In Situ Breast Carcinoma

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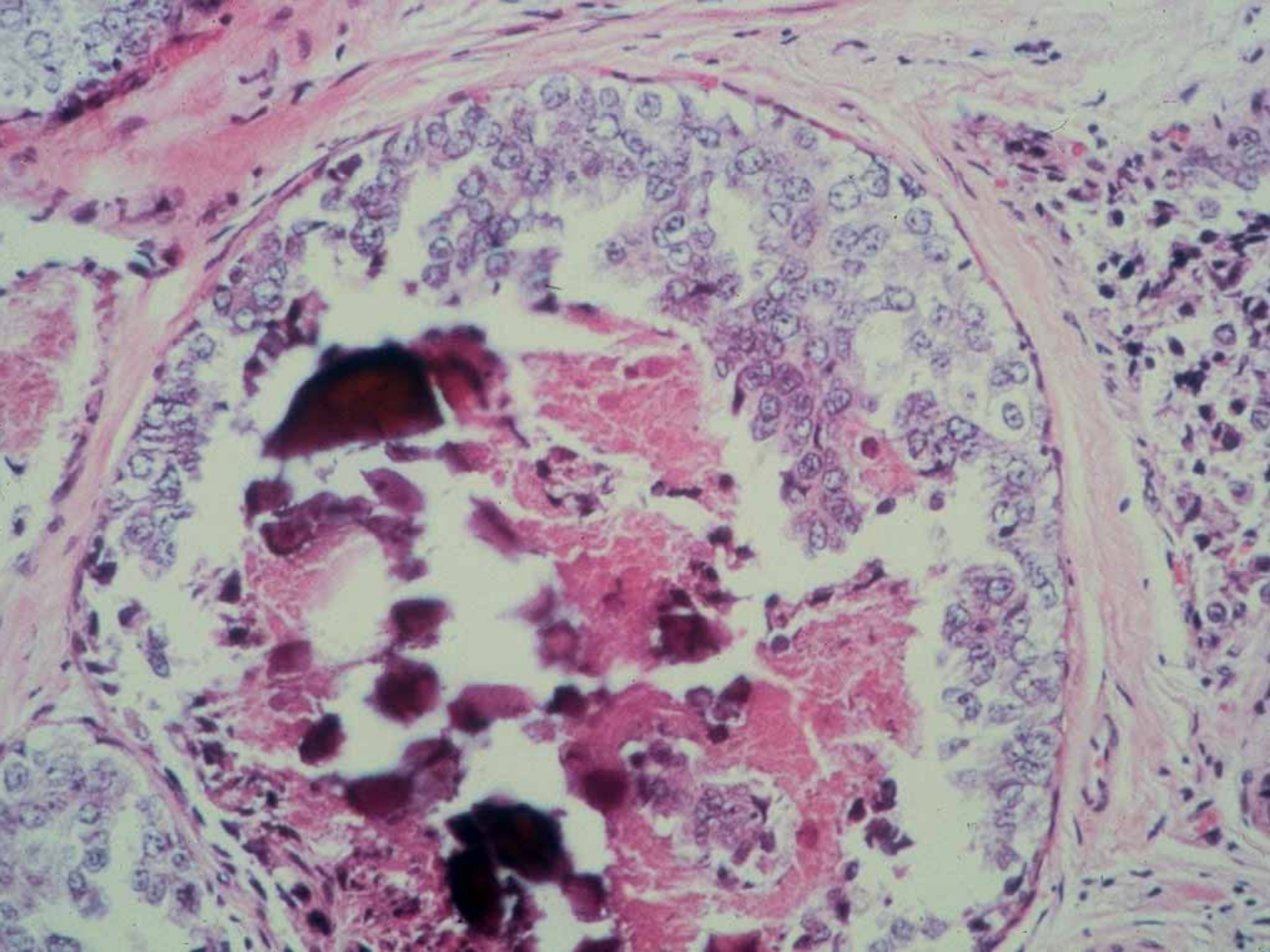
- In Situ Lobular Carcinoma
- Carcinoma with Mixed Ductal and Lobular Features/Pleomorphic Lobular Carcinoma In Situ
- Encysted Papillary Carcinoma

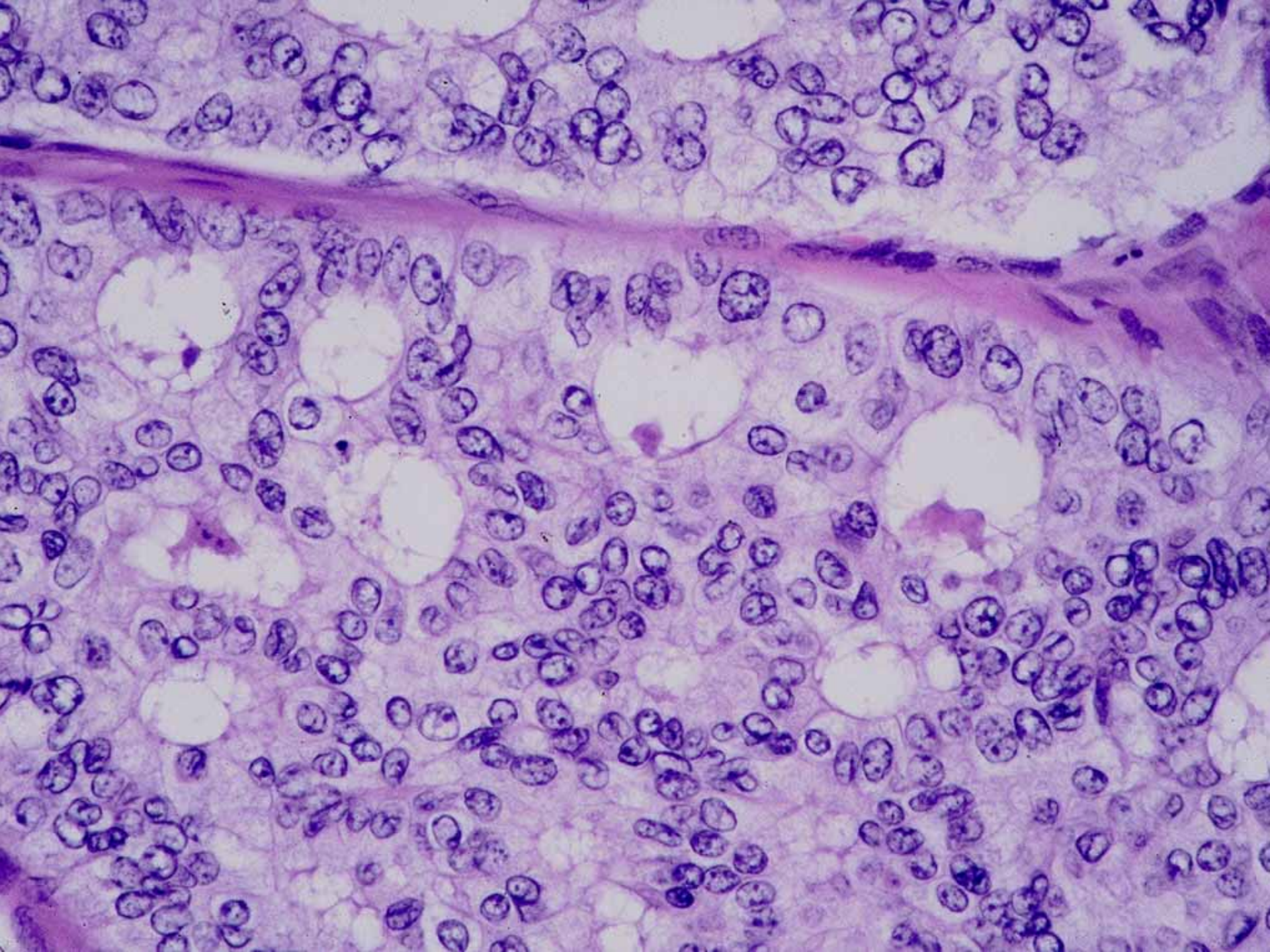
Ductal Carcinoma in Situ: Differential Diagnosis, Clinical Significance, and Prognostic Factors

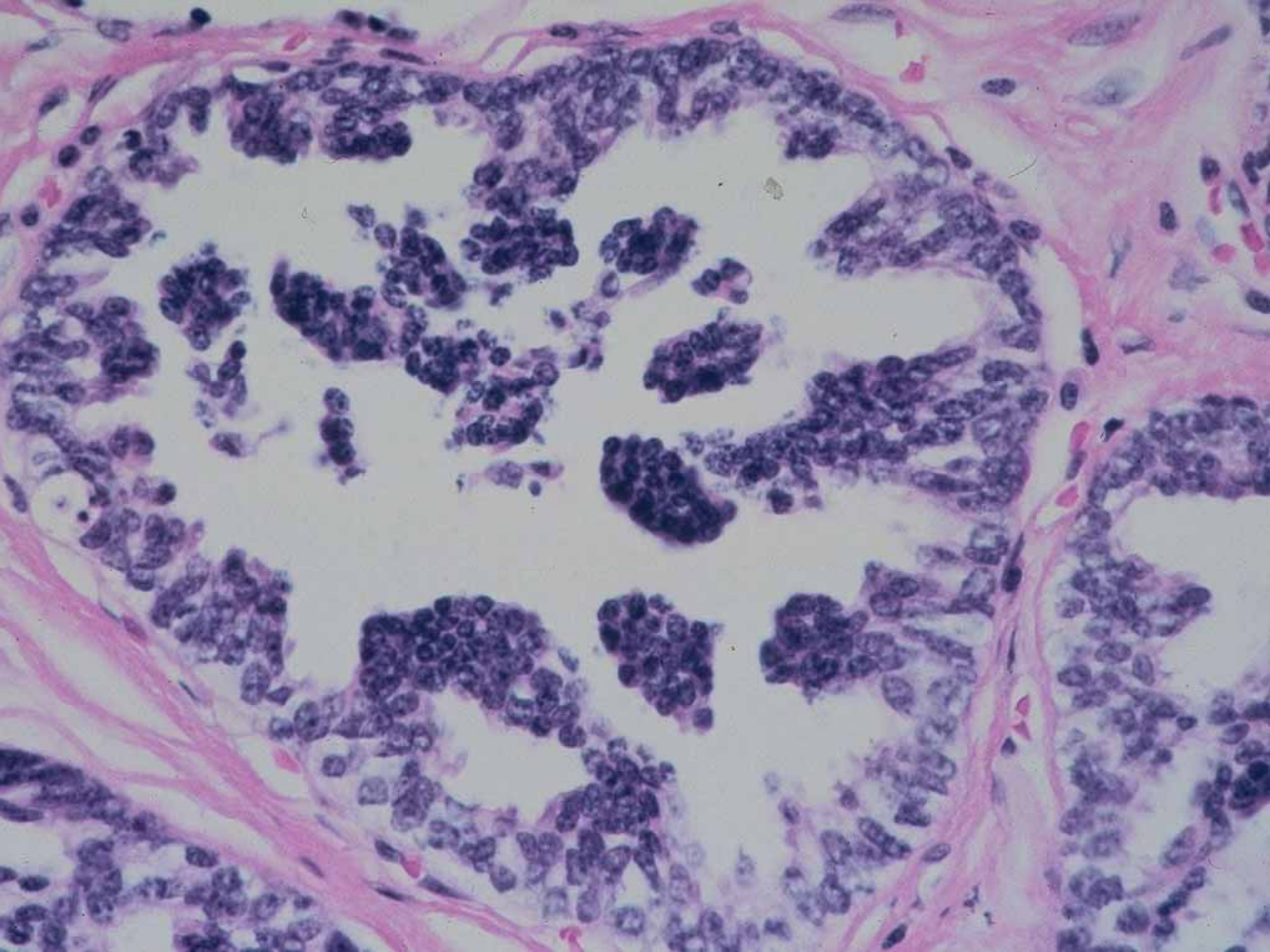
- Traditional (Architectural) Classification
- Controversies & Problems
- Biologic Differences
- Segmental Distribution
- New Classification Systems
- Treatment

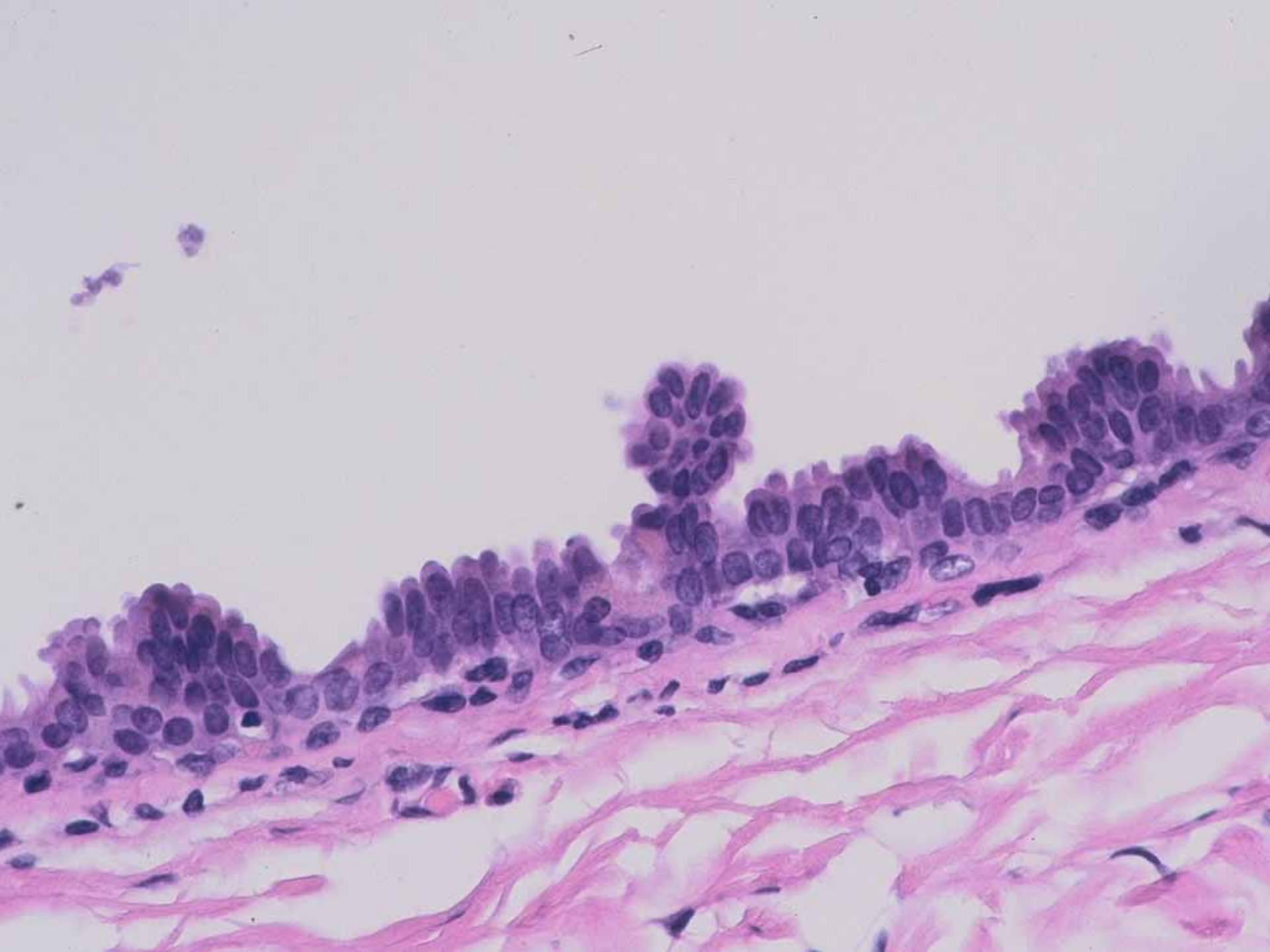
Classification of DCIS

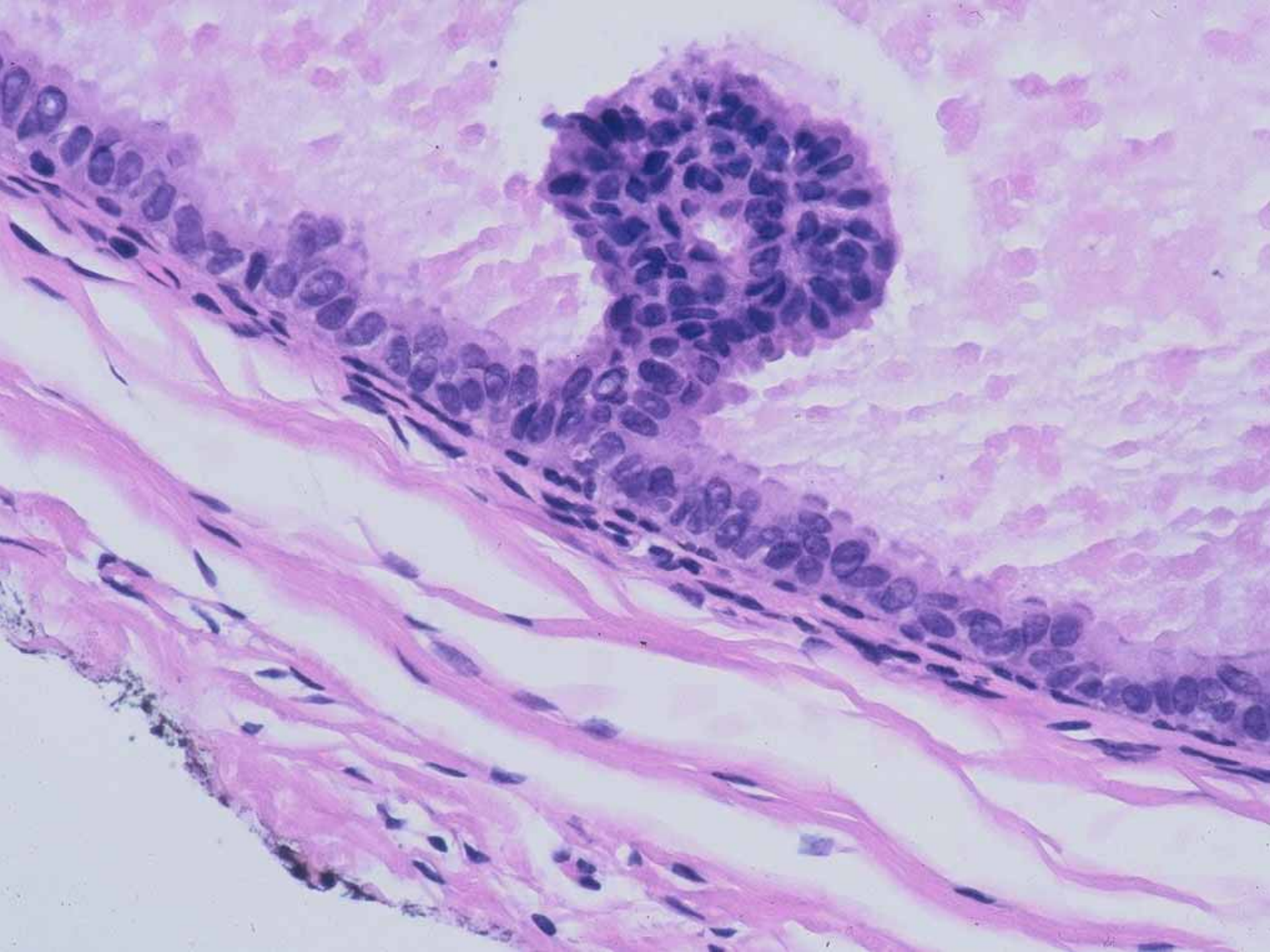
- Traditional classification based primarily on architecture
- Comedo, solid, cribriform, papillary micropapillary, clinging

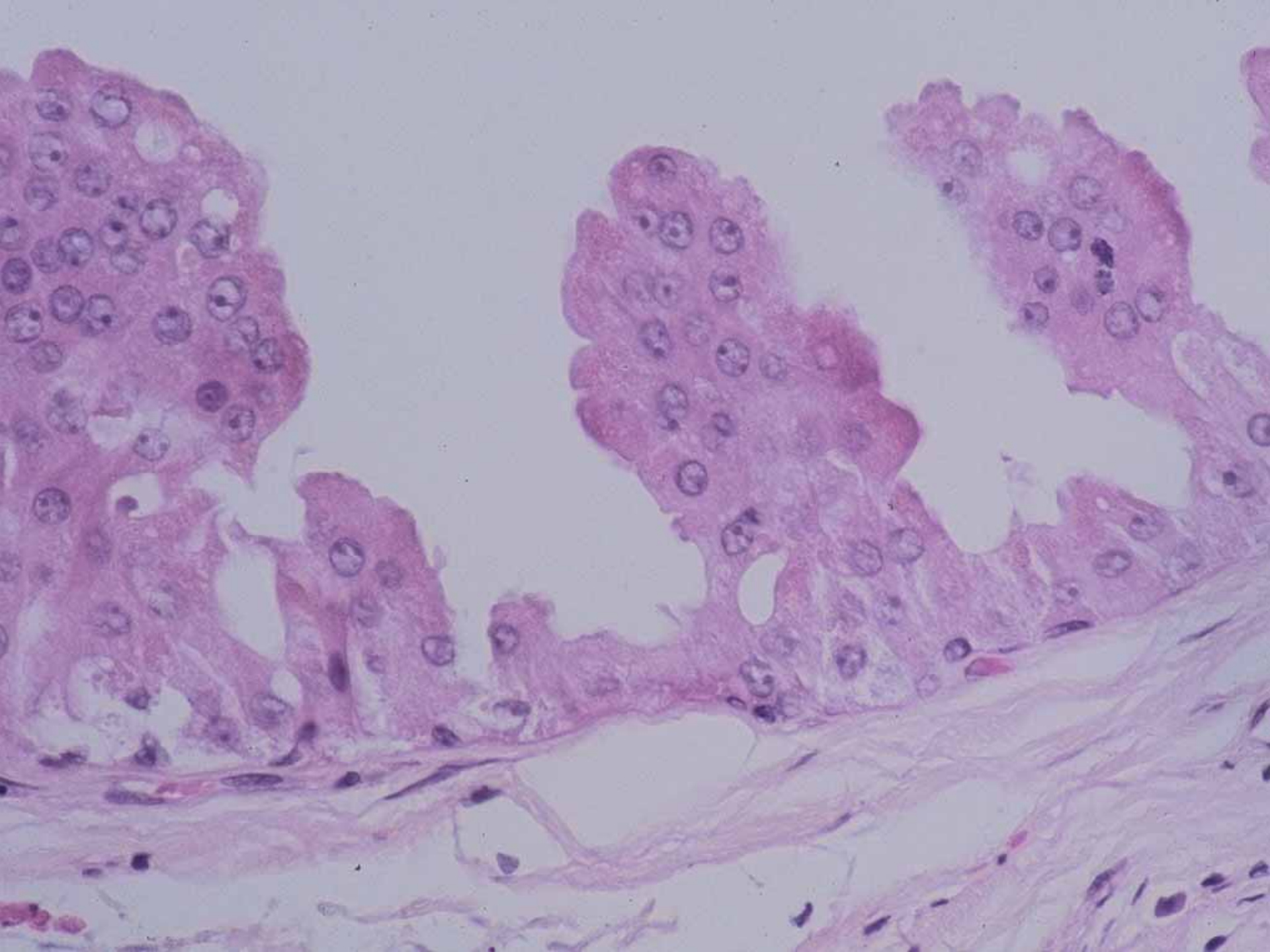






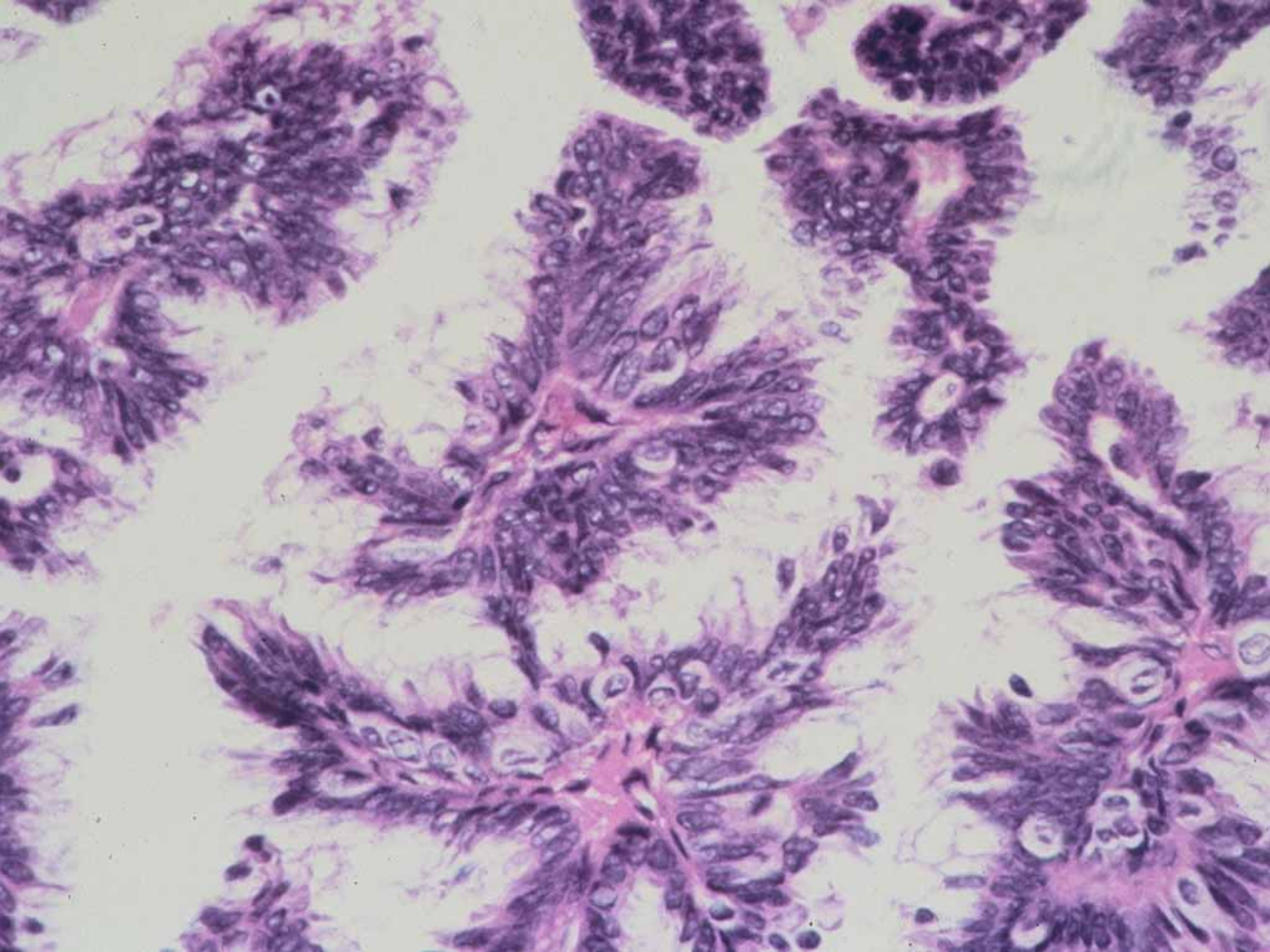


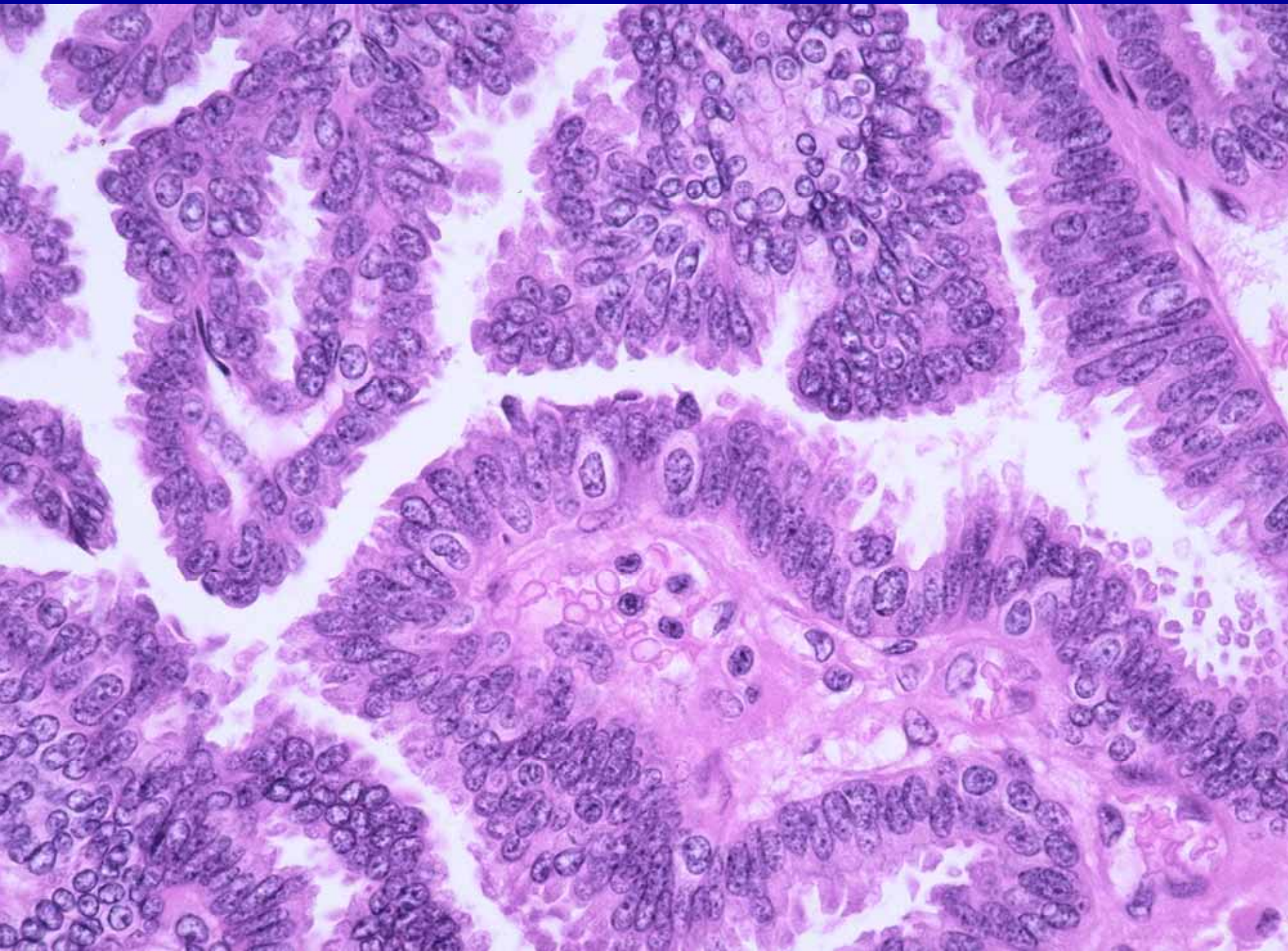


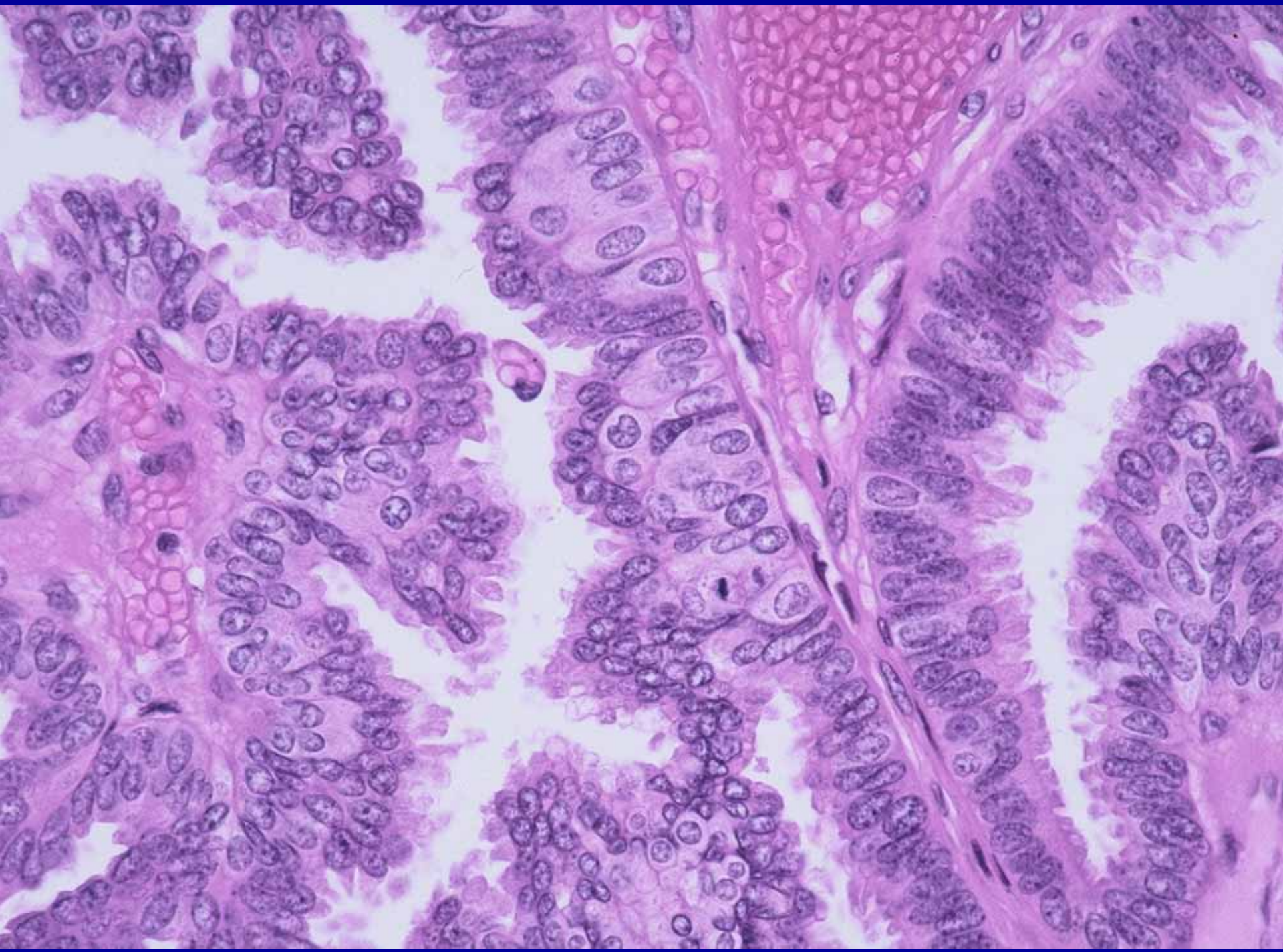


Papillary Ductal Carcinoma In Situ

- In contrast to papillomas, a uniform cell population
- Hyperchromatic cuboidal to columnar cells
- +/- clear epithelial cells near the base (globoid cells), which may mimic myoepithelial cells







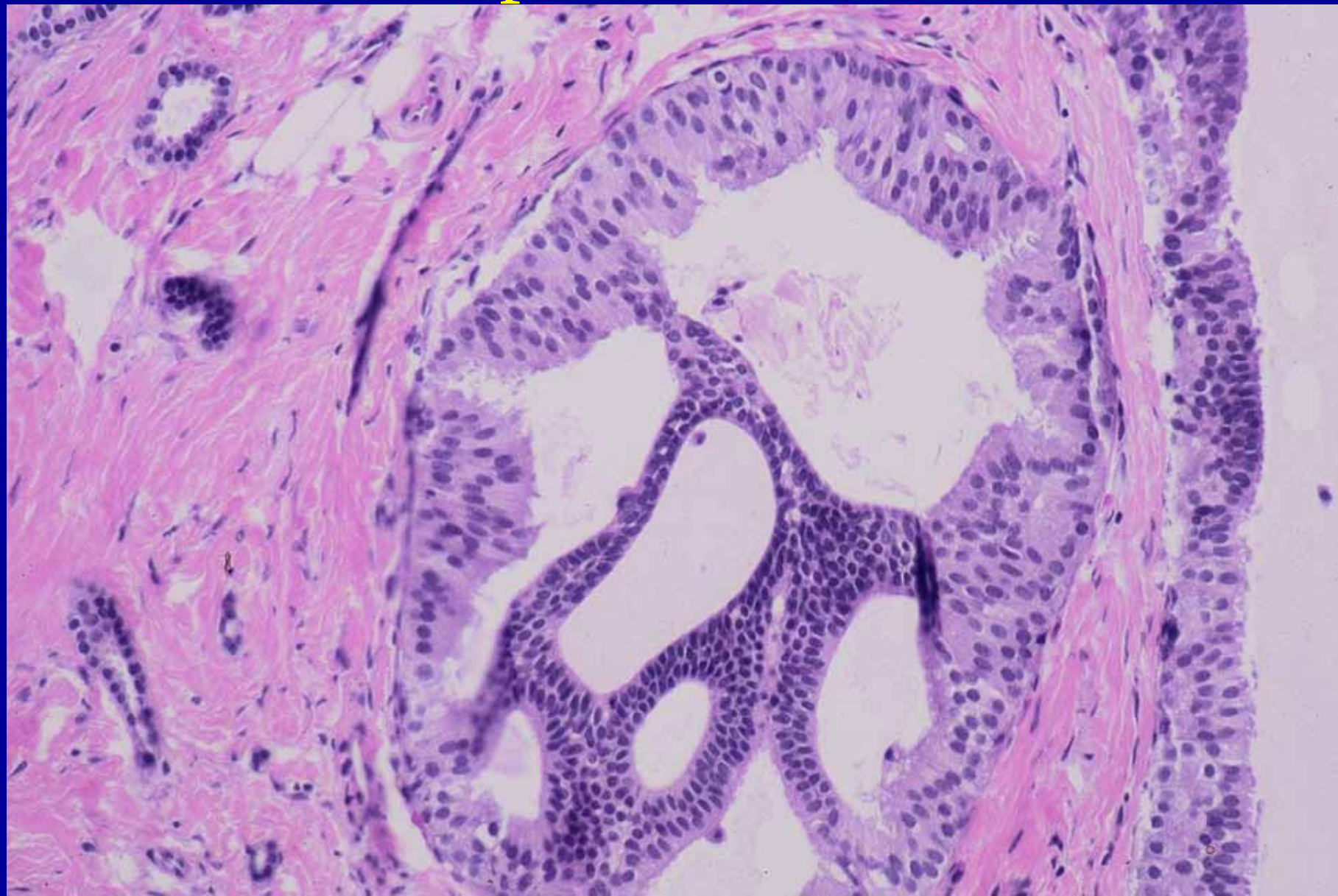
Papillary Ductal Carcinoma In Situ

- Differential includes papilloma/invasive carcinoma
- It has fibrovascular cores
- There are no myoepithelial cells in the fibrovascular cores
- The blood vessels mark with smooth muscle markers
- p63 is negative in the cores
- It has myoepithelial cells around the periphery of the duct

Papillary Ductal Carcinoma In Situ

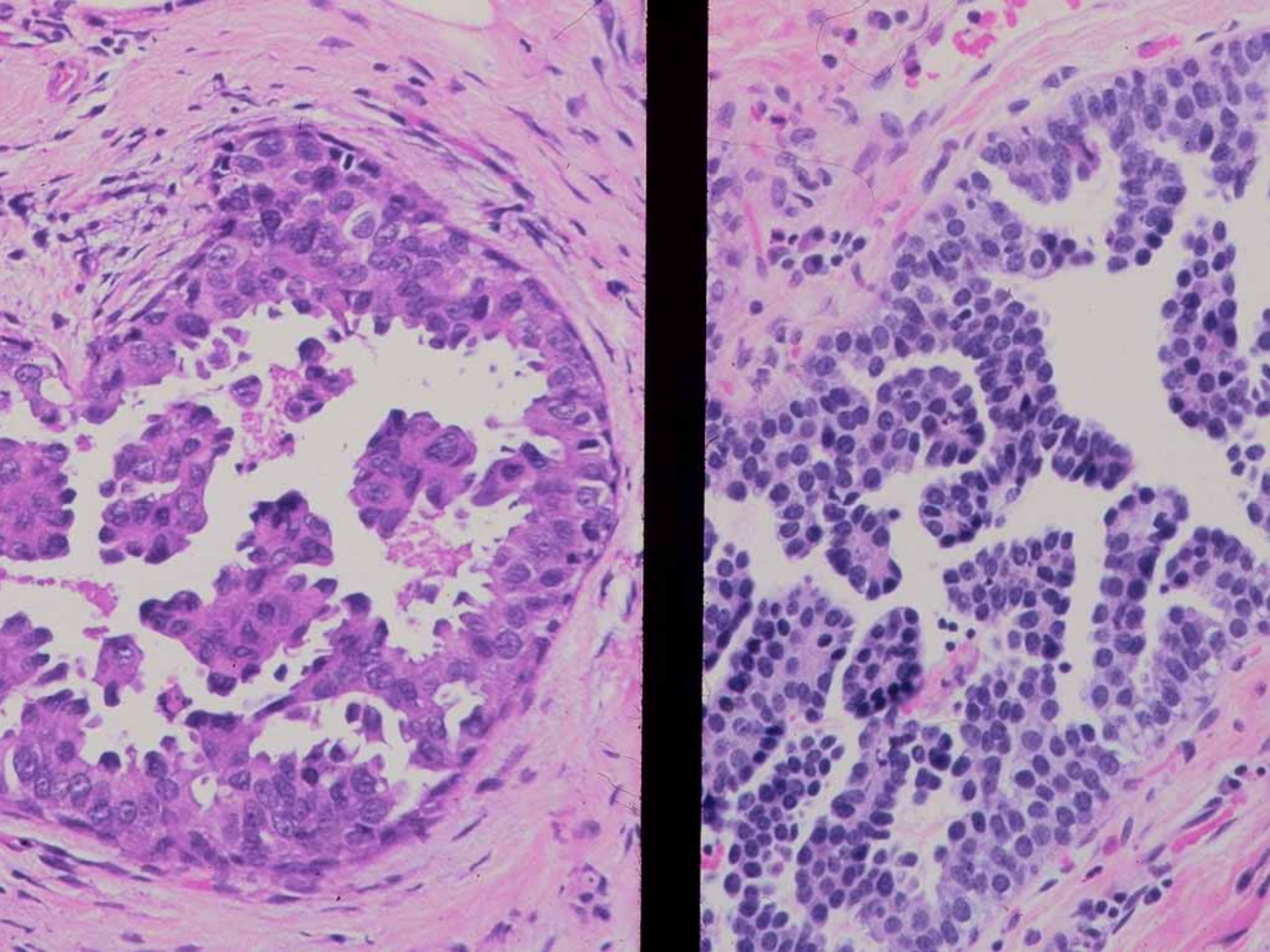
- The associated invasive carcinoma usually NOS/NST
- Occasionally invasive in nests maintaining fibrovascular cores
- Invasive papillary carcinoma may metastasize maintaining a nested papillary appearance mimicking DCIS

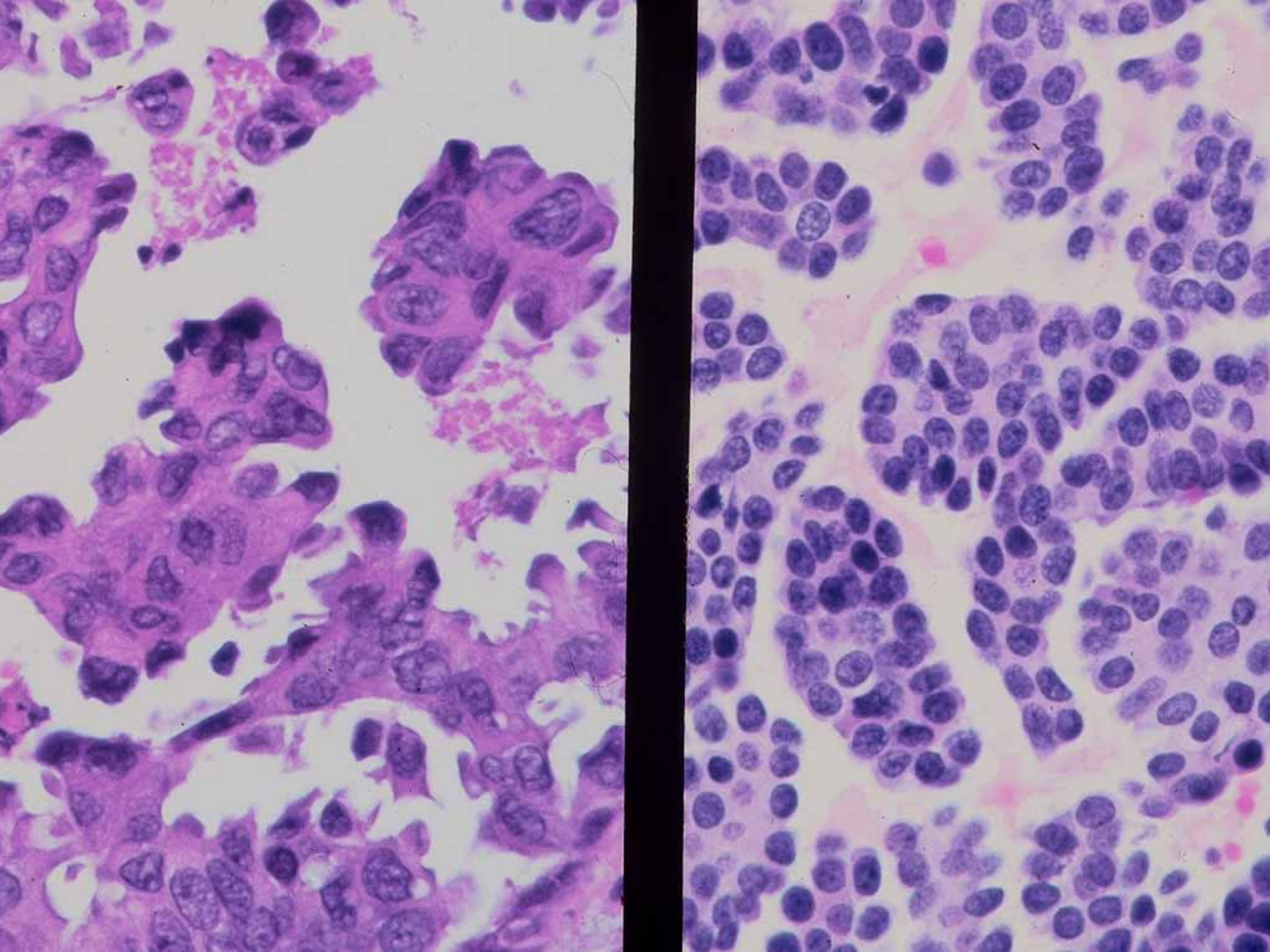
Biphasic DCIS

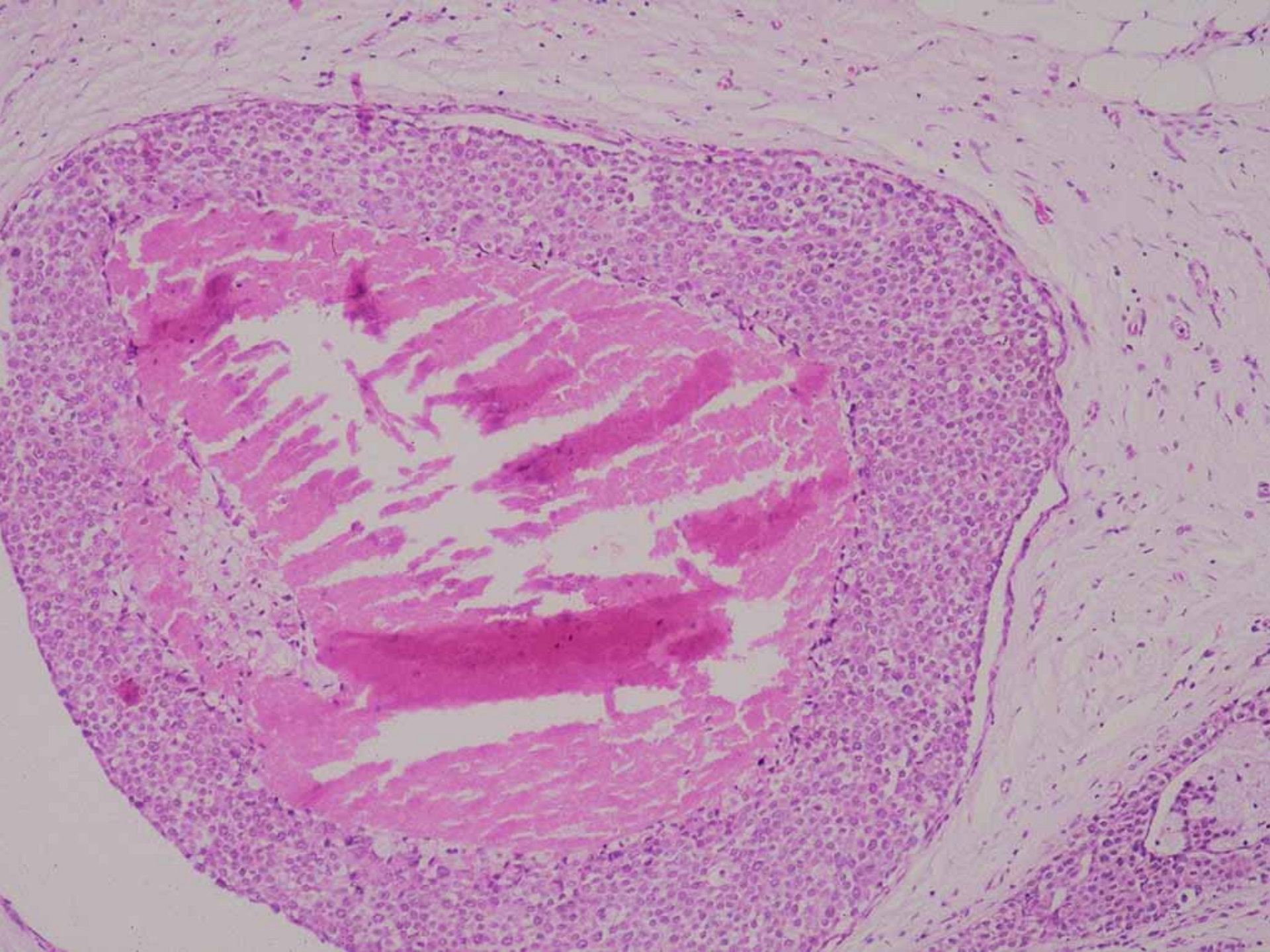


Problems with the Architectural Classification System

- Definitions for subtypes not uniform
- Many lesions have mixtures of subtypes

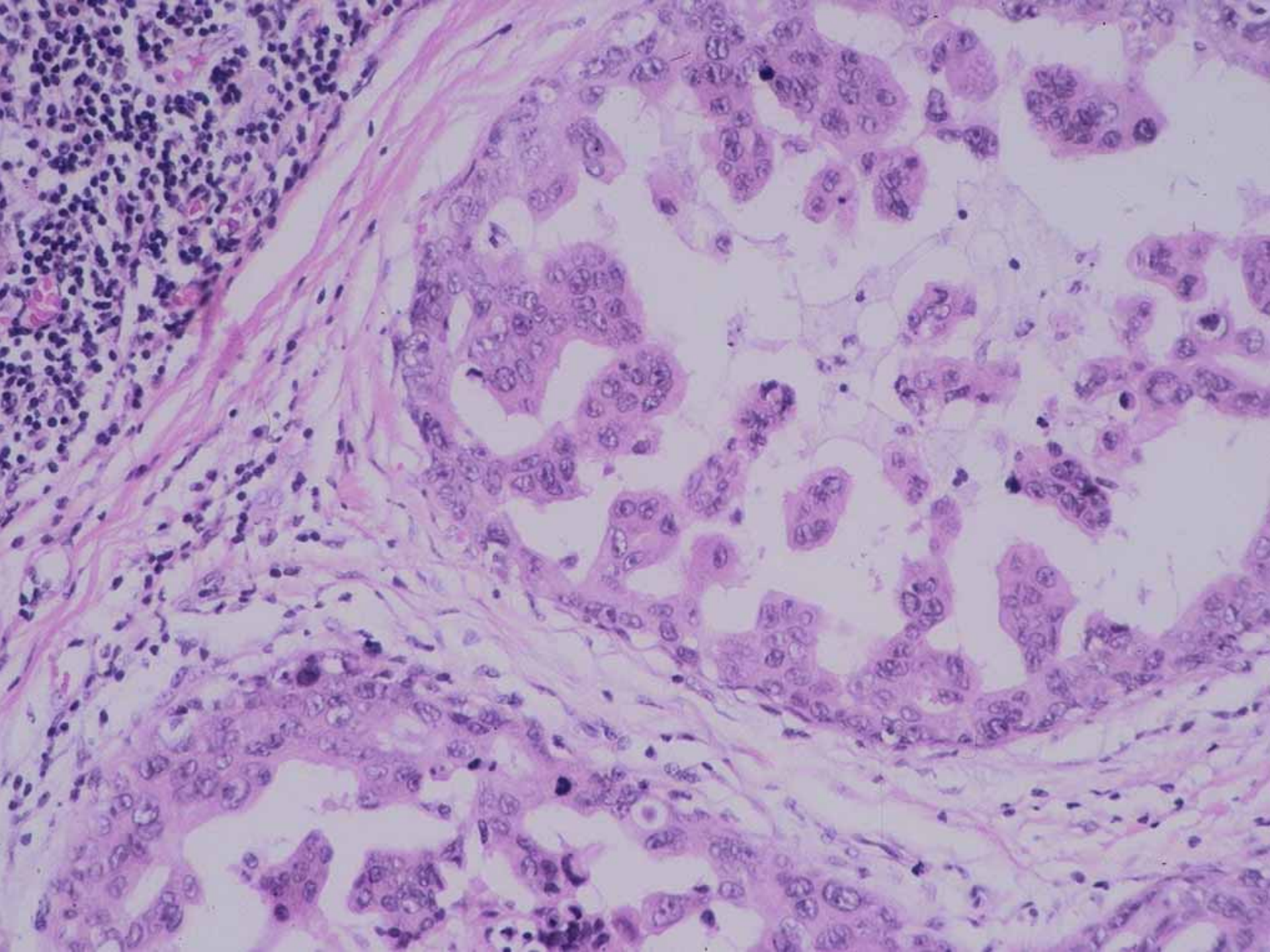


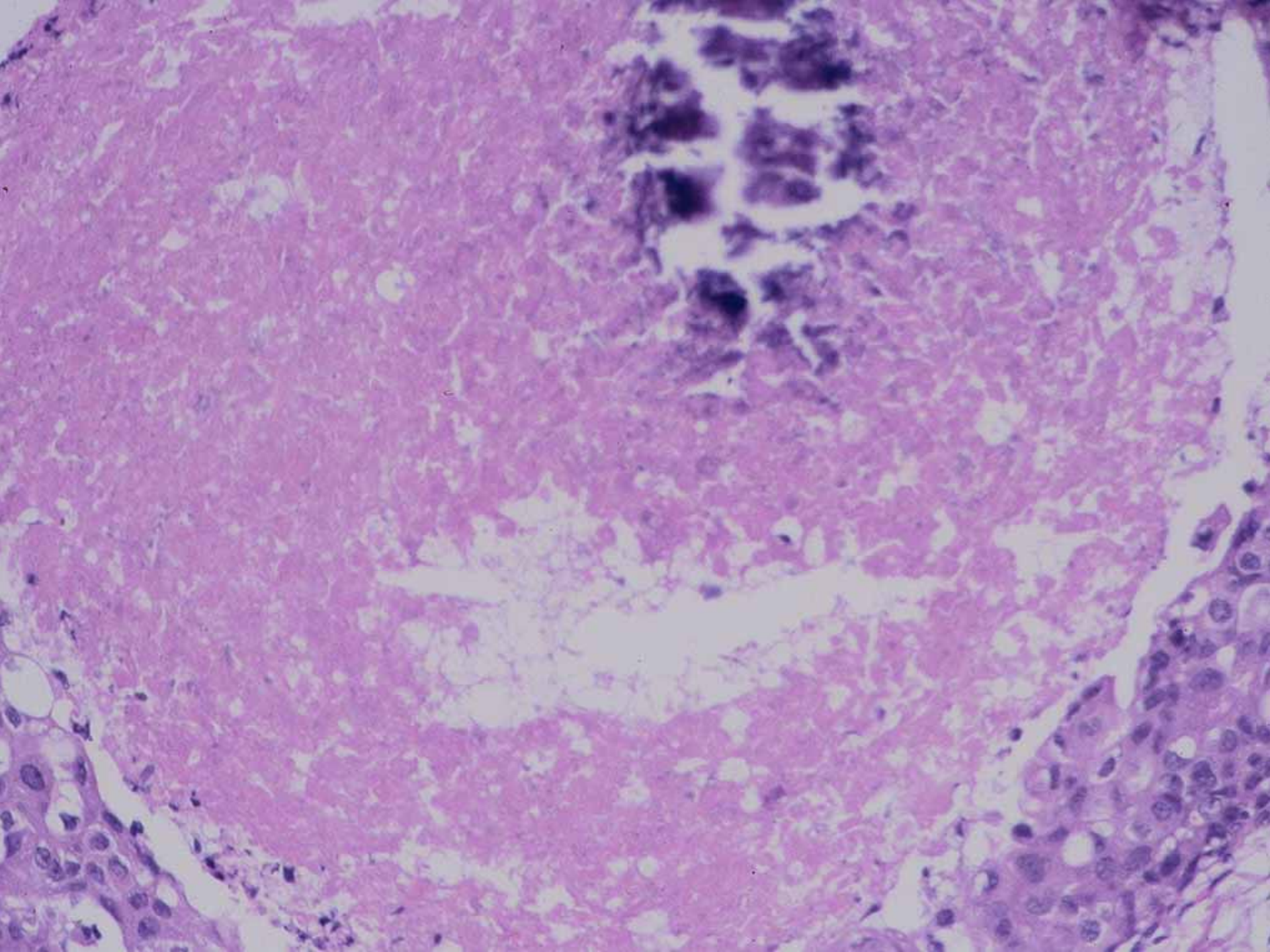




Heterogeneity of DCIS
100 consecutive cases

- 76 non-comedo lesions
  - mixture of patterns in 30%
  - most commonly crib + mp
- 24 comedo lesions
  - Non-comedo areas in 42%
    (Lennington, 1994)



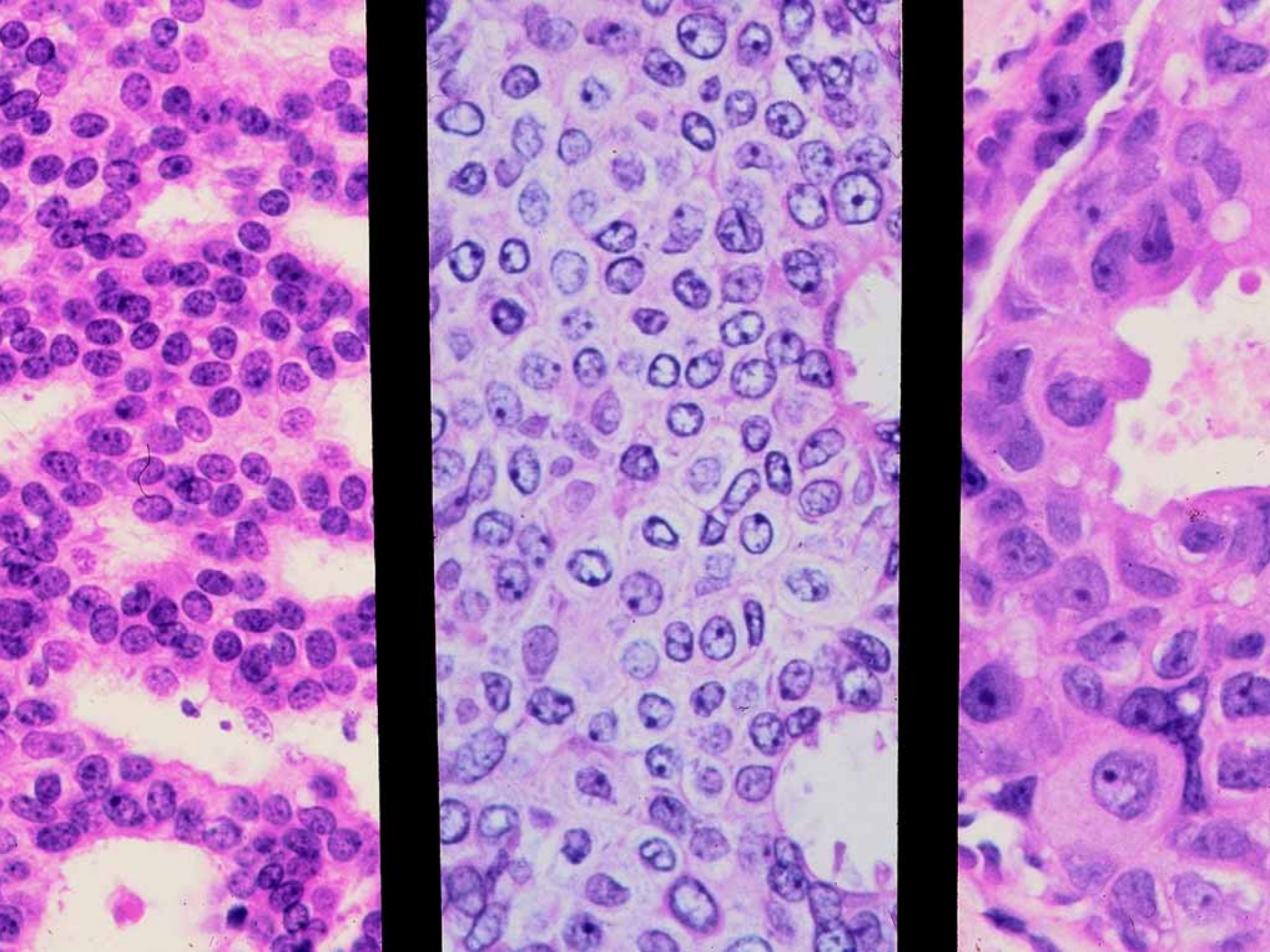


DCIS

- While architecture varies considerably within an individual case
- Nuclear morphology is much more constant

DCIS

- Most newly proposed classification systems rely primarily on Nuclear morphology
- And have 3 grades



Alternative Classification Proposal

Ductal Intraepithelial Neoplasia (DIN)

- Is appealing at some level
- UDH through high grade DCIS as a spectrum (DIN1-DIN3)
- There is no scientific evidence that ductal lesions progress in the breast following this pathway

DCIS: Differentiation

	High Grade	Low Grade
Cytology	High grade	Low grade
Necrosis	Frequent	Infrequent
Aneuploidy	Frequent	Infrequent

DCIS: Differentiation

	High Grade	Low Grade
ER+, PR+	Infrequent	Frequent
Proliferative rate	High	Low

DCIS: Differentiation

	High Grade	Low Grade
HER2/neu+	Frequent	Infrequent
bcl2+	Frequent	Infrequent
P53 mutations	Frequent	Infrequent
Angiogenesis	Frequent	Infrequent

DCIS: Differentiation

	High Grade	Low Grade
Microinvasion	More common	Less common
Calcifications	“Course granular”	“Psammomatous”
	Linear branching	Fine granular

Genetic Abnormalities In DCIS

High Grade	Intermediate	Low Grade
Amplifications 17q12, 11q13	>Losses on 16q	Losses on 16q

Buerger H. J Pathol 1999; 187:396

DCIS

- The molecular and genetic abnormalities seen with DCIS are the same seen with invasive cancer
- Low grade DCIS has changes of low grade invasive cancer and of the special types of invasive cancer
- High grade DCIS has changes seen in high grade invasive cancer

Microarray Profiling

Numerous studies have now documented that ductal carcinoma in situ has the same subtypes previously identified for invasive carcinoma

- Luminal a
- Luminal b
- HER-2/neu over expressing
- Basal like

DCIS: Size > 10 mm

HER2/neu+	83%
HER2/neu-	33%

De Potter C. Hum Pathol 1995; 26:601

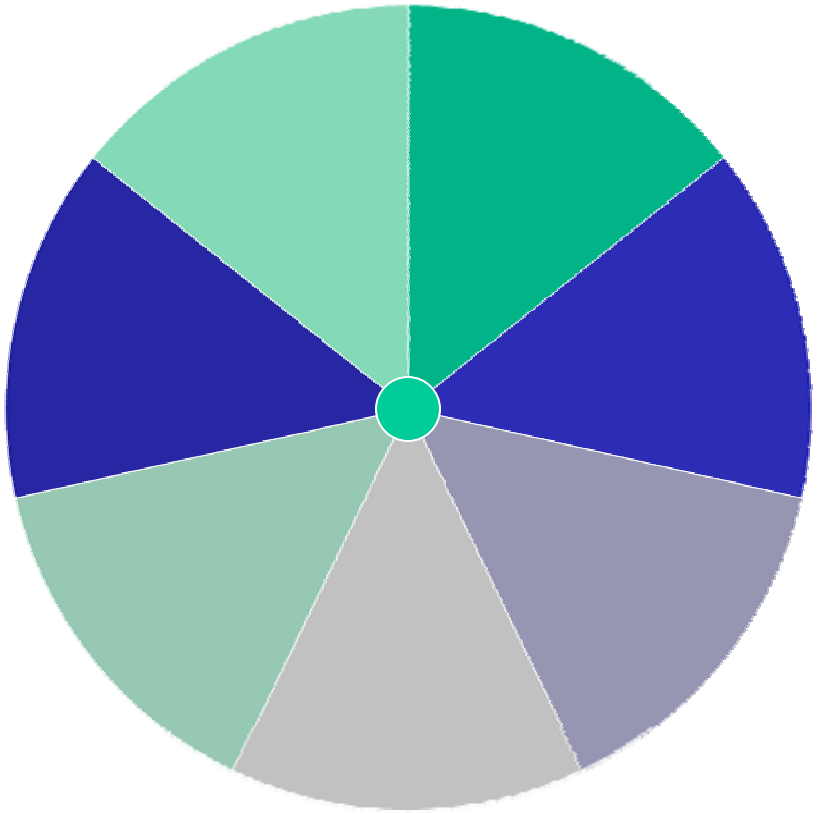
Mammographic Appearance of DCIS

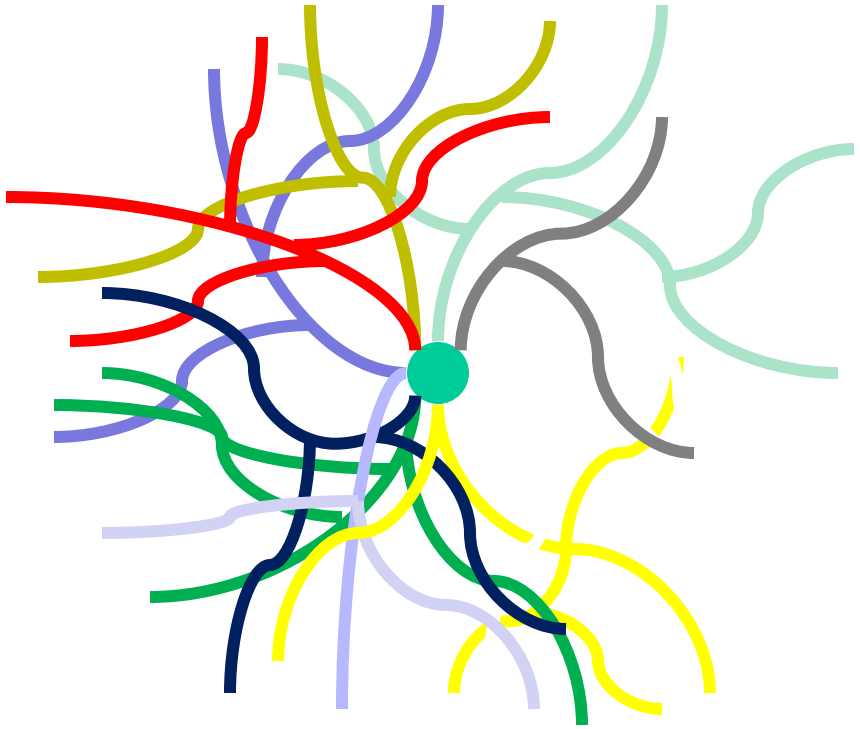
- Microcalcifications alone most common (~70%)
- Other (~30%)
  - Soft tissue abnormality with microcalcifications
  - Soft tissue abnormality alone
    - mass sometimes circumscribed
    - architectural distortion

DISTRIBUTION OF DCIS

- The myth of multicentricity
- Most cases show unicentric (segmental) distribution
- Involved segment may be large

“Segments” of the Breast





Mammographic vs Histologic Size (using standard views without magnification)

	Size discrepancy > 2cm
High Grade	8/50 (16%)
Low Grade	15/32 (47%)

Holland et al 1984

DCIS: Differentiation

	High Grade	Low Grade
+ excision margin	Less frequent	More frequent

Mammographic vs Pathologic Size (magnificaton views)

- 59 mastectomy specimens with DCIS
- Maximum size discrepancy ~1.5 cm; similar in High and Low Grade lesions

Holland et al 1994

Mammographic vs Pathologic Size Magnification Views

- High Grade 3/14 (21%)
- Intermediate Grade 1/7 (14%)
- Low Grade 2/14 (14%)

(Holland 1994)

Mammographic vs Pathologic Size

- Mammography still underestimated size of DCIS

- Size discrepancy < 2cm in ~80-85% of cases

(Holland ,1994)

Is there a relationship between Grade of DCIS and Outcome ?

Local Recurrence Related to Histologic Grade (Type)

	RX	F/U	DCIS "high"	Grade "low"
Lagios	CS	124 mos	33%	2%
Schwartz	CS	47 mos	48%	2%
Collins	CS	62 mos	25%	5%
Solin	CS+RT	5 yr	11%	2%
Solin	CS+Rt	15 yr	18%	15%
B-17	CS	8yr	34%	29%
B-17	CS+RT	8yr	15%	12%

“Low Grade” or “Non-Comedo” Groups

Lagios	NG 1 without necrosis
Silverstein	NG 1 or 2 without necrosis
Solin	NG 1 or 2 with necrosis, NG 1 or 2 without necrosis, NG 3 without necrosis
Fisher	NG 1 or 2 with necrosis, NG 1 or 2 without necrosis, NG 3 without necrosis, NG 3 with necrosis in <1/3

DCIS

In evaluating
studies of histologic type
and risk of local recurrence,
it is essential to understand
the composition of the
groups being compared

(NOT EVERYONE'S "LOW GRADE" IS THE SAME)

Considerations Regarding Recurrence and Histologic Type

- Poorly differentiated lesions are associated with necrosis and calcification
- Poorly differentiated lesions grow more rapidly
- Studies have relatively short follow-up
- Well differentiated lesions can recur up to 4 decades after biopsy(Sanders M., Cancer 2005)

- The higher recurrence rate in poorly differentiated DCIS may be a function of short follow-up and ease of detection

Local Recurrence Related to Histologic Type

Influence of Length of F/U (Solin et al, CS+RT)

Follow-up (act)	Local Recurrence	
	high grade	low grade
5 years	11%	2%
8 years	20%	5%
10 years	18%	15%

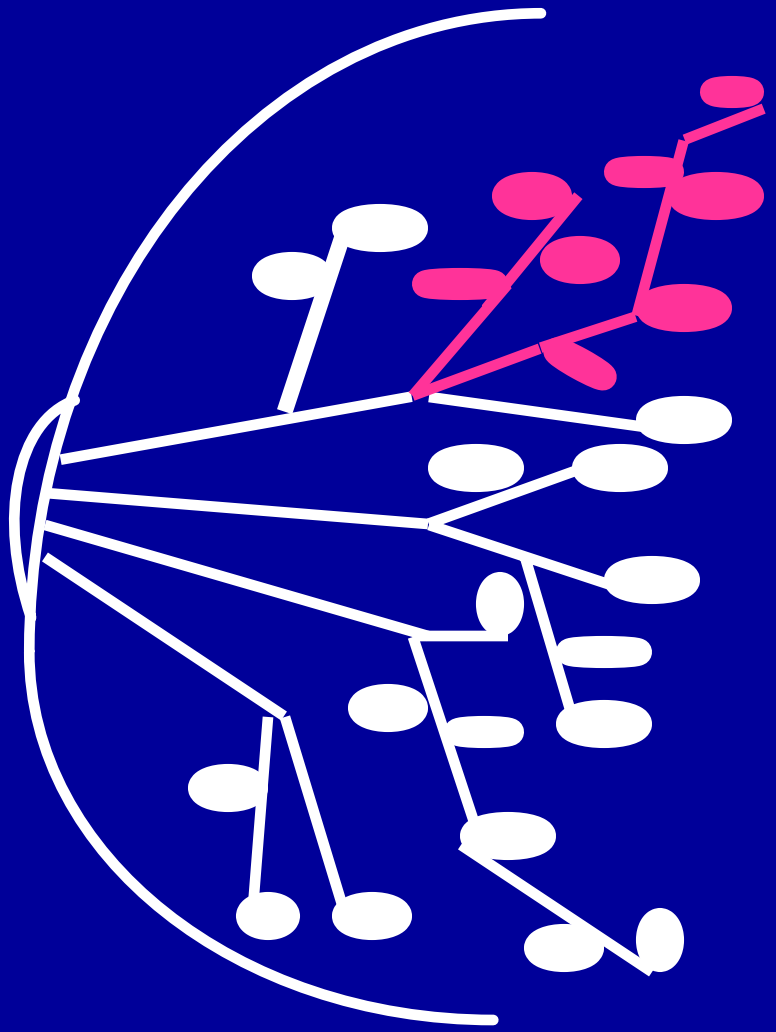
Importance of Margin Assessment: DCIS

- Positive margins identified in many studies as the most important risk factor for local recurrence
- However, margin status alone may be suboptimal in defining adequacy of excision

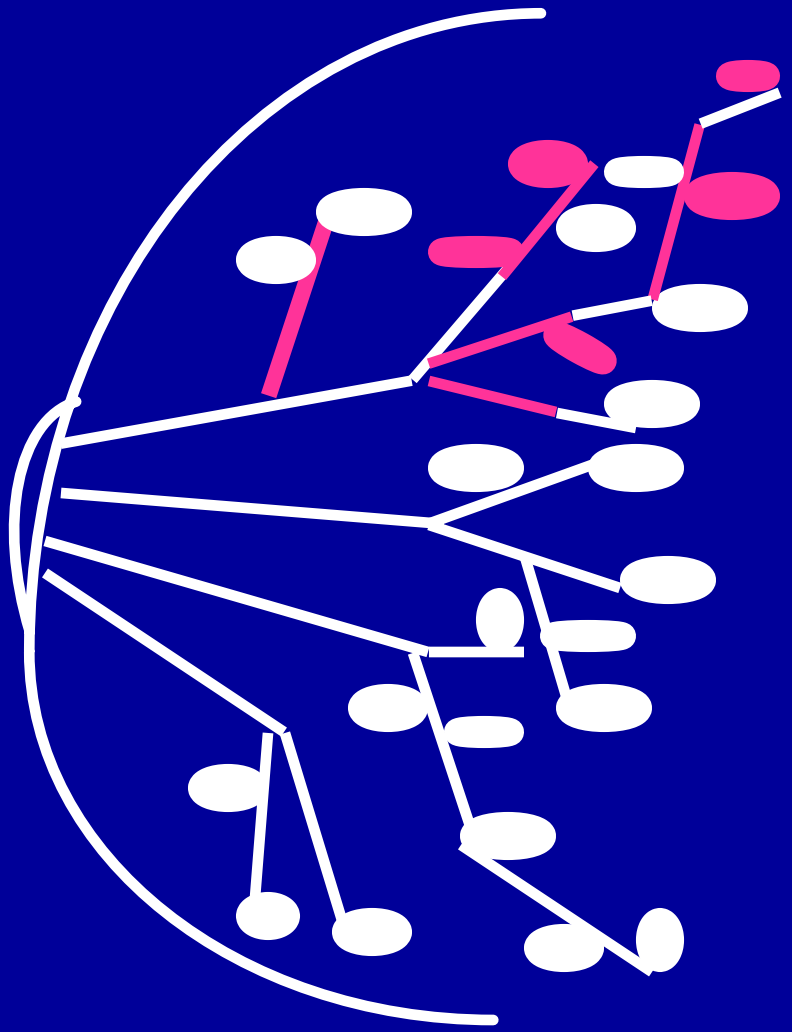
NSABP B-17
Pathologic Subset Analysis, 1995
Margins and Local Recurrence (mean f/u 48 mos)

	CS	CS +RT
Positive/unk	25%	10%
Negative	11%	4%

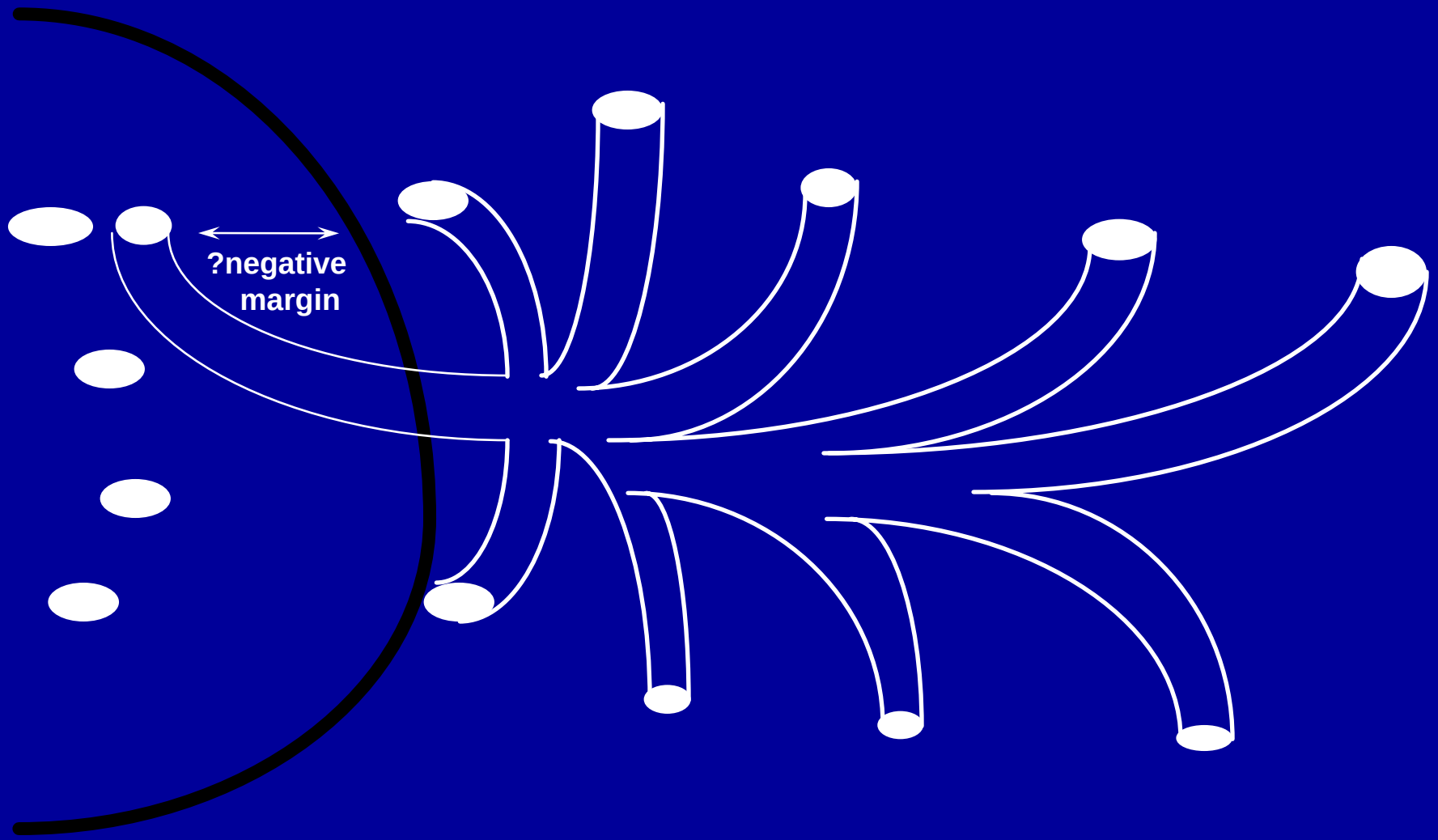
Unicentric (Segmental) Involvement



Continuous



Multifocal (gaps)


?negative
margin

Gaps Between Foci of DCIS

(Faverly, Holland; 1994)

Gap Size	# (%)
No gap	30 (50%)
<5mm	19 (32%)
5-10mm	6(10%)
>10mm	5 (8%)

Gap Size Related to DCIS Grade

(Faverly, Holland; 1994)

Gap size	Grade		
	Low (n=27)	Int. (n=9)	High (n=19)
None	30%	45%	90%
<5mm	44%	33%	5%
5-10mm	11%	11%	5%
>10mm	15%	11%	0%

Gaps in Low Grade DCIS

Large histologic sections

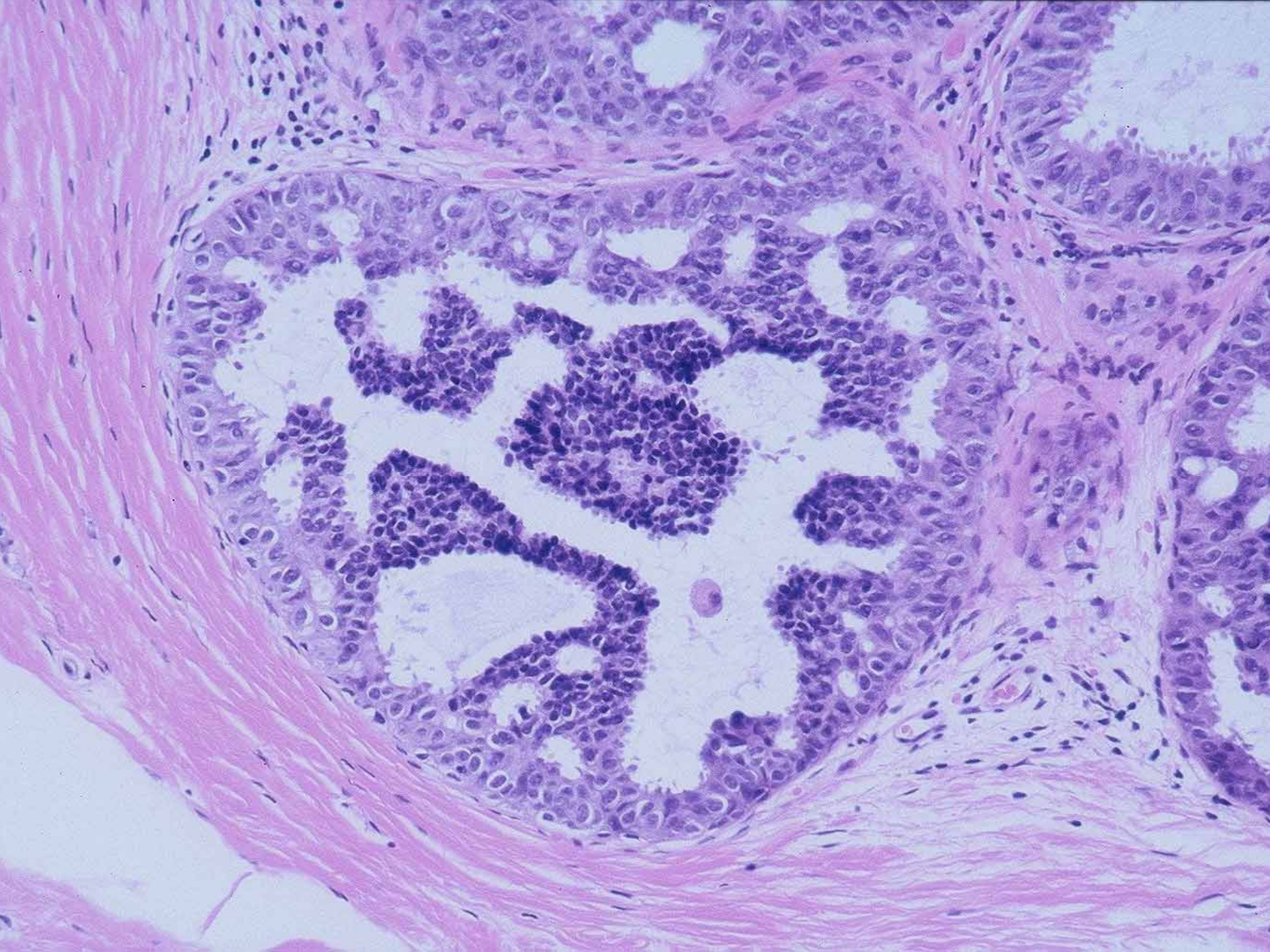
High grade DCIS usually unifocal

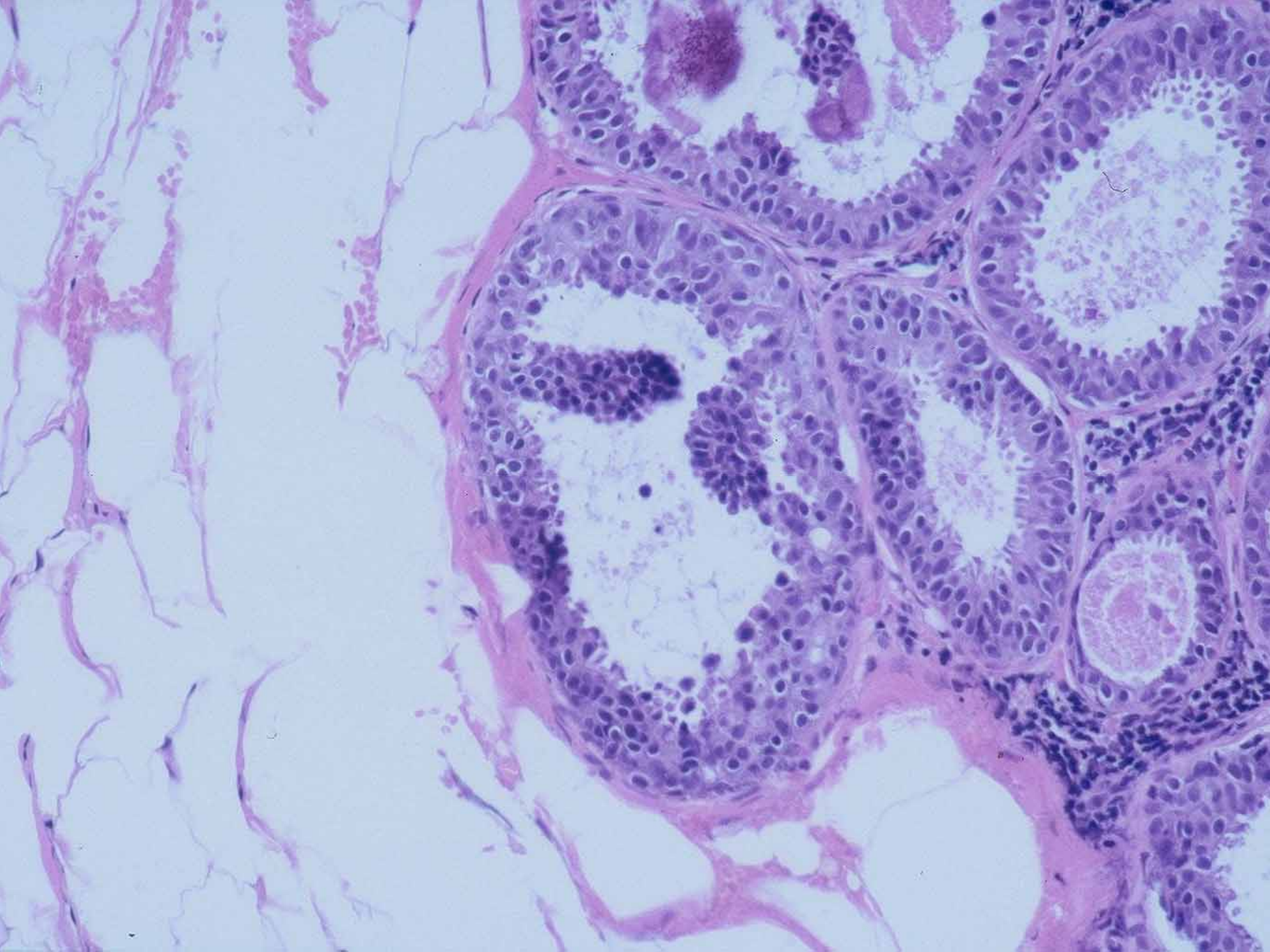
Low grade DCIS often multifocal

Foschini MP., Human Pathology 2007

Gaps in Low Grade DCIS

- In order to diagnose low grade DCIS you need cellular monomorphism and architectural change
- Some areas of low grade DCIS are diagnostic while other areas lack sufficient architectural change
- The Gaps may be diagnostic not biological





Clonal Analysis of DCIS

- 7 cases of “predominantly intraductal carcinoma” studied: all monoclonal
- 3 cases with multiple foci of DCIS: every sample monoclonal, and same allele of PGK gene inactivated in each case
- All cases comedo type

Breast Failure in Patients with Negative Margins: The Wm Beaumont Experience

of Ducts With DCIS Near Margin

# Ducts with DCIS	12 yr Recurrence Rate
0	9
1-7	11
≥8	25

DCIS

- 33% of patients with negative excision margins who had post-operative mammography performed, which revealed microcalcifications, had residual DCIS

Waddell B, 2000

- Even with “free” margins, if there is a significant amount of DCIS near the margins, a re-excision should be considered

Margin Width and Local Recurrence

(Silverstein, 1999)

- Margin width ≥10mm:
  - low risk of local recurrence for patients treated with CS+RT or CS alone

  risk of local recurrence not affected by

  - Use of radiotherapy
  - nuclear grade
  - presence of comedo necrosis
  - lesion size

Margin Width and Local Recurrence

(Silverstein ,2006)

- Margin width ≥10mm:

  12Year probability of local recurrence

  – with CS alone 13.9% (3.4% invasive)

  – with CS+RT 2.5% (1.6% invasive)

How Wide is Wide Enough?

- Not a resolved issue
- Wider excisions associated with lower local recurrence but poorer cosmetic outcome
- Optimal margin width likely differs for patients treated with CS+RT and CS alone

Margin Width and Local Recurrence

Wong, 2006(JCRT)

- Prospective study for small (2.5 cm) non-HG DCIS
- Margin width 1 cm
- No RT
- Accrual closed early due to high LR rate
- 5year LR 12%

ECOG ES5194 Excision +/- Tam

- DCIS Excised minimum 3mm margin
- Two arms

  Low or intermediate grade 2.5 cm or smaller

  High grade (NG3 + necrosis 1 cm or smaller)
- Specimen sequentially sectioned and completely embedded
- Post excision Mag mammo negative for calcs

ECOG ES5194 Excision +/- Tam 2006

- Ipsilateral Breast recurrence at 5 years
- High grade **14.8%** (7.2-22.3%)
- Low or intermediate **6.1%** (4.0-8.2%)
- The use of radiotherapy decreased recurrence in all groups

Size (Extent) of DCIS

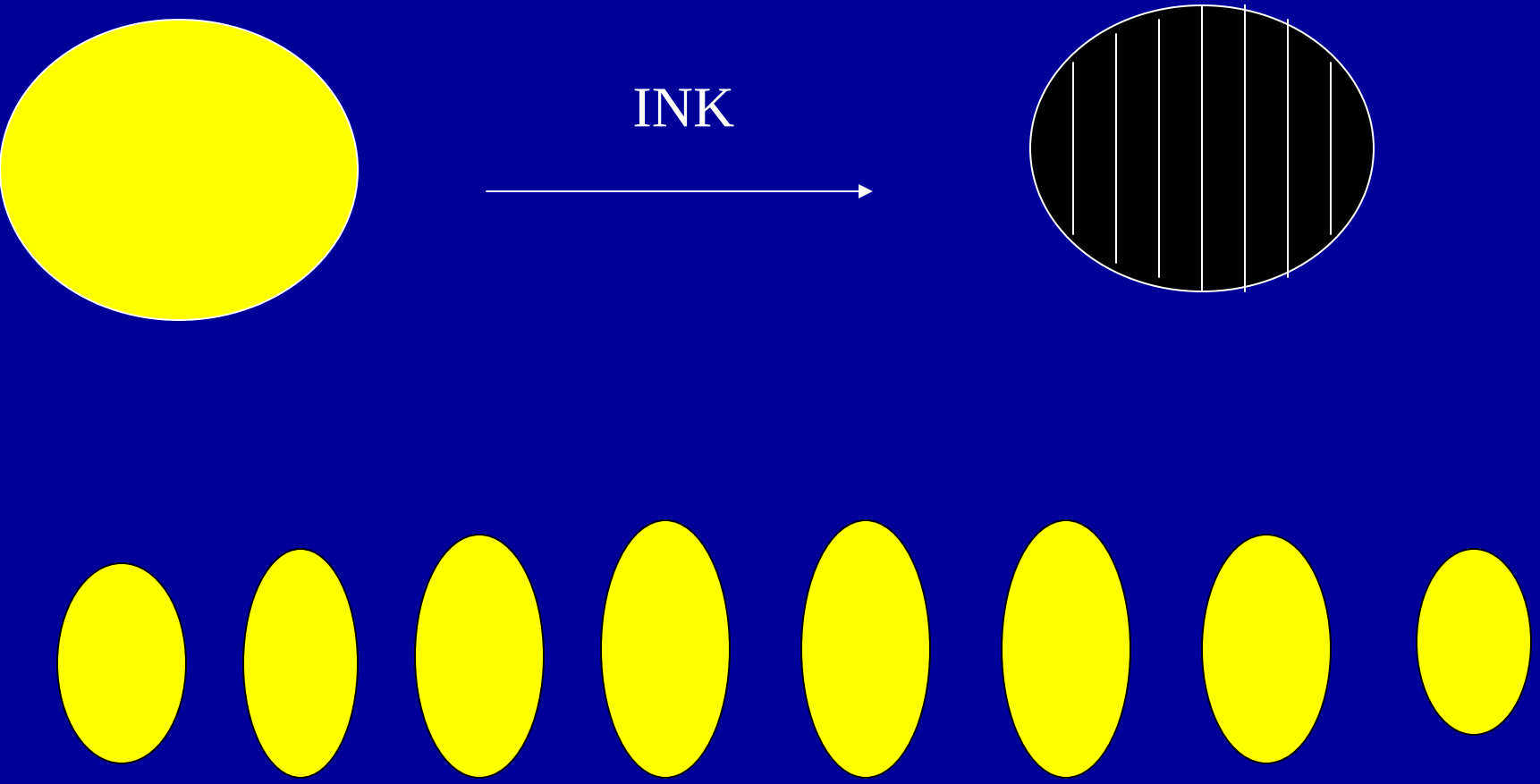
- Size related to likelihood of finding
  - occult invasion
  - lymph node metastases
- Size related to ability to perform adequate excision and achieve satisfactory cosmesis

Problems in Determining Size

- Often underestimated by mammography
- Grossly evident “tumor” rarely present
- Microscopically, lesion often present on >1 slide
- Accurate assessment requires total, sequential embedding or some modification thereof

Estimation of Size

- If mammo-path discrepant, use larger size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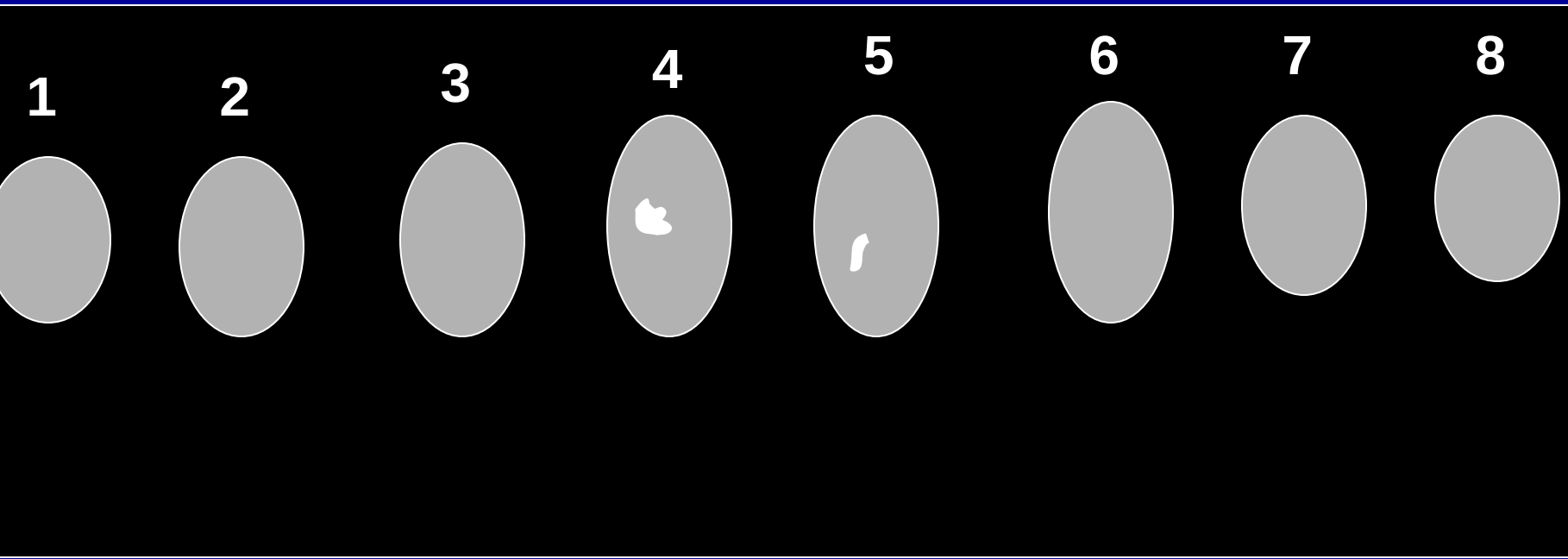
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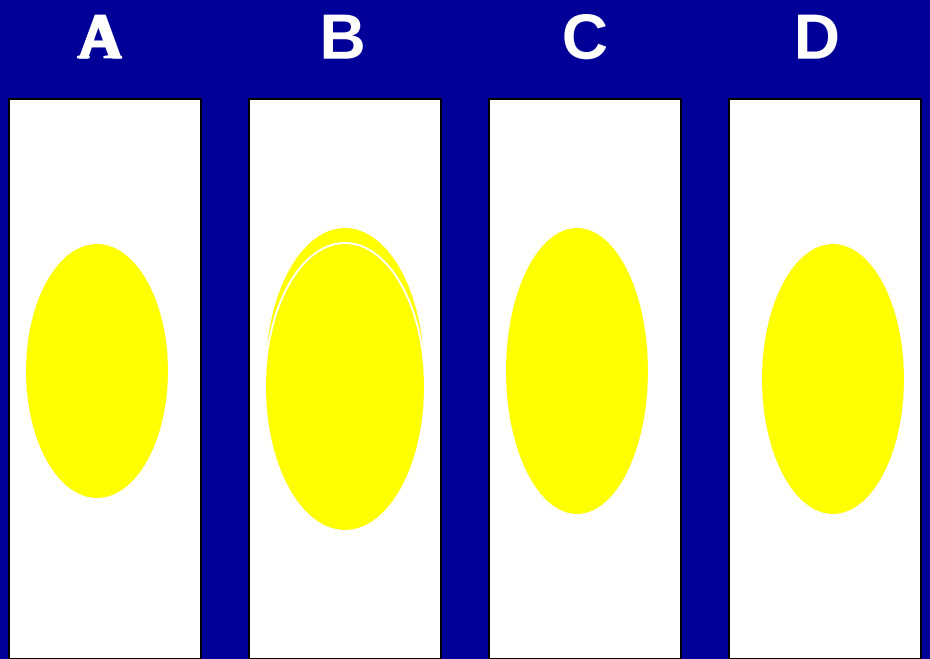

A
B
C
D

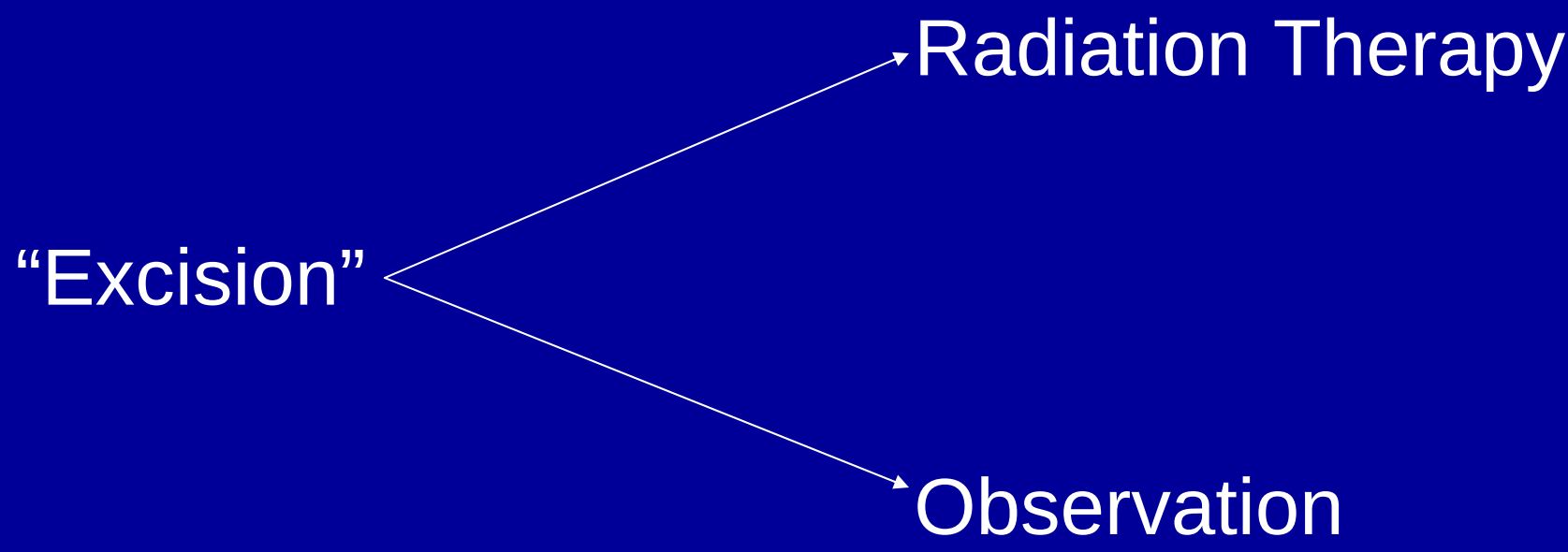
The BIDMC Approach

- All tissue is placed in disposable cassettes
  Labeled numerically and sequentially
- If the calcifications are associated with benign findings ,no more sampling
- If DCIS , additional cassettes can be submitted maintaining orientation

Estimation of Size

- Blocks 3 mm thick x # of involved blocks

First Generation Randomized Clinical Trials



First Generation Randomized Trials With Available Results

NSABP-B17

EORTC 10853

Local Recurrence Rates in NSABP-B17 and EORTC 10853 Trials

	NSABP-B17	EORTC 10853
Excision	27% (3.6%/yr)	26% (3.8%/yr)
Excision+RT	12% (1.6%/yr)	15% (2.1%/yr)
% Red'n	56%	47%

NSABP B17
8 Year Update

Breast Recurrence

	LE	LE+RT
Margins		
Free	29%	13%
Involved/unk	39%	17%

p=NS

NSABP B17
8 Year Update

Breast Recurrence

	LE	LE+RT
Comedo Necrosis		
Abs/SI	23%	13%
Mod/marked	40%	14%

Risk Factors For Local Recurrence EORTC 10853

- Age < or = 40
- Palpable lesion
- No radiation
- Intermediate or high grade DCIS
- Solid or Cribriform v Micropapillary or Clinging Pattern
- Doubtful margin
- All groups benefited from Radiation

Bijker, N et. al. JCO, 2006

Second Generation Randomized Clinical Trials

NSABP B-24 Trial (5 yr actuarial results)

	Placebo	Tam	%redn	p
LR	9.3%	6.0%	35%	0.04
Invasive LR	4.2%	2.1%	50%	0.03
Non-inv LR	5.1%	3.9%	24%	0.43
CBC	3.4%	2.0%	41%	0.01

Lancet, 1999

Comparison of the 5-Year Local Recurrence Rates in NSABP B17 and B24 Trials

B24	Tamoxifen	7%
B24	Placebo	12%
B17	Lumpectomy+XRT	12%
B17	Lumpectomy	25%

Reduction in Recurrence

- Seen only in ER+ cases
- For this reason we are currently testing our cases of DCIS for estrogen receptors

Mortality of DCIS Treated by Mastectomy

- Historically up to 2% of patients with DCIS developed metastatic disease
- For patients with mammographically detected disease the risk is lower

Axillary Node Involvement in DCIS (Pre-Sentinel)

- In the National Cancer Data Base 3.7% had positive nodes (10946 women)
- Other modern series 0-0.5%

Sentinel Lymph Node (SLN) Involvement in DCIS

- With the SNL procedure and IHC it is not unusual to find positive nodes
- In recent series 6 to 13 % of cases are positive
- Most of these cases are identified by IHC alone or first
- These patients are generally offered adjuvant therapy

Sentinel Lymph Node (SLN) Involvement in DCIS

- Given that fewer than 2% of patients with DCIS will develop distant metastasis it is clear that IHC identification does not translate to a known risk

SLN in DCIS

- Two large studies have shown no relationship between positive SLN and recurrence in patients with DCIS

Marby H., Giuliano A. E. and Silverstein MJ, A J Surg 2006, 192 : 455

Broekhuizen LN, Eur J Surg Oncol,2006, 32: 502

Sentinel Lymph Node (SLN) Involvement in DCIS

- For this reason we do not generally advocate for the use of IHC in those rare patients who undergo a SLN procedure

DCIS Consensus Conferences

- The European Organization for Research and Treatment of Cancer (EORTC) has held a number of DCIS Consensus Meetings
- In addition Gordon Schwartz MD organized Meetings in the USA

DCIS Consensus Conferences Recommendations for Reporting

- Nuclear grade
- Necrosis
- Polarization
- Architectural pattern(s)
- Margins
- Size of DCIS

DCIS Consensus Conferences Recommendations for Reporting

- Location of Microcalcifications
- Correlation of tissue specimens with specimen x-ray and mammographic findings

DCIS Consensus Conferences

- In terms of Pathology Reporting the conclusions were essentially the same

Conclusions

- Distribution in breast, histologic features, size, and adequacy of excision appear to be important considerations in selecting appropriate therapy for patients with DCIS

Conclusions

- Difficulties in assessing each of these factors
- Relative importance and interactions among them not well defined

Where Do We Go From Here?

- Long term results from clinical trials
- Methods to assess full extent of lesion and to assure its removal
- Methods to assess biologic potential
- Agents to prevent or suppress progression to invasion

Final Pathology Report for DCIS

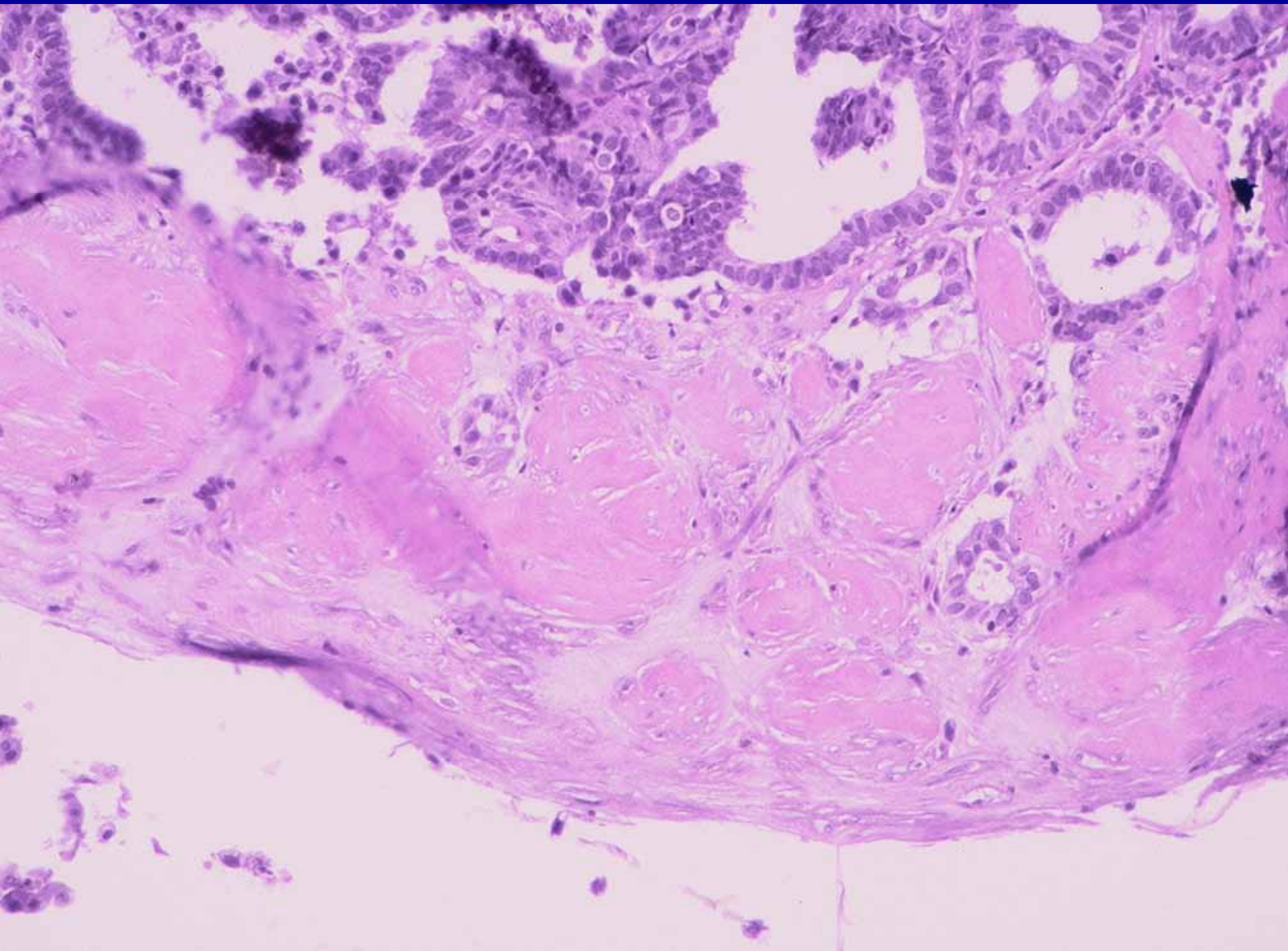
- Specimen size
- Nuclear grade
- Architectural pattern(s)
- Necrosis
- Lesion size/extent
- Location of calcifications
- Margins

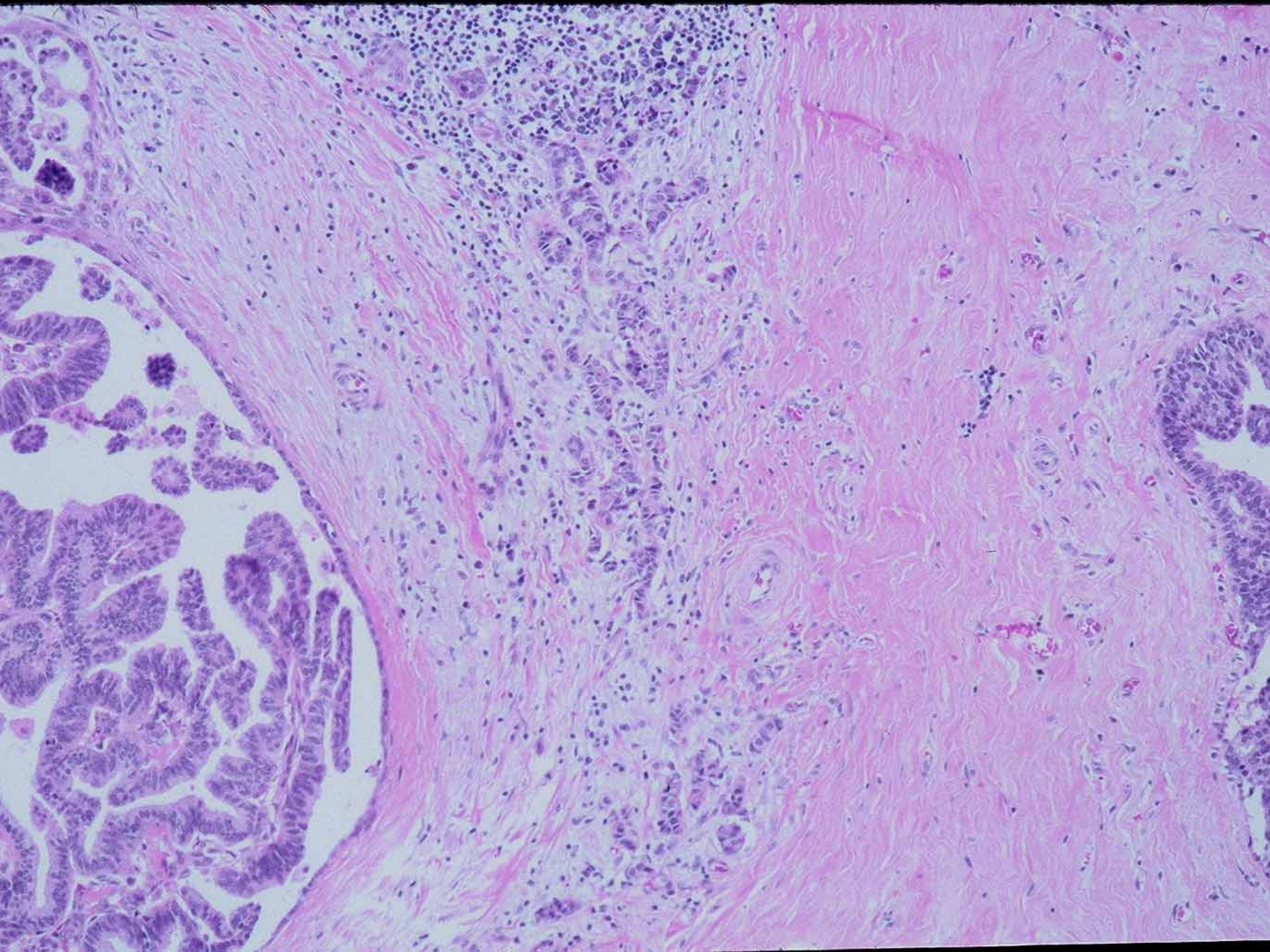
Intracystic Carcinoma

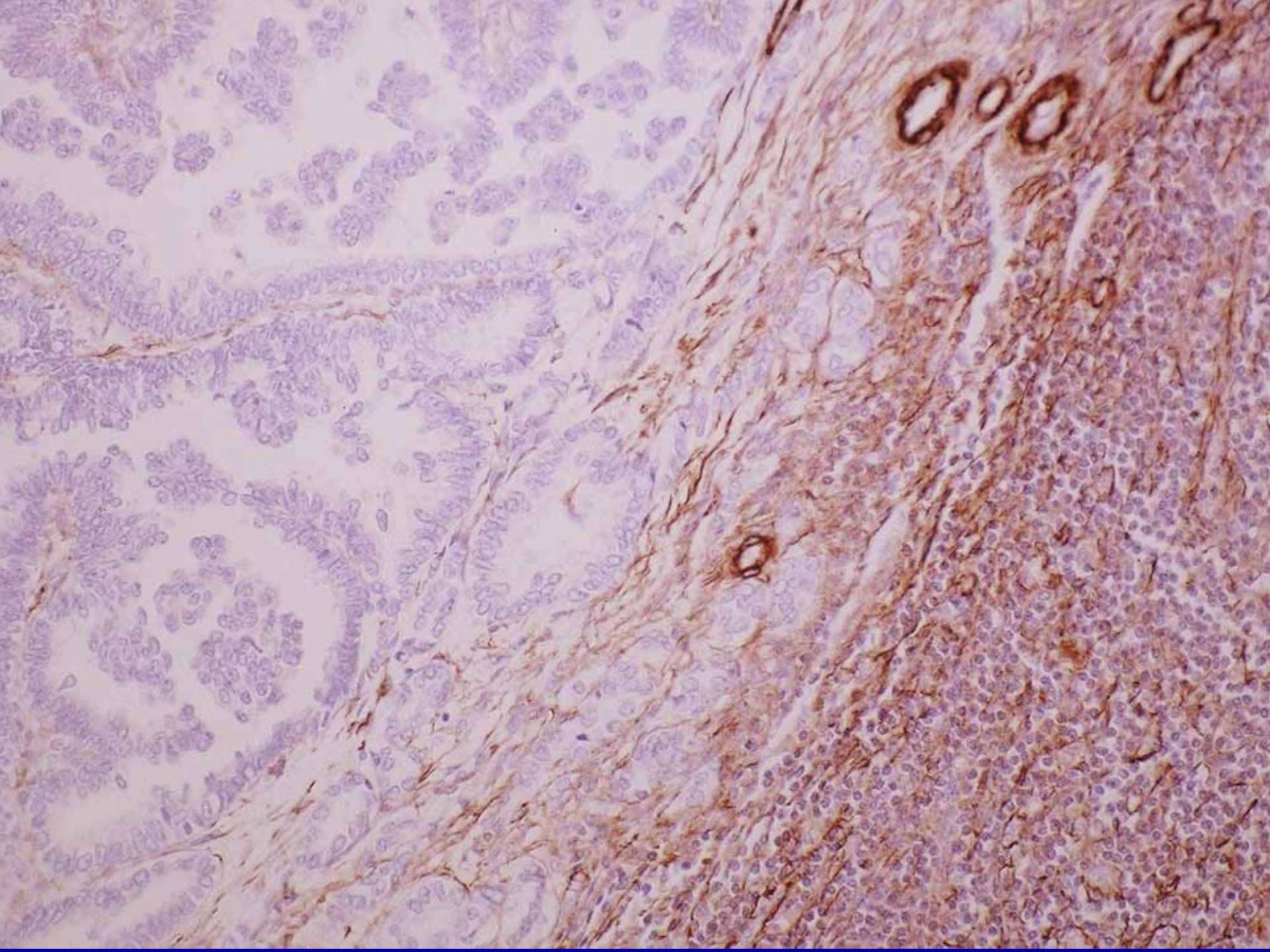
- Stains for myoepithelial cells are generally negative
- Is it DCIS is an enlarged duct or an expansile invasive carcinoma
- If a single cystic space is involved, excision is generally curative
- Examine adjacent tissue
- If DCIS adjacent, prognosis same as any DCIS

Intracystic Carcinoma

- The proliferation may be papillary, cribriform or solid
- The wall is often thick and may have entrapped epithelium
- Entrapped epithelium does not qualify for invasive carcinoma







Intracystic Papillary Carcinoma

917 cases from the California Tumor Registry from 1988-2005

53% classified as having invasion

At 10 years the relative cumulative survival

- Insitu 96.8%
- With invasion 94.4%
- P.NS

Grabowski, J Cancer 2008, 113: 916

Lobular Neoplasia

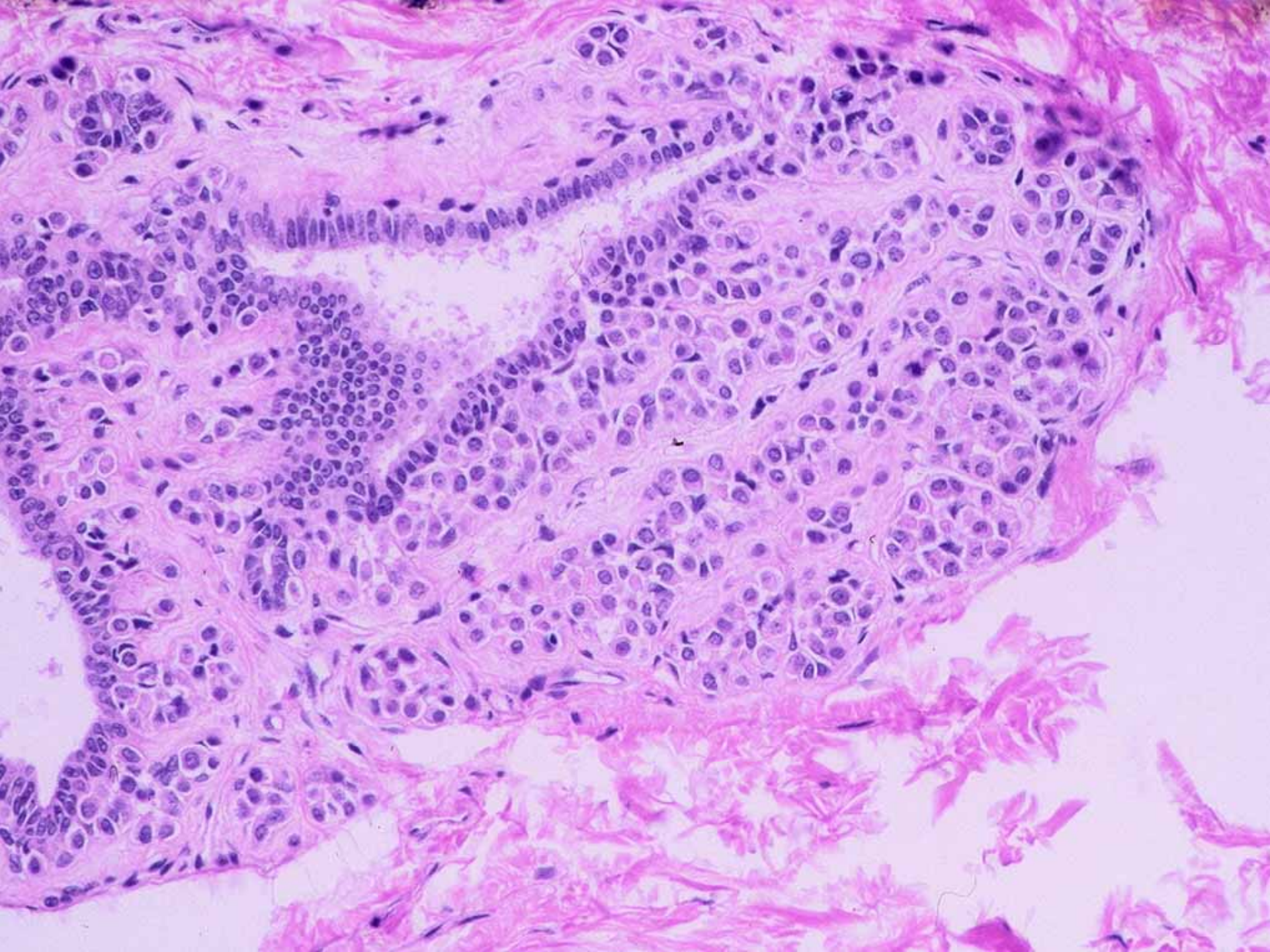
- Atypical Lobular Hyperplasia
- Lobular Carcinoma insitu

Lobular Neoplasia (LCIS/ALH)

- Cytologically both lesions are identical
- Monomorphic cell population (usually small)
- May have signet ring cells
- Pagetoid spread common
- Hallmark is lack of cellular cohesion (e-cadherin negative)

Lobular Neoplasia (LCIS/ALH)

- The difference between LCIS and ALH depends on the degree of lobular involvement and distention
- Both lesions are generally felt to indicate elevated risk for subsequent development of breast cancer.
- There is a greater risk associated with LCIS than ALH



Classical LCIS

- Type A- Small cells with uniform nuclei
- Type B- Larger cells with more variable nuclei; with or without prominent nucleoli

Markers in Classic LCIS

ER	Positive
Proliferation Rate	Low
HER2	Negative
p53	Negative
E-Cadherin	Negative

Lobular Neoplasia (LCIS/ALH)

- In most women it is thought of as a risk factor for development of any type of breast cancer
- In women who develop Invasive Lobular Carcinoma (ILC) it is a direct precursor

Lobular Neoplasia (LCIS/ALH)

FREQUENCY

- Depends on definition
- Between 0.5-3.8% of biopsies done for a mass
- Much higher in mammographically driven biopsies ~ 5-15%
- 80-90% found in pre menopausal women

Lobular Neoplasia (LCIS/ALH)

- It is almost always an incidental finding
- While not usually a cause of microcalcifications frequently present near calcifications
- Multicentric in 60-80% of mastectomy specimens with LCIS/ALH
- Bilateral in ~ 25-35% of cases

Lobular Neoplasia (LCIS/ALH)

NATURAL HISTORY

- Subsequent invasive carcinoma 7-34.5%
- Relative Risk 5-12 times control populations
- % invasive breast cancer per year of FU 0.7-1.5

6 studies with greater than 5 years of follow up

Lobular Neoplasia (LCIS/ALH)

MANAGEMENT

- NSABP trials show a 50% reduction in breast cancer when these patients receive Tamoxifen
- Bilateral Mastectomy
- Observation
- Some advocate Unilateral Subcutaneous Mastectomy

Pleomorphic LCIS

- A lesion that lacks cohesion
- It has major biologic differences from what is usually felt to be LCIS
- Often has necrosis and apoptosis
- Has a high proliferative rate

Pleomorphic LCIS

- An E cadherin negative in situ carcinoma
- High nuclear grade
- Usually ER positive
- High proliferative rate (47-92% of cases)
- Her2/neu positive (5-25% of cases)

LCIS with Comedo Necrosis

18 cases of E cadherin negative LIN

- Usually associated with mammographic calcifications
- Invasive carcinoma present in 67% of cases

Pleomorphic LCIS / LCIS with Comedo Necrosis

- More aggressive biological characteristics
- More frequently associated with invasive carcinoma

Pleomorphic LCIS

- We do not have outcome studies of observation alone with these lesions
- In order not to confuse the clinicians, at this time, I diagnose these lesions as insitu carcinoma with mixed ductal and lobular features
- And advise they be treated as one would a comparable DCIS

Histologic Differential Diagnosis between LCIS and Solid Small Cell DCIS

Feature	LCIS	DCIS
Loss of cohesion	Yes	No
Intracytoplasmic vacuoles	Present	Absent
Pagetoid ductal spread	Present	Absent
Microacini	Absent	Present
Polarity of cells at periphery	Absent	Present

Questions