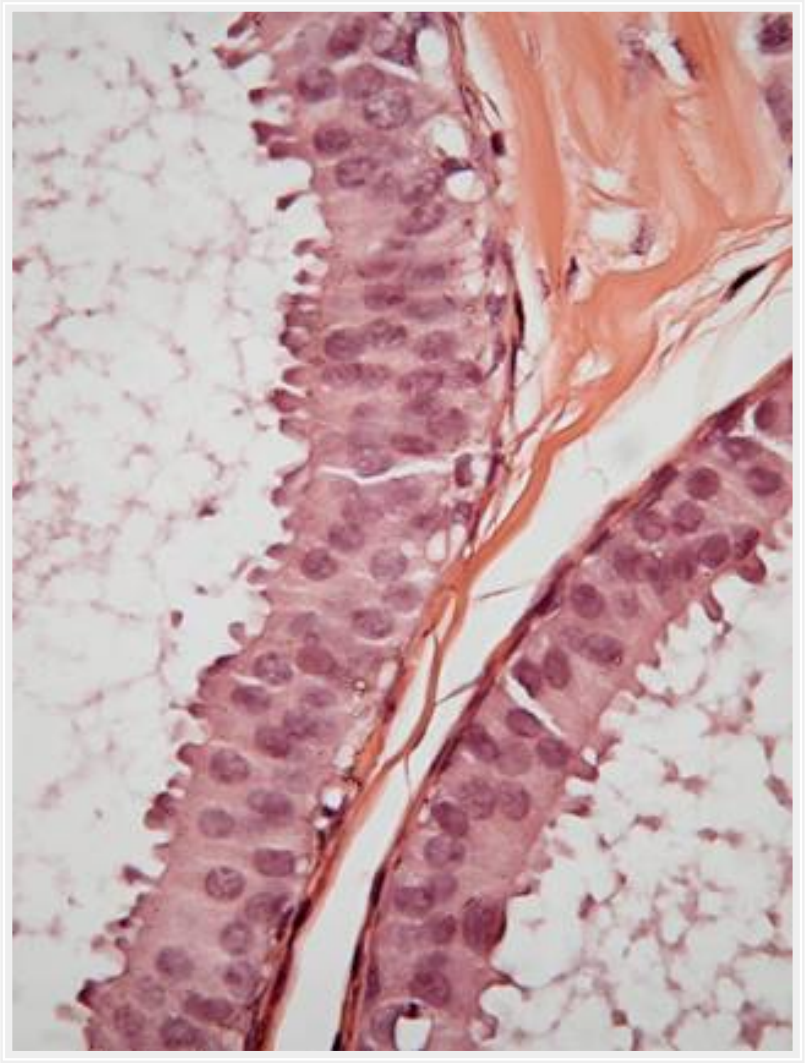
FLAT EPITHELIAL ATYPIA = DIN 1a

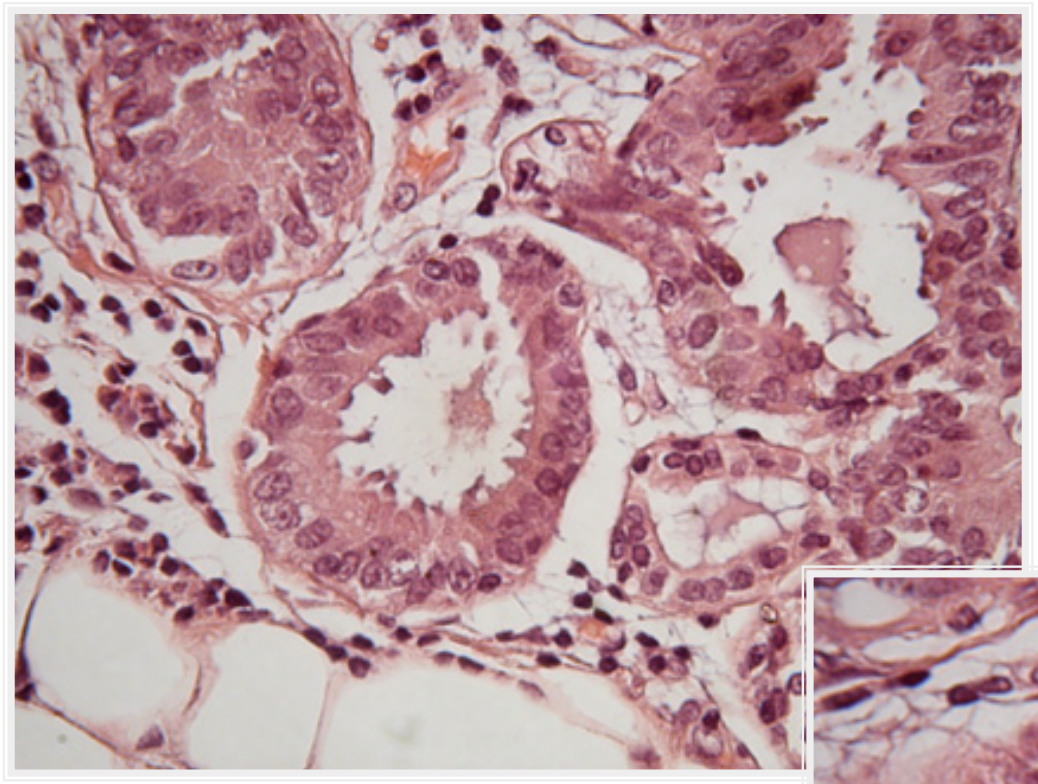
- Hyperplastic lesions (not filling the lumen)
- Minimal:
  - architectural distorsion
  - nuclear pleomorphism
- Low risk of association with invasive cancer
- 3 major morphological presentations:
  - Columnar cell lesions
  - Clinging carcinoma
  - Atypical cystic lobules

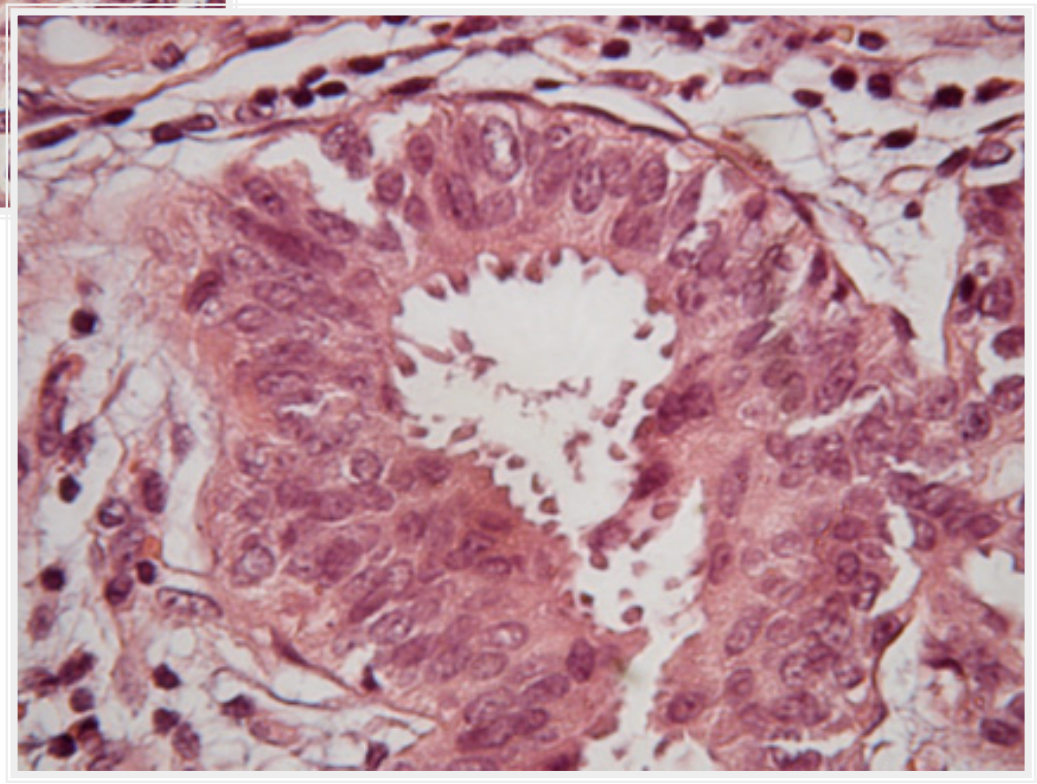
FLAT EPITHELIAL ATYPIA = DIN 1a
COLUMNAR CELL LESIONS

Columnar cells with abundant cytoplasm
Apical vesicles (snouts)
Hobnail morphology
Intraluminal secretion
Bridges & micropapillae
Polistratification
Microcalcifications

Nuclear atypia may be present
(tubular) carcinoma may coexist

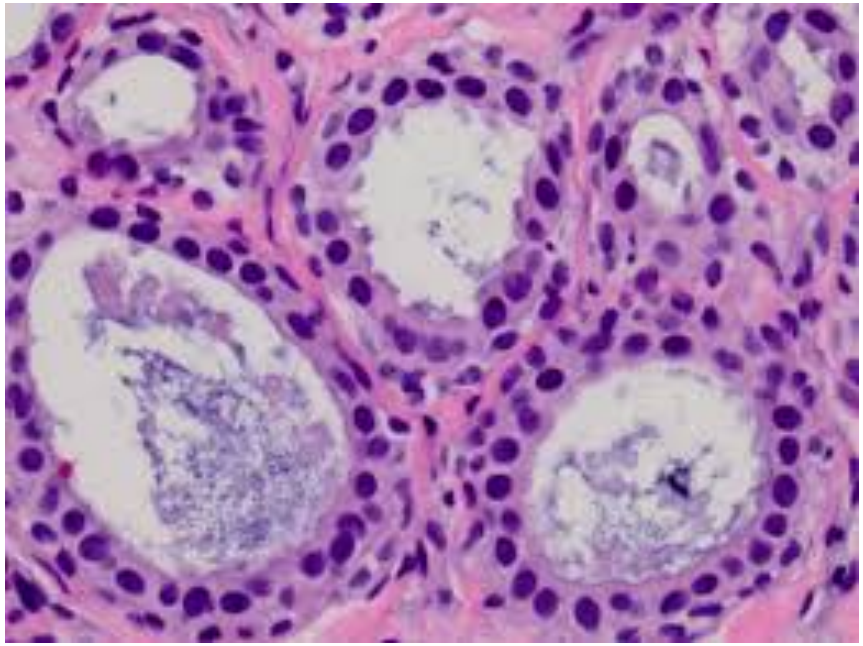






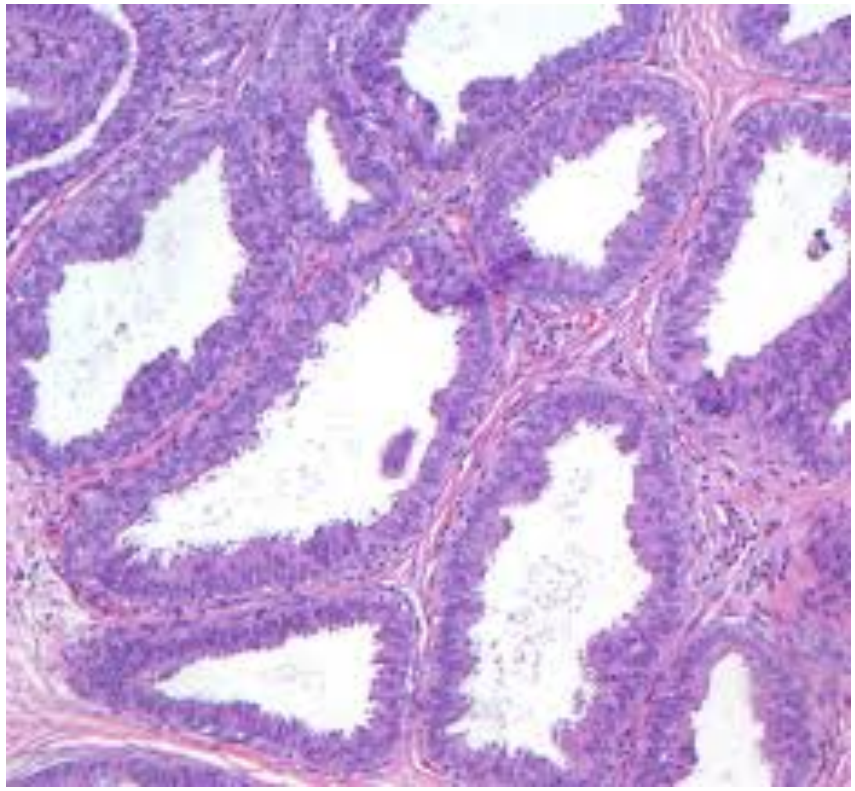
FLAT EPITHELIAL ATYPIA = DIN 1a
CLINGING CARCINOMA

Flat cells with scarce cytoplasm
Nuclear hyperchromasia
Intraluminal secretion
Polistratification
Microcalcifications



FLAT EPITHELIAL ATYPIA = DIN 1a
ATYPICAL CYSTIC LOBULES

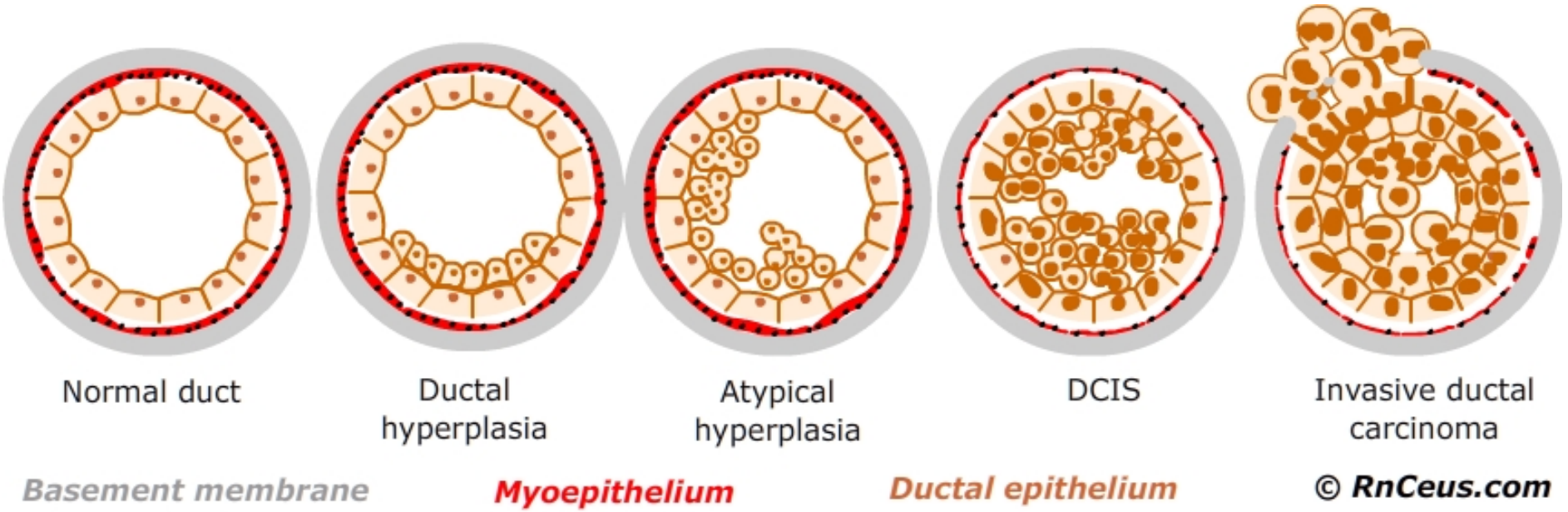
Enlarged lobular architecture
Hypercellular lobules
Cystic spaces
Columnar cell morphology
Intraluminal secretion
Polistratification
Microcalcifications



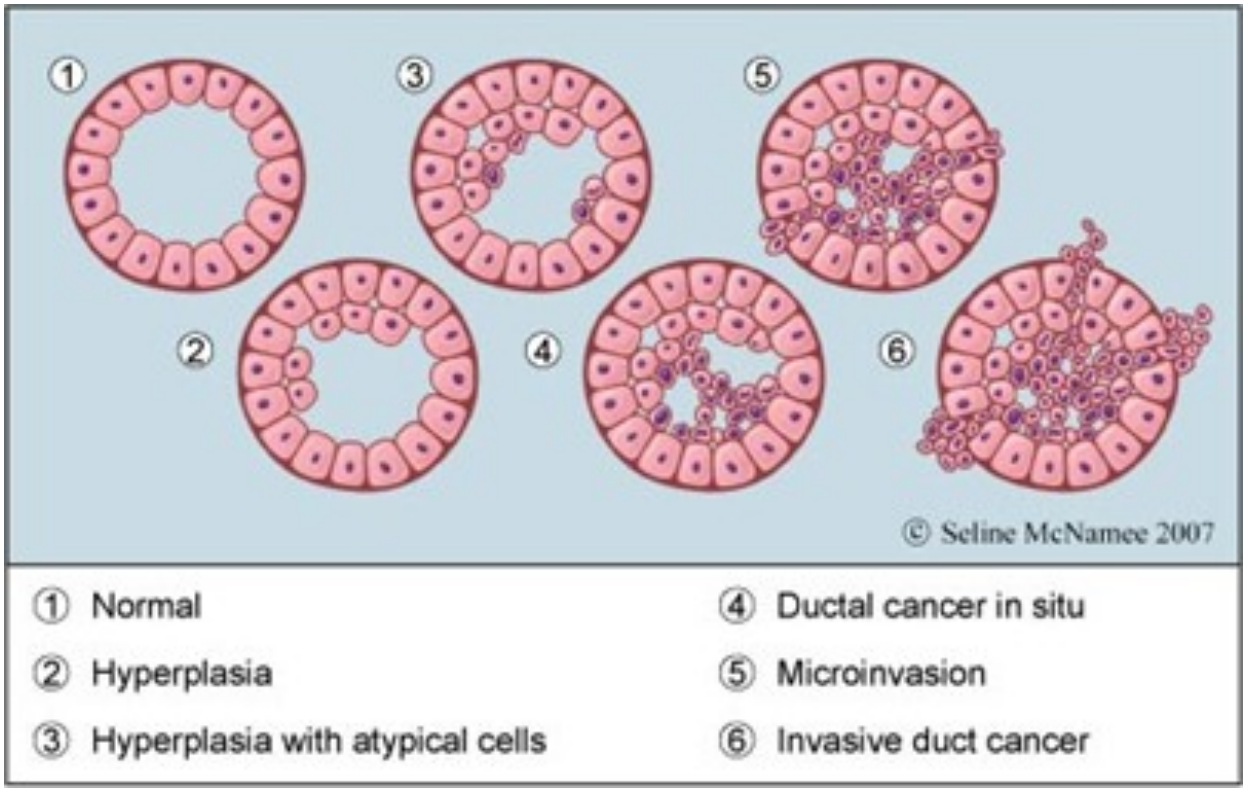
ATYPICAL DUCTAL HYPERPLASIA = DIN 1b

- Hyperplastic lesions growing within the lumen
- Minimal:
  - extension (≤2 mm.)
  - architectural distorsion
  - nuclear pleomorphism
- Low risk of association with invasive cancer

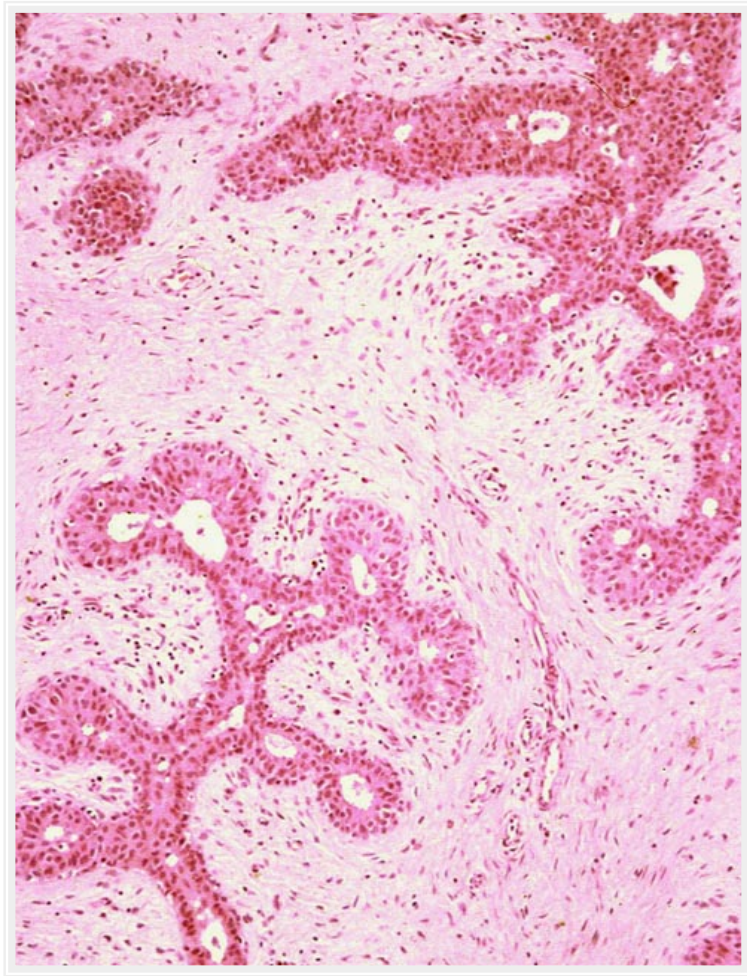
MORPHOLOGICAL BREAST CHANGES FROM NORMAL TO INVASIVE CANCER



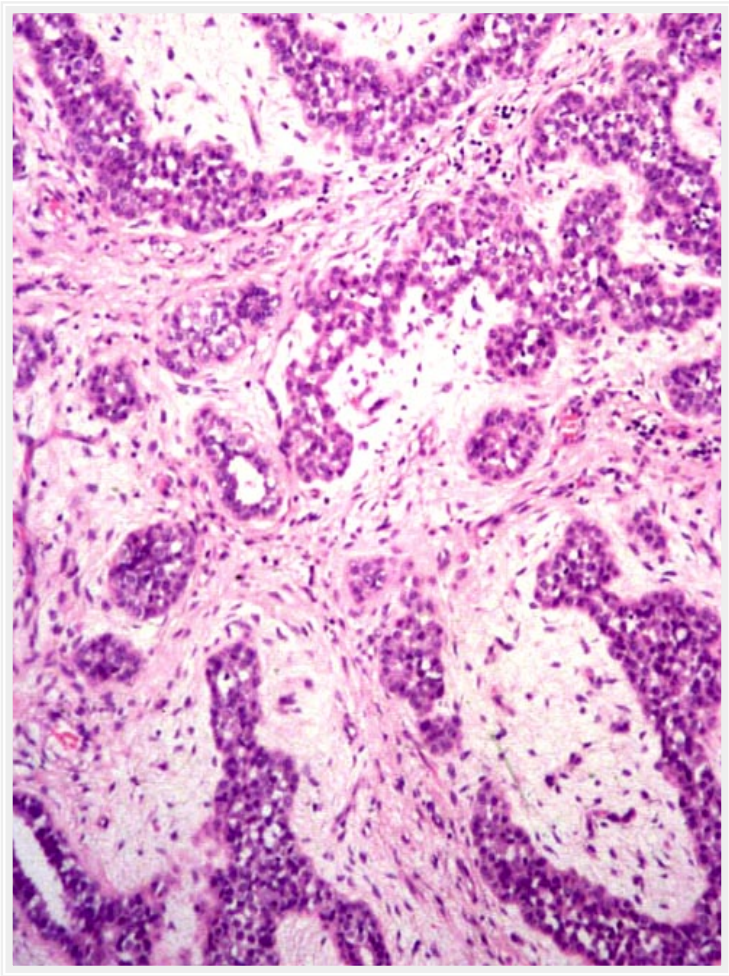
MORPHOLOGICAL BREAST CHANGES FROM NORMAL TO INVASIVE CANCER



ATYPICAL DUCTAL HYPERPLASIA = DIN 1b

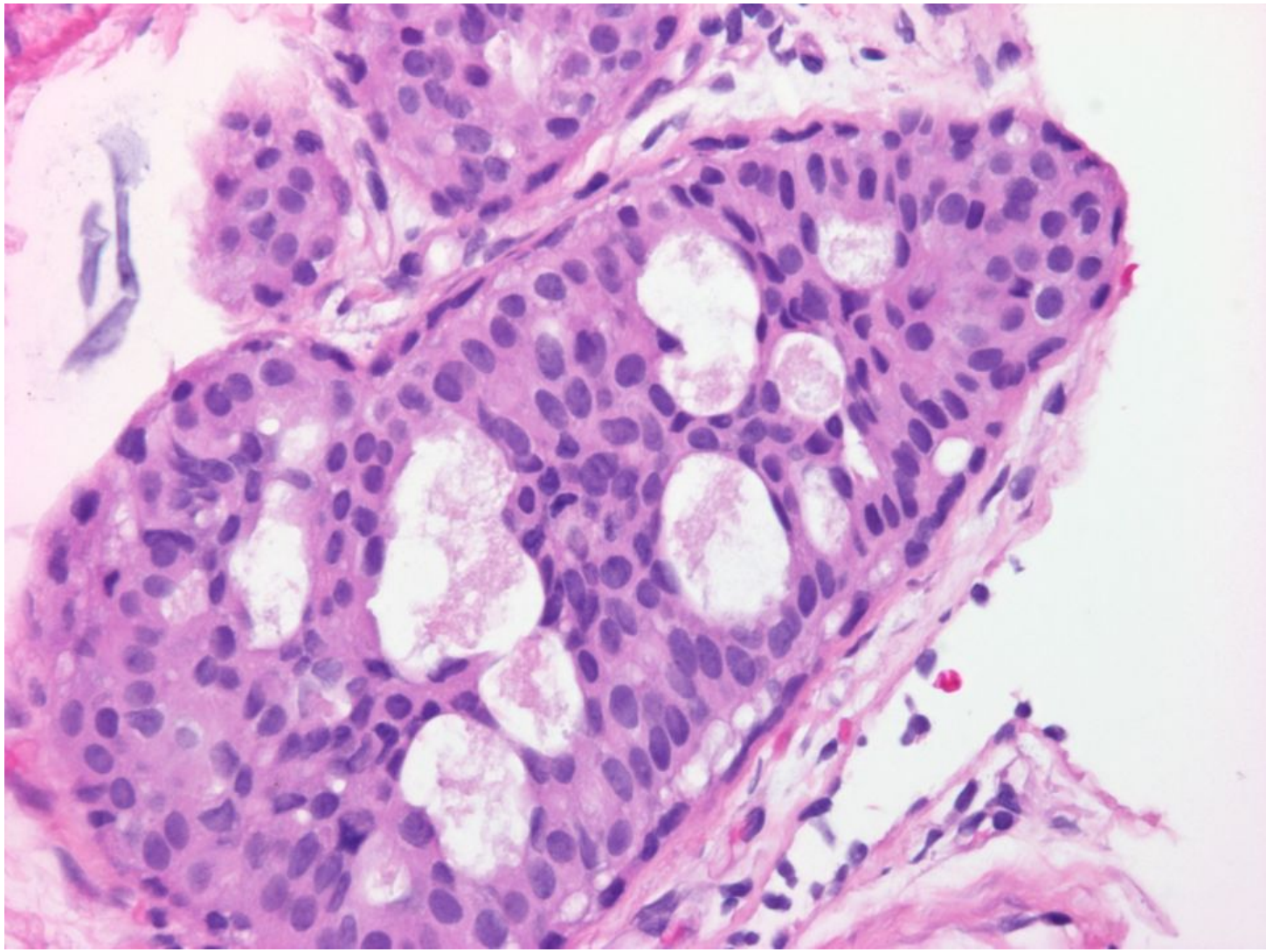


Usual ductal hyperplasia



Atypical ductal hyperplasia
DIN 1b

ATYPICAL DUCTAL HYPERPLASIA = DIN 1b

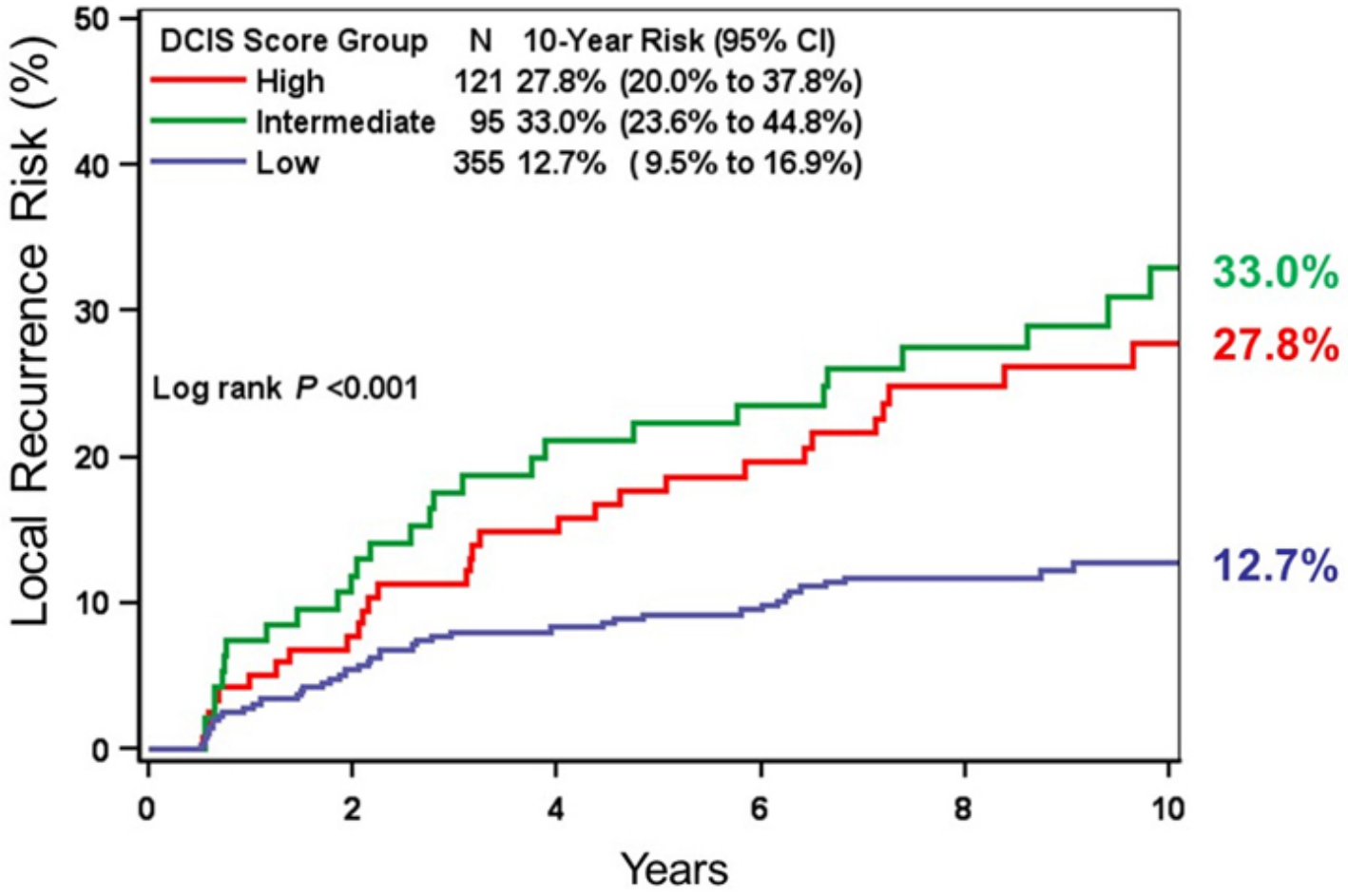


DUCTAL CARCINOMA IN SITU = DIN 1c-3

- Neoplastic lesions extensively growing within the lumen
- Increased:
  - extension (≥2 mm.)
  - architectural distorsion
  - nuclear pleomorphism
- Higher risk of recurrence (DCIS)
- Higher risk of association with invasive cancer

DUCTAL CARCINOMA IN SITU = DIN 1c-3

10-Year Risk of Local Recurrence, Based on DCIS score



DUCTAL CARCINOMA IN SITU = DIN 1c-3

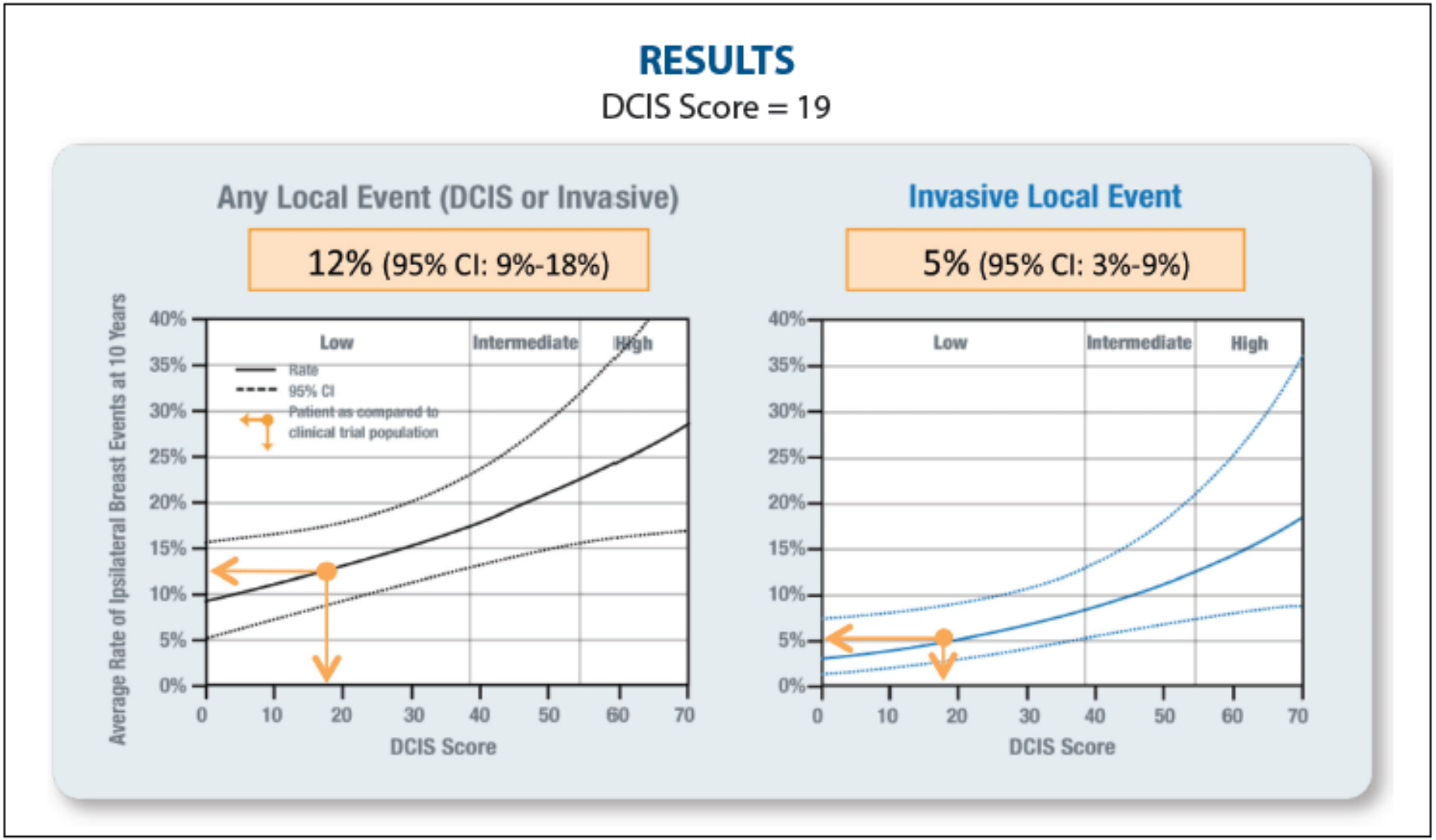
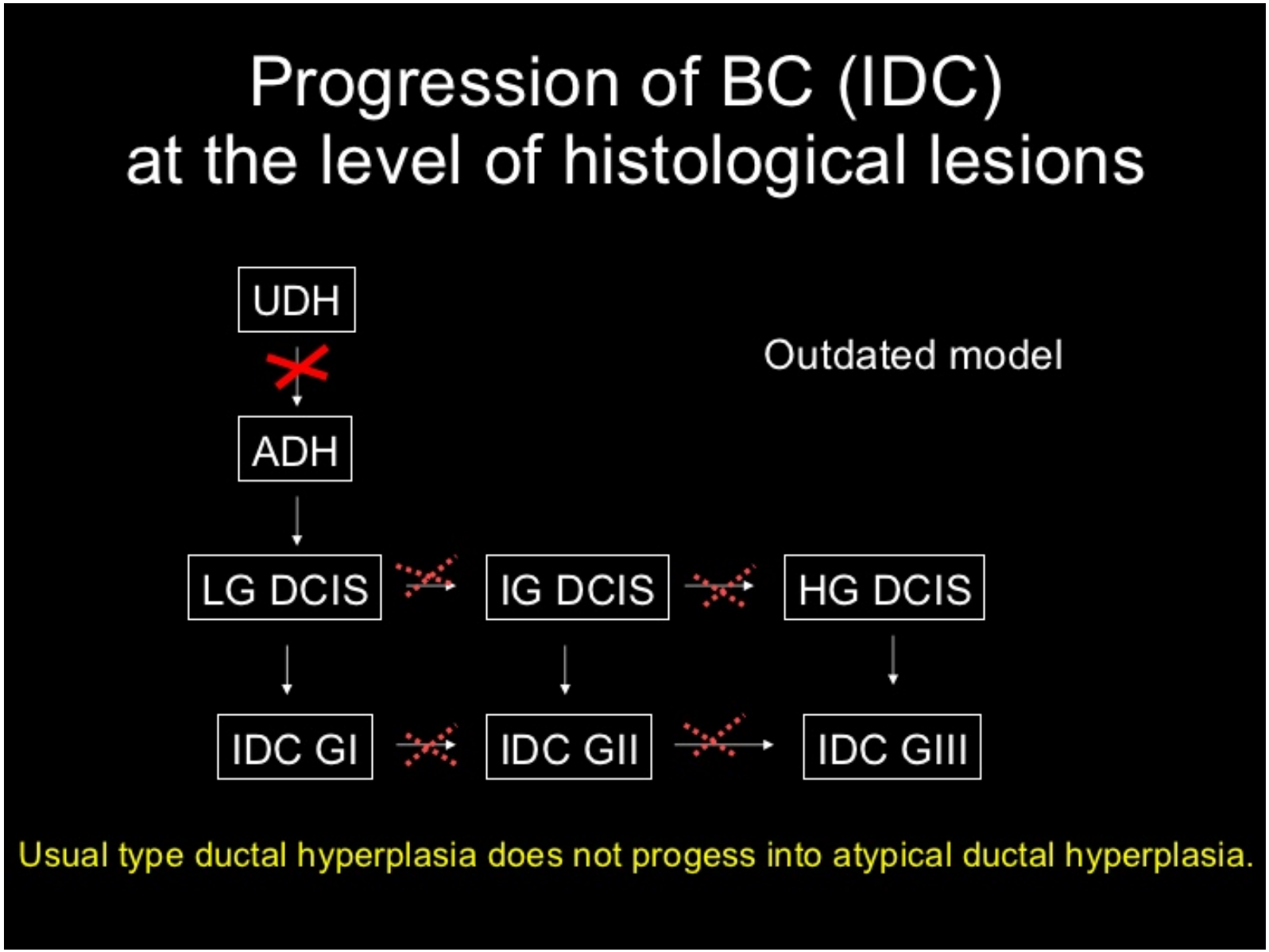
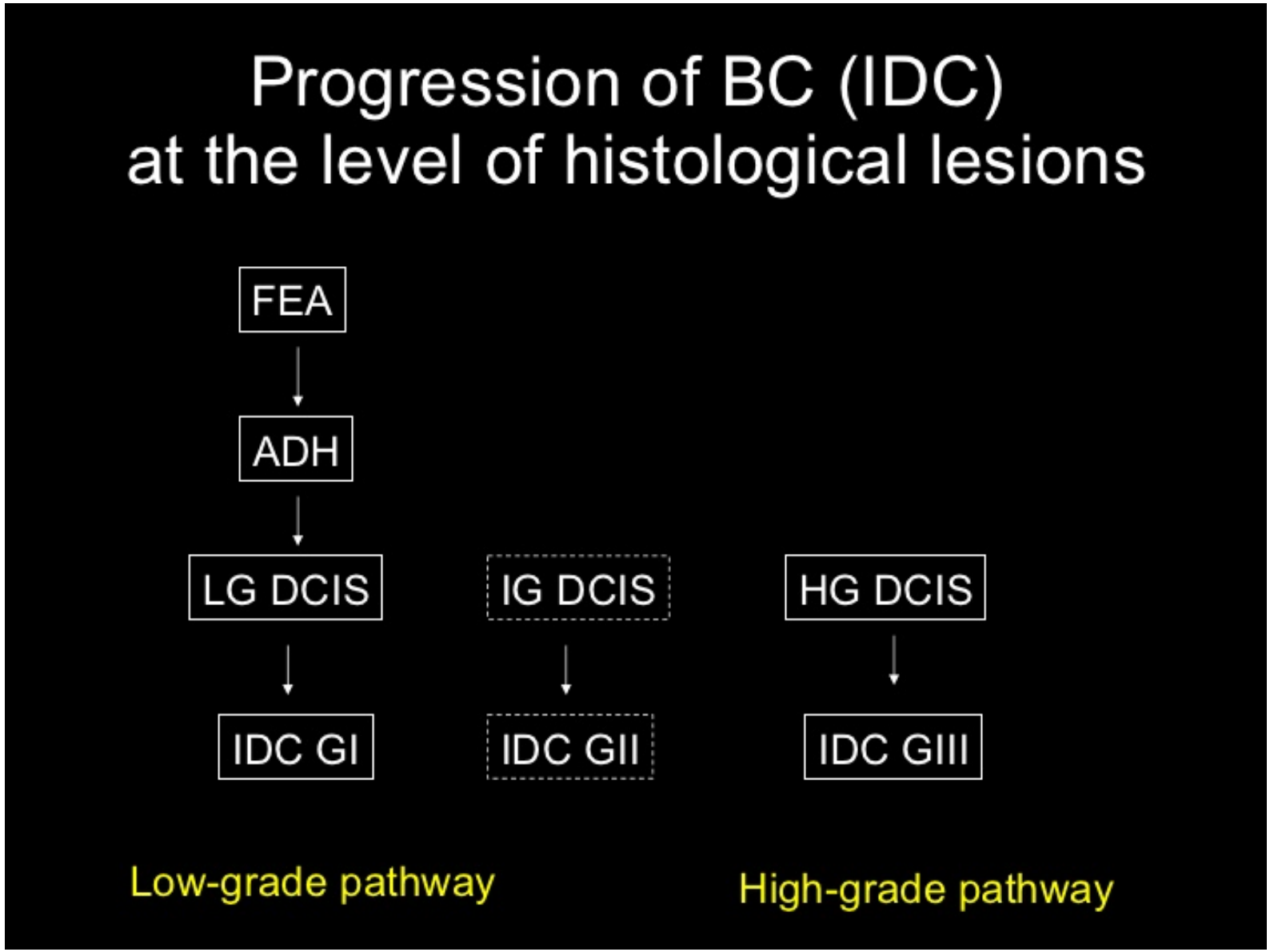


Figure 3: Using the DCIS Score to Determine 10-Year Risk Estimates for an Ipsilateral Breast Event (left) and Invasive Breast Cancer (right)—CI = confidence interval; DCIS = ductal carcinoma in situ.

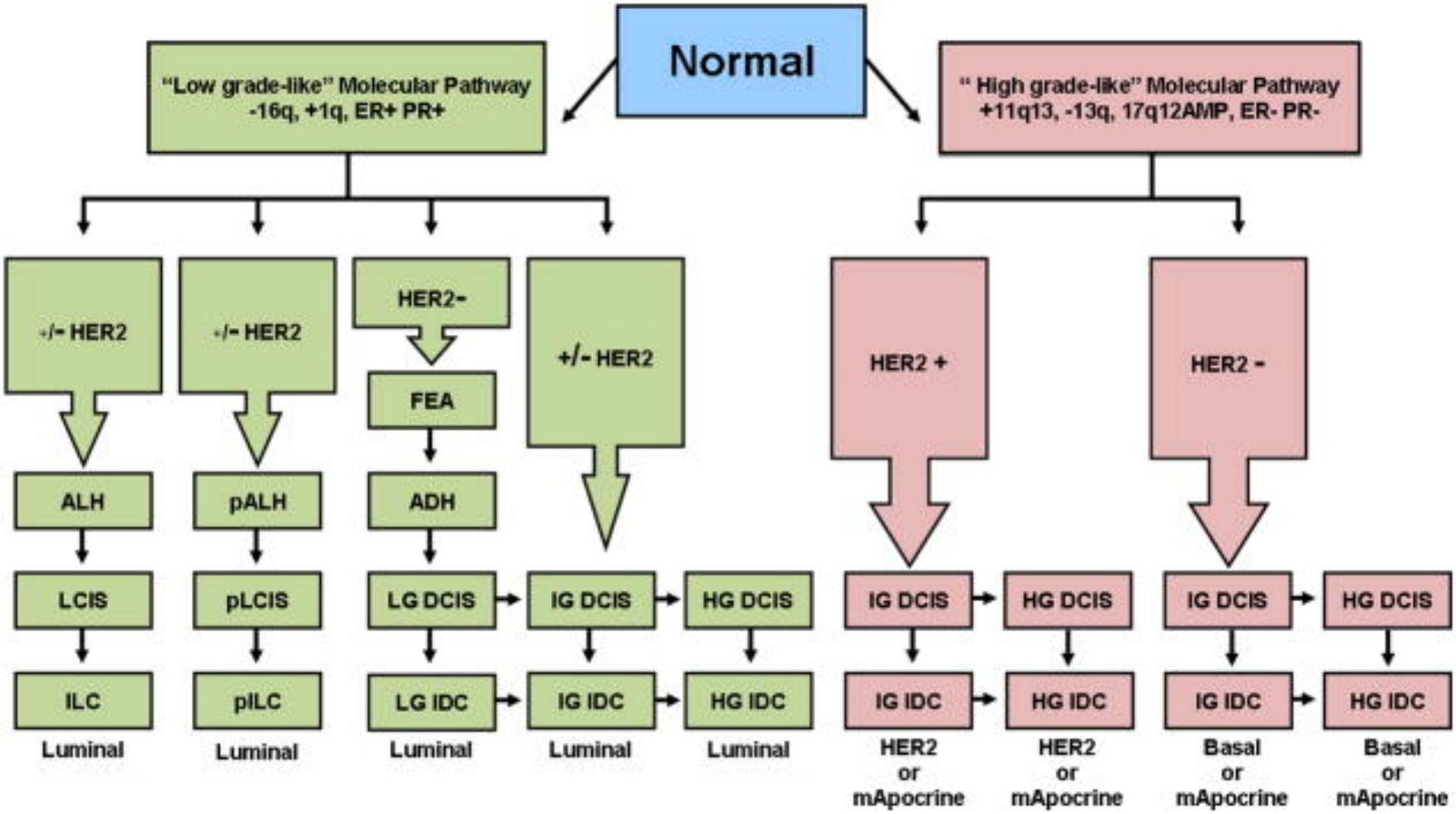
PROGRESSION TO CANCER = OLD



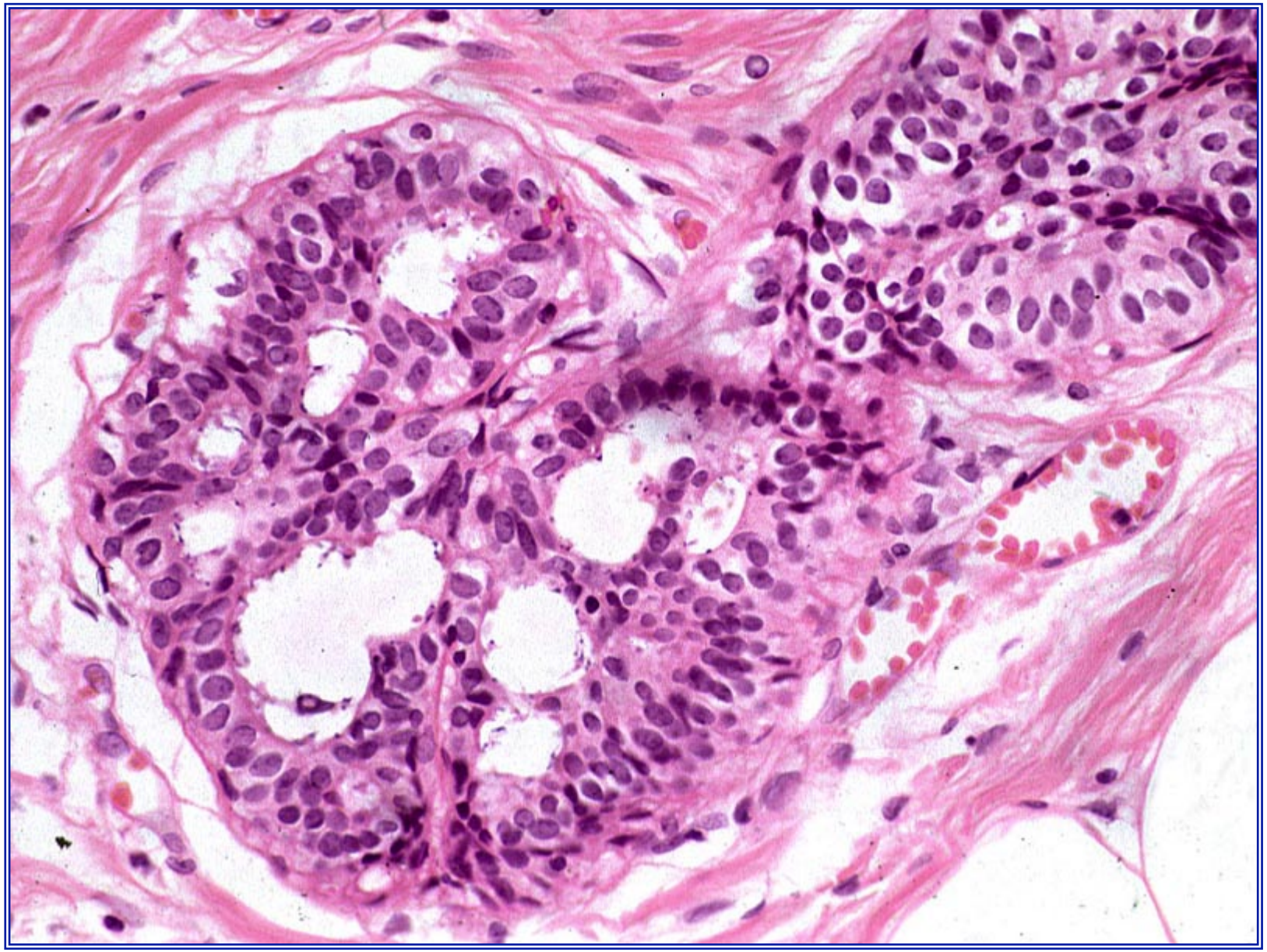
PROGRESSION TO CANCER = NEW



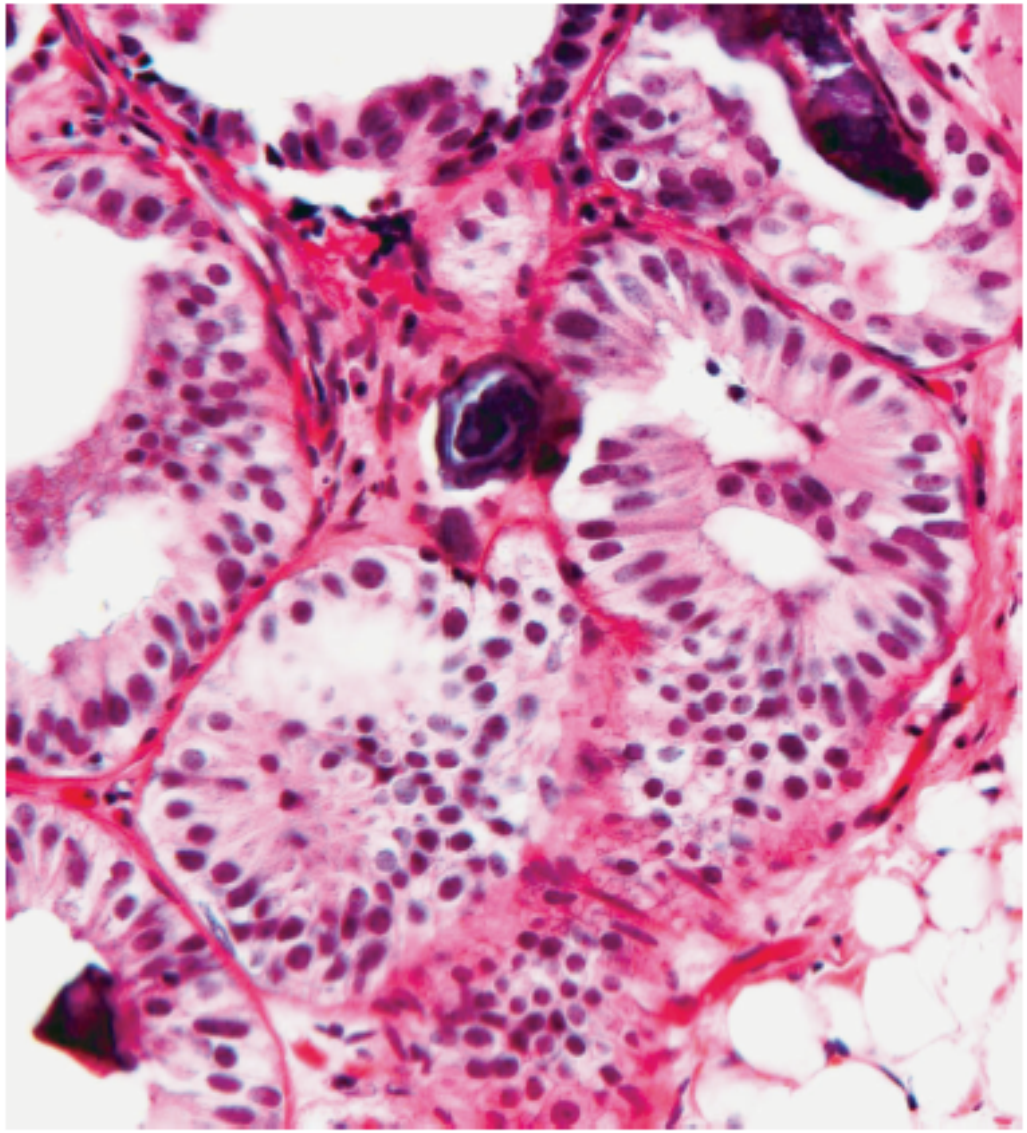
PROGRESSION TO CANCER = NEW



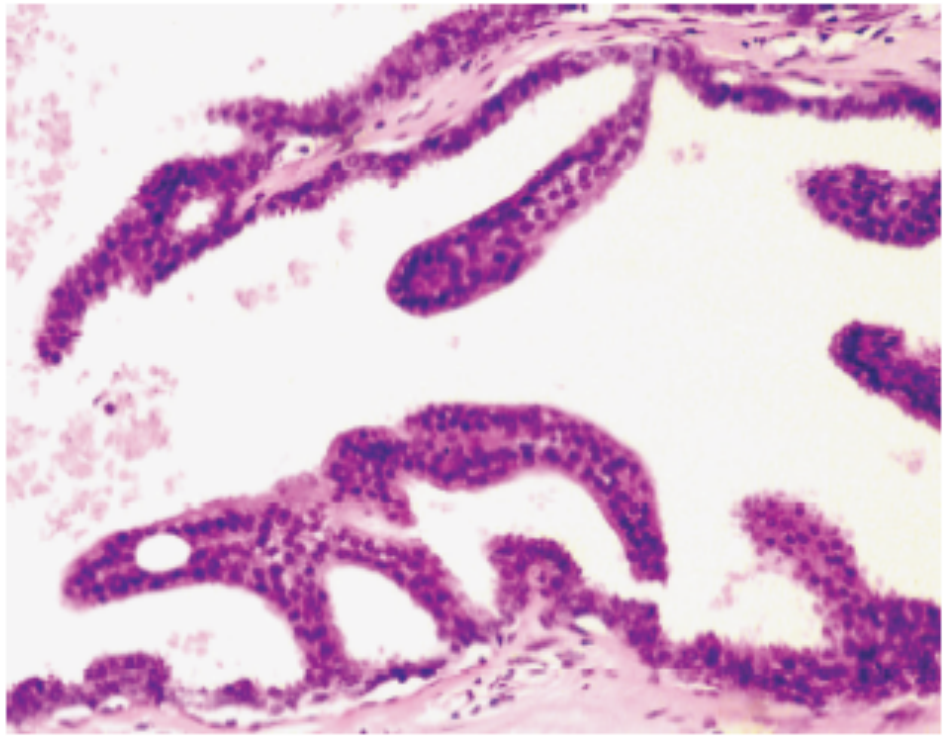
Well differentiated DCIS – DIN 1c



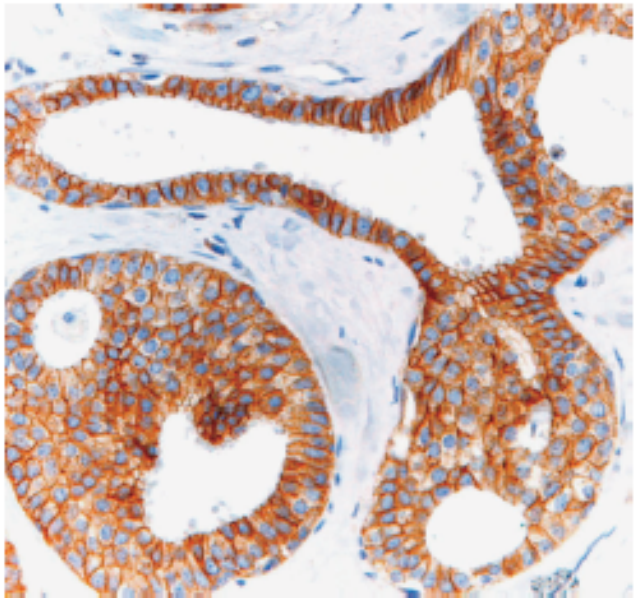
Well differentiated DCIS – DIN 1c with microcalcifications



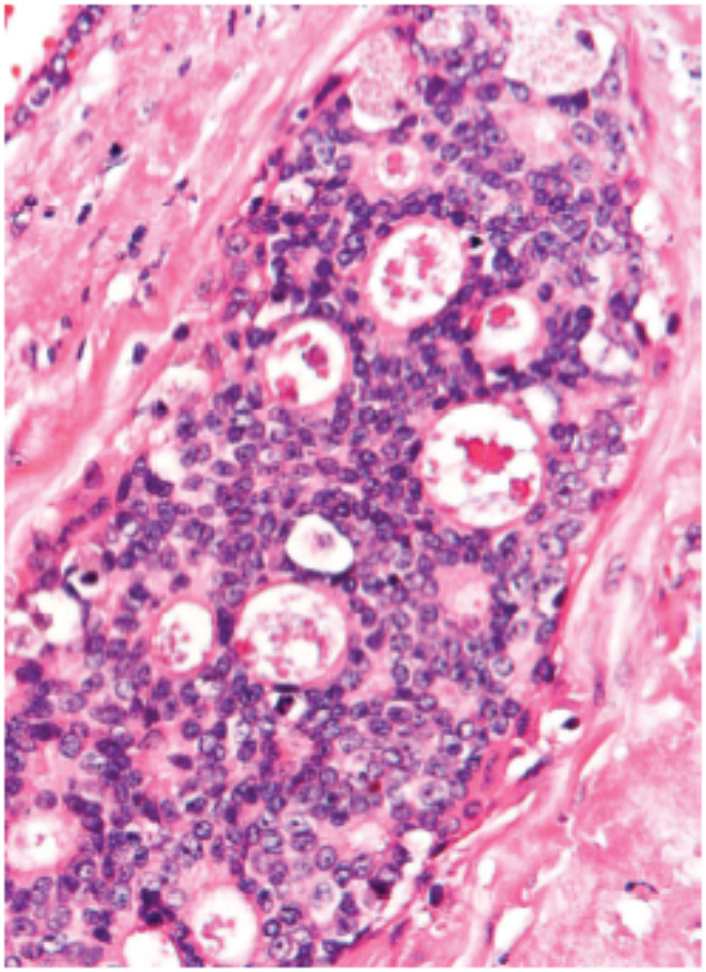
Well differentiated DCIS – DIN 1c with micropapillae (a) or cribriform pattern (b)



a

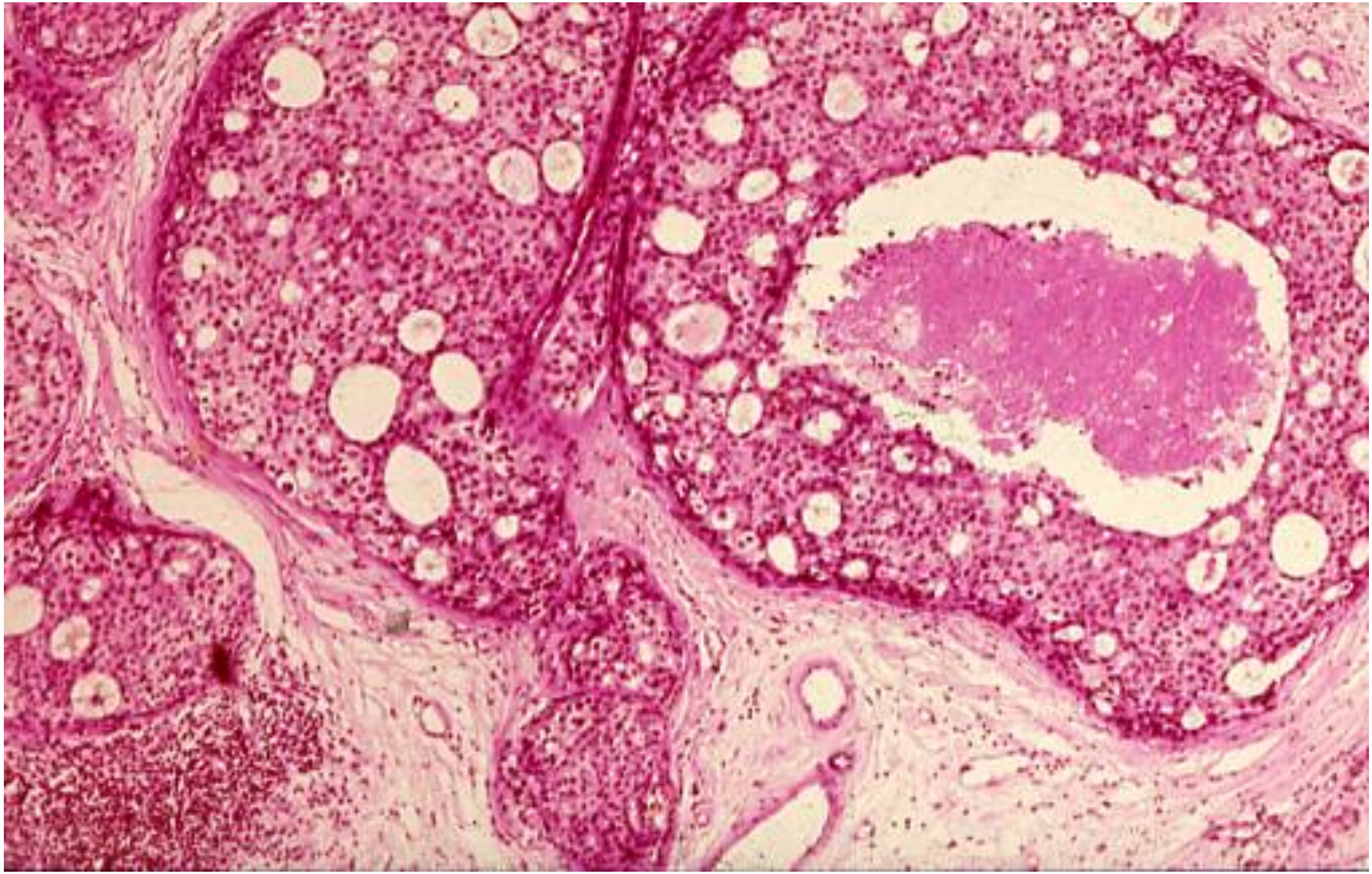


c

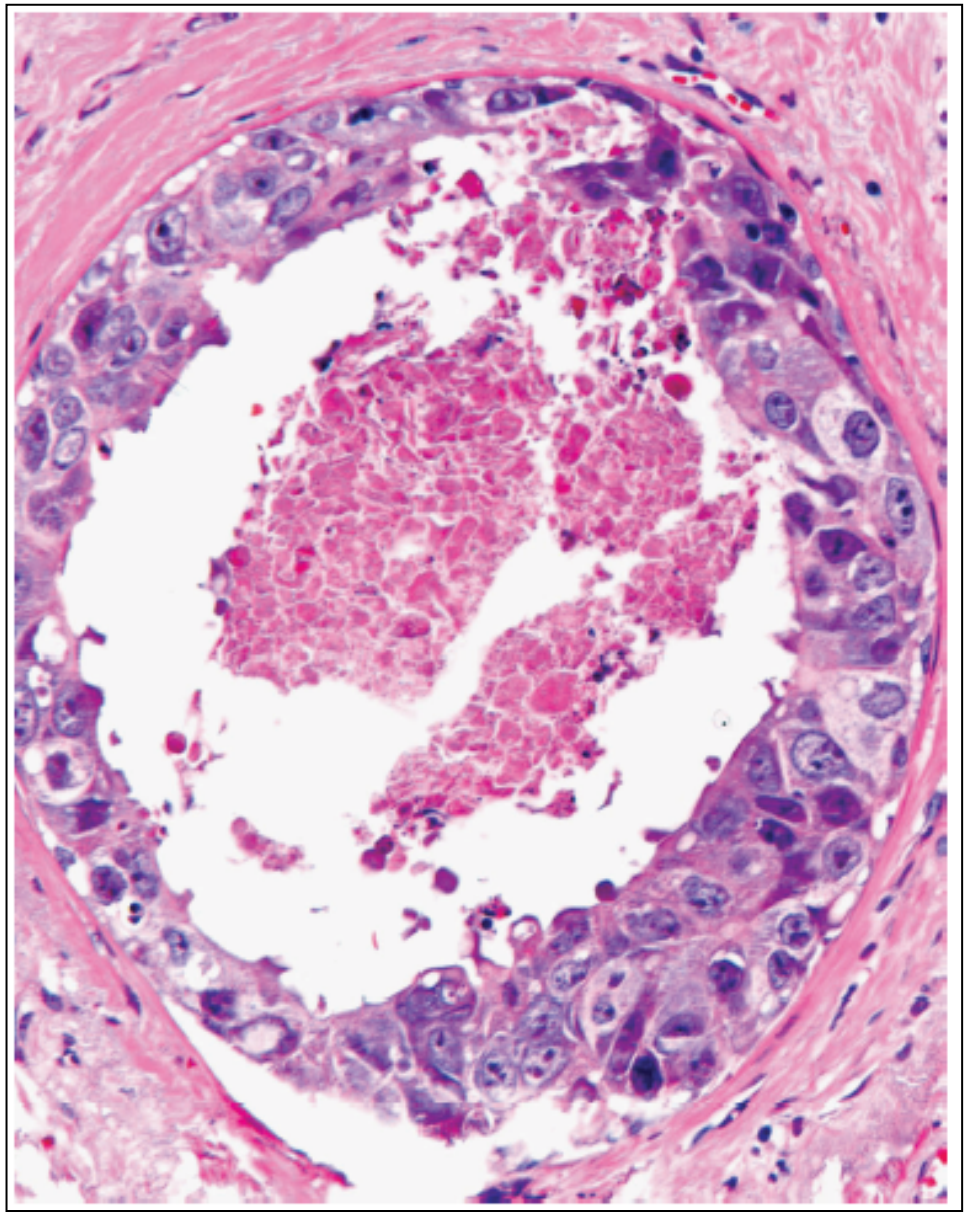


b

Moderately differentiated DCIS – DIN 2 with microcalcifications and necrosis

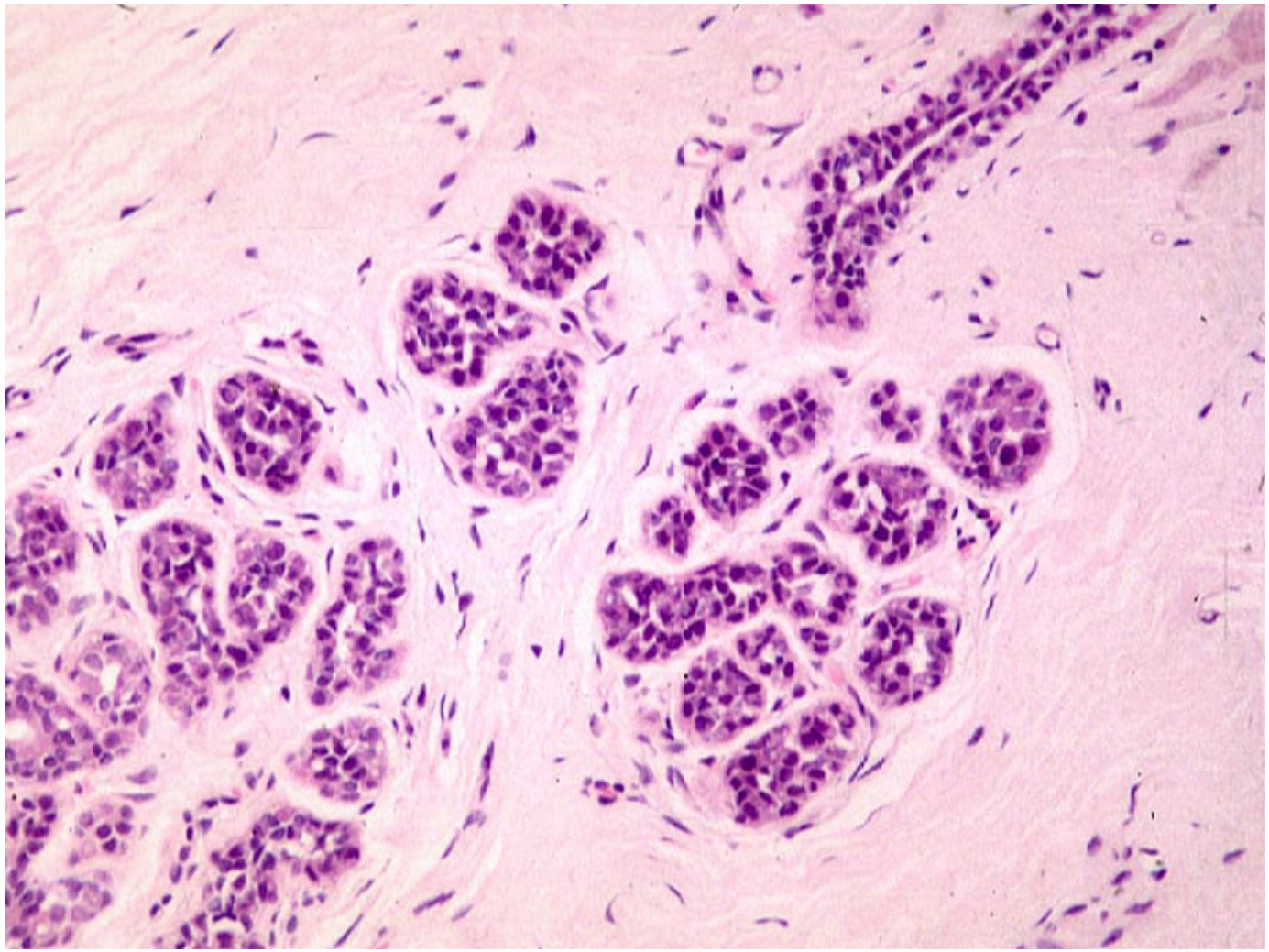


Poorly differentiated DCIS – DIN 3 with microcalcifications, necrosis and nuclear pleomorphism



LOBULAR HYPERPLASTIC LESIONS

USUAL	Non-distended acini, partly or completely filled with monomorphic cells
ATYPICAL	Poorly distended acini, filled with poorly cohesive monomorphic cells; partial or complete lobular involvement
LOBULAR CARCINOMA IN SITU	Severely distended acini, filled with cells that may be pleomorphic; possible confluence of adjacent acini; expansion of lobules



LIN 1-2-3

Traditional terminology	LIN terminology
Usual lobular hyperplasia	Usual lobular hyperplasia (ULH)
Atypical lobular hyperplasia	LIN Grade 1
Lobular carcinoma in situ (LCIS) low grade	LIN Grade 2
Lobular carcinoma in situ (LCIS) high grade	DIN Grade 3

LIN 1-2-3

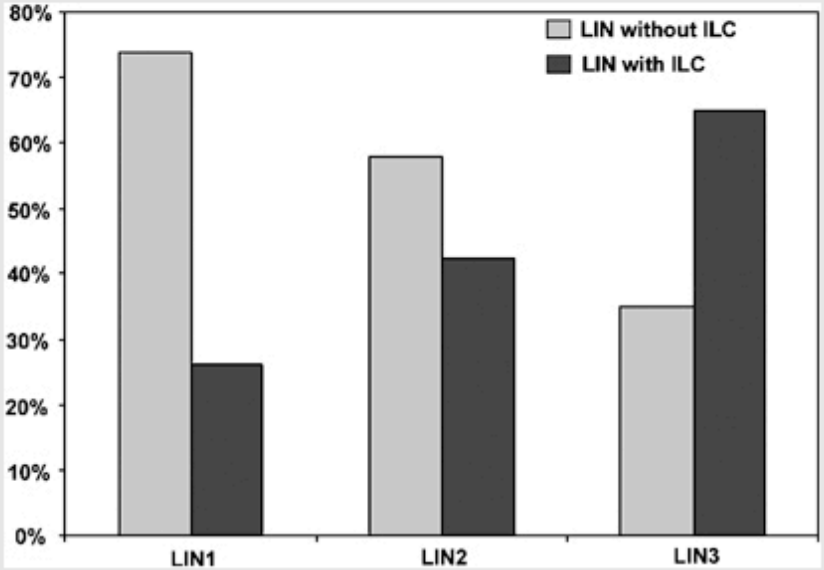
Figure and tables index

Next table

	LIN, grade 1	*LIN, grade 2*	*LIN, grade 3*
Loosely cohesive cellular proliferation	+	+	+
Preserving distinct ductular outlines	+	+	- (Virtual confluence)
Filling the acinar space	±	+	+
Acinar distension	-	+	+++ (Maximally)
Nuclear pleomorphism[a]	-	-	Rarely
Pure classic signet ring cell population[a]	-	-	Rarely

LIN, lobular intraepithelial neoplasia.

[a] If present, maximum distension of acini is not required.



Relationship between lobular intraepithelial neoplasia and invasive lobular carcinoma. The increasing grade of lobular intraepithelial neoplasia directly correlates with association of invasive lobular carcinoma (P=0.01).

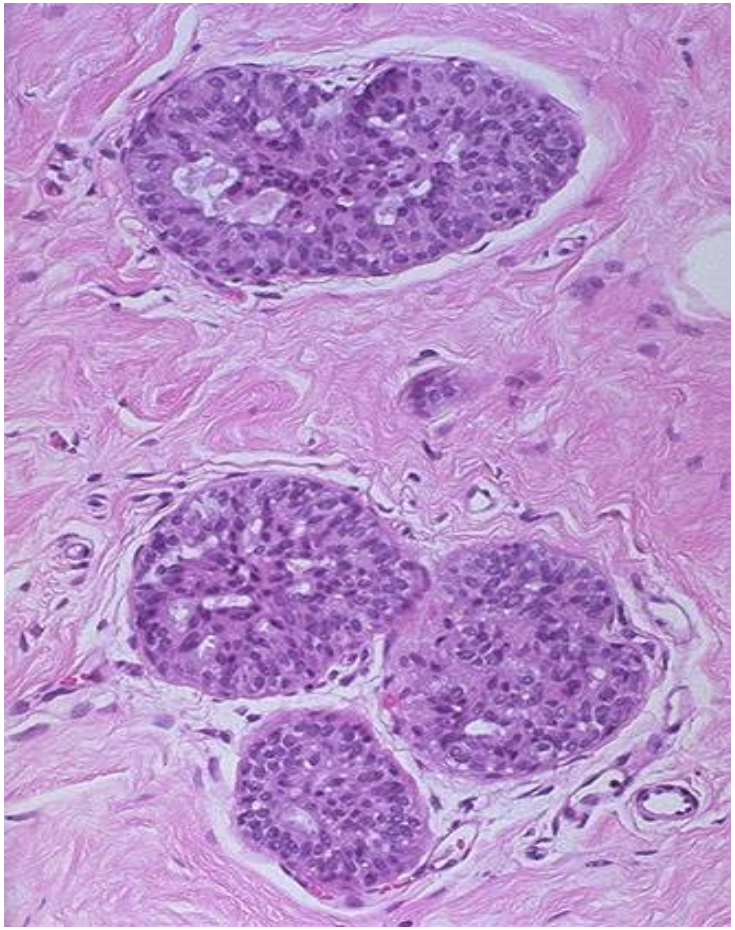
LCIS facts

- 25% of all CIS
- Frequently multicentric/bilateral
- ILC in 20-30% (life-time)
- No palpable mass (biopsy incidental finding)
- Better detected by US

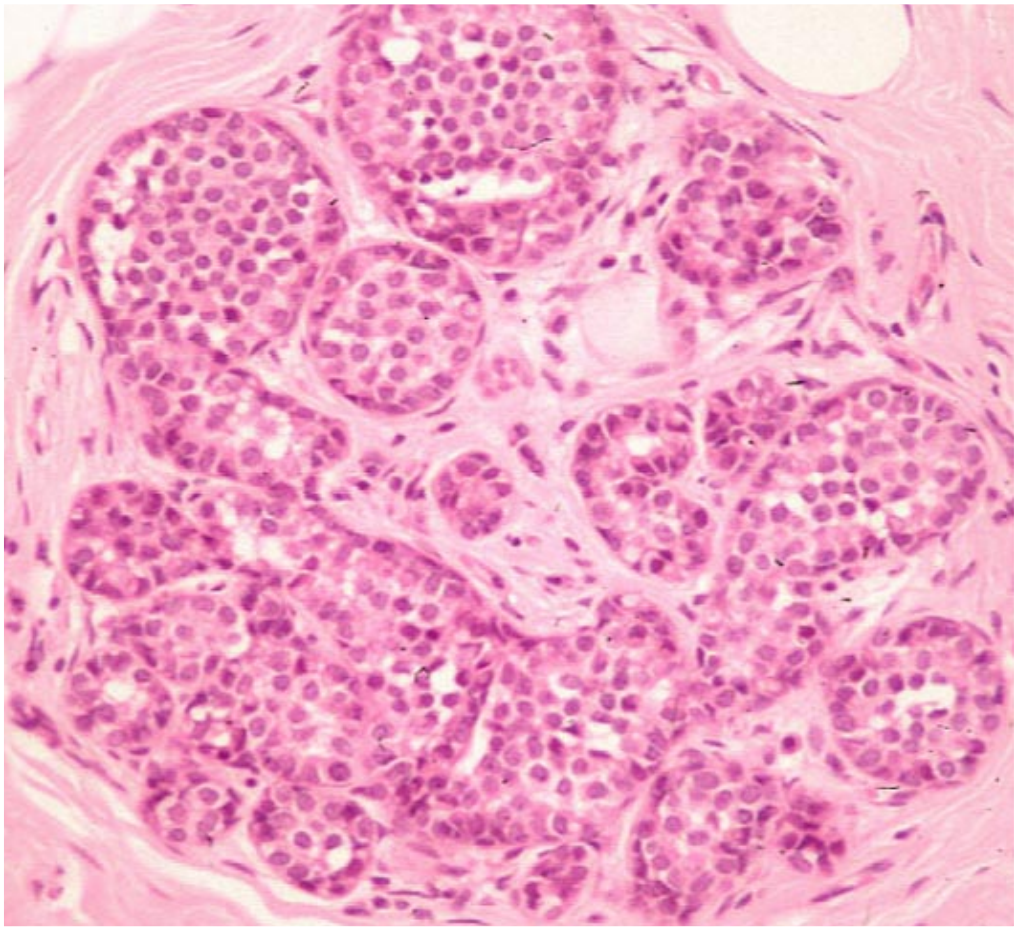
Management:

- Clinical + US follow-up (4 mo.)
- Mammography (yearly)
- Chemoprevention (anti-hormonal tx)
- Consider surgery for LIN3 and larger lesions

DUCTAL vs. LOBULAR HYPERPLASIA

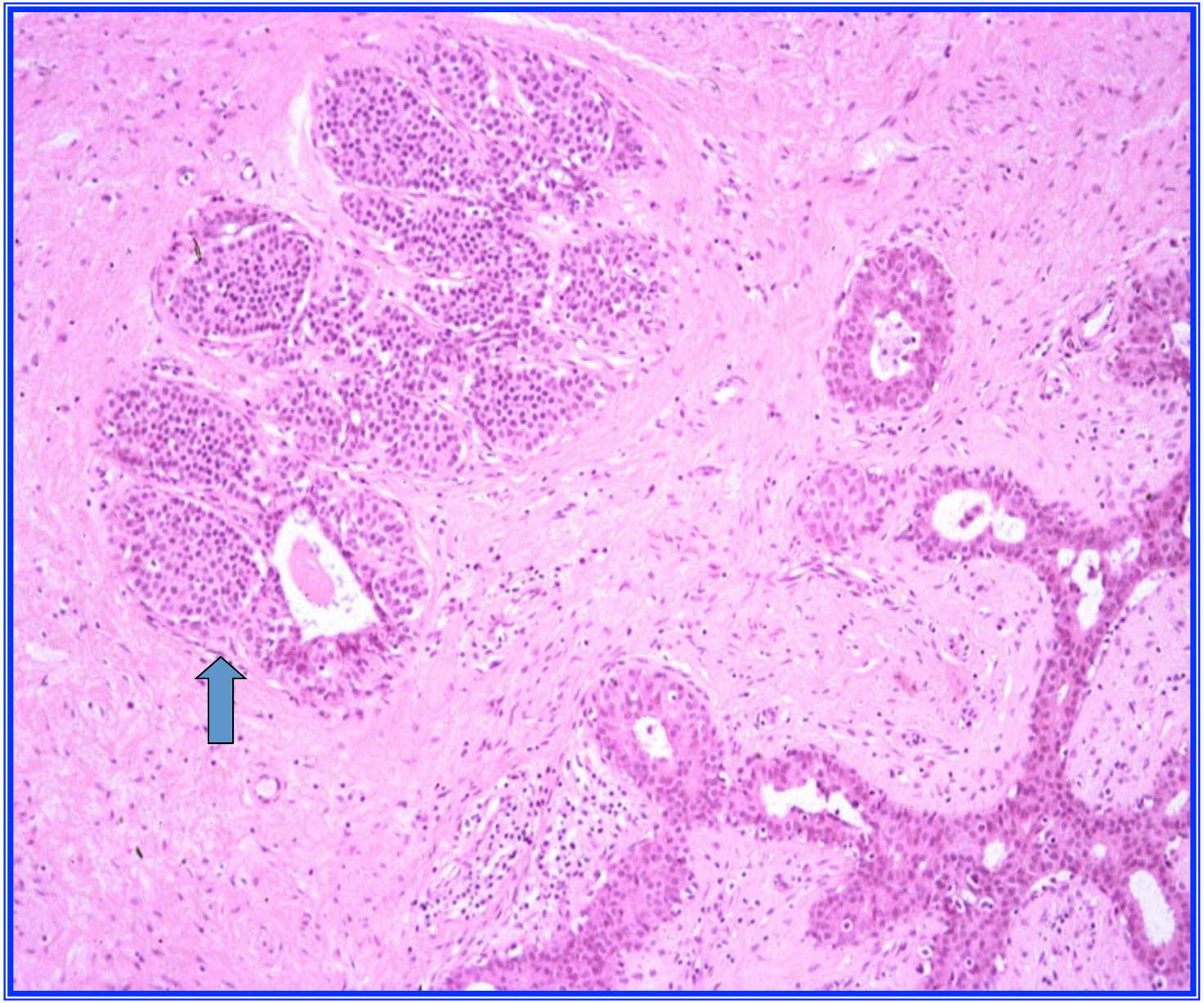


Ductal

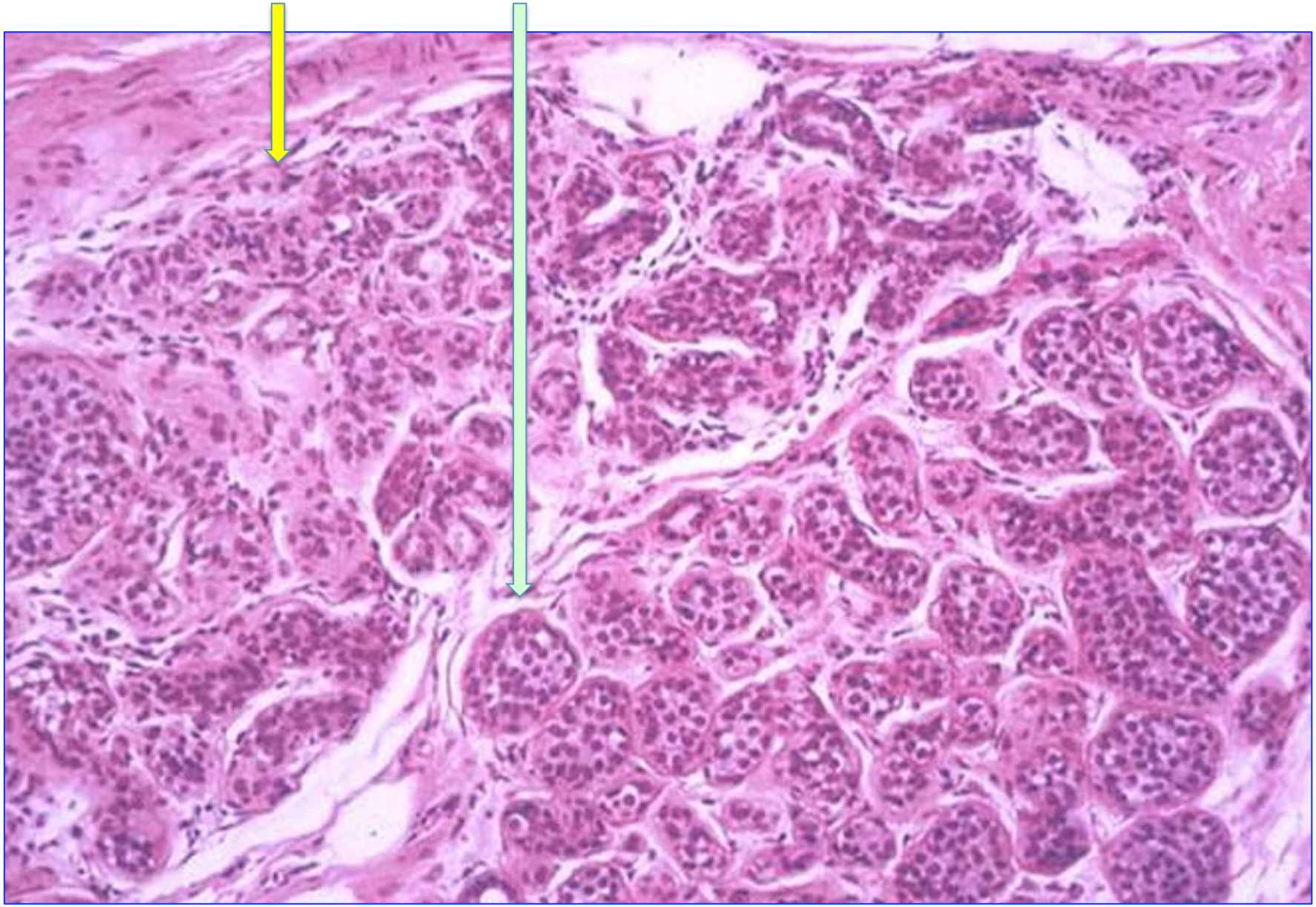


Lobular

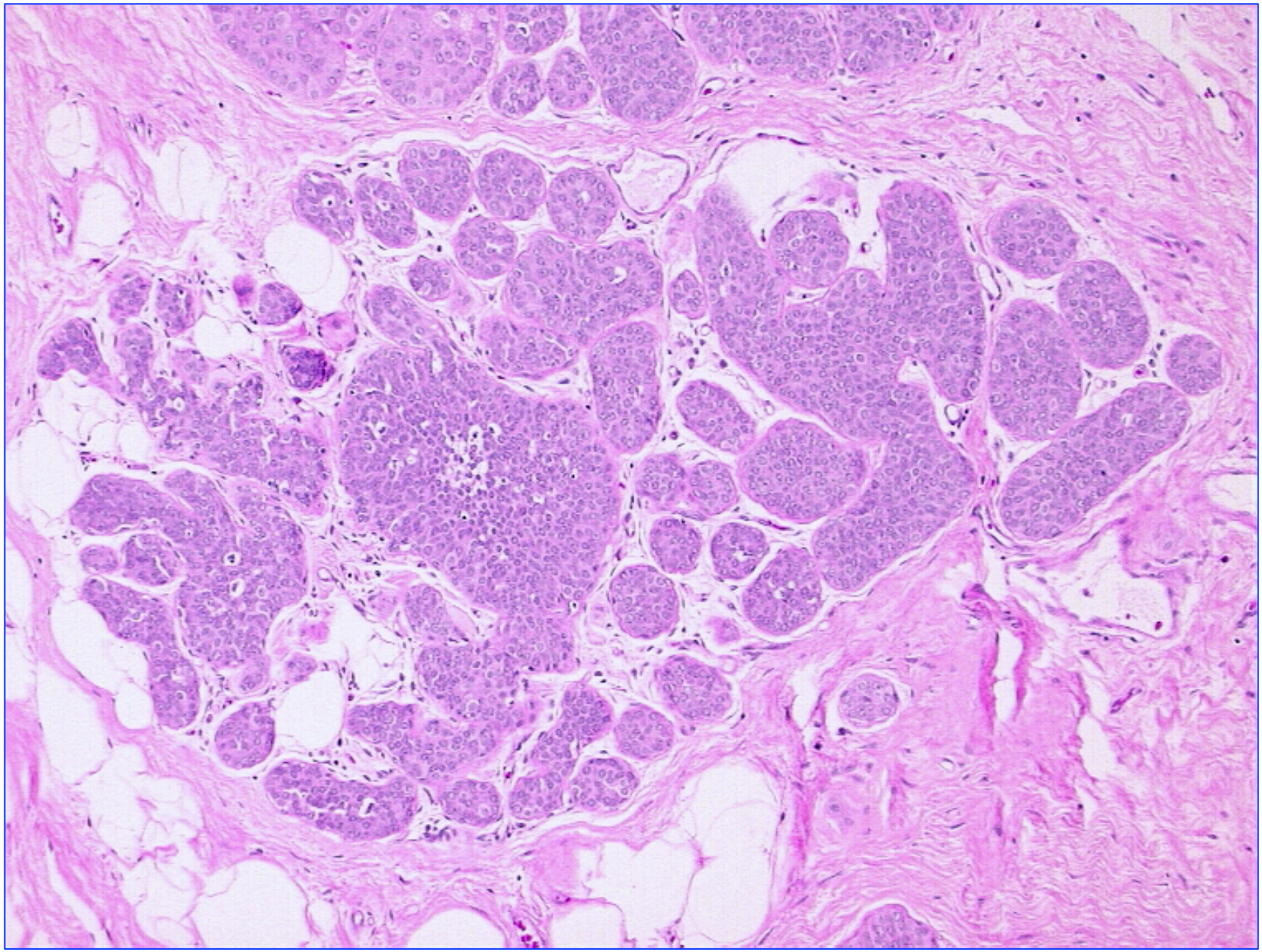
Lobular carcinoma in situ



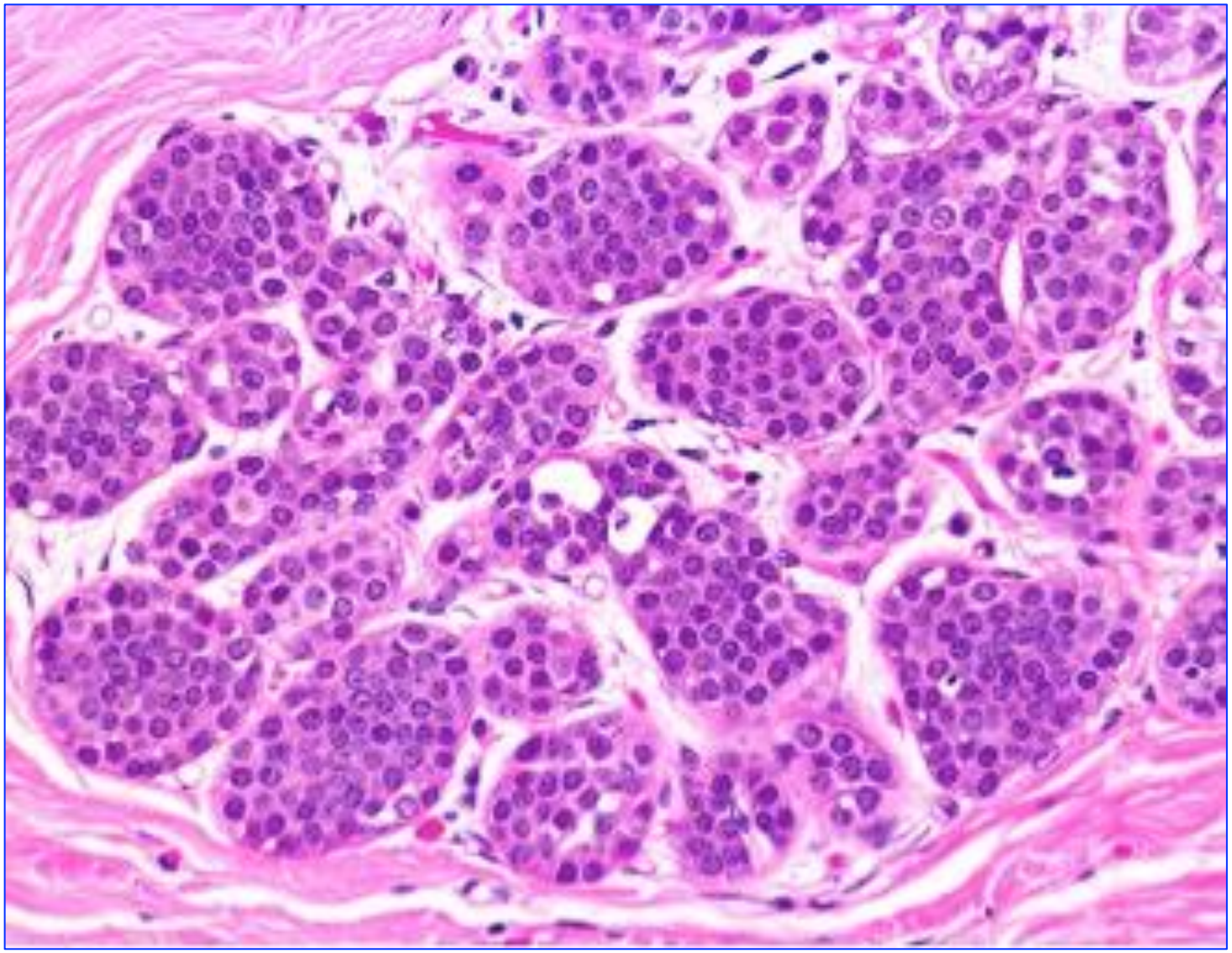
Usual & atypical lobular hyperplasia = LIN1



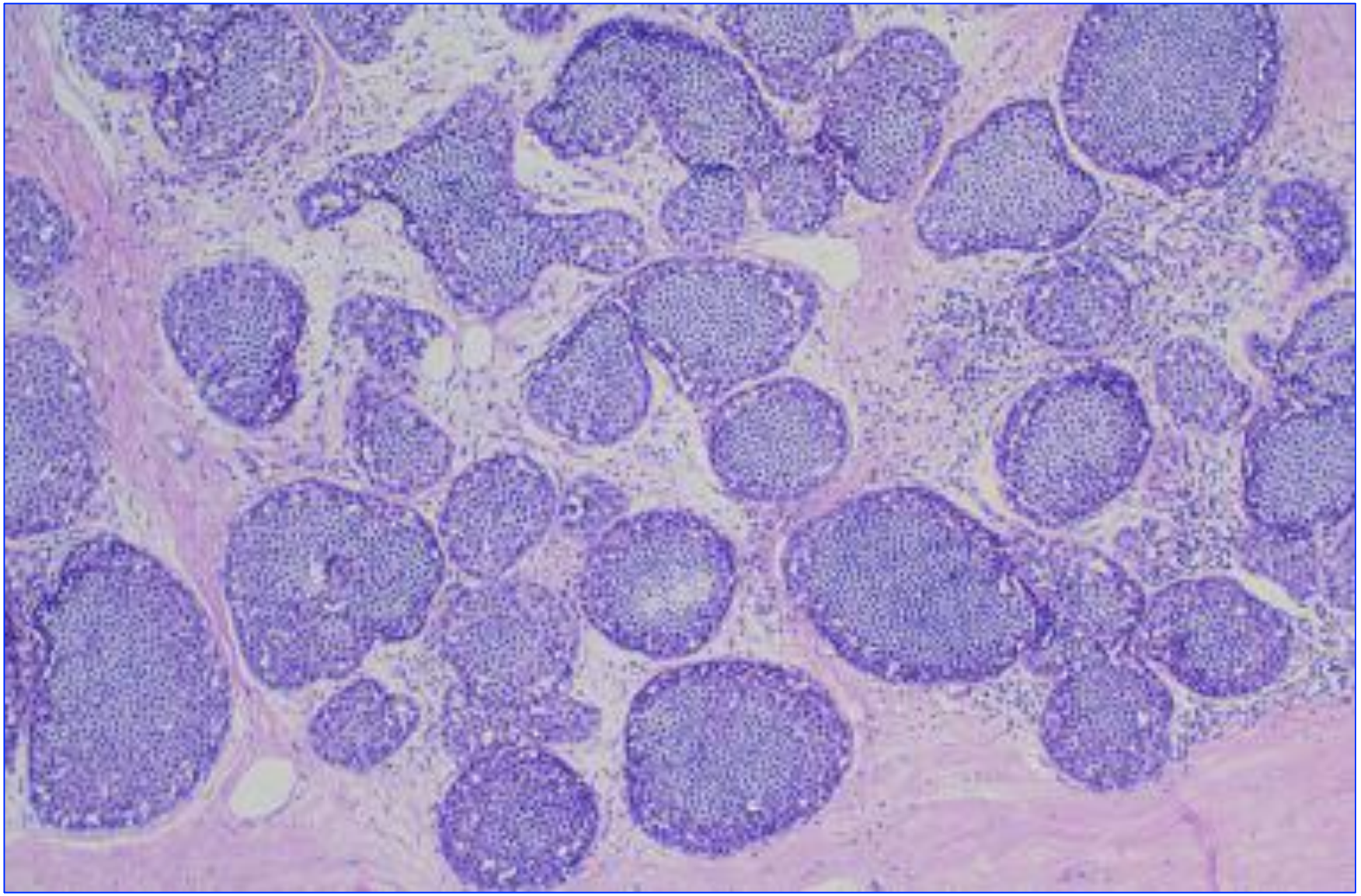
Lobular carcinoma in situ, low grade = LIN2



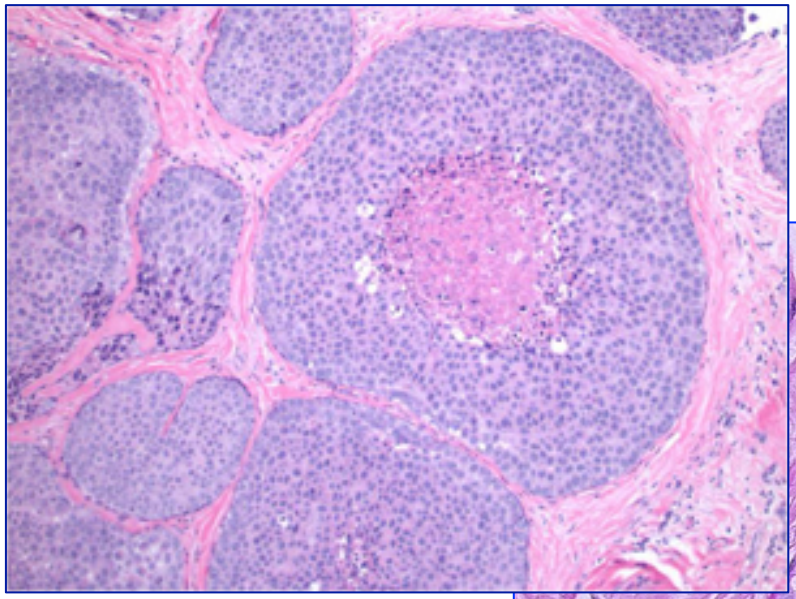
Lobular carcinoma in situ, low grade = LIN2

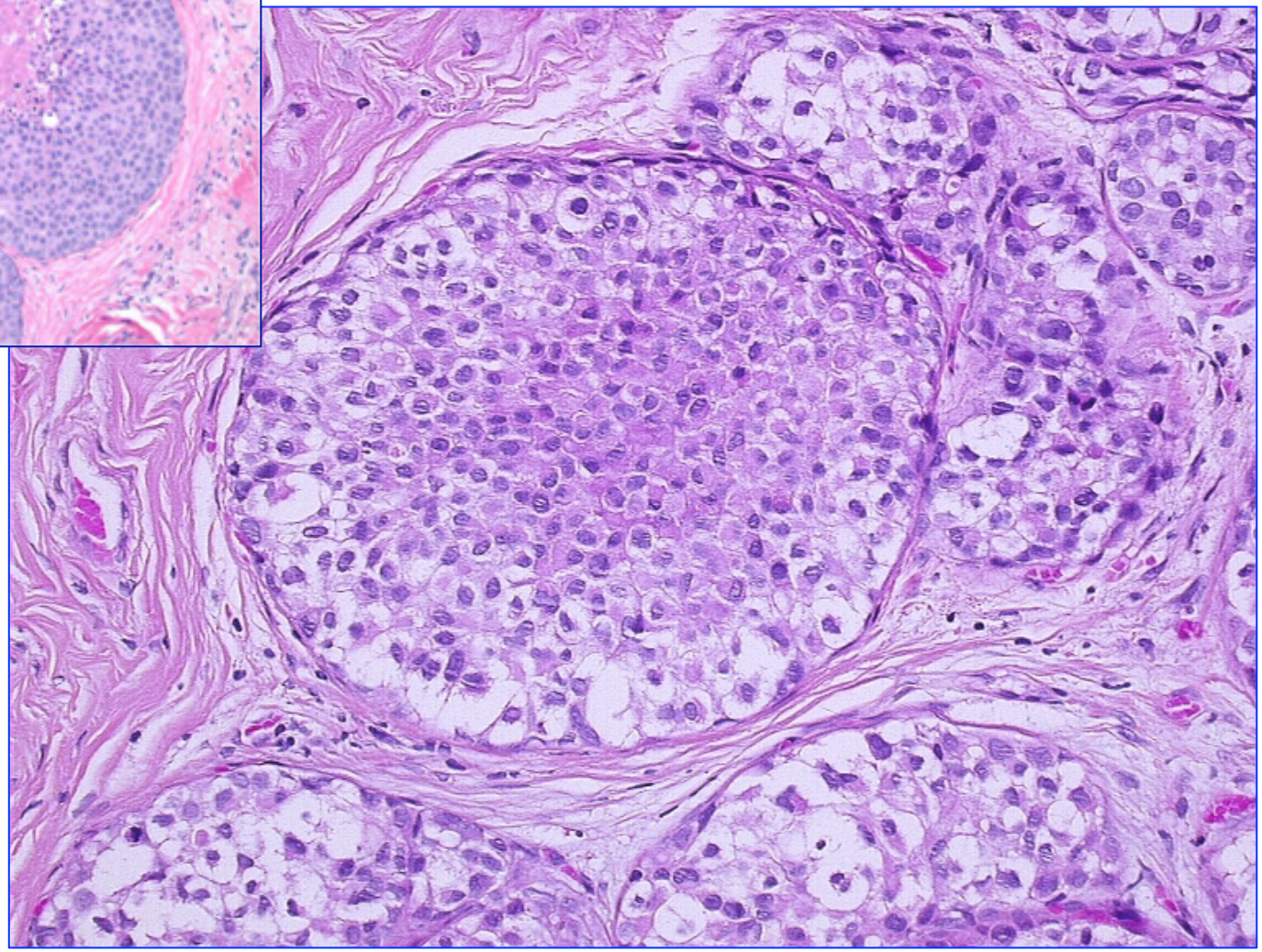


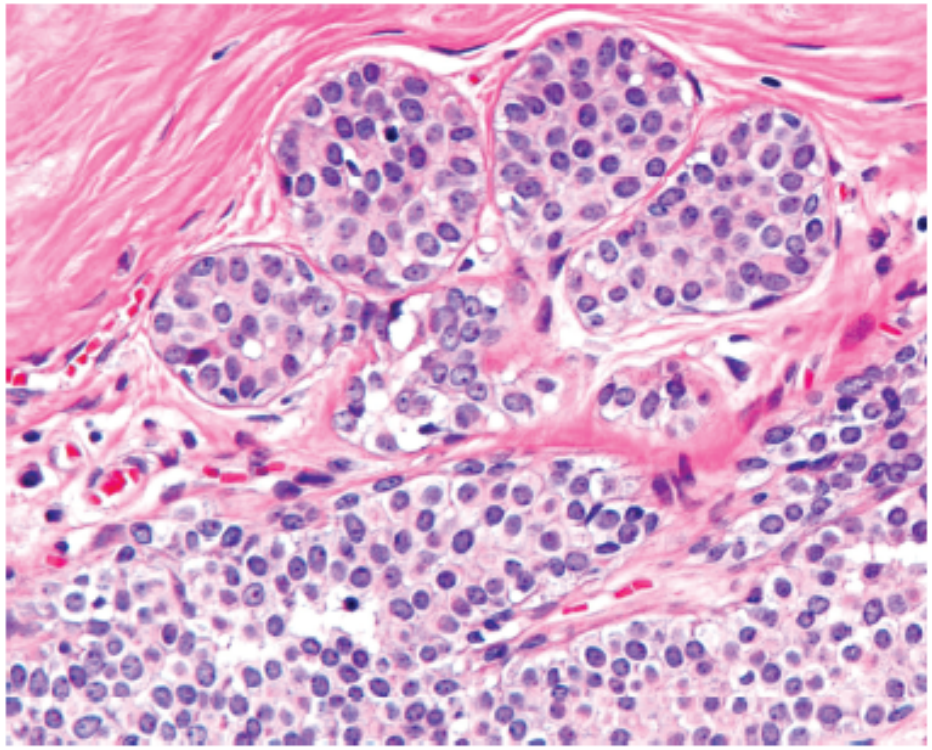
Lobular carcinoma in situ, high grade = LIN3



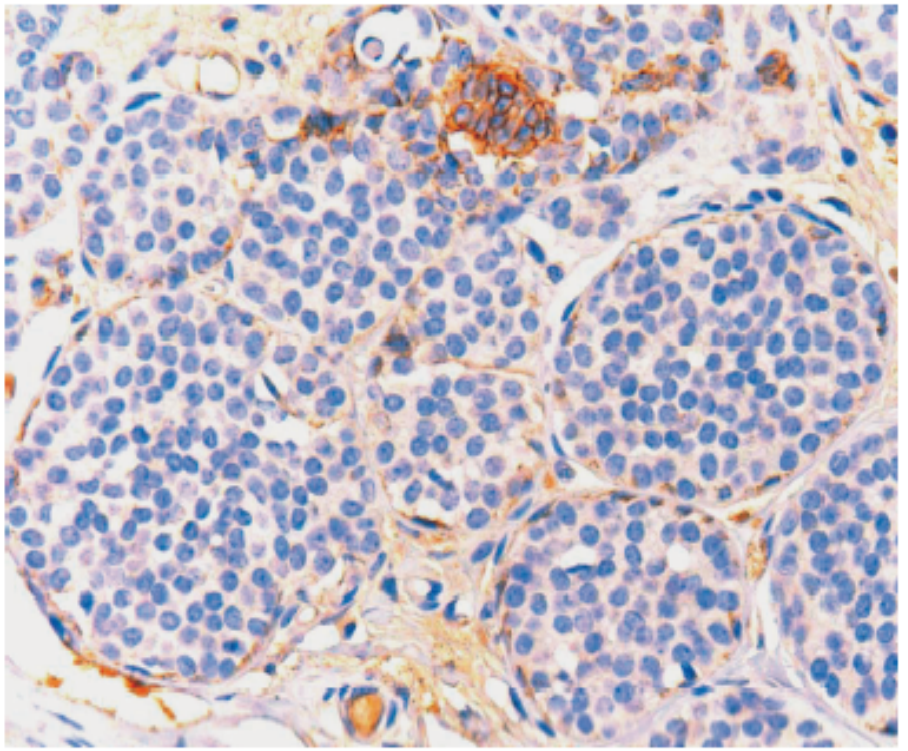
Lobular carcinoma in situ, high grade = LIN3



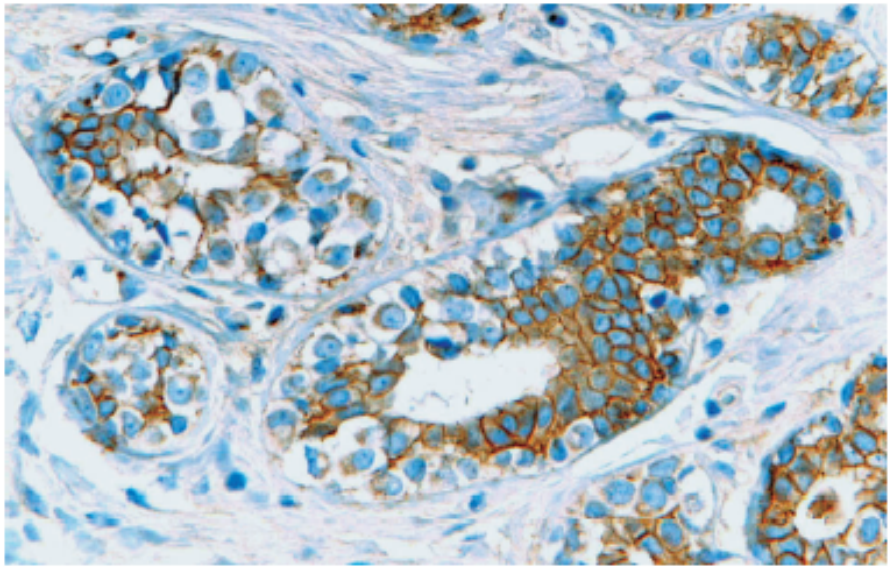




a



b



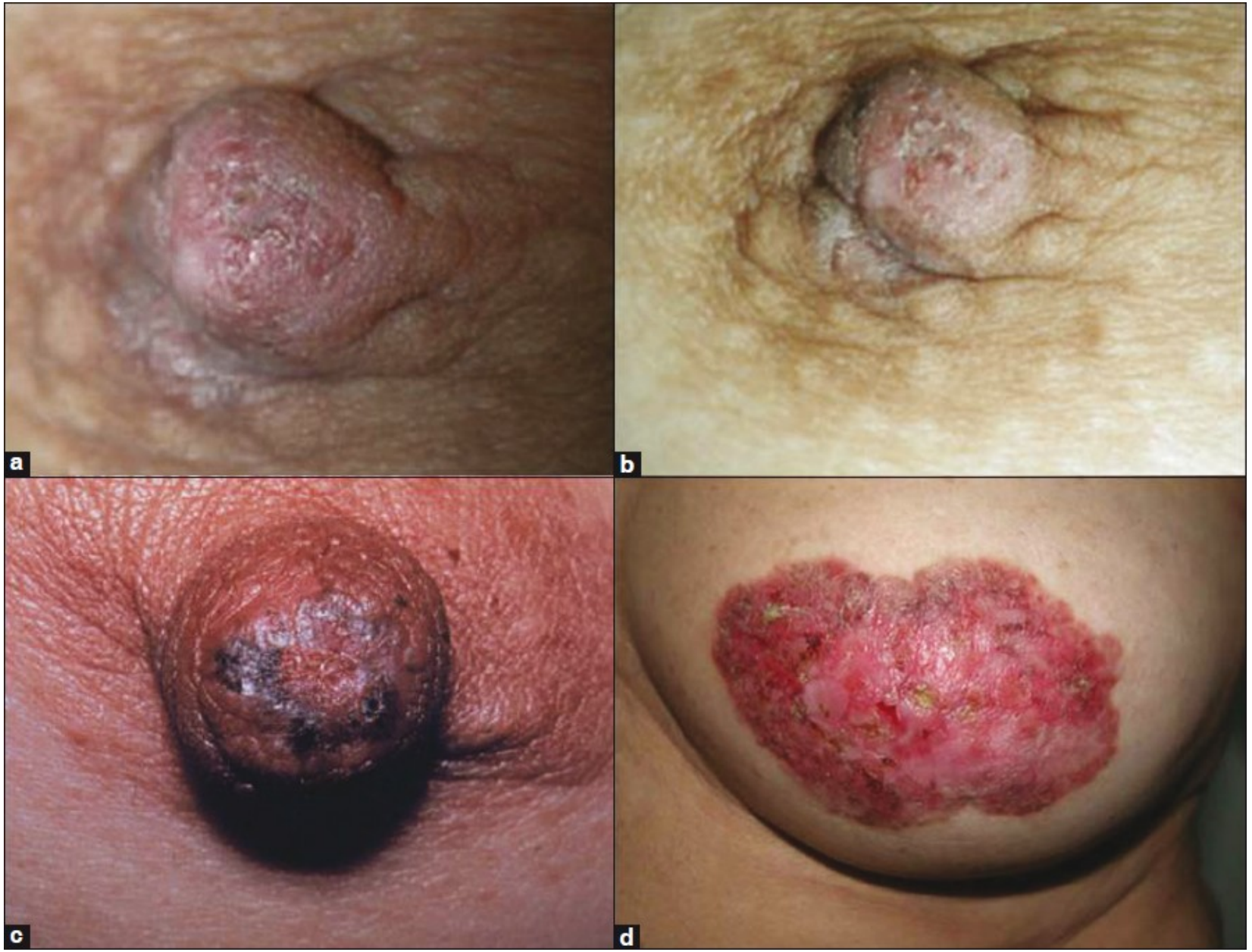
c

Fig. 40 – a) Neoplasia lobulare classica con acini espansi da cellule regolari. **b)** Neoplasia lobulare con cellule negative per *caderina e*. **c)** Diffusione Pagetoide: le cellule della neoplasia lobulare, negative per *caderina e*, si insinuano tra il mioepitelio e l'epitelio secretorio del lume. Queste ultime si riconoscono in quanto conservano la colorazione della membrana cellulare per *caderina e*.

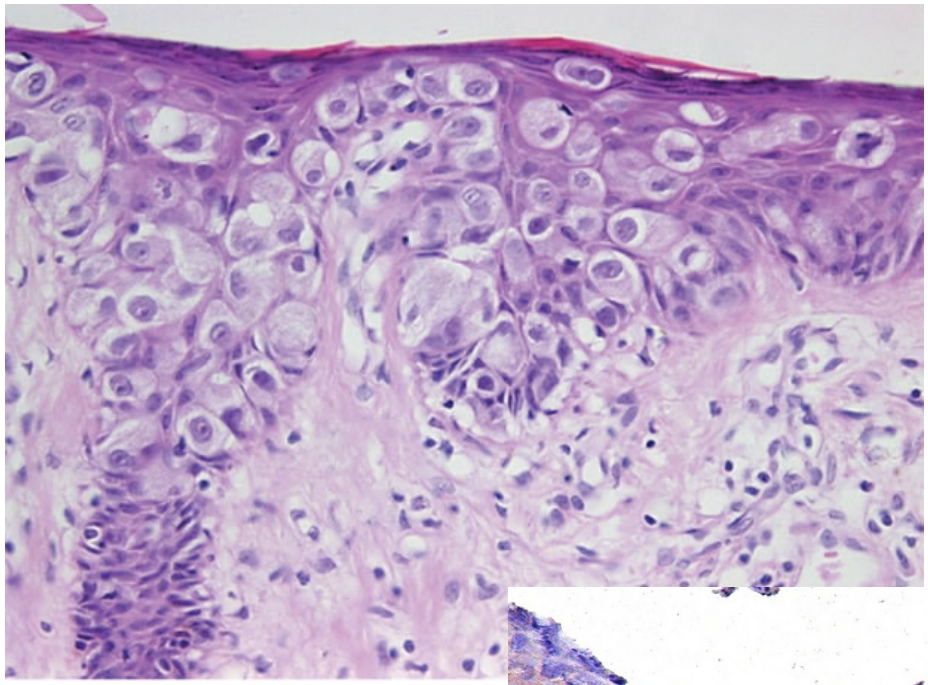
Paget's disease of the nipple

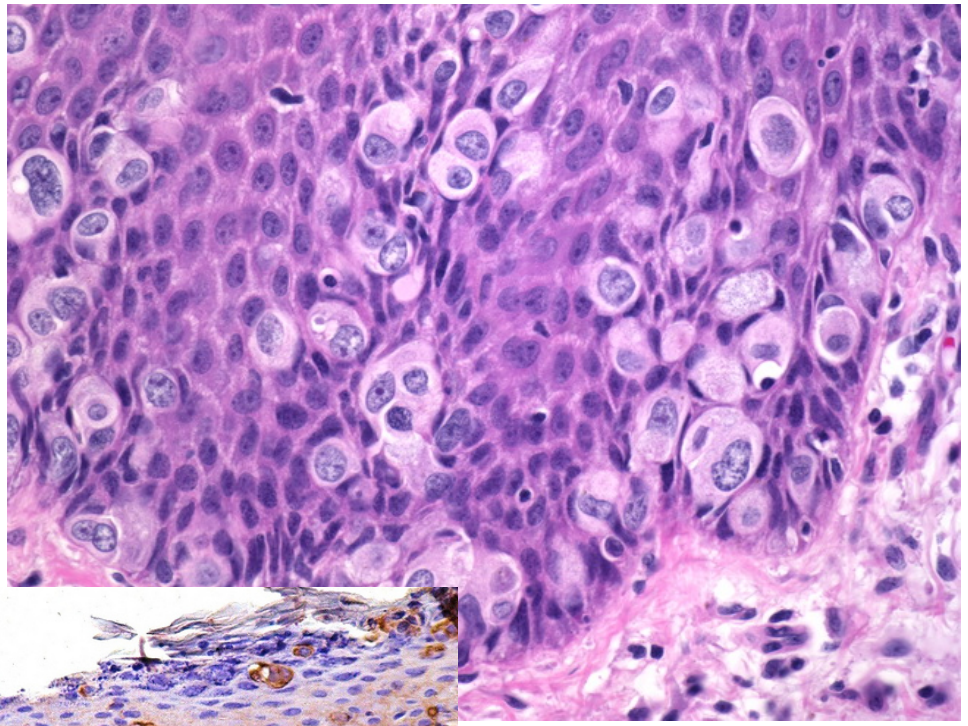
Erosive-ulcerative lesion
Mature-older patients
Blood nipple discharge
Intra-epidermal neoplastic epithelial cells
Her2-positive
Frequent DCIS in lactiferous ducts
Similar to vulvar Paget's disease

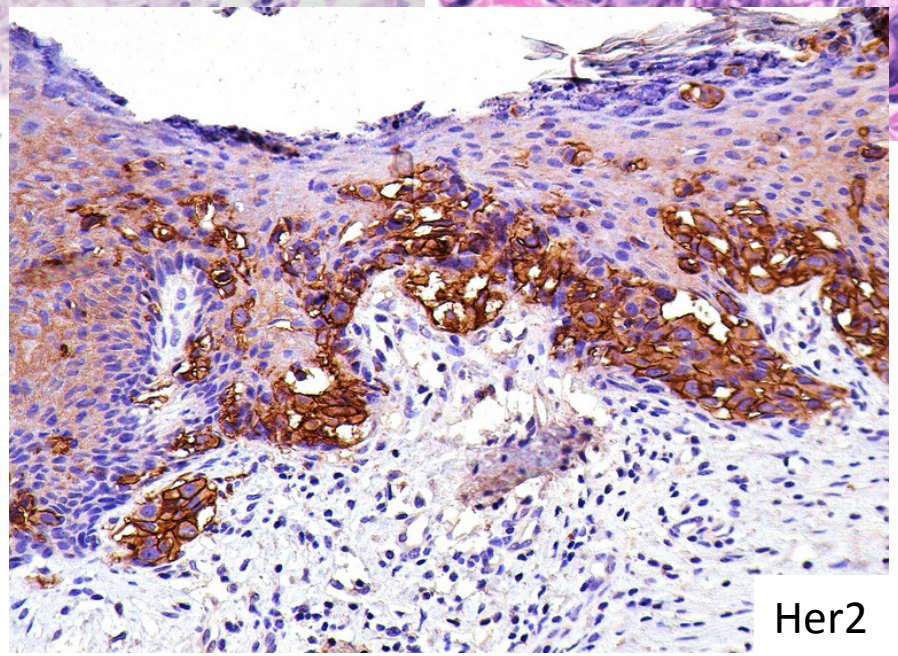
Paget's disease of the nipple



Paget's disease of the nipple





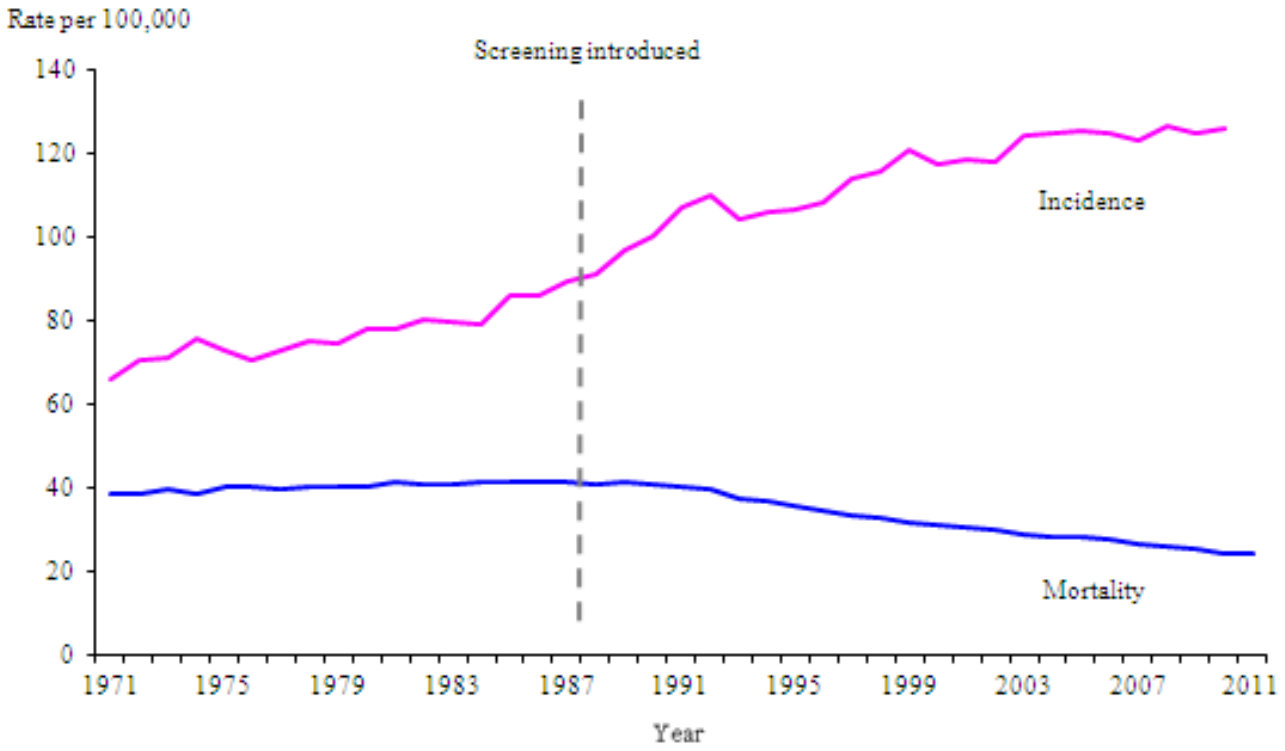


Her2

INVASIVE BREAST CARCINOMA

- Most frequent cancer in women
- 22% of all malignant neoplasms in women (≤1% in men)
- 6-8% of women develop breast cancer
- 1st cause of cancer-related death in women
- Up to 33% cancer-specific mortality
- Increasing incidence, decreasing mortality in western countries

INVASIVE BREAST CARCINOMA



INVASIVE BREAST CARCINOMA

Predisposing factors:

-Geographical: industrialization, breast-feeding, hypercaloric diet, alcohol intake, low physical activity
-Early menarch (< 12 ys)
-Late menopause (> 54 ys)
-Nulliparity
-Late pregnancy
-Short (< 3 mo.)/no breast-feeding
-Familiarity (mother & sisters)
-Obesity (BMI >25Kg/mq)
-Genetic factors: BRCA1 (17q), BRCA2 (12q12-13)
-Irradiation (Hiroshima, radiotherapy)

INVASIVE BREAST CARCINOMA

Risk factors:

Personal:

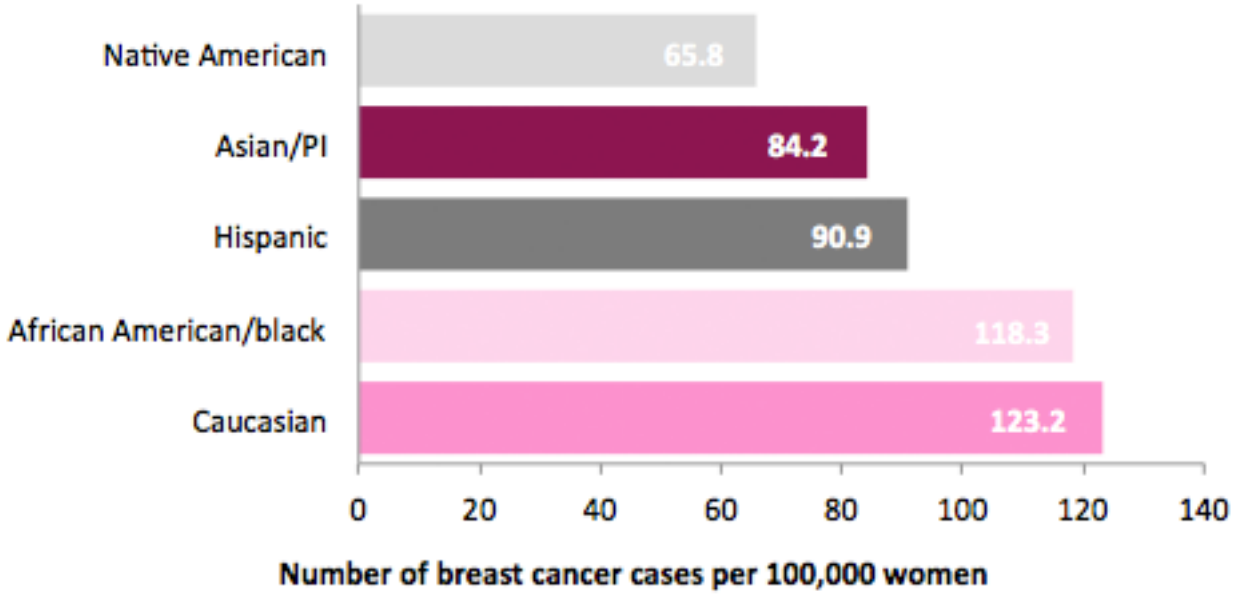
- Previous breast cancer (invasive >> in situ)
- Previous DIN/LIN
- Ductal papilloma
- Ovarian / endometrial cancer

Familial: mother or sisters with breast cancer

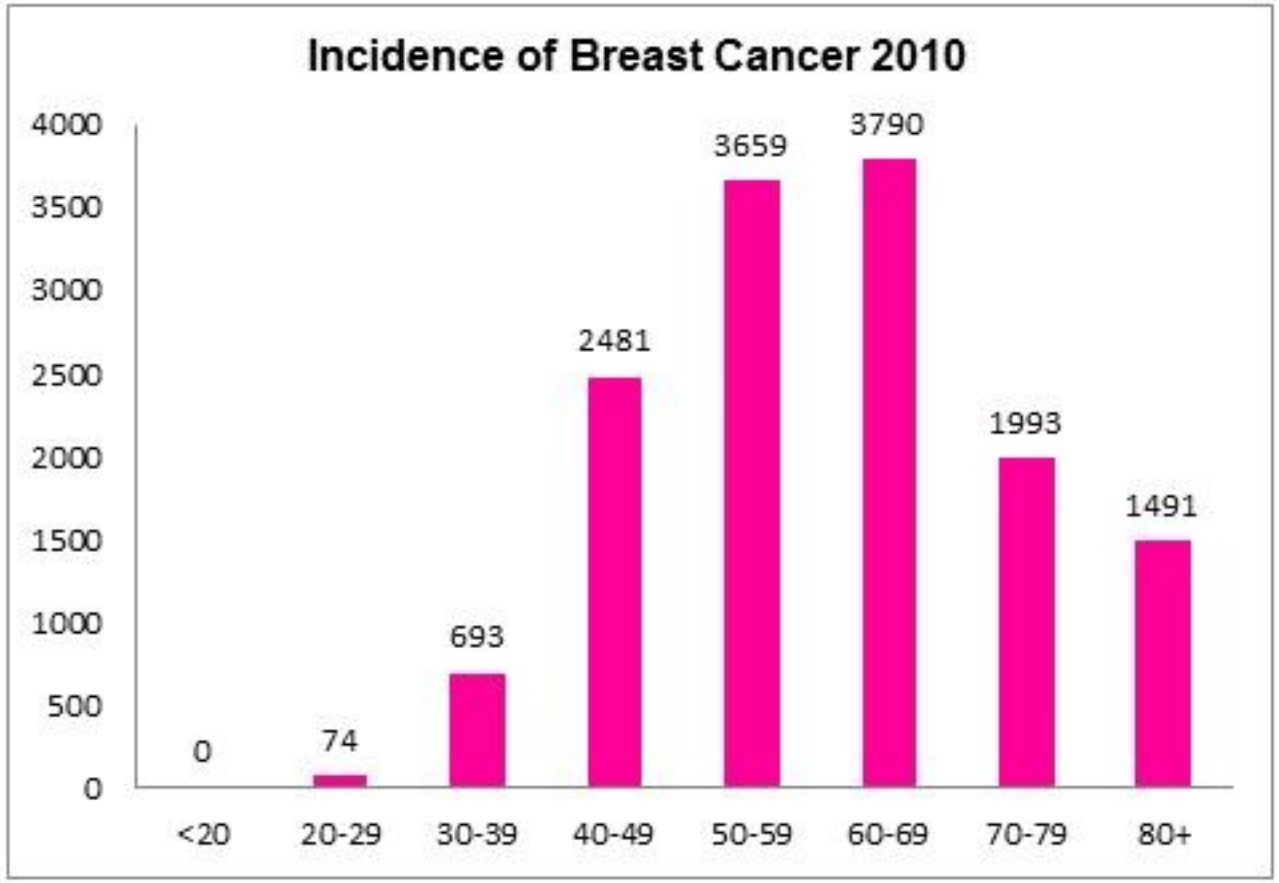
Li-Fraumeni syndrome

BRCA1 or BRCA2 syndrome

INVASIVE BREAST CARCINOMA



INVASIVE BREAST CARCINOMA



INVASIVE BREAST CARCINOMA

Role of oestrogens:

- Bind to specific nuclear receptors
- Induce specific proliferative effects
- Accentuated in obese and persistent in menopause
- Genotoxic direct effect, mediated by P450 (increased free radicals)
- Phytoestrogens (pesticides, biphenyl-poly-clorurates) accumulates in breast adipose tissue
- Hormone replacement therapy in menopause
- Oral contraceptive?

SYNDROMIC BREAST CARCINOMA

Li-Fraumeni

- Constitutive mutation of p53
- Multiple neoplasms at < 30 ys.
- Breast cancer at < 40 ys.
- Osteosarcoma
- Soft tissue sarcomas at < 45 ys.
- Brain tumours
- Leukemia

BRCA1

- Constitutive mutation of BRCA1 (17q21)
- Juvenile ovarian or breast cancer
  - No previous DIN/LIN
  - ER & PgR negative
  - Her2 negative
- Additional carcinomas (colon, liver, endometrium, cervix)
- Profilactic surgery
- Chemoprevention (Tamoxifen)

BRCA2

- Constitutive mutation of BRCA1 (13q12-13)
- Juvenile ovarian or breast cancer
  - DCIS
  - ER & PgR positive
  - Additional cancers (ovary, salpynx, pancreas, gallbladder)
- Melanoma
- Profilactic surgery
- Chemoprevention (Tamoxifen)

HEREDITARY BREAST CARCINOMA

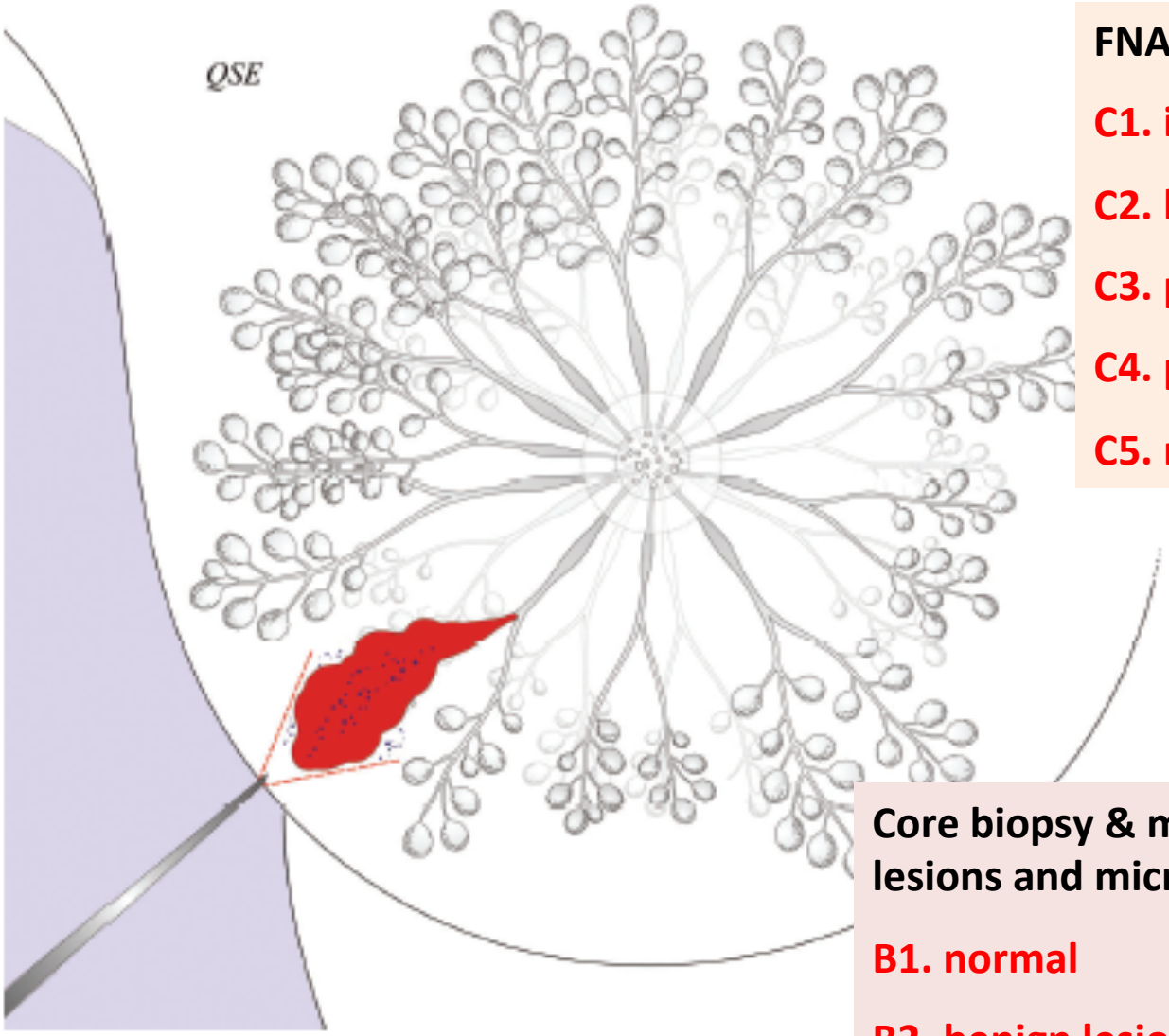
- BRCA1 & 2 in 80% hereditary breast cancers
- 6-10% of all breast cancers

Molecular screening:

- In high risk patients
- Identification of 1st case
- High cost
- Complex techniques
- Germline mutations
- No cost/effective

INVASIVE BREAST CARCINOMA

- Maximal prevalence: > 45 ys.
- More frequently asymptomatic
- Site: >50 % in UEQ
- Firm nodule with stellate borders
- Skin or nipple retraction = late events
- Association with pre-neoplastic lesions:
  - Carcinoma in situ (DIN or LIN)
  - Ductal papilloma



FNAB: palpable nodules

C1. inadequate

C2. benign lesion

C3. possibly benign lesion

C4. possibly malignant lesion

C5. malignant

Core biopsy & mammotome: non-palpable lesions and microcalcifications

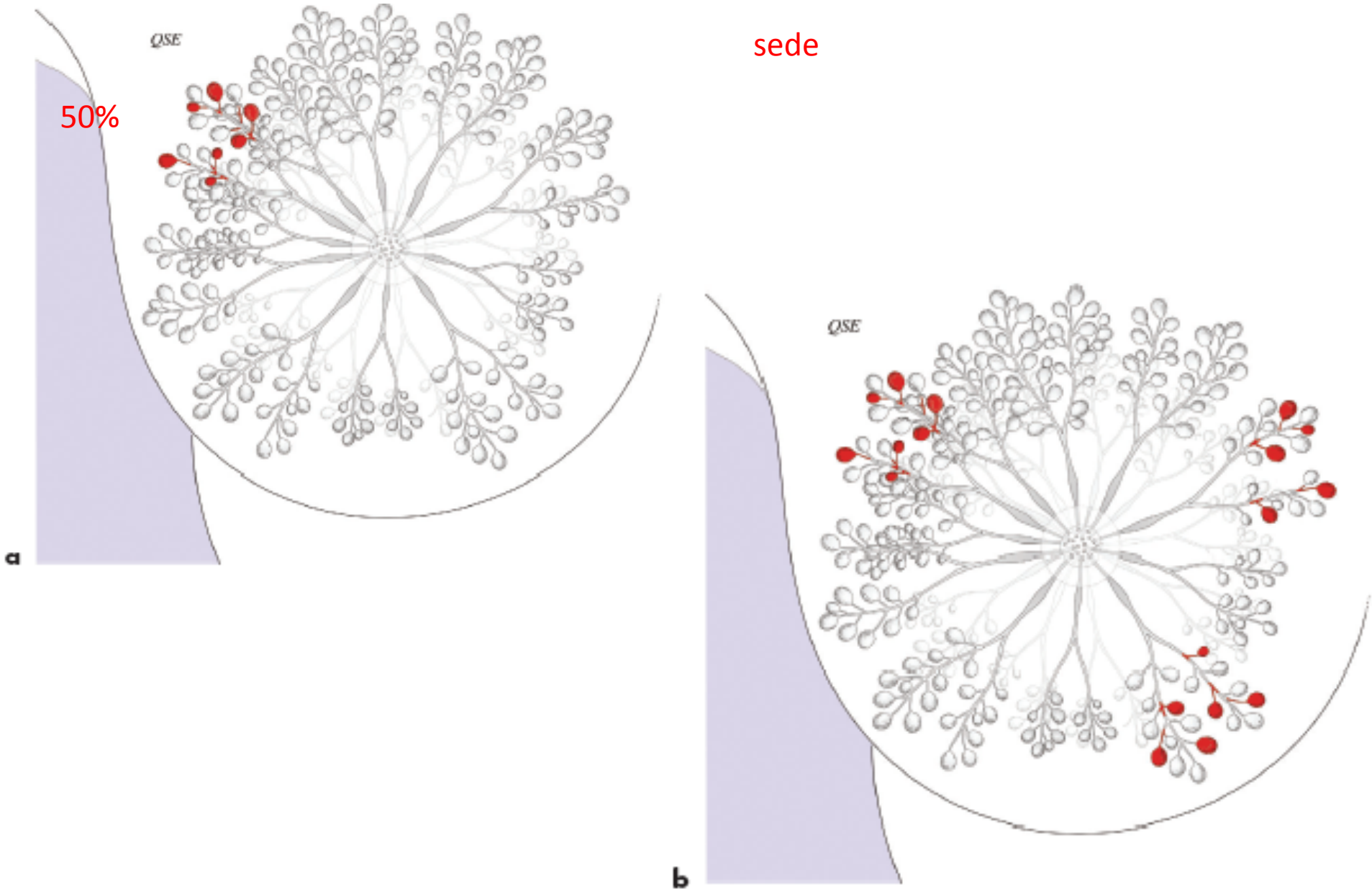
B1. normal

B2. benign lesion

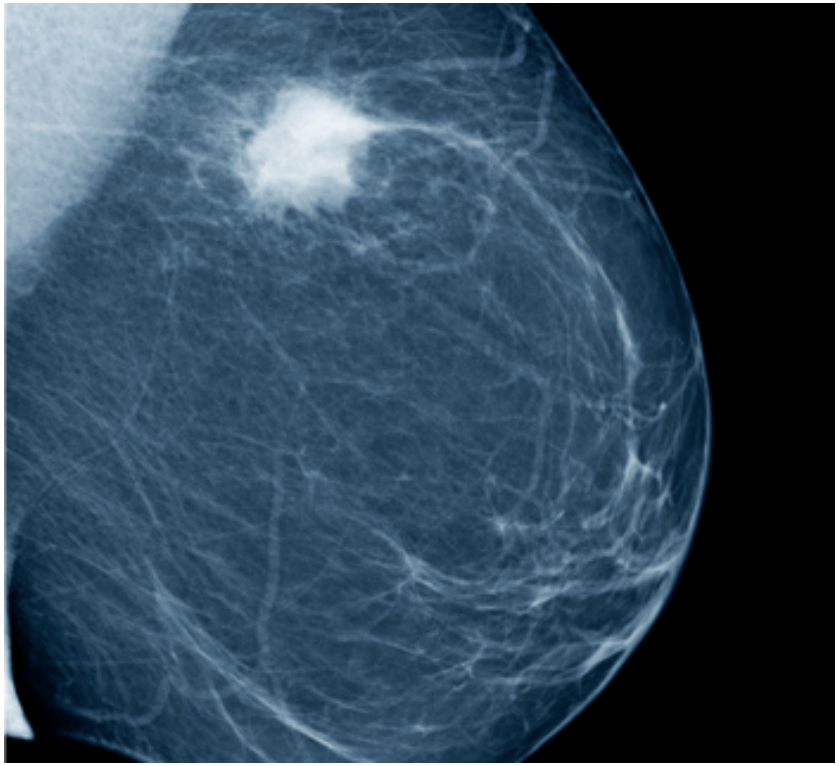
B3. uncertain malignant potential

B4. possibly malignant lesion

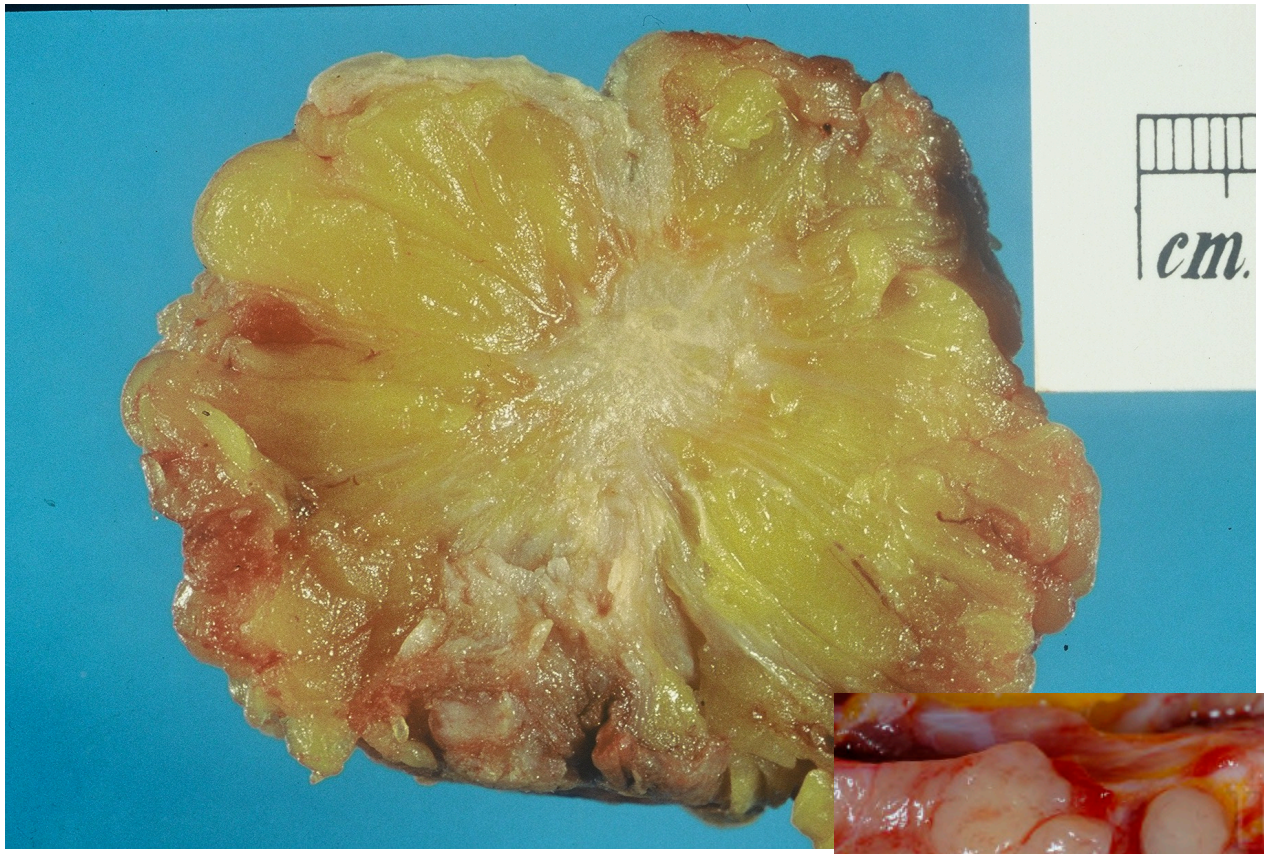
B5. malignant

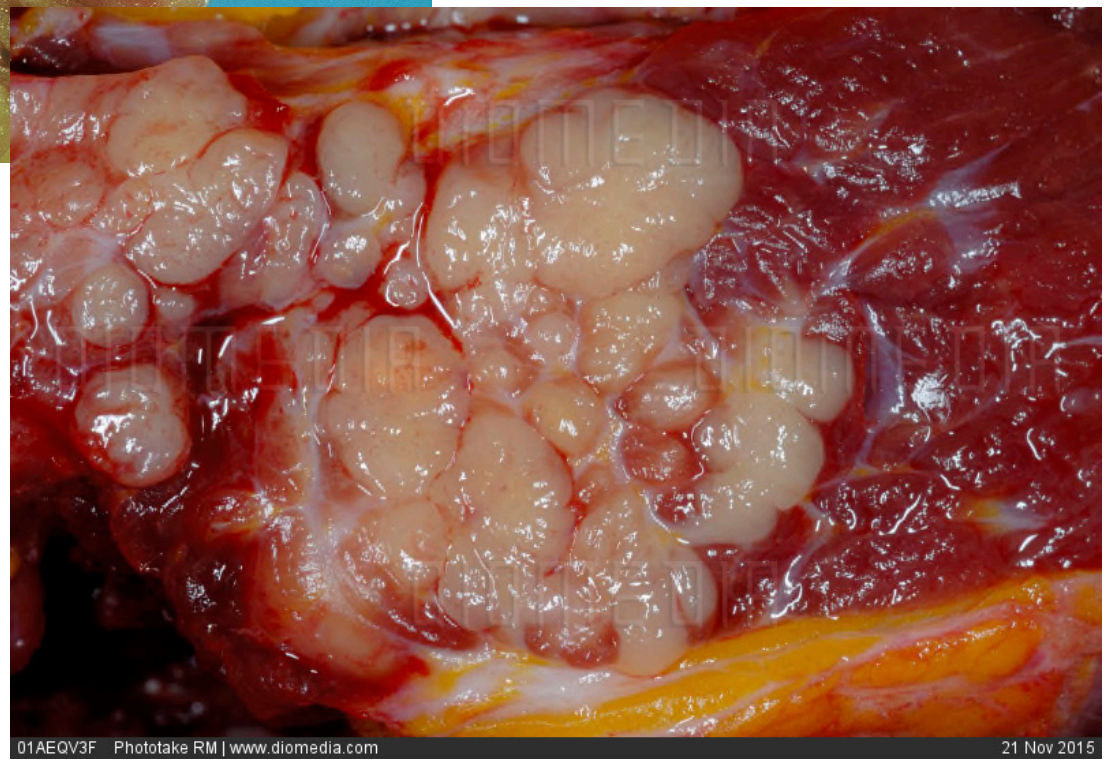

QSE
50%
a
sede
QSE
b

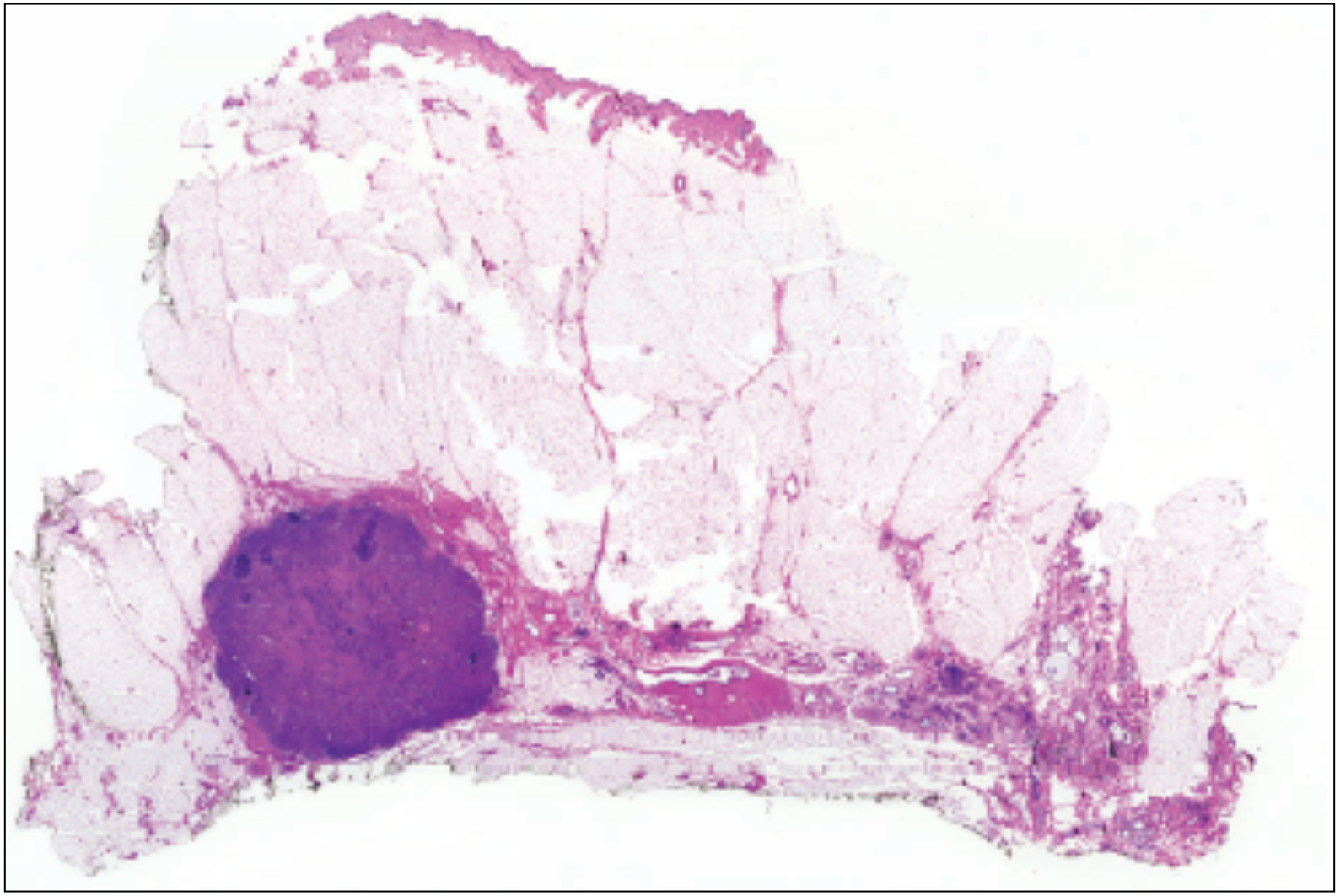

How dense are you?
LEVEL 1
LEVEL 2
LEVEL 3
LEVEL 4
<25% Density
Fatty Breast Tissue
<50% Density
Scattered Density
>50% Density
Heterogeneously Dense
>75% Density
Extremely Dense




Breast MRI


cm.


01AEQV3F Phototake RM | www.diomedia.com
21 Nov 2015



INVASIVE BREAST CARCINOMA
PROGNOSTIC FACTORS

Patient characteristics	Age (Race)
Disease characteristics	Tumor size Tumor type Tumor grade Axillary lymph node status Peritumoral vascular invasion
Biomarkers	Receptor status (ER, PgR) HER2 expression Ki-67 labeling index
Genetic profile (!)	*Mammaprint* *OncotypeDx* *PAM50*

INVASIVE BREAST CARCINOMA

Main histotypes:

→ Ductal (70%)

→ Lobular (20%)

→ Special types (10%)

Good prognosis:

- Tubular
- Cribriform
- Mucinous
- Papillary
- Adenoid-cystic
- Lobular (classic) G1
- Medullary

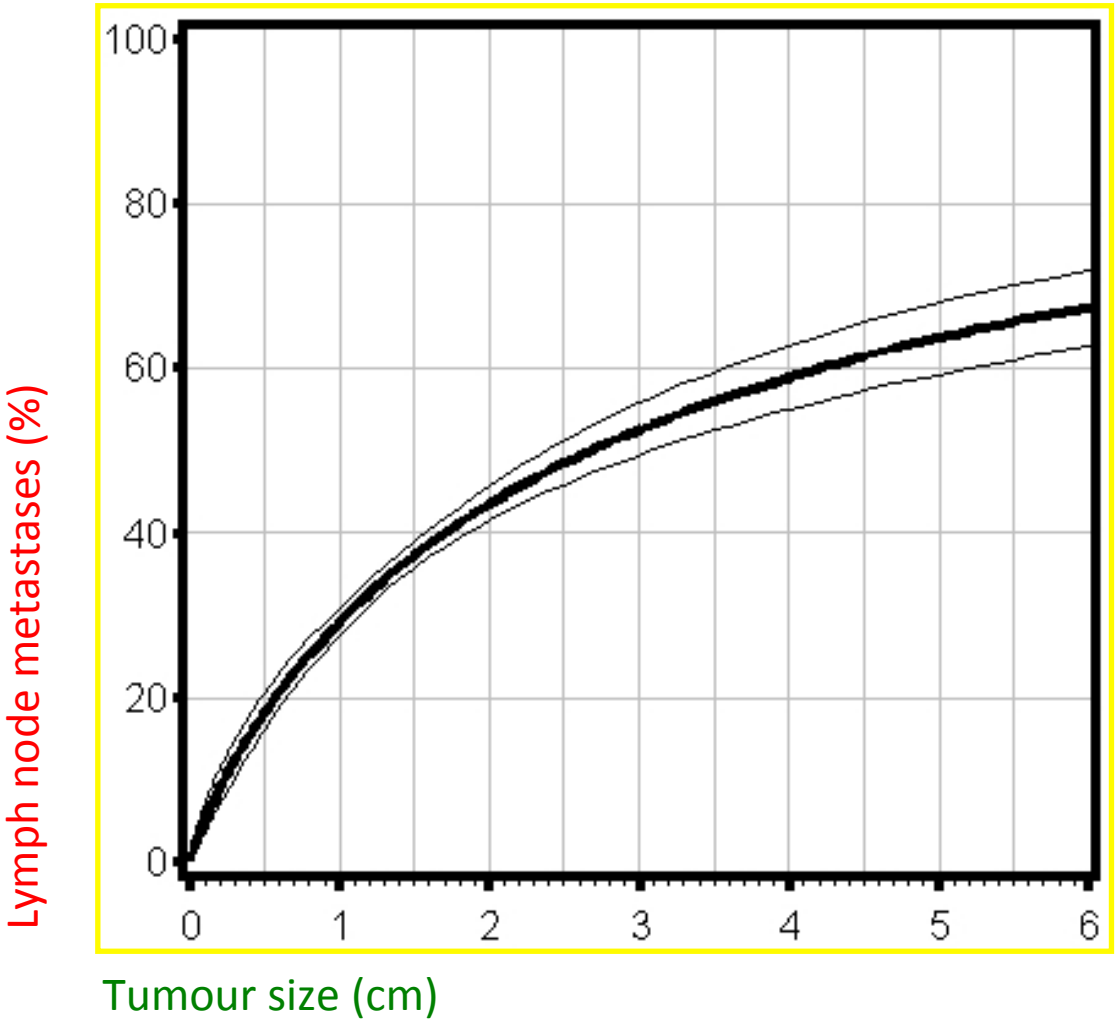
Poor prognosis:

- Extensive central necrosis
- Extensive central fibrosis
- Lobular (pleomorphic) G3
- Matrix-producing
- Metaplastic
- Micropapillary
- Apocrine

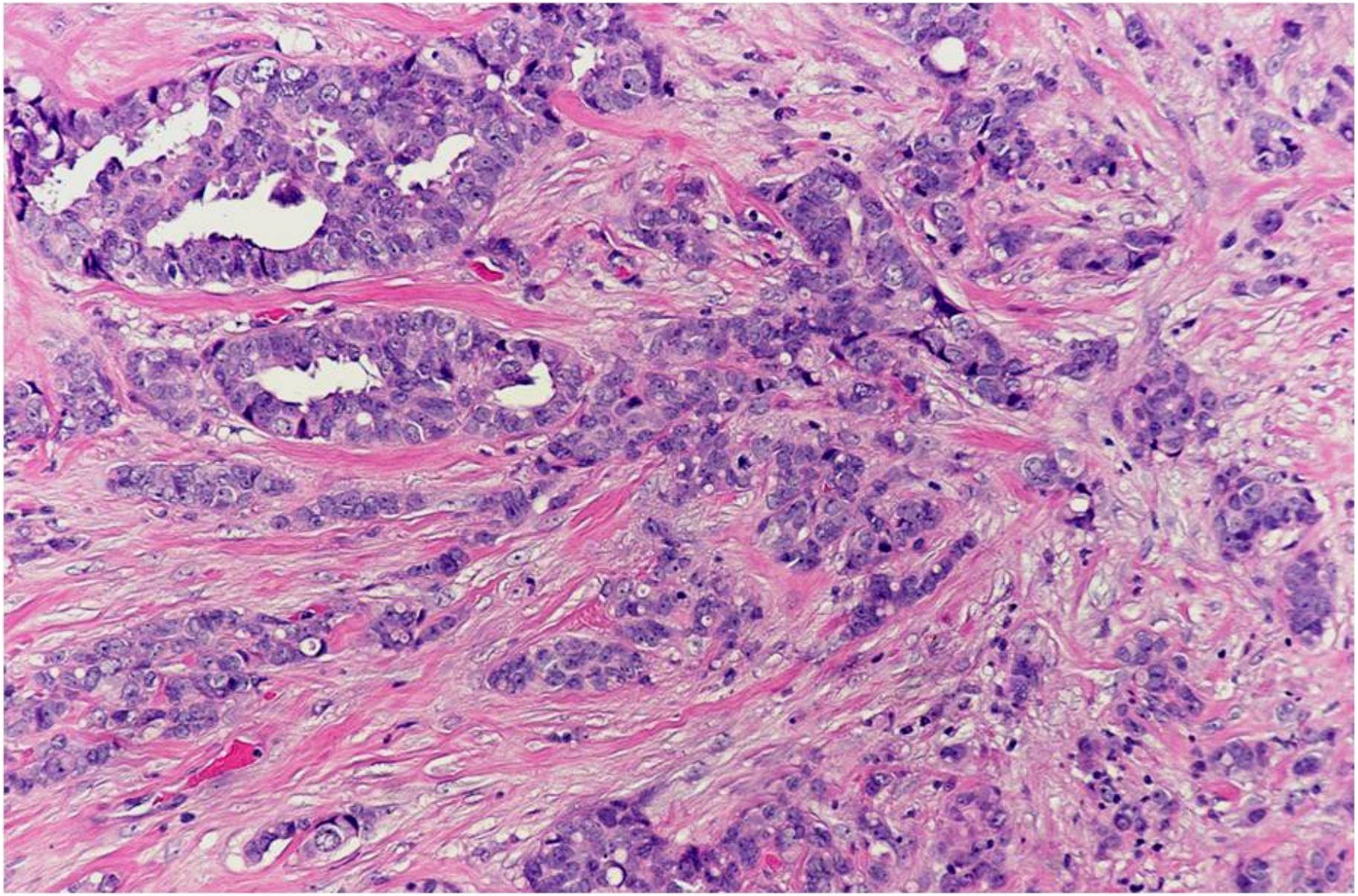
St. Gallen
Endocrine-responsiveness

Highly responsive	Incompletely responsive	Non-responsive
•High ER & PgR *and* •Low Ki-67 *and* •No HER2 overexpr.	• Low ER & PgR *or* • PgR absent *or* • HER2 overexpr *or* • High Ki-67	•ER & PgR both absent

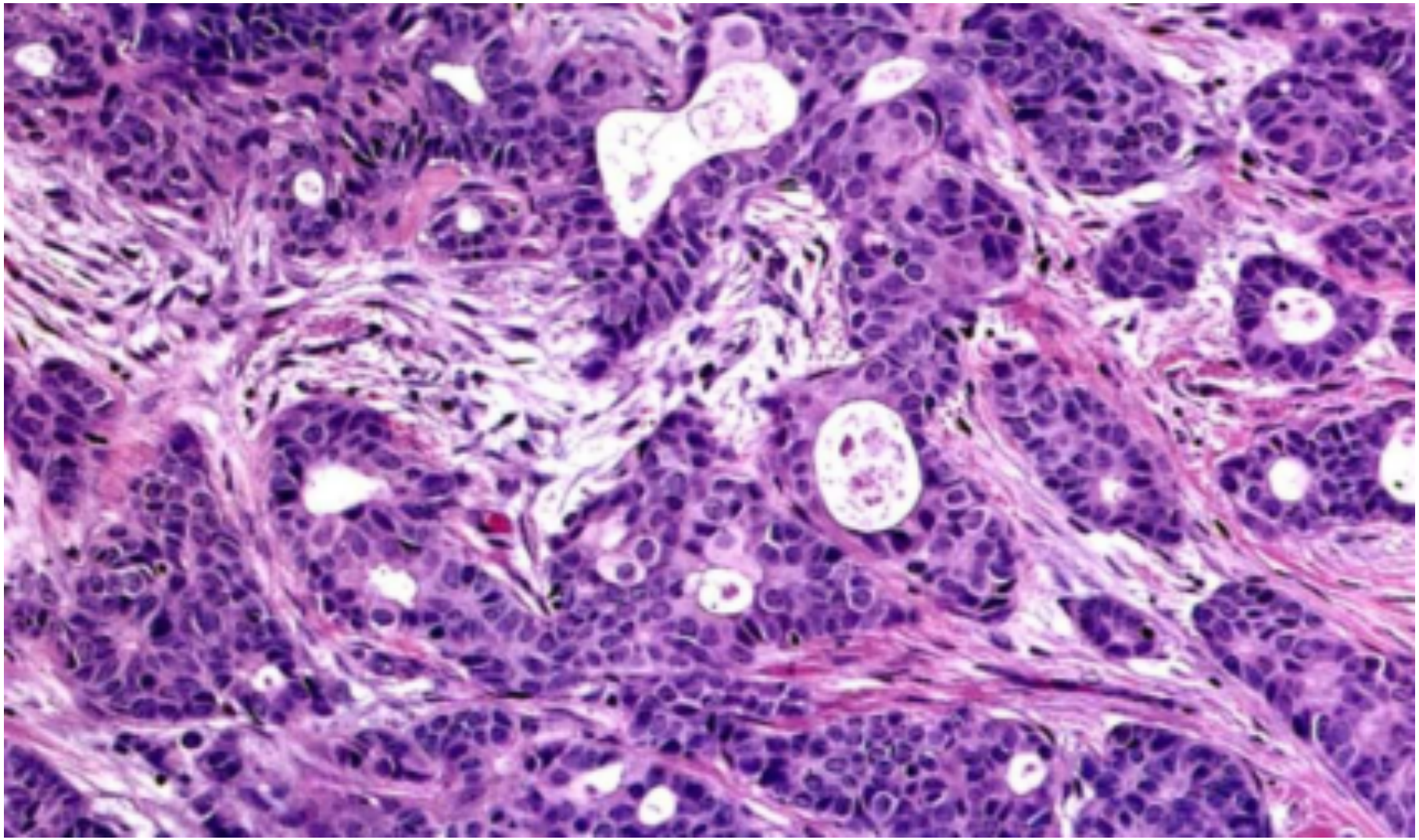
INVASIVE BREAST CARCINOMA



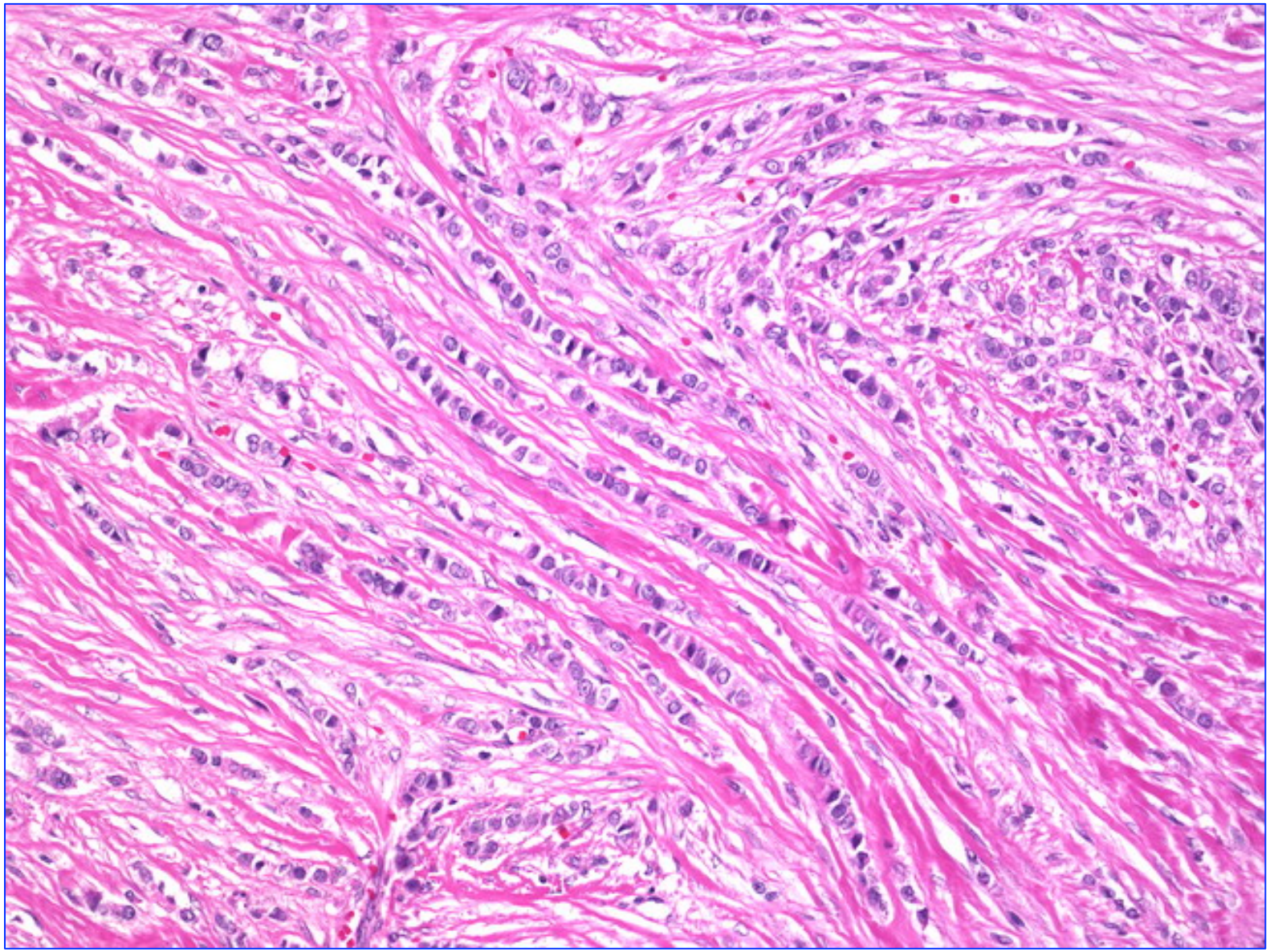
Invasive (infiltrating) ductal carcinoma



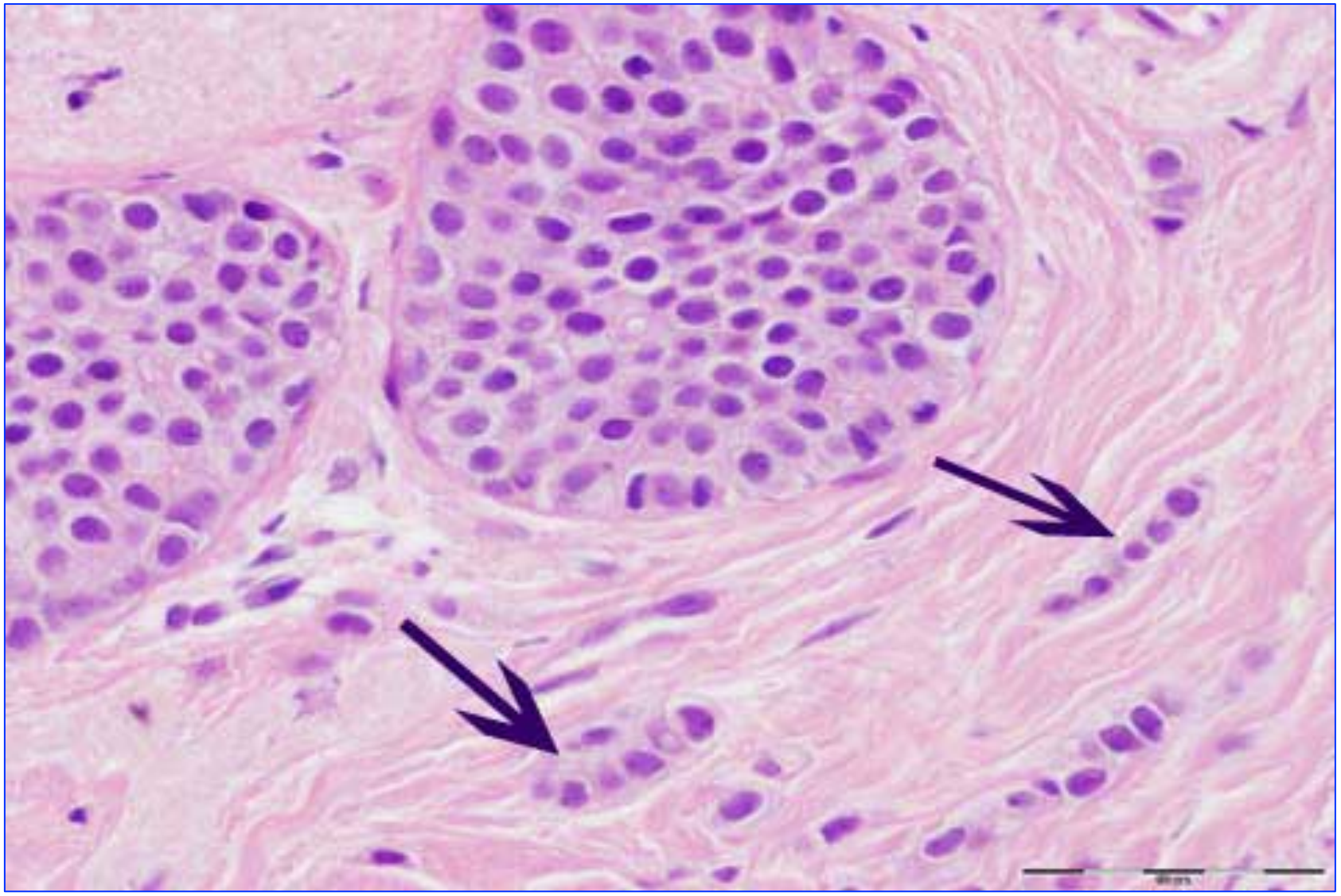
Invasive (infiltrating) ductal carcinoma

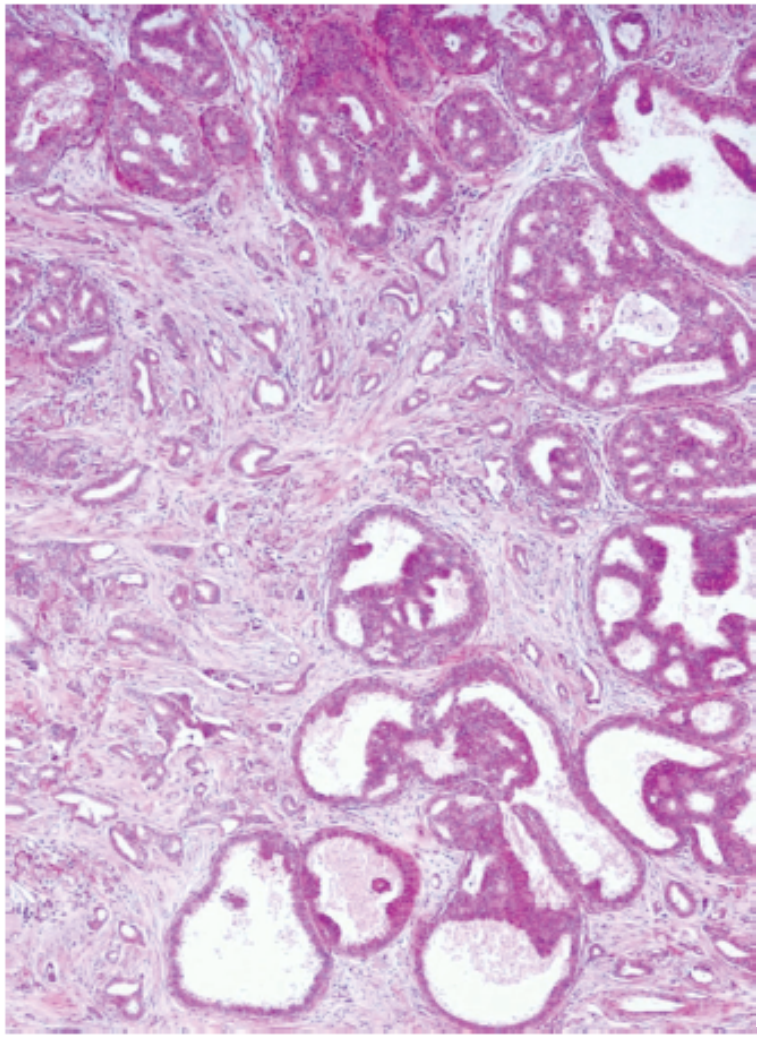


Invasive (infiltrating) lobular carcinoma

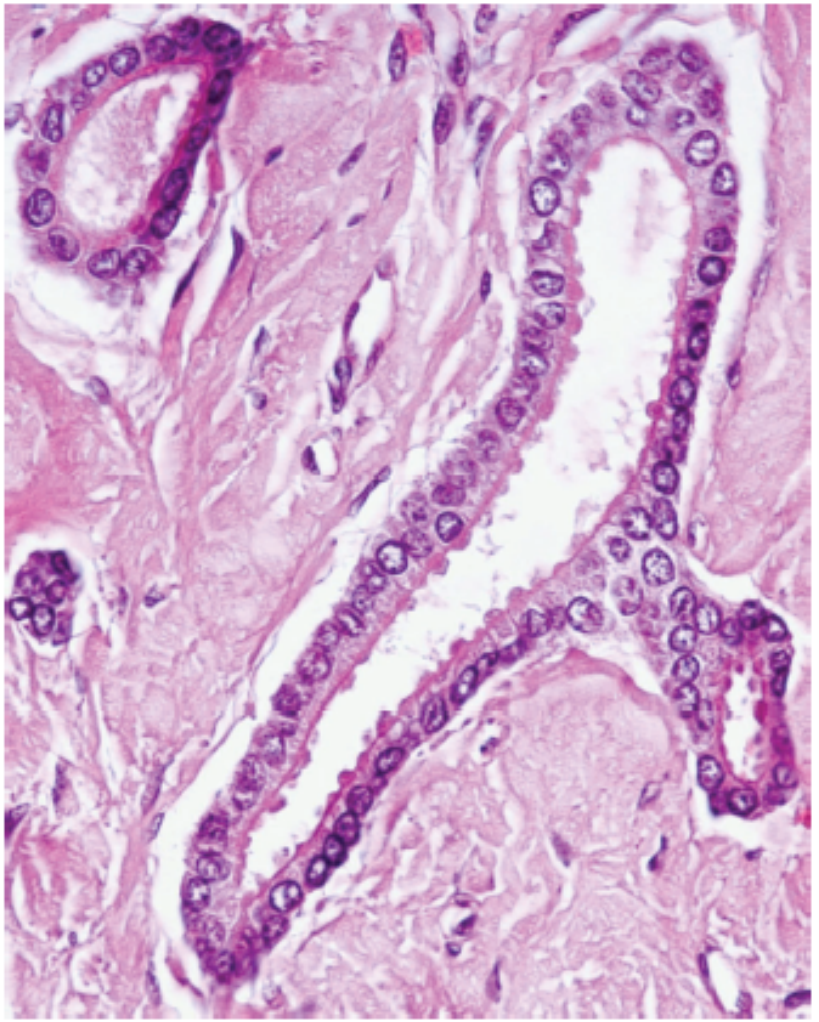


Invasive (infiltrating) lobular carcinoma



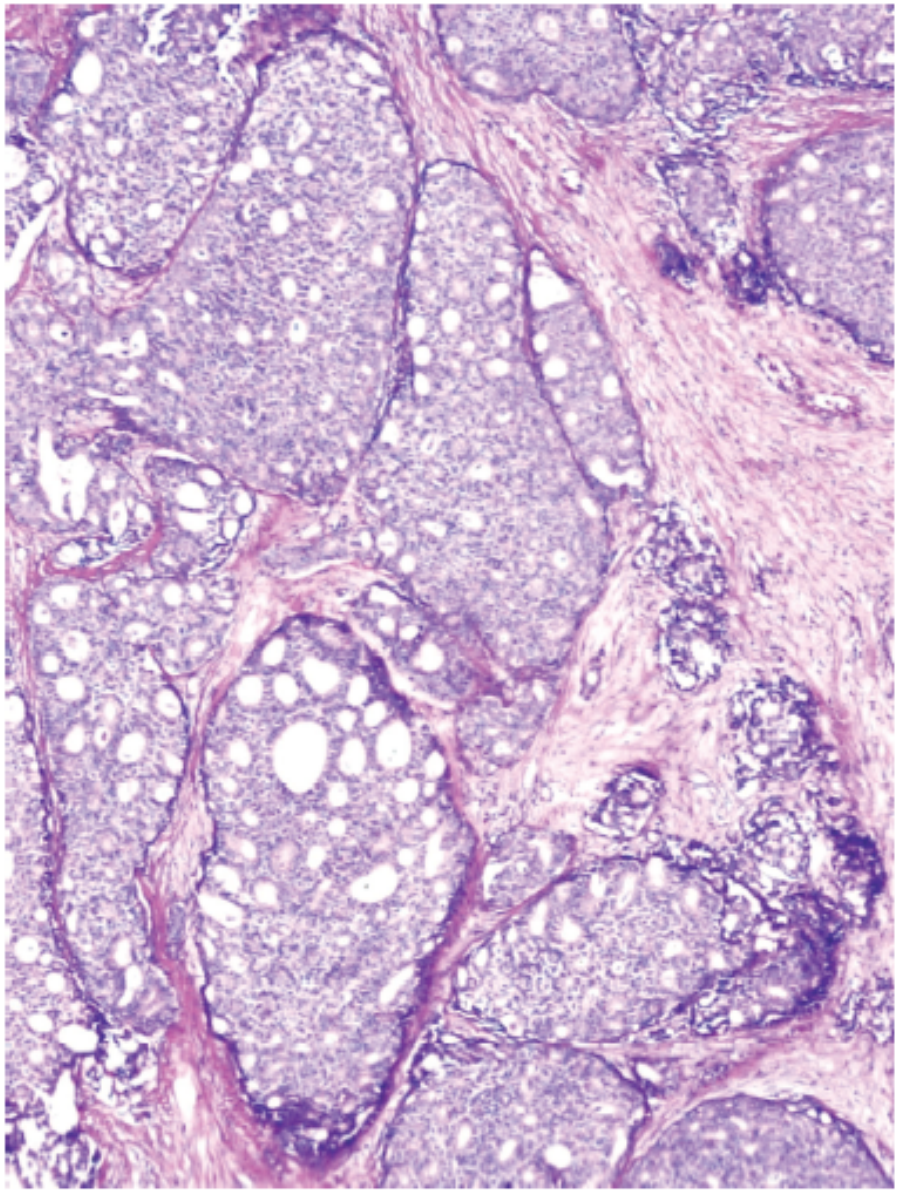


a

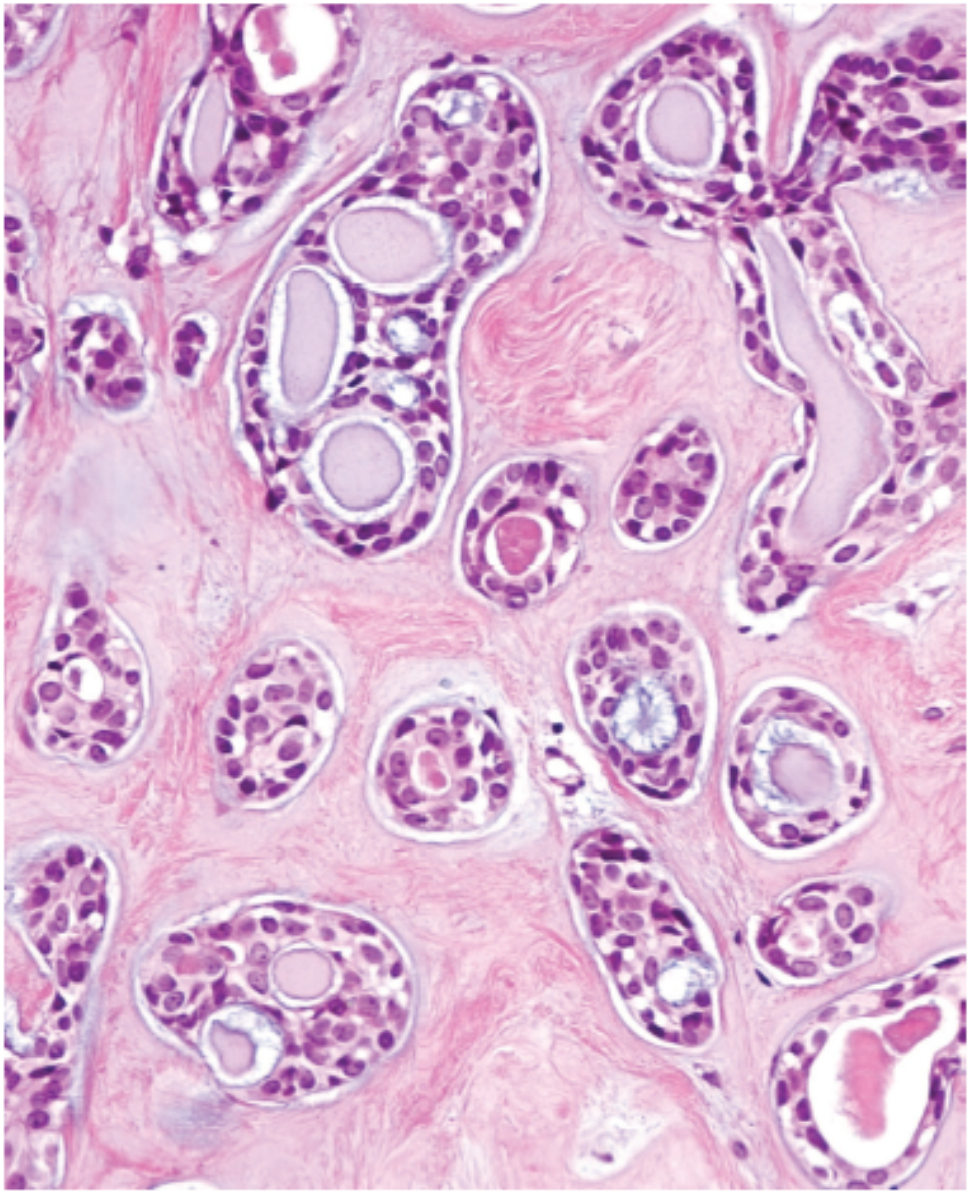


b

Fig. 49 – a) Carcinoma tubulare frammisto a CDIS ben differenziato. **b)** Tipico tubulo mostrante una sola fila di cellule.

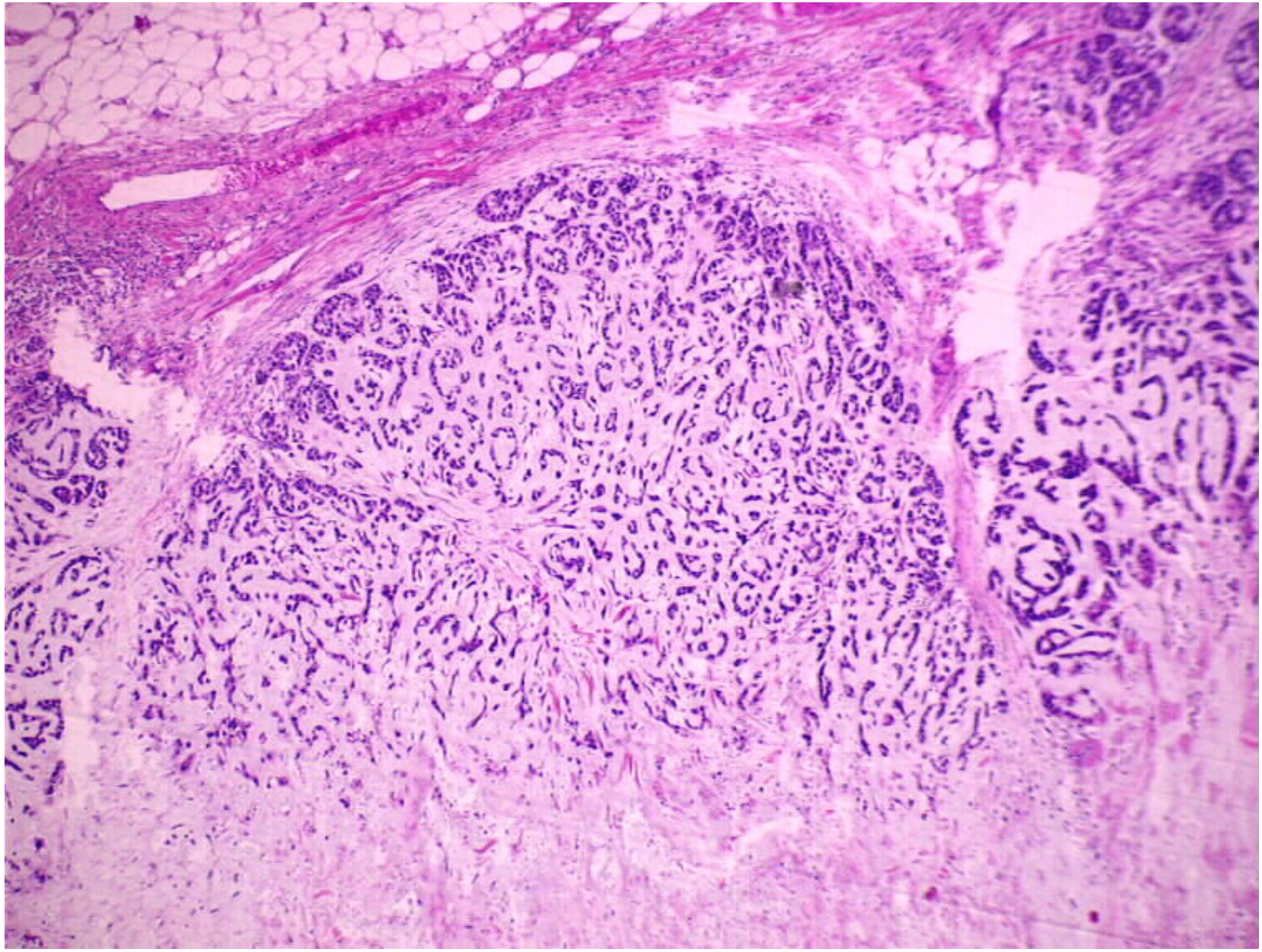


Cribriform in situ and invasive ca.

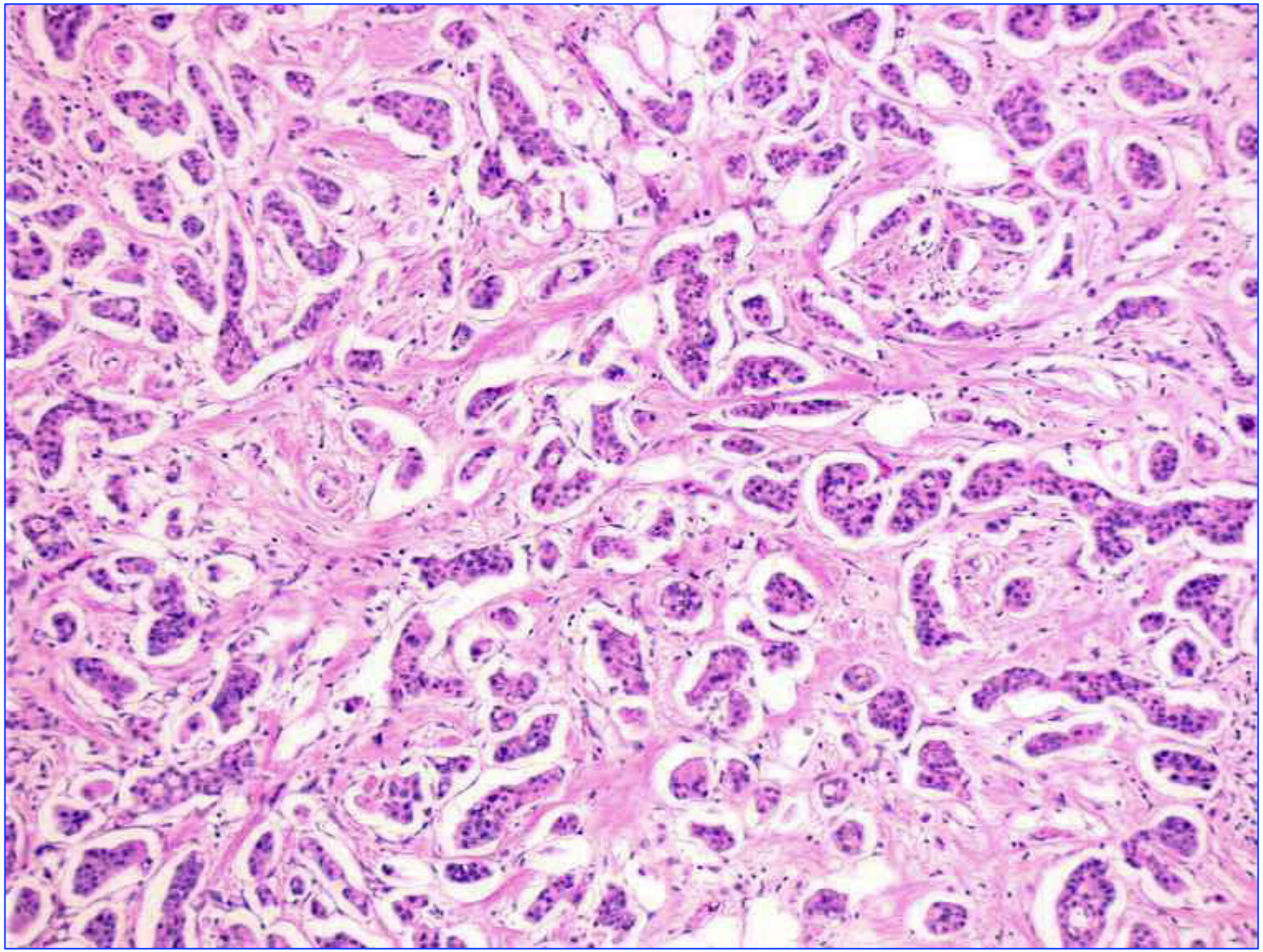


Adenoid-cystic carcinoma

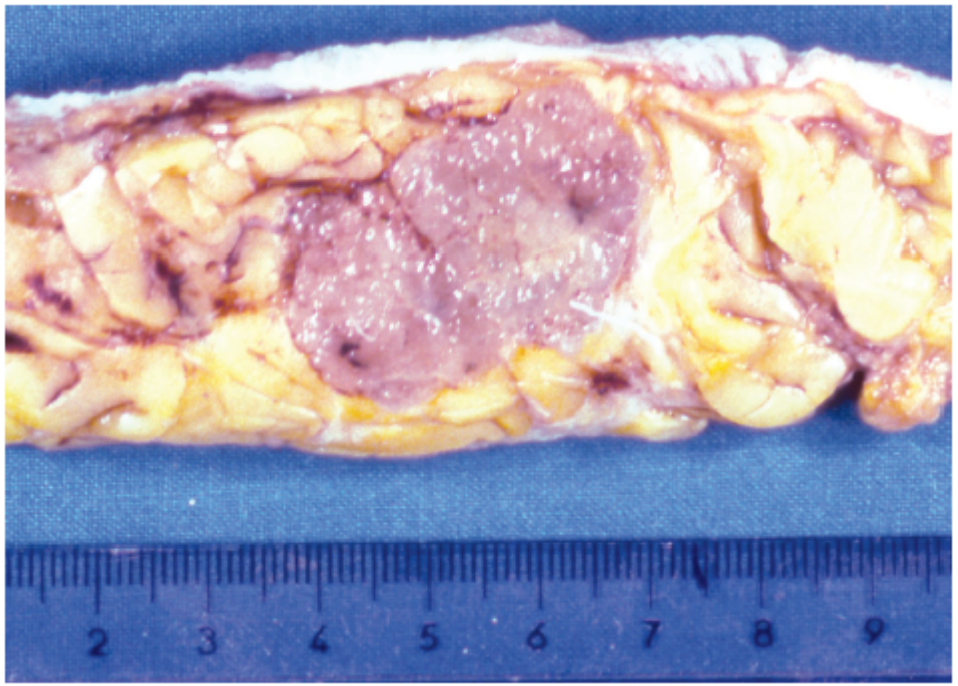
Matrix-producing carcinoma



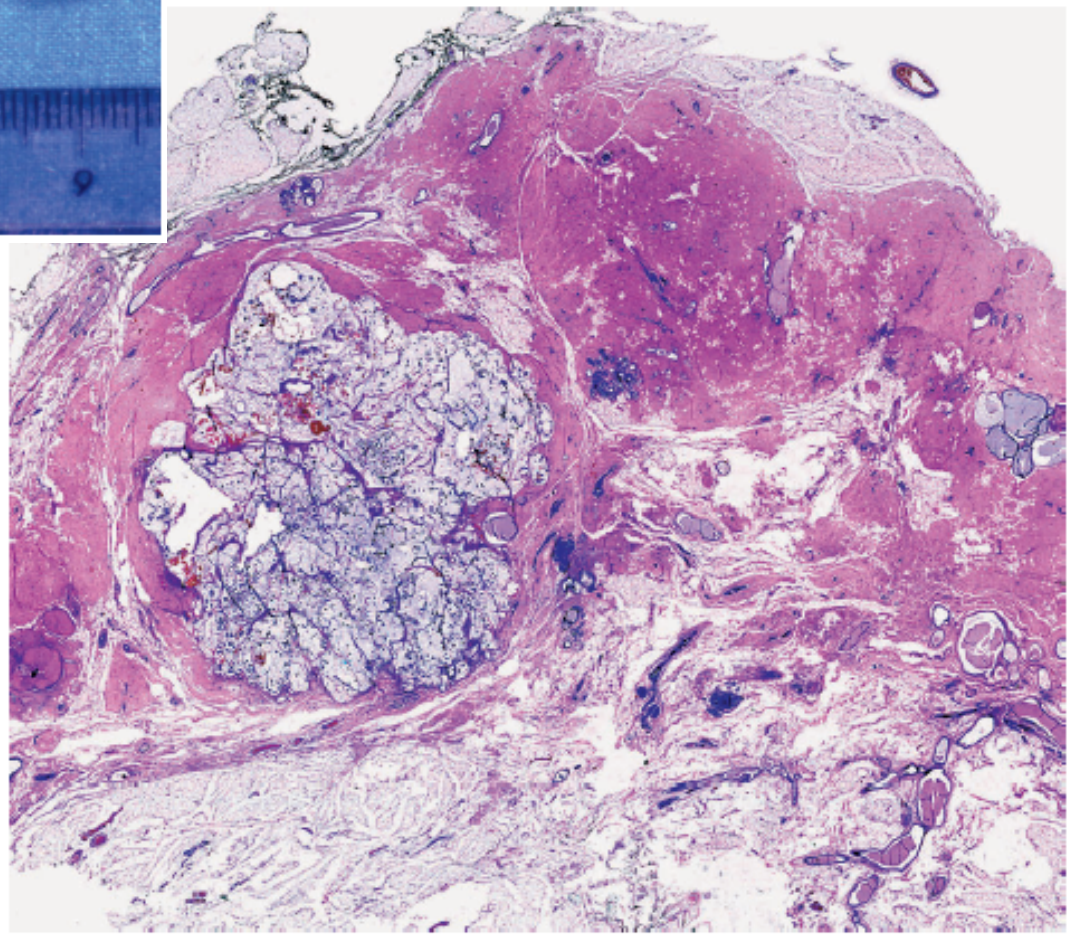
Micropapillary carcinoma



Mucinous carcinoma



a



b

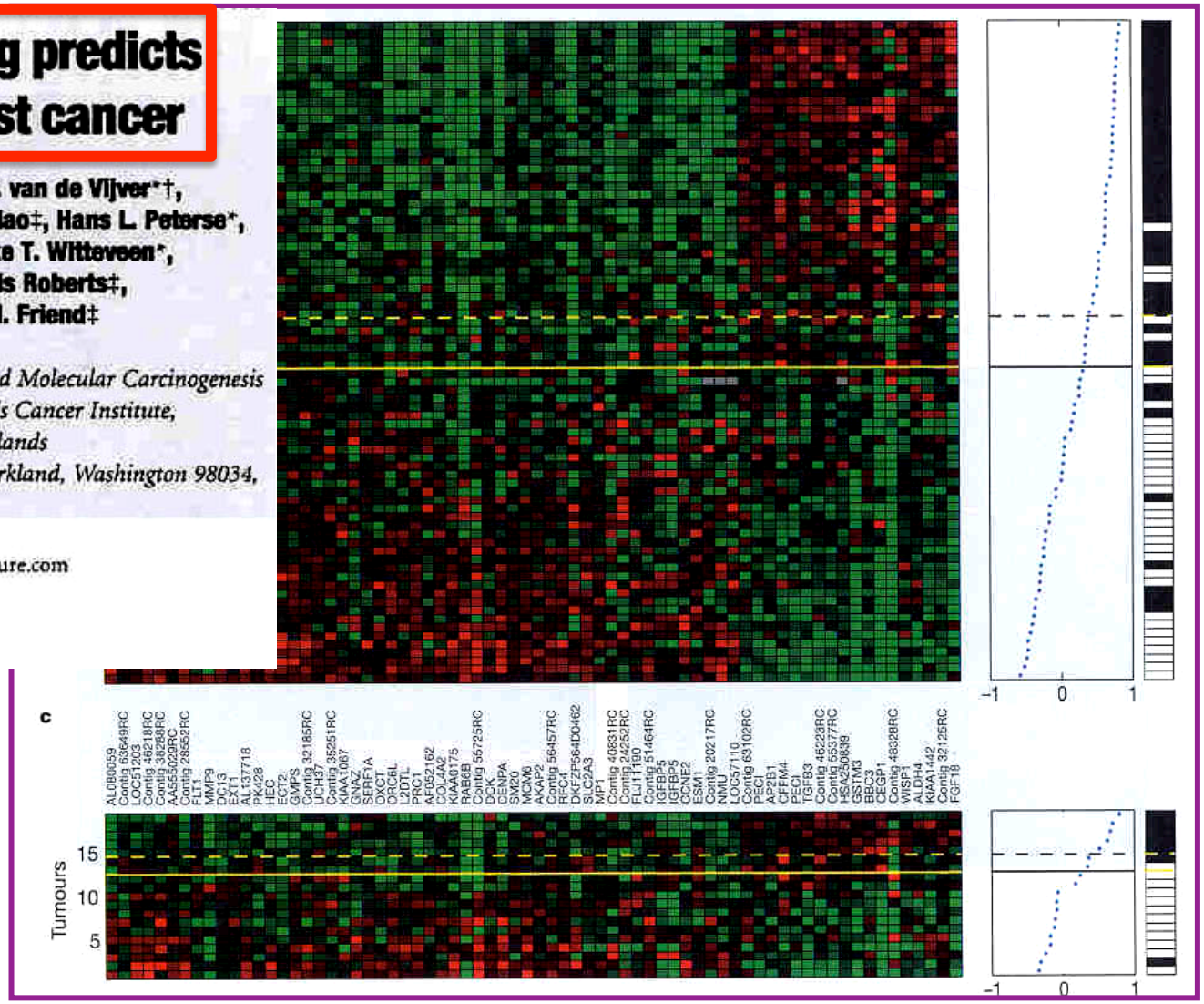
Present or future?

Gene expression profiling predicts clinical outcome of breast cancer

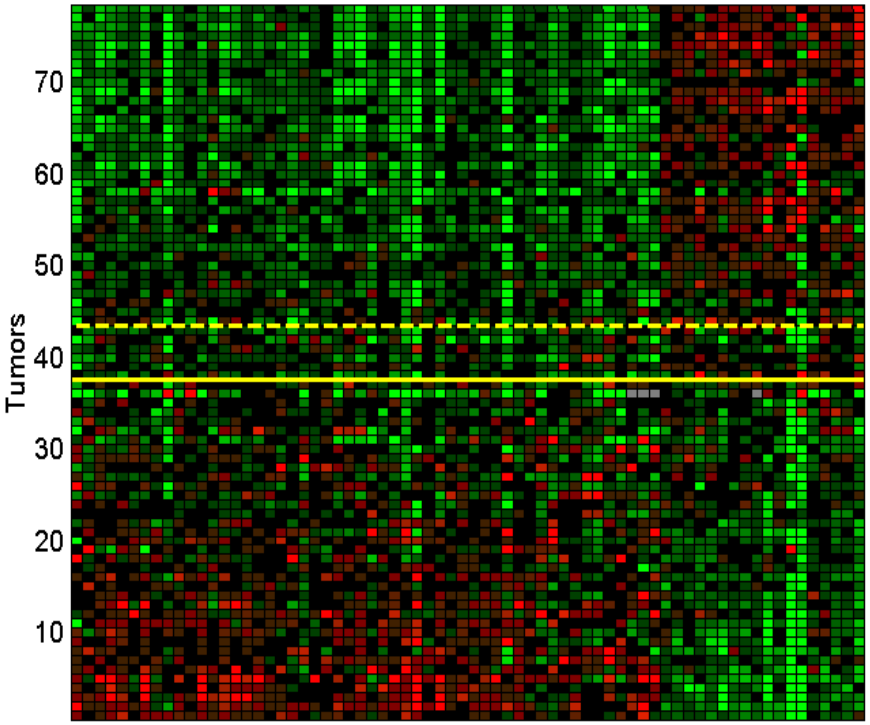
Laura J. van 't Veer*†, Hongyue Dai†‡, Marc J. van de Vijver*†, Yudong D. He‡, Augustinus A. M. Hart*, Mao Mao‡, Hans L. Peterse*, Karin van der Kooy*, Matthew J. Marton‡, Anke T. Witteveen*, George J. Schreiber‡, Ron M. Kerkhoven*, Chris Roberts‡, Peter S. Linsley‡, René Bernards* & Stephen H. Friend‡

* *Divisions of Diagnostic Oncology, Radiotherapy and Molecular Carcinogenesis and Center for Biomedical Genetics, The Netherlands Cancer Institute, 121 Plesmanlaan, 1066 CX Amsterdam, The Netherlands*
‡ *Rosetta Inpharmatics, 12040 115th Avenue NE, Kirkland, Washington 98034, USA*

NATURE | VOL 415 | 31 JANUARY 2002 | www.nature.com

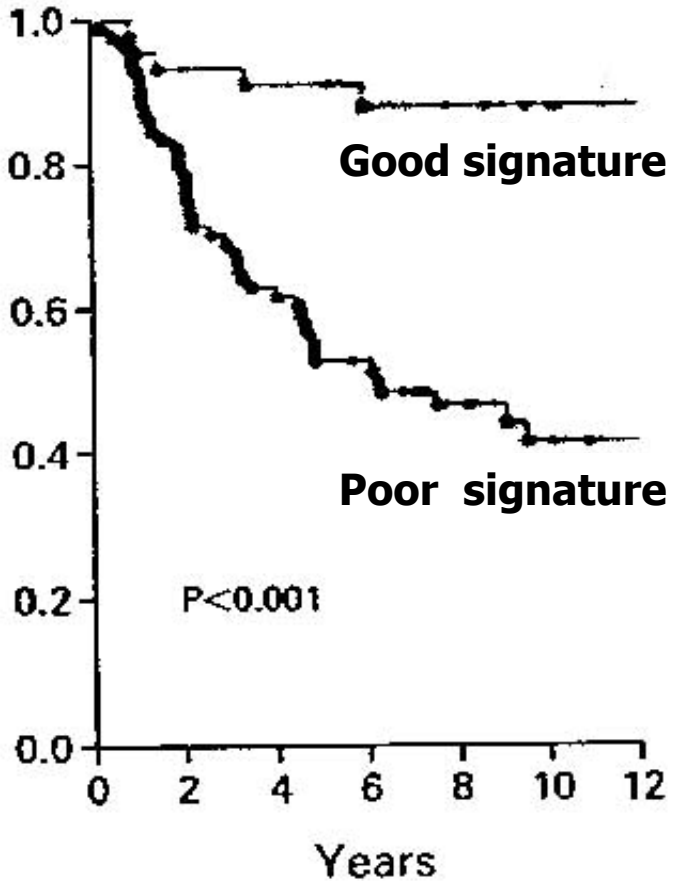


Present or future?

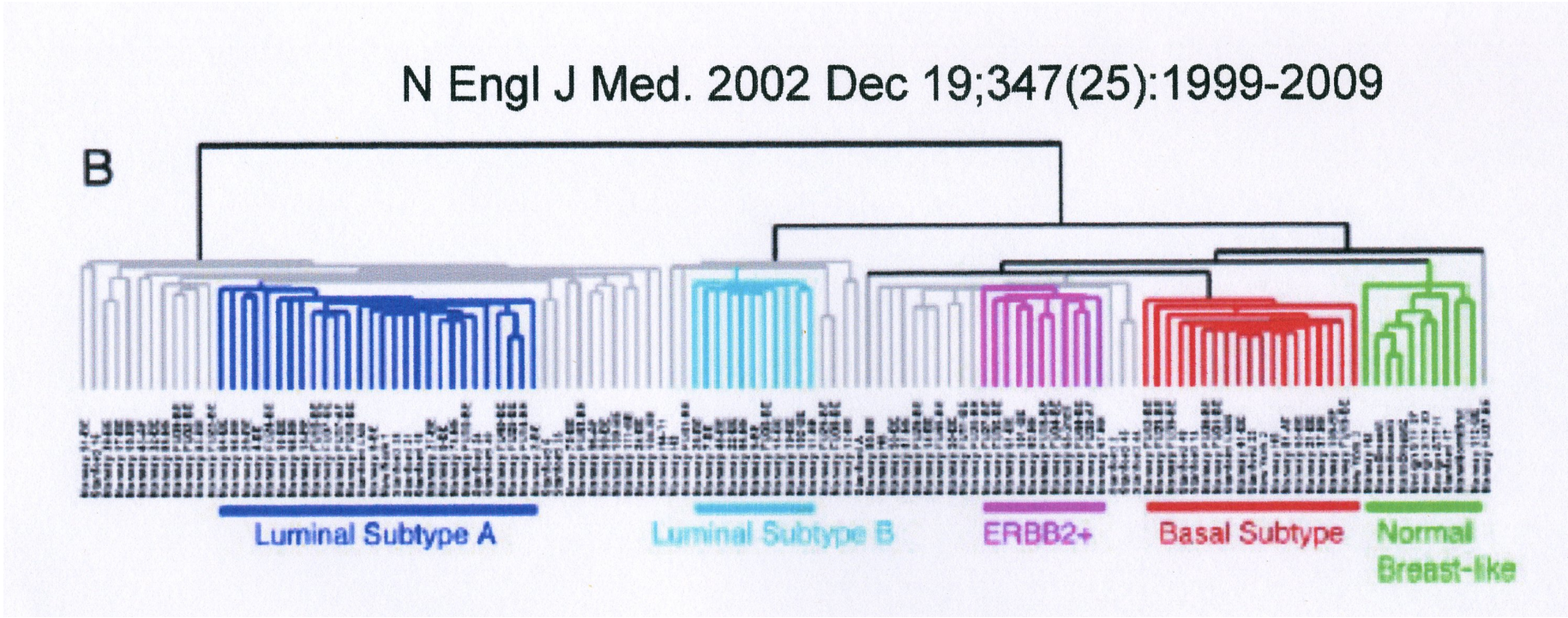


microarray

Gene-expression profile



N Engl J Med, Vol 347 (25), Dec. 2002



LUMINAL A
LUMINAL B
ERB B2+
BASAL LIKE
NORMAL BREAST

Molecular apocrine
Claudin-low

INVASIVE BREAST CANCER PROGRESSION

- Recurrence (ipsi-controlateral)
- Lymphatic invasion
  - Axillary or internal mammary nodes
- Haematogenous dissemination (lung, liver, bone, CNS, adrenal)
- Contiguity dissemination (pleura)
- Ovarian colonization

INVASIVE BREAST CANCER PROGRESSION

OVERALL SURVIVAL

5 ys.: St. I = 80%, St. II = 65%, St. III = 40%, St. IV = 10%

30 ys.:

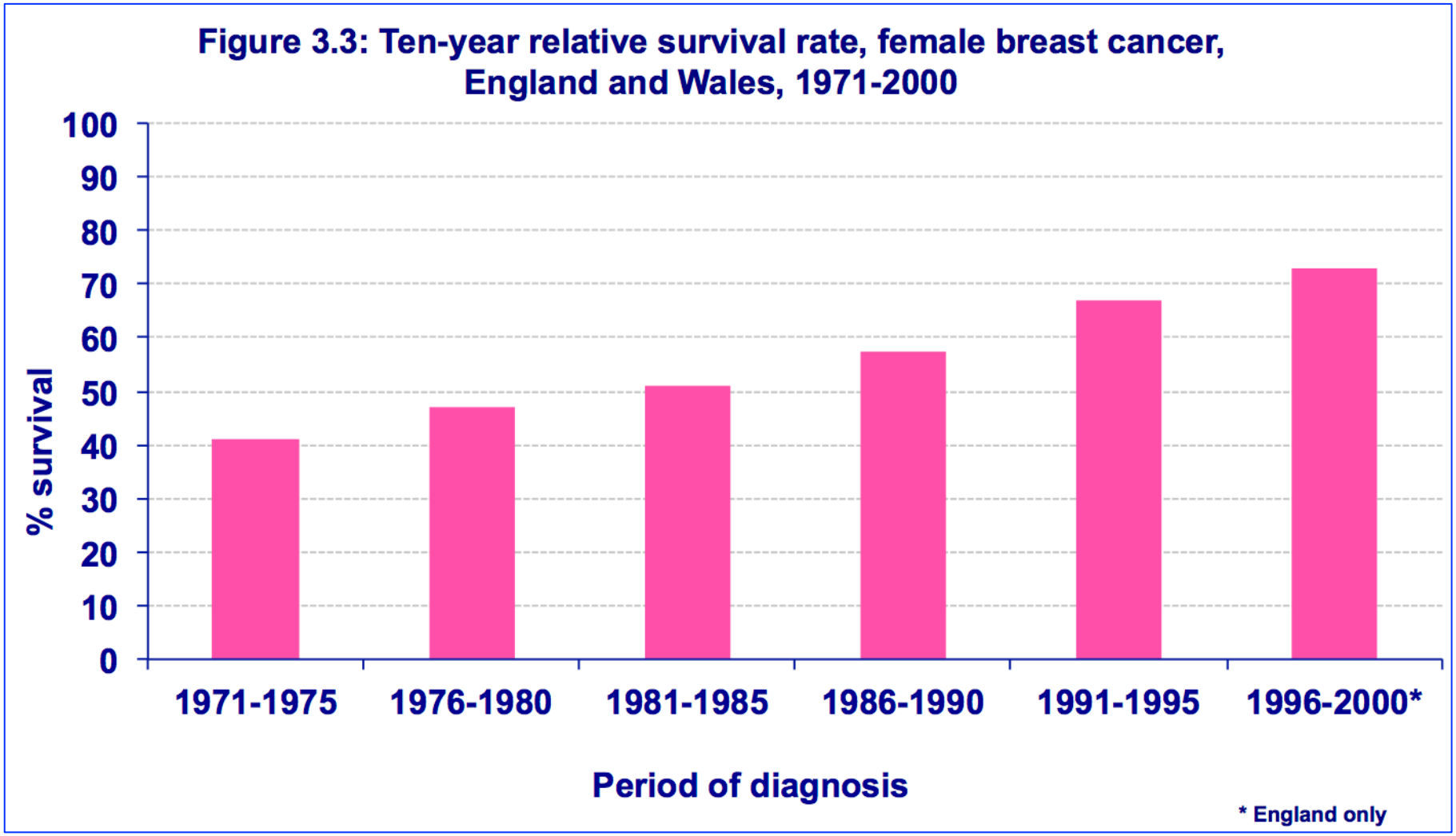
- DCIS: 74%
- Papillary: 65%
- Medullary: 58%
- Ductal: 34%
- Lobular: 29%

INVASIVE BREAST CANCER PROGRESSION

Stage	5-year Relative Survival Rate
0	100%
I	100%
IIA	92%
IIB	81%
IIIA	67%
IIIB	54%
IV	20%

Table 2-1 - Breast cancer mortality rate by stage. Source: American Cancer Society

INVASIVE BREAST CANCER PROGRESSION



INVASIVE BREAST CANCER
Increasing survival and QoL

Early detection

Accurate (clinico-pathological) characterization (NO "*one-fits-all*")

Conservative surgical treatments:

- Lumpectomy / quadrantectomy + RT
- Mastectomy (subcutaneous, nipple-sparing)
- Breast reconstrucion

Tailored systemic treatments

- Neo-adjuvant (pre-surgical)
- Adjuvant (prophilactic = hormonal, chemo, targeted)
- Metastatic setting
- Palliative