

Problems in the Diagnosis of Ductal Carcinoma in Situ

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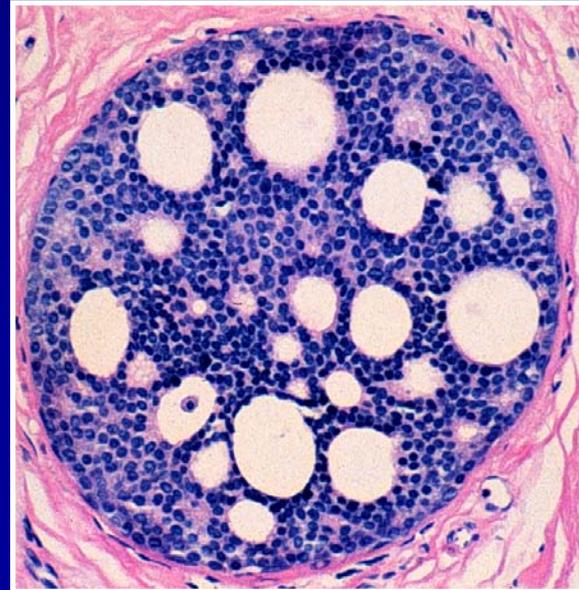
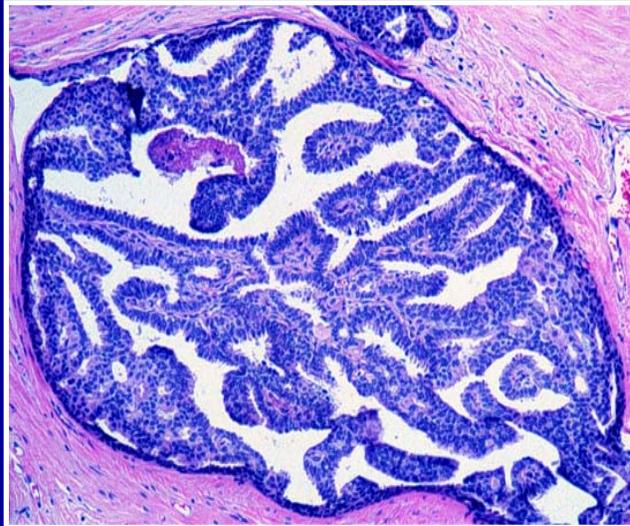
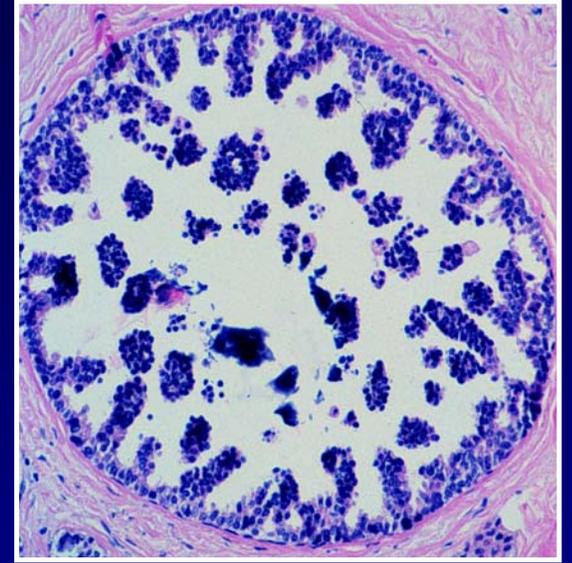
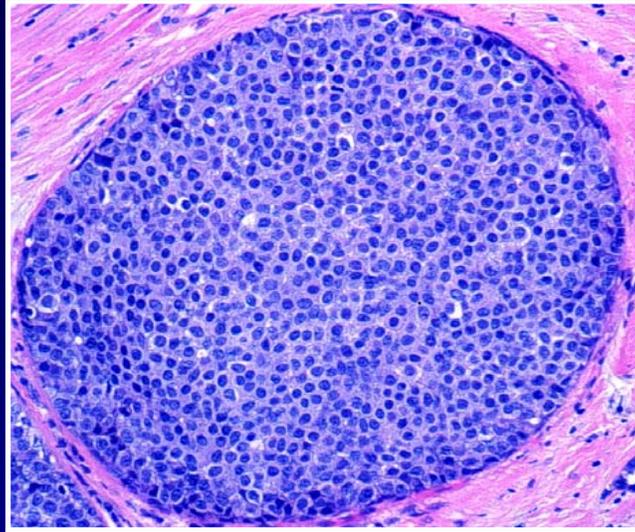
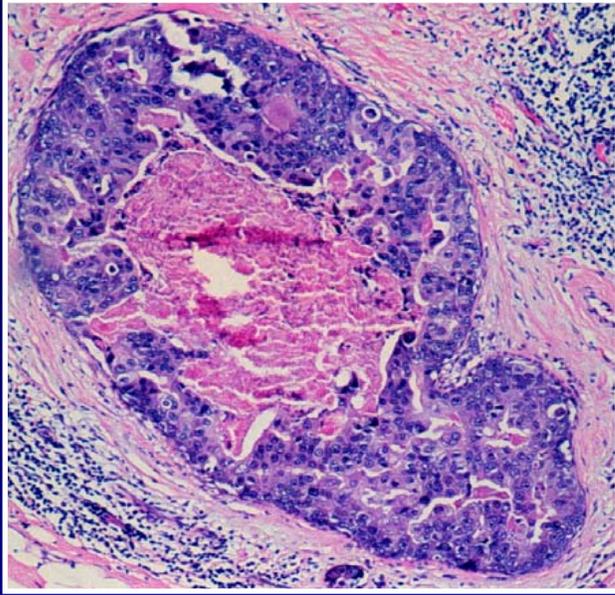
Department of Pathology

**Beth Israel Deaconess Medical Center
and Harvard Medical School**

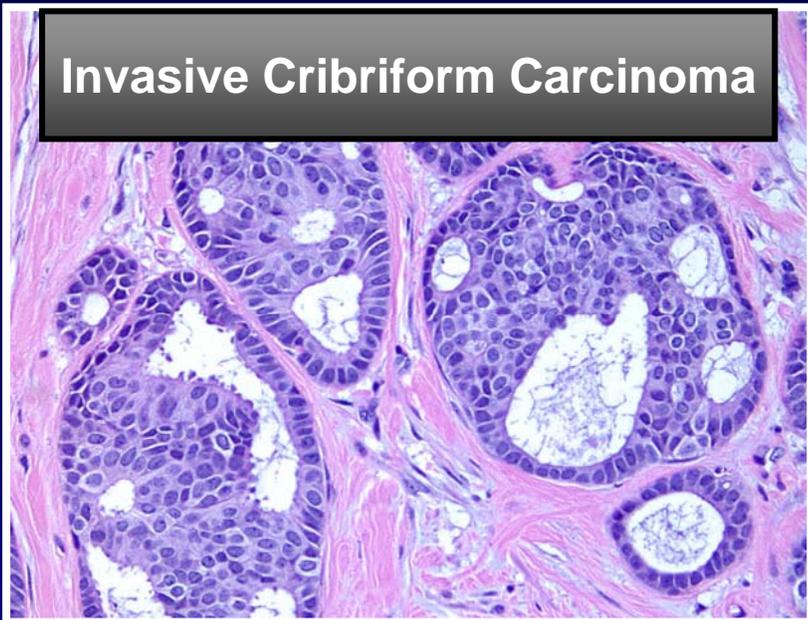
Boston, MA

**The Diagnosis of DCIS
Is Straightforward
in Most Cases**

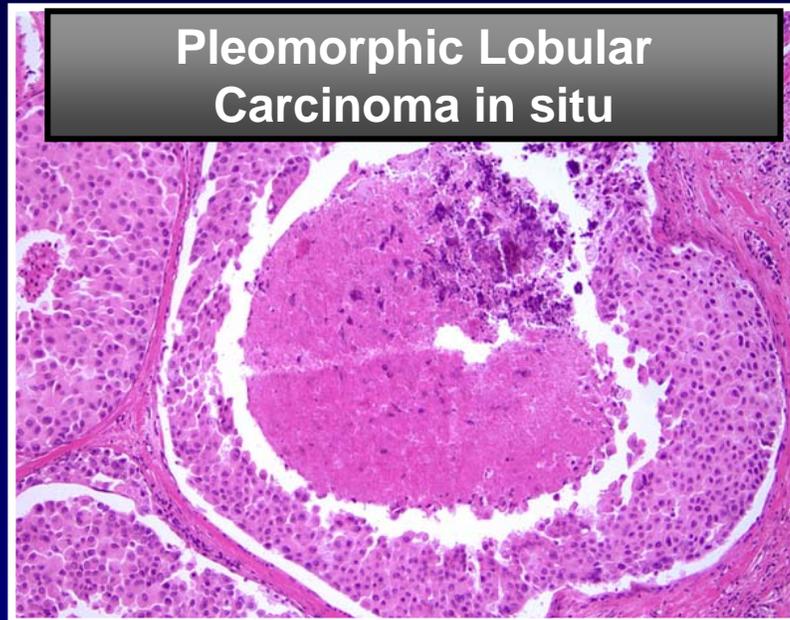
But, DCIS Has Many Faces.....



Invasive Cribriform Carcinoma



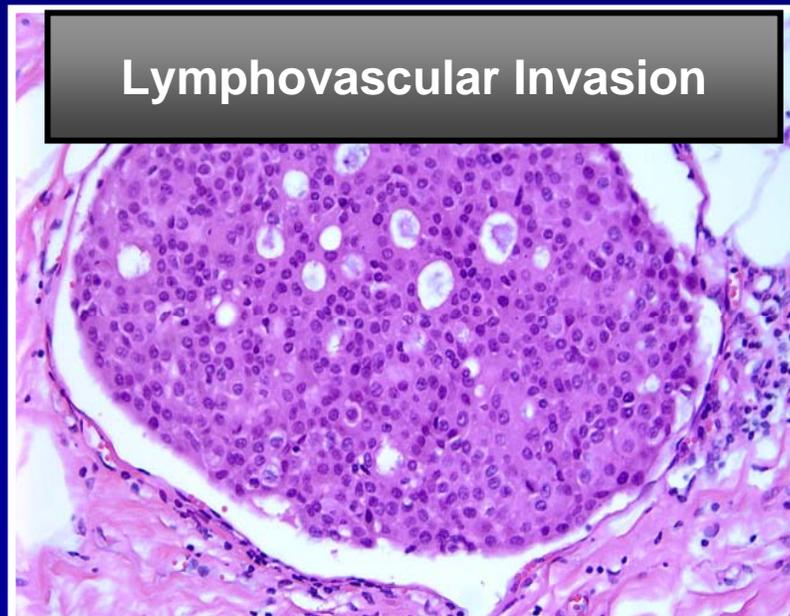
Pleomorphic Lobular Carcinoma in situ



Collagenous Spherulosis



Lymphovascular Invasion



**The Diagnosis of DCIS Is
NOT ALWAYS
Straightforward**

**How Often is the
Diagnosis of DCIS a
Problem?**

Pathologist Agreement: Local vs Central Dx

NSABP B-17, 1993

- 818 women with DCIS
- 6.2% not DCIS on central review
 - 1.5% invasive ca
 - 4.7% ADH

Pathologist Agreement: Local vs Central Dx

RDOG 5 Study
Collins, et al, 2004

- **Prospective, randomized trial comparing FNA and CNB for non-palpable breast lesions**
- **596 pts underwent open surgical biopsy following needle biopsy**
 - **Local pathology review**
 - **Central pathology review**
- **Local and central diagnoses compared**

Pathologist Agreement: Local vs Central

RDOG 5 Study
Collins, et al, 2004

**Central Pathology Review in Agreement
with Local Pathologist Dx of DCIS in 114/123 cases (93%)**

Local Diagnosis	Central Diagnosis					Total
	Benign	ADH	ALH/LCIS	DCIS	Invasive	
Benign	140	11	1	2	2	156
ADH	2	15	1	3	0	21
ALH/LCIS	1	4	11	0	0	16
DCIS	2	2	1	114	4	123
Invasive	0	1	1	6	272	280

Pathologist Agreement: Local vs Central Dx

Cancer Research Network
DCIS Case-Control Study

- Pathology review completed in 606 subjects with DCIS
- 58 (9.6%) not DCIS on central review
 - 36 (5.9%) microinvasive or invasive carcinoma
 - 11 (1.8%) ADH
 - 5 (0.8%) LCIS
 - 6 (1.0%) other benign diagnoses

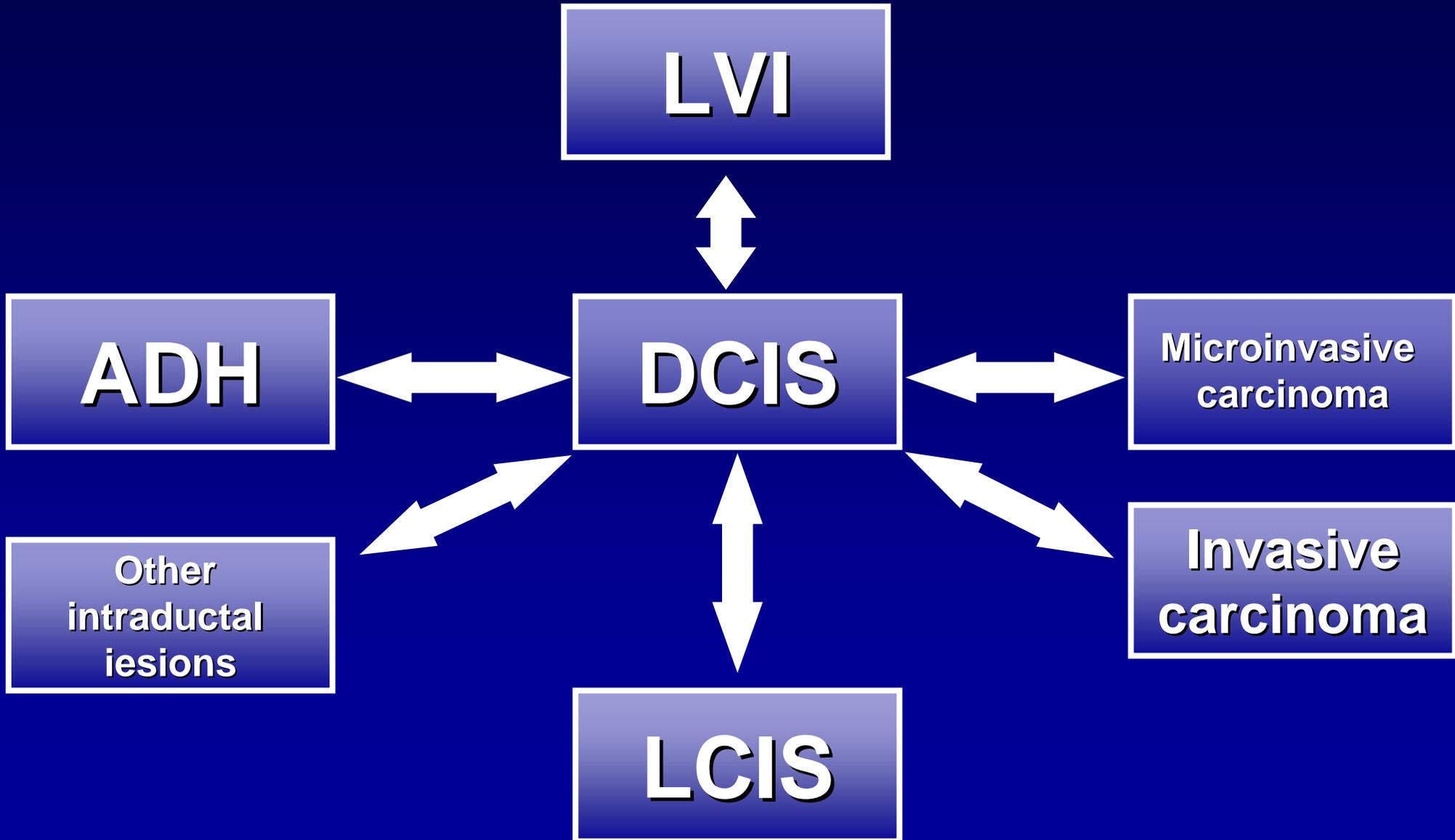
Pathologist Agreement: Local vs Central Dx

Summary

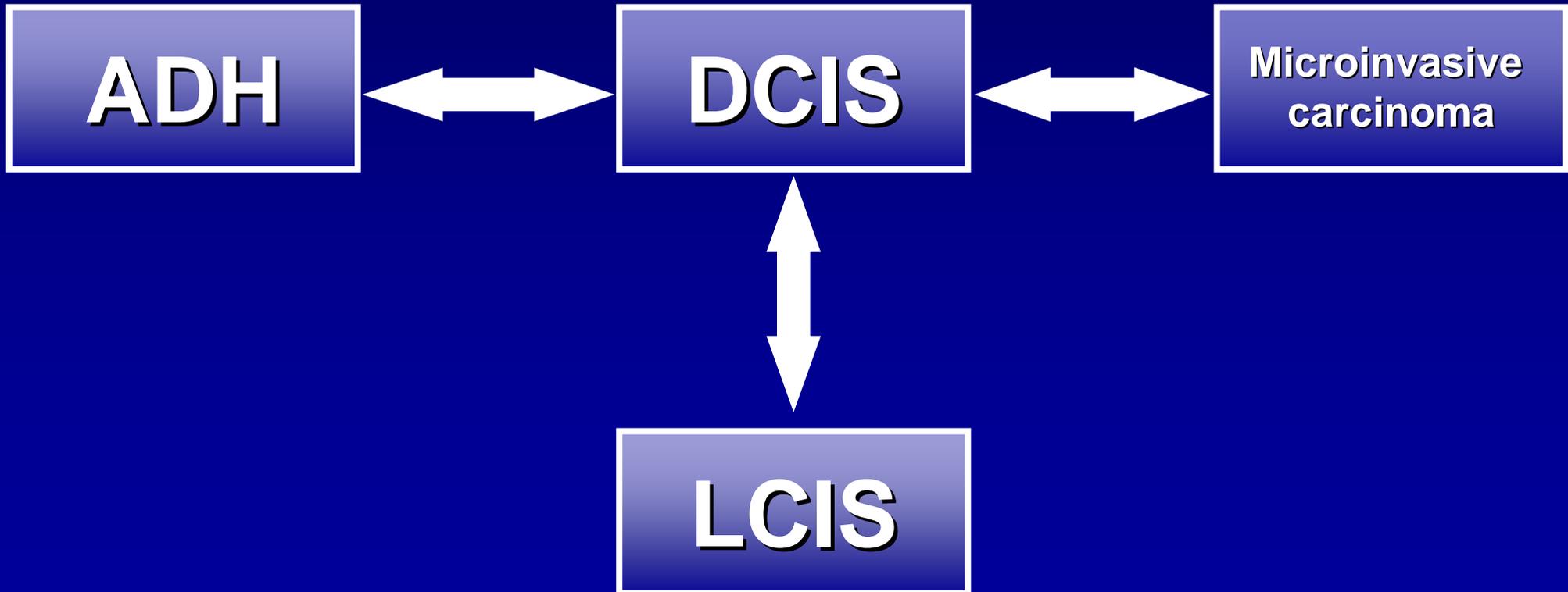
Study	#	% Not DCIS
NSABP B-17	818	6.2%
RDOG 5	123	7.0%
CRN DCIS	606	9.6%

Problems with both under-diagnosis and over-diagnosis

Problems in the Diagnosis of DCIS



Problems in the Diagnosis of DCIS



Problems in the Diagnosis of DCIS

**ADH vs DCIS:
Why do we care?**

DCIS

Clinically Important Differences Between ADH and LG-DCIS

	ADH	LG-DCIS
Magnitude of risk	lower (3-5x)	higher (8-10x)
Laterality of risk	either	ipsilateral (same site)
Type of subsequent cancer	any histology; any grade	usually low grade
Management	observation ± tamoxifen	complete local eradication

Distinction of ADH from DCIS

- **Qualitative features
(architecture, cytology)**
- **Quantitative features
(size/extent)**

Qualitative Features of ADH

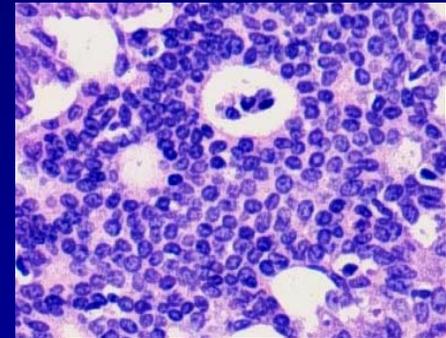
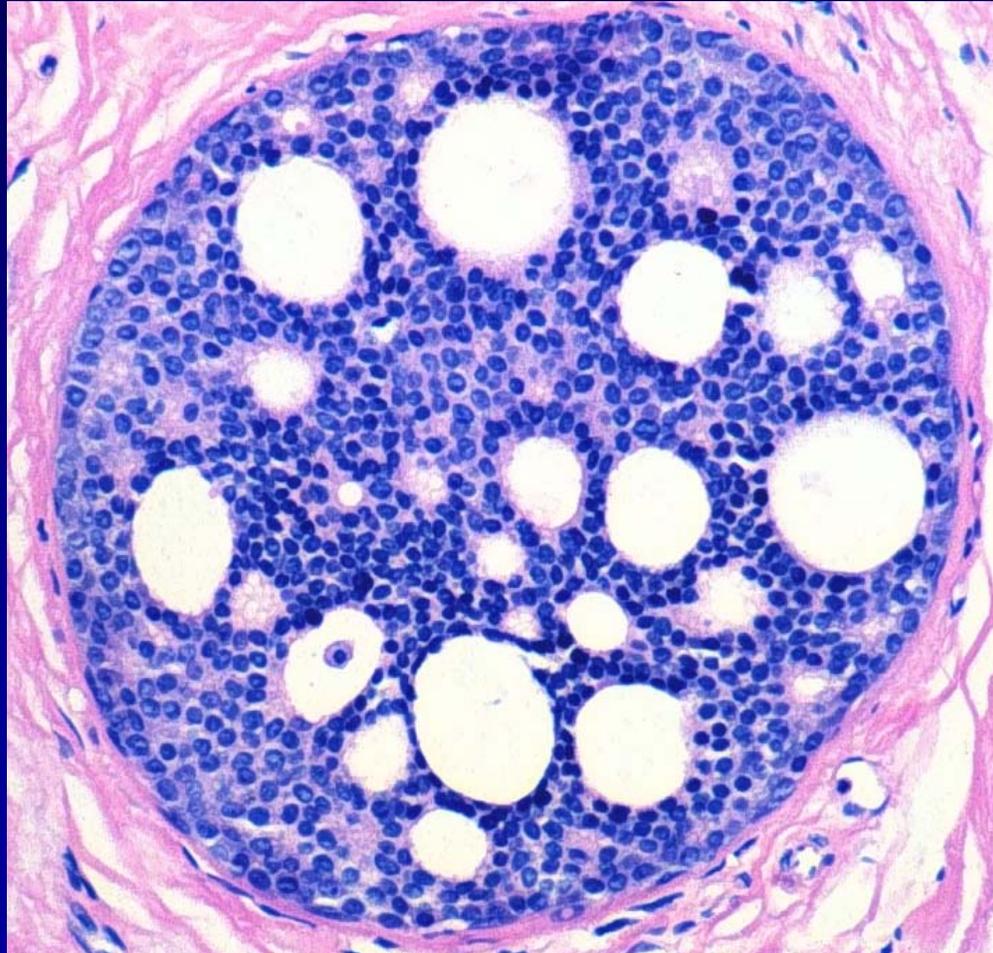
- ***Architecture:***

- Some features of usual ductal hyperplasia and some features of DCIS (e.g., rigid, non-tapering bridges, club-shaped micropapillae, round fenestrations)

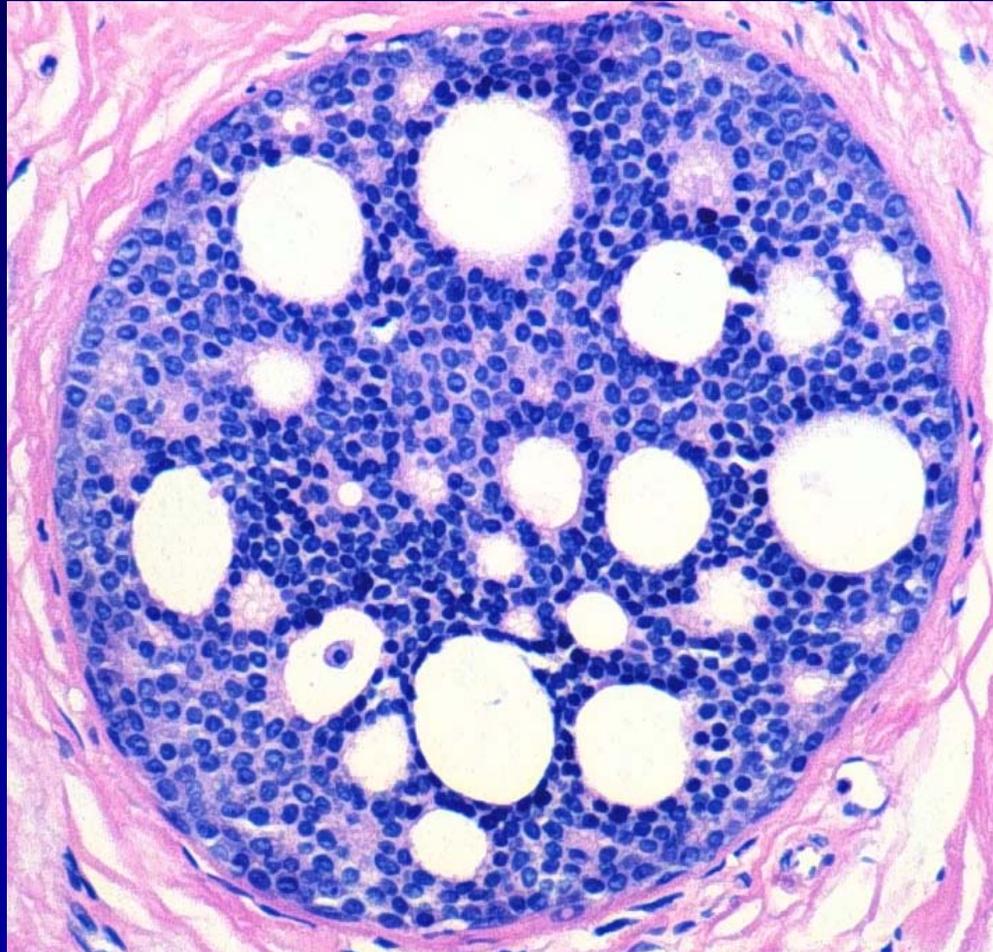
- ***Cytology:***

- Cells similar to those seen in low grade DCIS present in a portion of the space (e.g., monomorphism, polarization around lumina or within micropapillae)

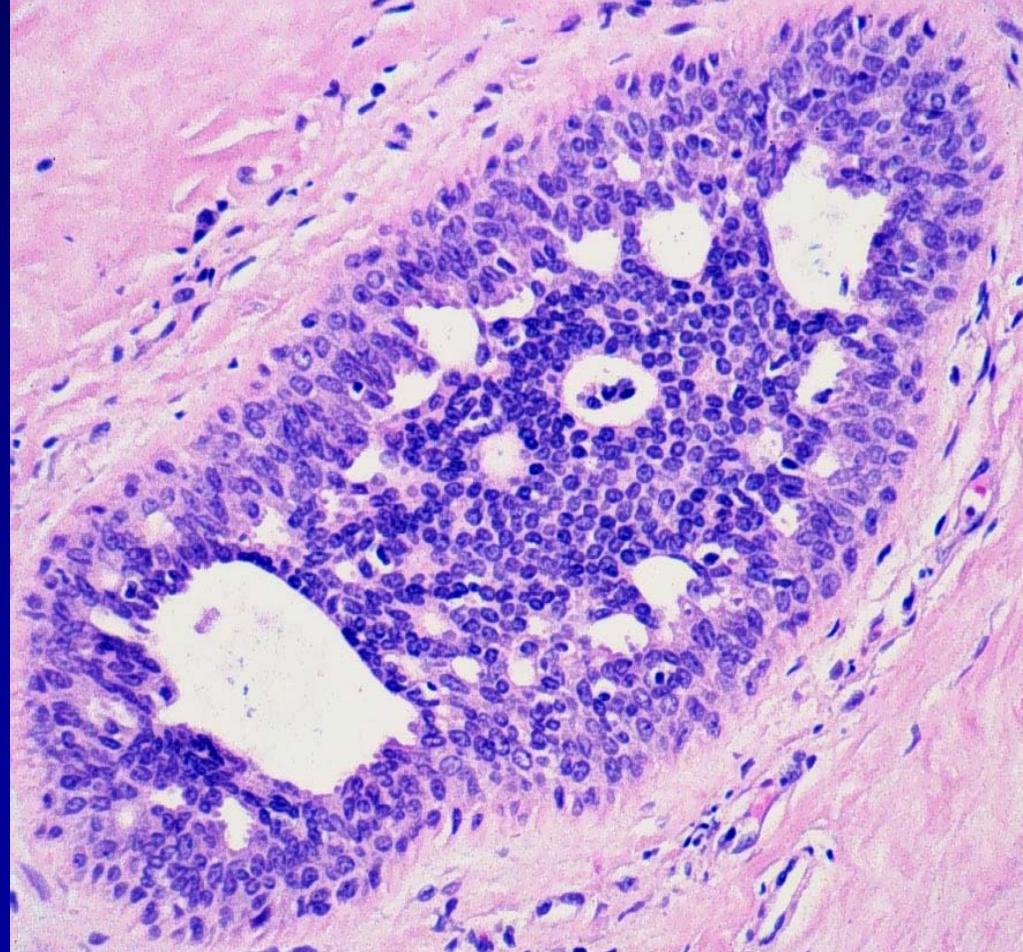
LG-DCIS



LG-DCIS



ADH



- **Observer agreement in equivocal cases is fostered by the standardization of diagnostic criteria**

Diagnostic Reproducibility

Standardized criteria?

No

Yes

Complete Agreement

0%

58%

All But 1 Agree

18%

71%

The Major Problem

- **There are no qualitative histologic features, singly or in combination, that permit the reliable distinction between ADH and LG-DCIS in all cases**

Quantitative Features

- Lesions that possess ALL of the qualitative features of LG-DCIS but are limited in extent are given the diagnosis of ADH:
 - 1985, Page et al: <2 spaces
 - 1990, Tavassoli and Norris: ≤2mm
 - 1998, Jensen and Page: <2-3mm

ADH

```
graph TD; ADH --> A["Partial involvement of spaces by cells identical to those seen in LG-DCIS"]; ADH --> B["Complete involvement of spaces by cells identical to those seen in LG-DCIS, but of limited extent (i.e., small LG-DCIS)"]; A --> C["? Same Clinical Implications"]; B --> C;
```

Partial involvement of spaces by cells identical to those seen in LG-DCIS

Complete involvement of spaces by cells identical to those seen in LG-DCIS, but of ***limited extent*** (i.e., small LG-DCIS)

? Same Clinical Implications

**Are there more objective
means to help distinguish
ADH from LG-DCIS?**

UDH



•HMW-CK

ADH

LG-DCIS

•Ploidy
•Proliferation



•ER

HG-DCIS

•HER2

•p53

•bcl-2

UDH

no consistent losses/gains

ADH

16q, 17p losses
1q gains

**Genetic Alterations
(LOH, CGH)**

LG-DCIS

16q, 17p losses
1q gains

HG-DCIS

11q, 13q, 17q gains

Biomarkers and Genetic Alterations

- No apparent differences between ADH and LG-DCIS
- But, many studies include as “ADH” small DCIS

Should We Continue to Attempt to Distinguish ADH from LG-DCIS?

- **NO:**
 - Histologic criteria poorly defined; low level of interobserver agreement
 - Morphologic similarities; any differences are only quantitative
 - Immunophenotypic similarities
 - Genetic similarities

Should We Continue to Attempt to Distinguish ADH from LG-DCIS?

- **YES:**
 - Problematic cases account for only a minority of lesions
 - Observer agreement improves with standardization of criteria
 - Genetic/molecular studies incomplete; have used relatively crude techniques (LOH, CGH) and definitions of ADH that include small LG-DCIS

- Immunophenotypic or even genetic similarity does not necessarily imply similar clinical behavior**
- Follow-up studies have documented clinically important differences between ADH and LG-DCIS that are considered in formulating patient management**

ADH: Conceptual vs Practical View

- **Conceptually:**

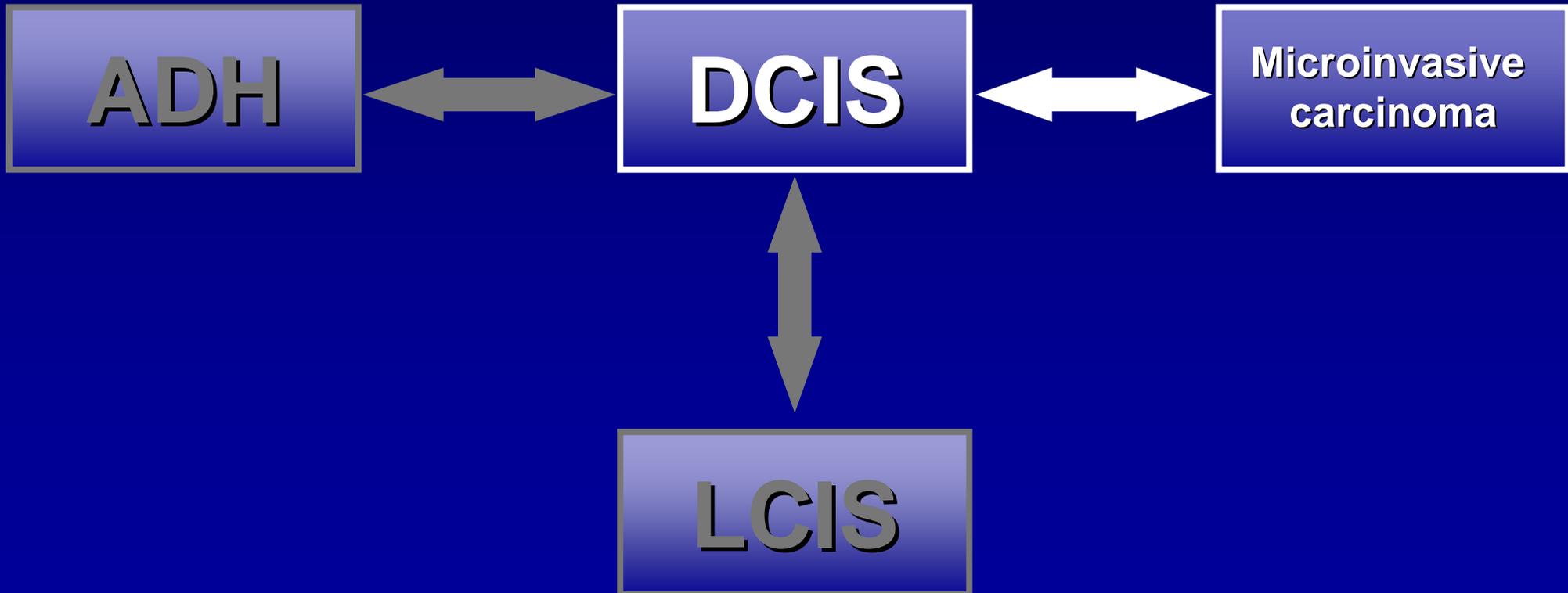
- ADH appears to be a neoplastic, clonal proliferation of cells identical to those of LG-DCIS (at least using currently available techniques)

- However, lesion less completely developed than LG-DCIS (“LG-DCIS in situ”)

- **Practically:**

- Given that there are documented, clinically important differences between ADH and fully developed LG-DCIS, these two processes should still be considered distinct with regard to patient management

Problems in the Diagnosis of DCIS



What is Microinvasive Carcinoma?

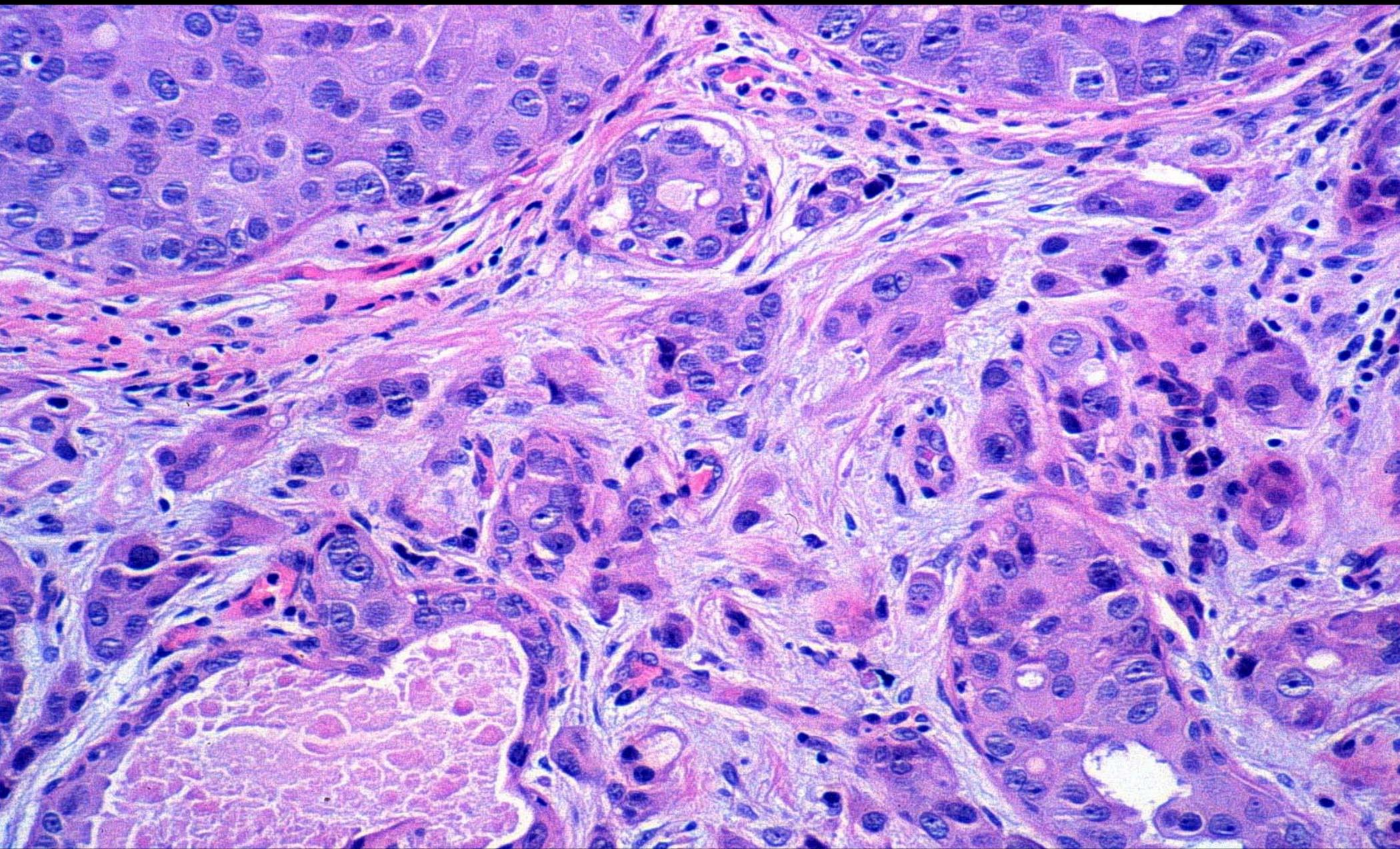
AJCC-UICC Definition (1997)

- “Extension of cancer cells beyond the basement membrane...with no focus more than 0.1 cm in greatest dimension”
- T1mic
- If multiple foci, should not be added together

Features of DCIS Associated with Microinvasion

- **High grade/comedo histology**
 - but, may also be seen in association with other grades/types of DCIS and with LCIS
- **Extent (size, number of involved ducts)**
- **Periductal lymphoid infiltrates**





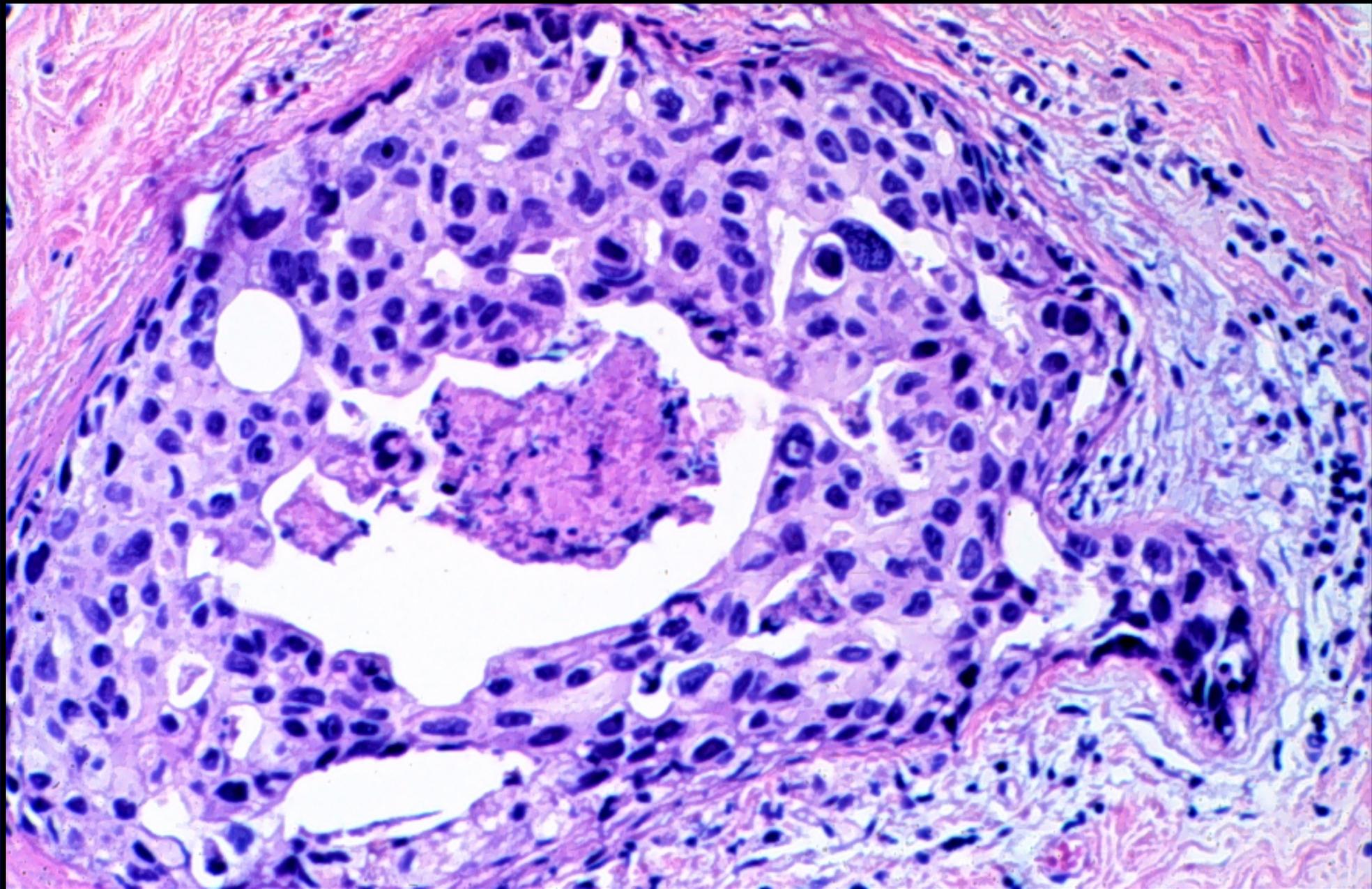
Problems in Distinguishing “Pure” DCIS from DCIS with Microinvasion

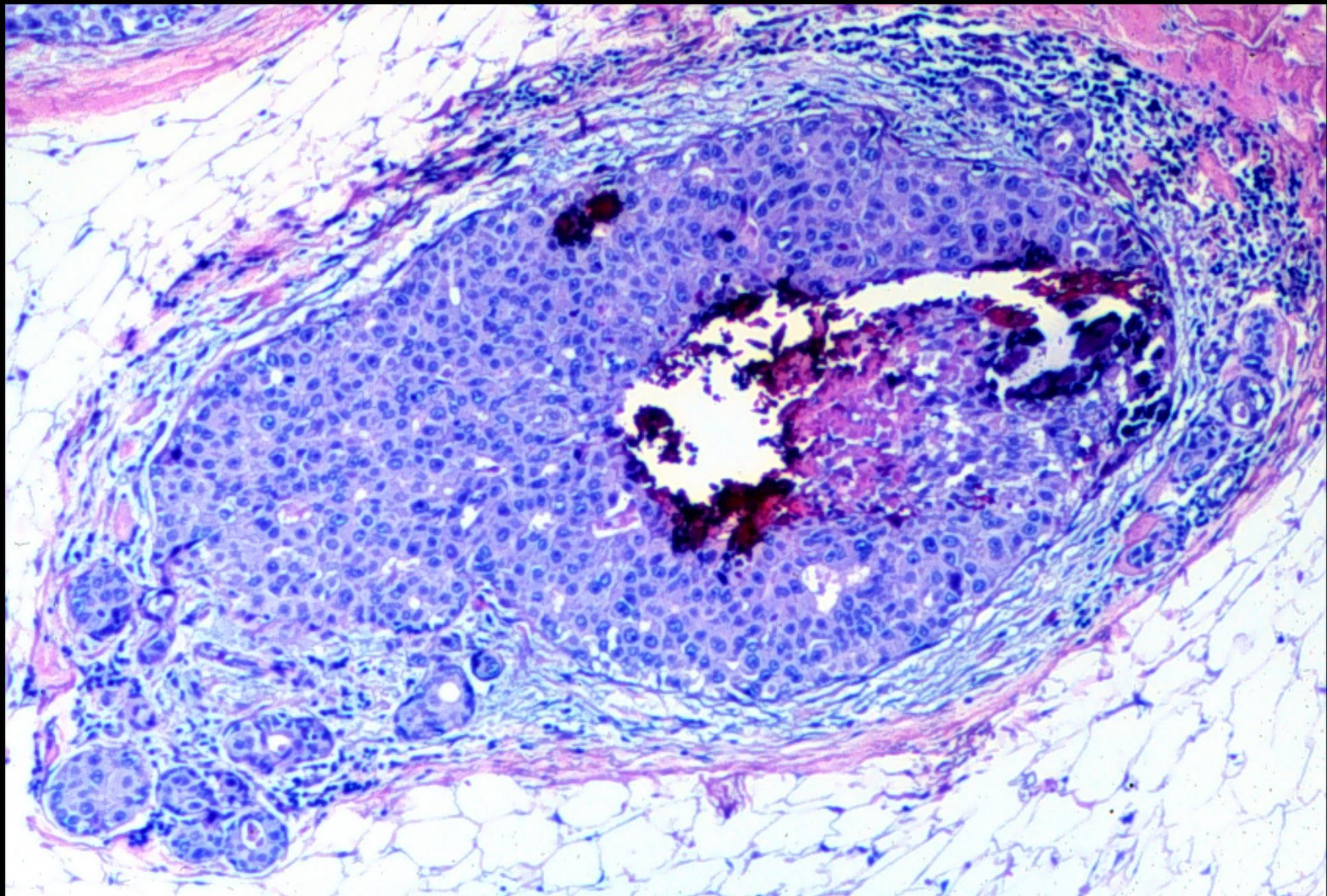
- Over-diagnosis

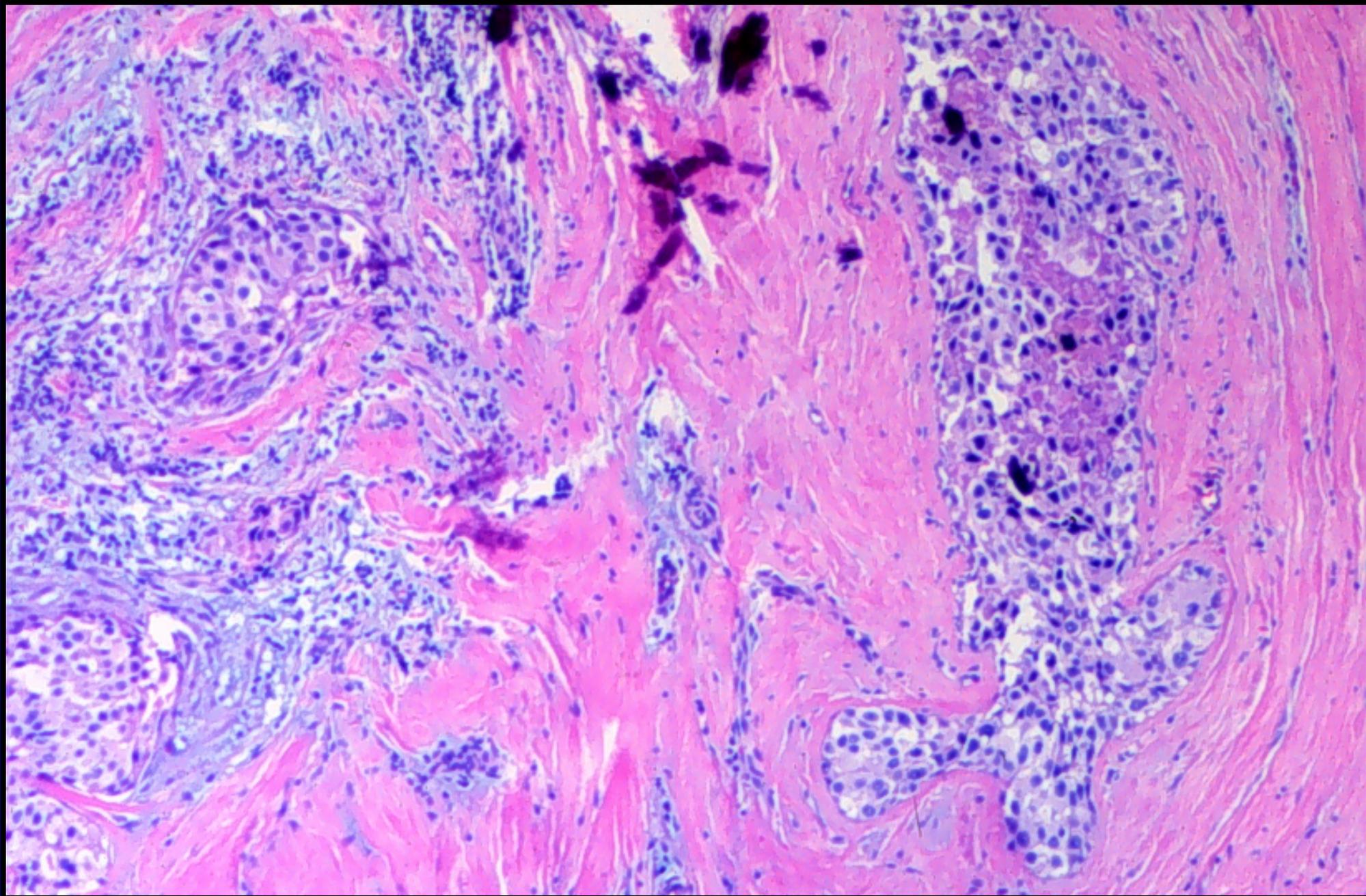
--DCIS may have areas that mimic invasion

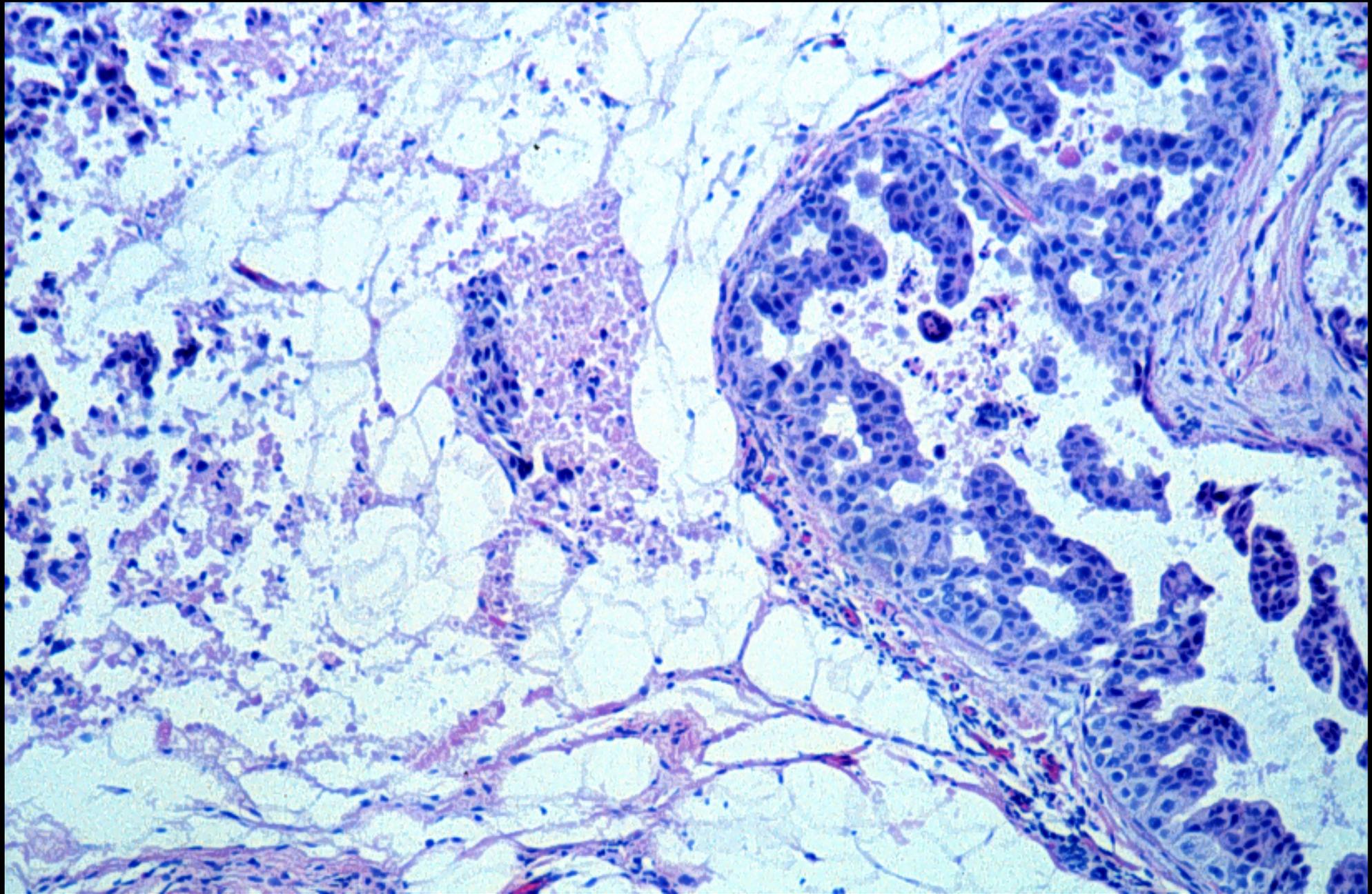
- » Duct branching
- » Involvement of lobules
- » Involvement of benign sclerosing lesions
- » Distortion of involved spaces
- » Tangential sectioning
- » Crush artifact
- » Cautery effect
- » Artifactual displacement of DCIS cells

--Defensive pathology



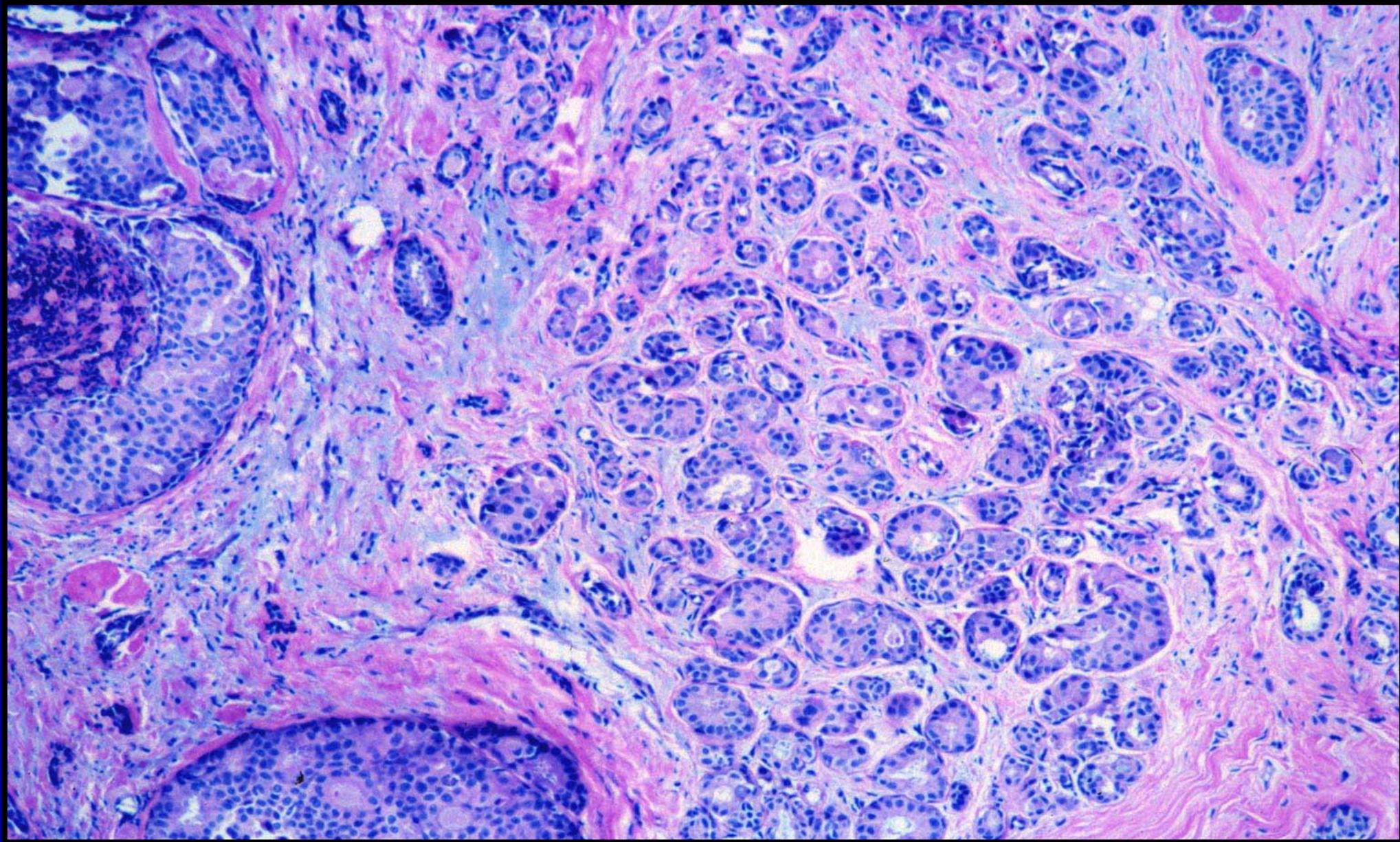




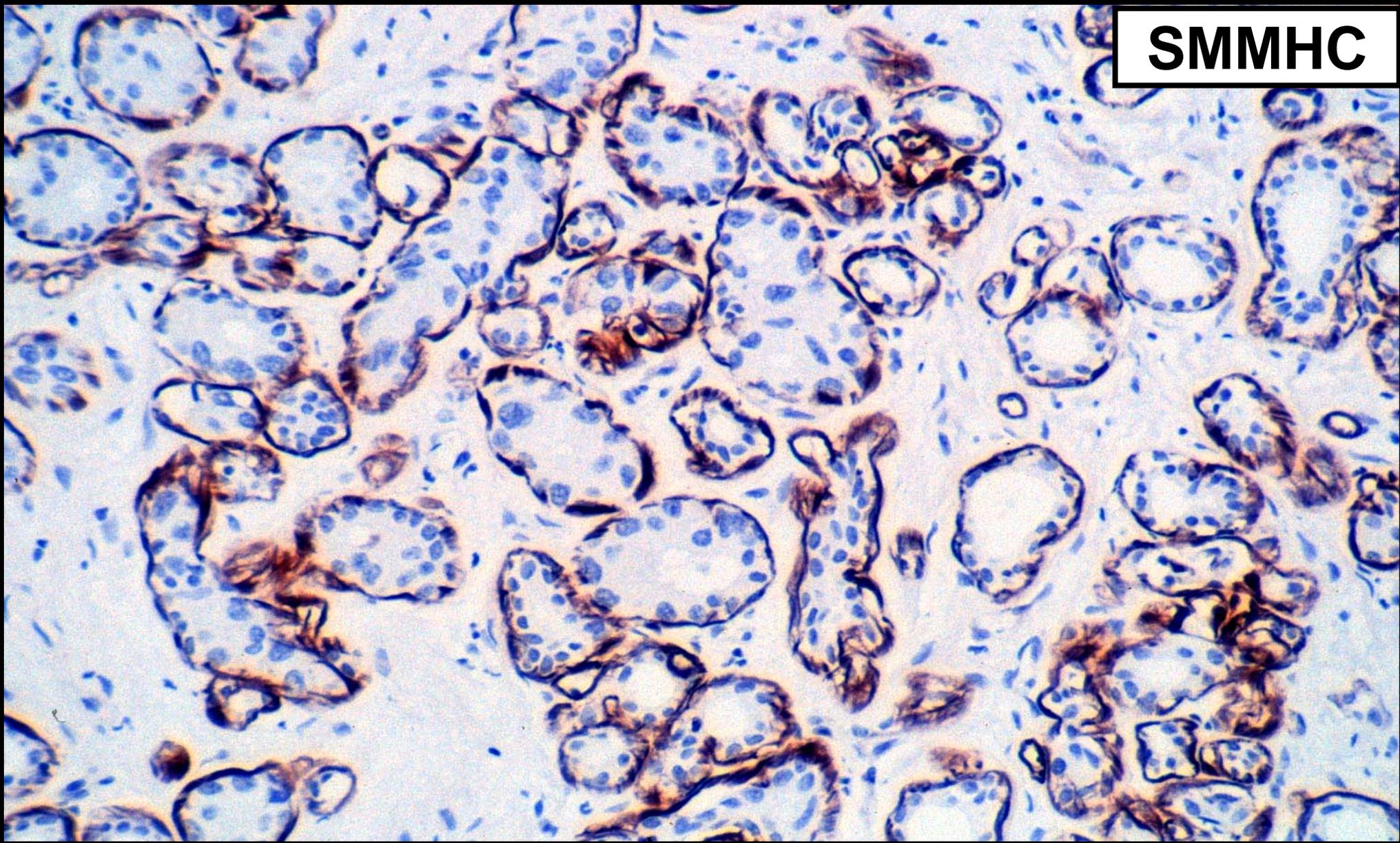


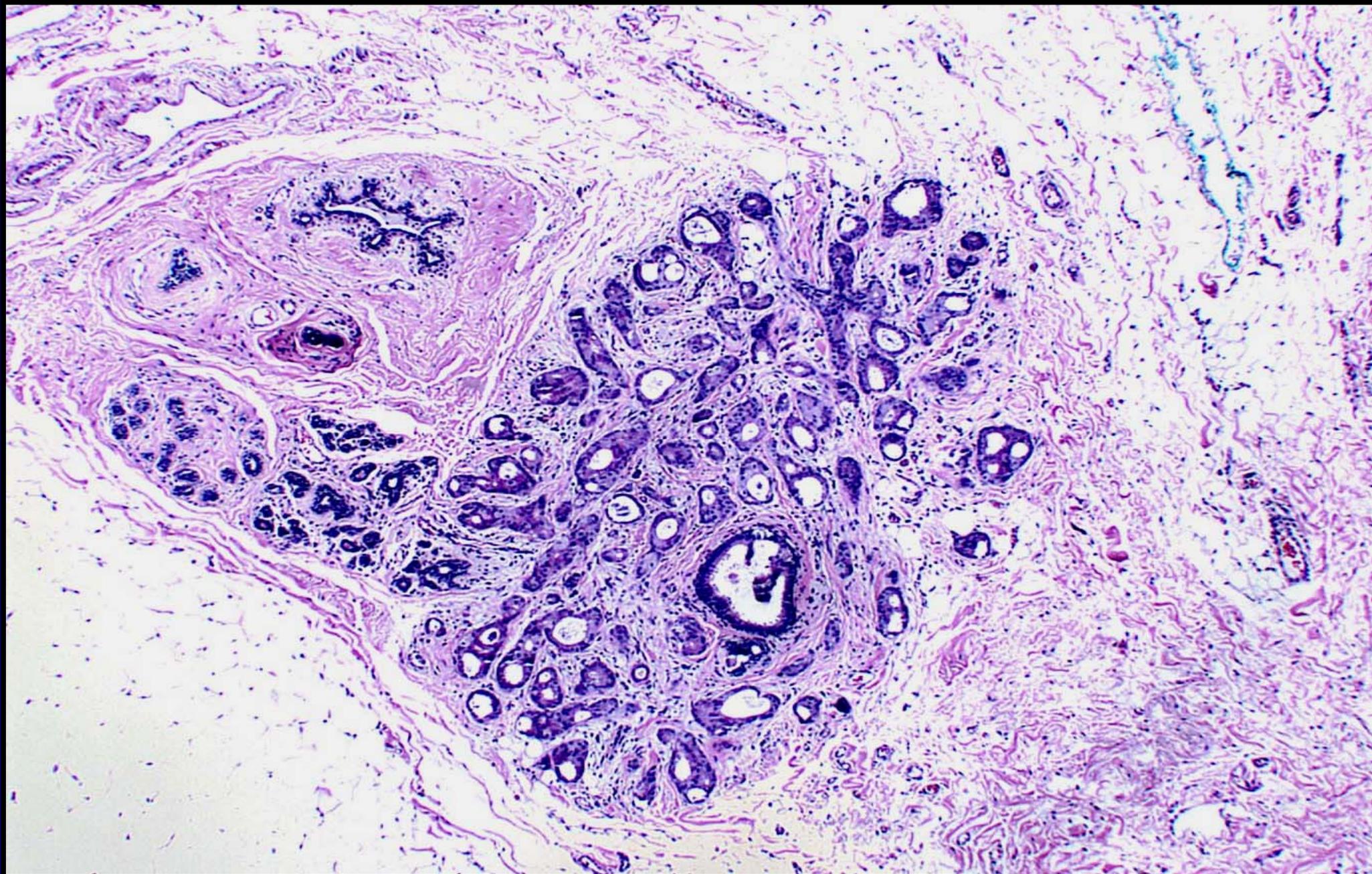
Distinction Between Mimics of Invasion and Real Invasion

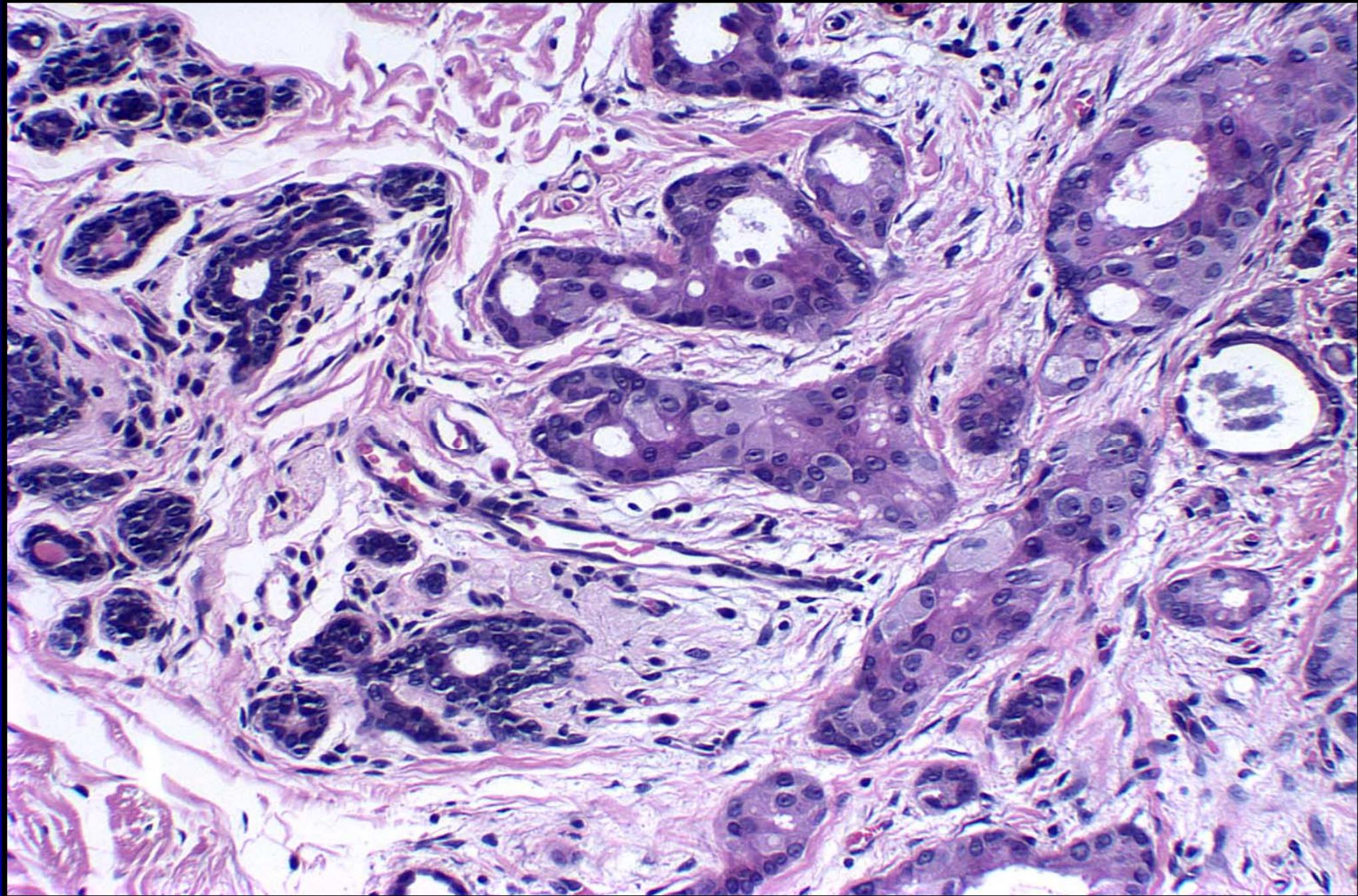
- **Not always possible on H and E sections, even with multiple levels**
- **Immunostains for myoepithelial cells**



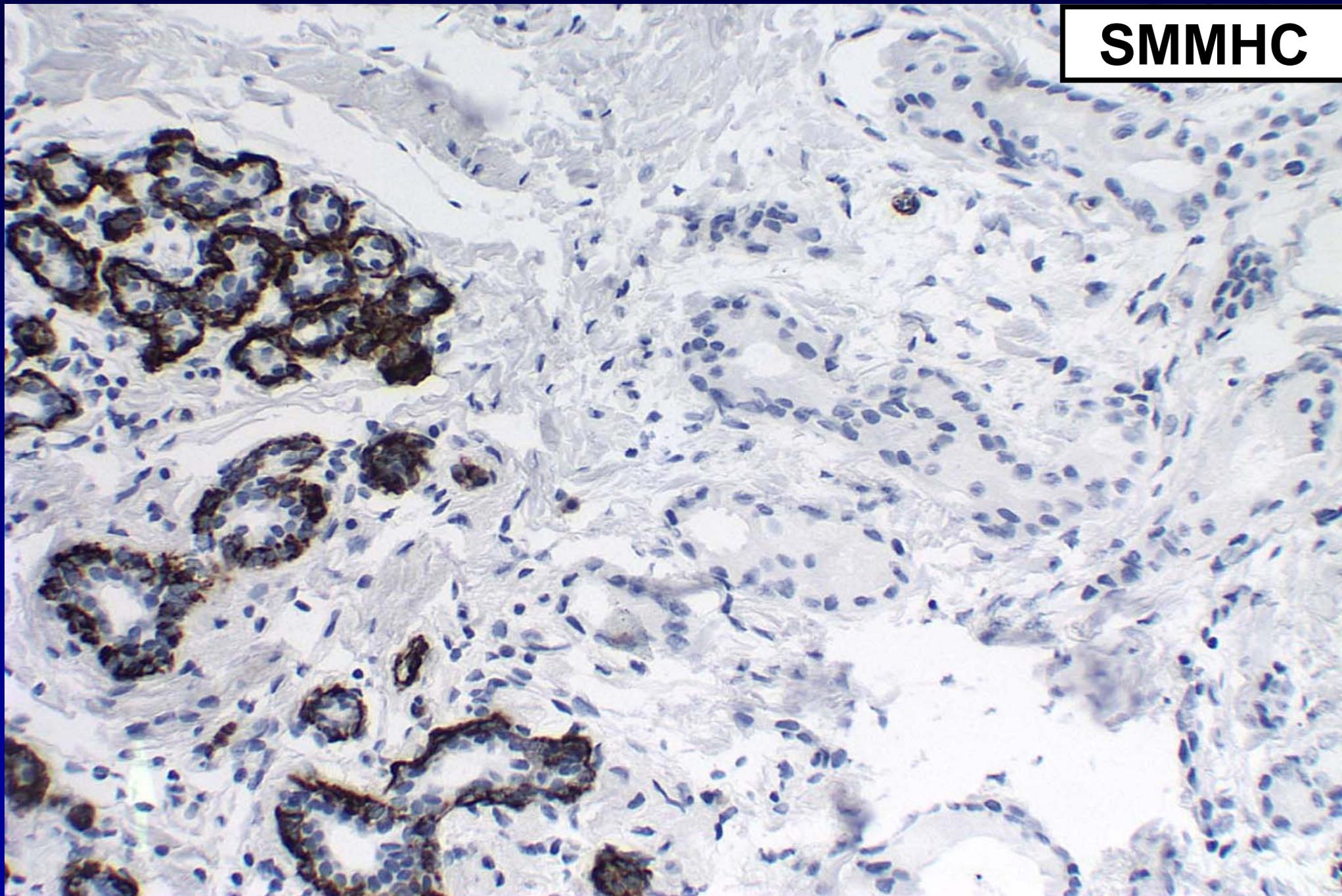
SMMHC







SMMHC



Problems in Distinguishing “Pure” DCIS from DCIS with Microinvasion

- Over-diagnosis

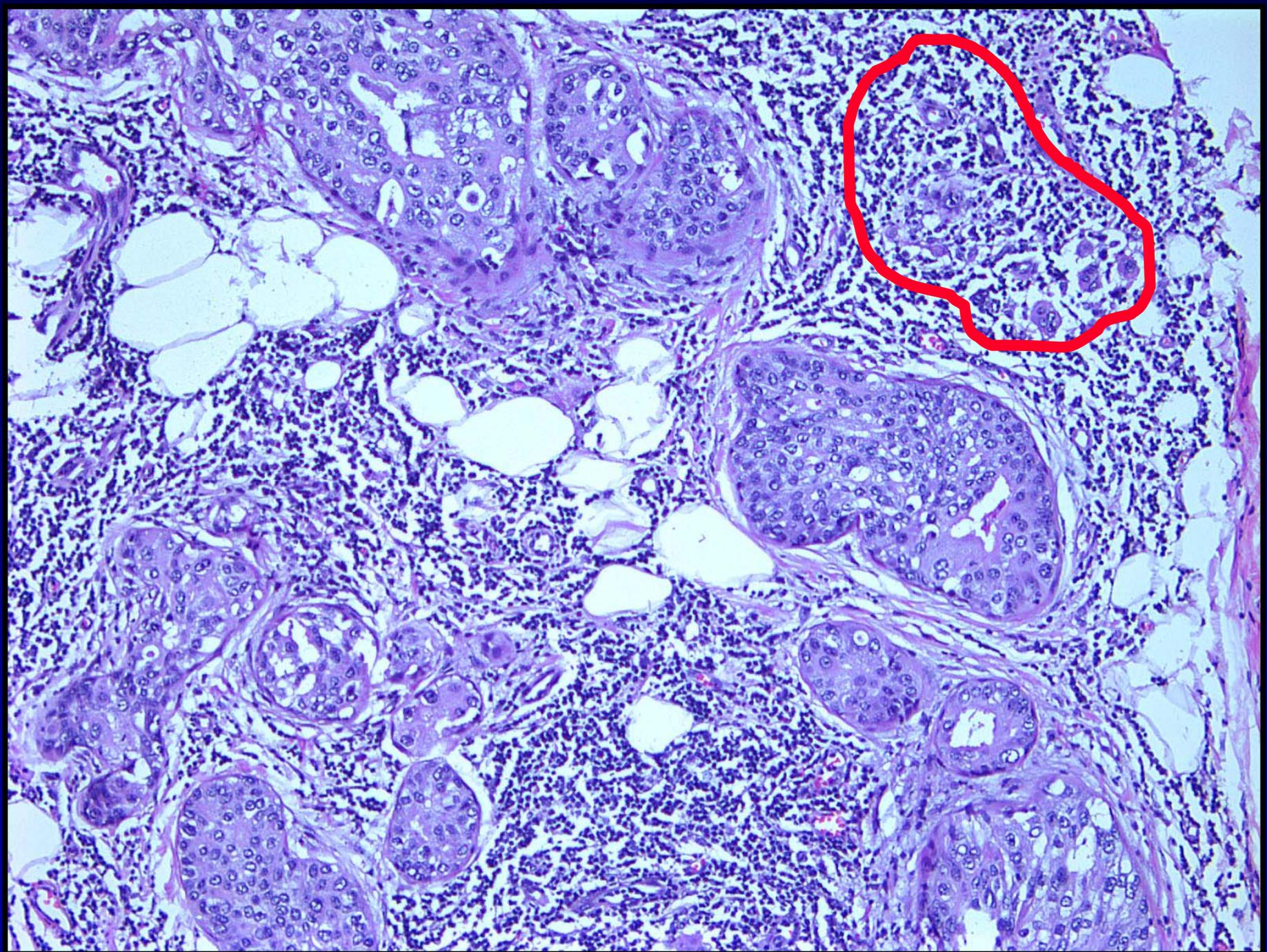
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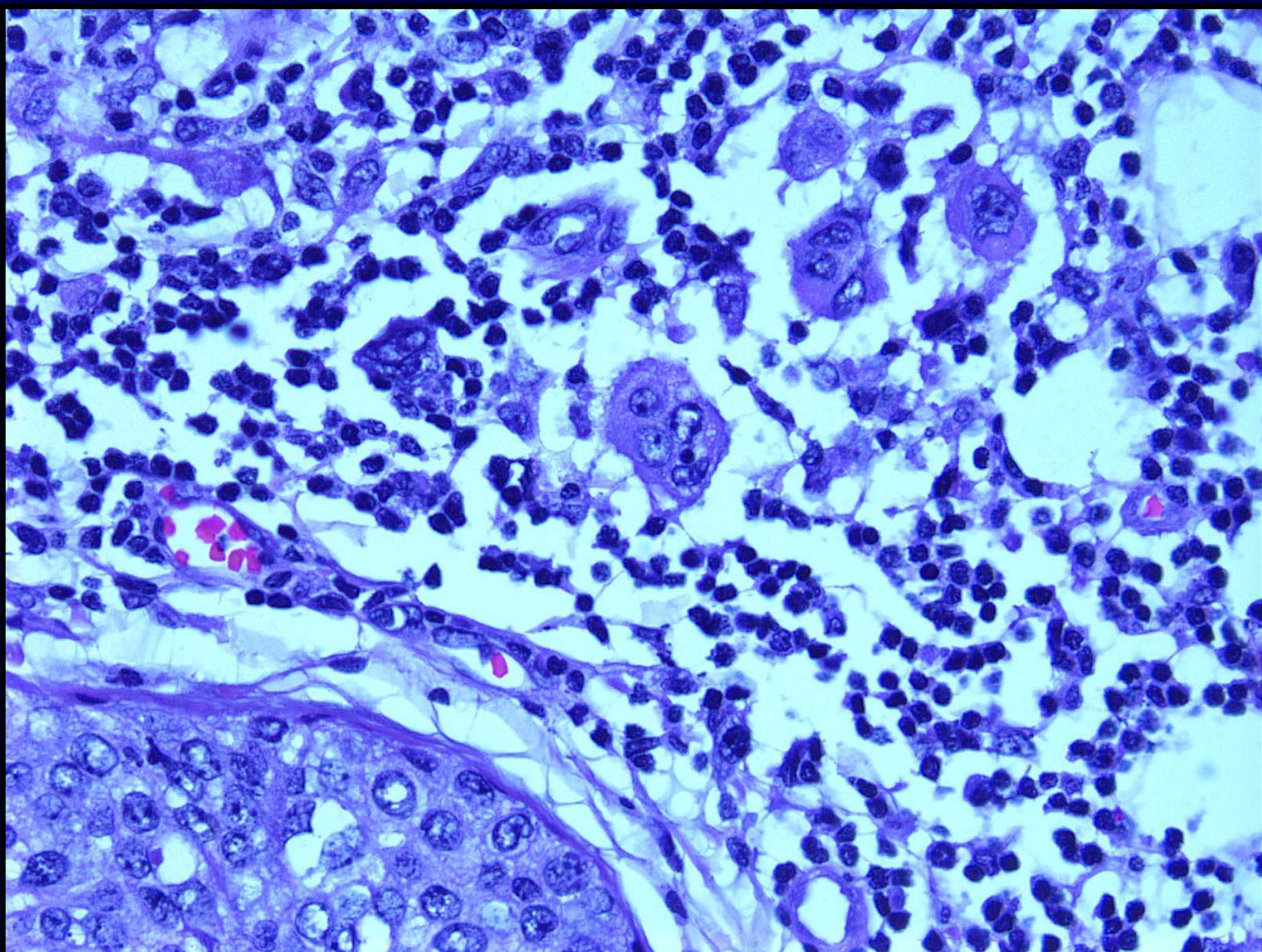
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--Defensive pathology

- Under-diagnosis

- Microinvasive foci may be over-looked
- Microinvasive foci may not be sampled





Clinical Significance of Microinvasion

- **Varying definitions used in the past**
- **Clinical significance is unclear**
(? any worse than “pure” DCIS of
equivalent size and grade)

Axillary Lymph Node Involvement with Microinvasion

<u>Study</u>	<u>#pts</u>	<u>% node +</u>
Wong	33	0
Silverstein	17	0
Akhtar	25	0
Padmore	11	0
Mann	18	0
Silver	38	0
Rosner	34	3%
Solin	39	5%
Penault-Llorca	58	5%
Klauber-De More	31	10% (sentinel)
Patchefsky	16	12%
Prasad	15	13%
Zavotsky	14	14% (sentinel)
Schuh	30	20%

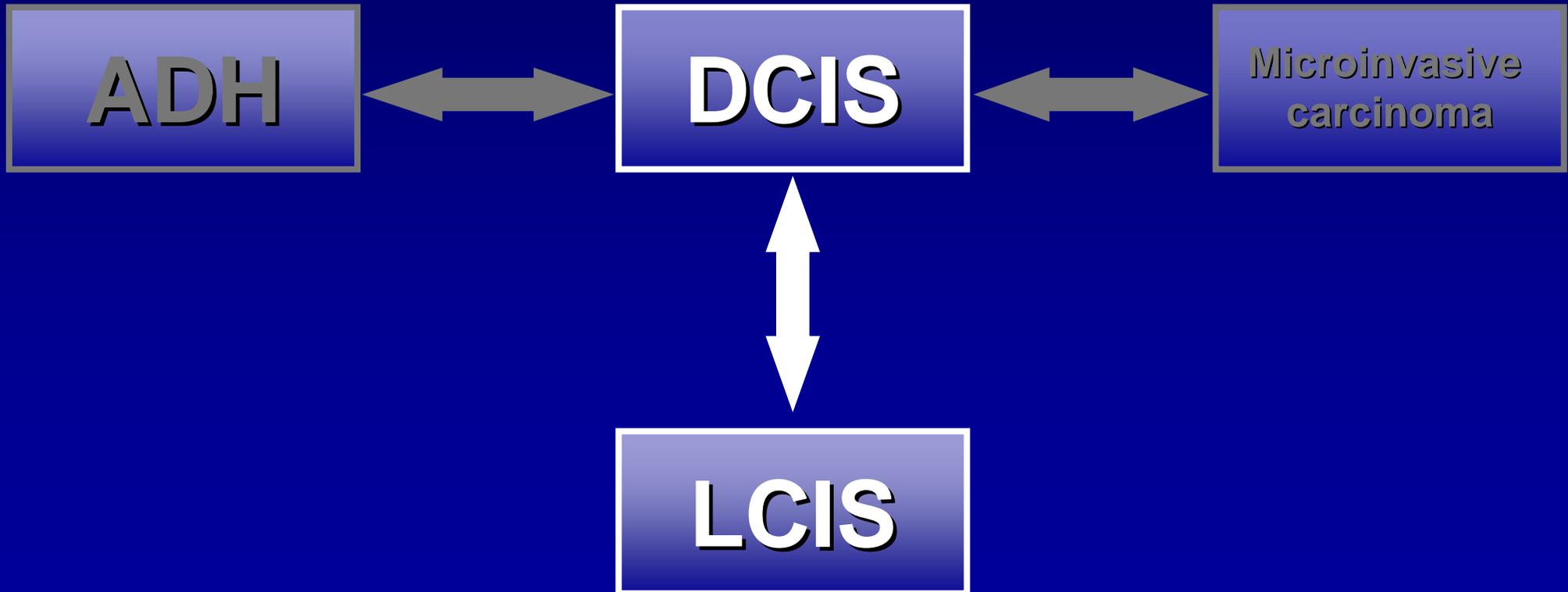
Outcome of Patients with Microinvasion

- **Studies have small numbers, varying definitions, and varying degrees of tissue sampling**
- **No clear differences from “pure” DCIS with regard to DFS or OS**
 - especially likely to be true when current AJCC-UICC definition is used

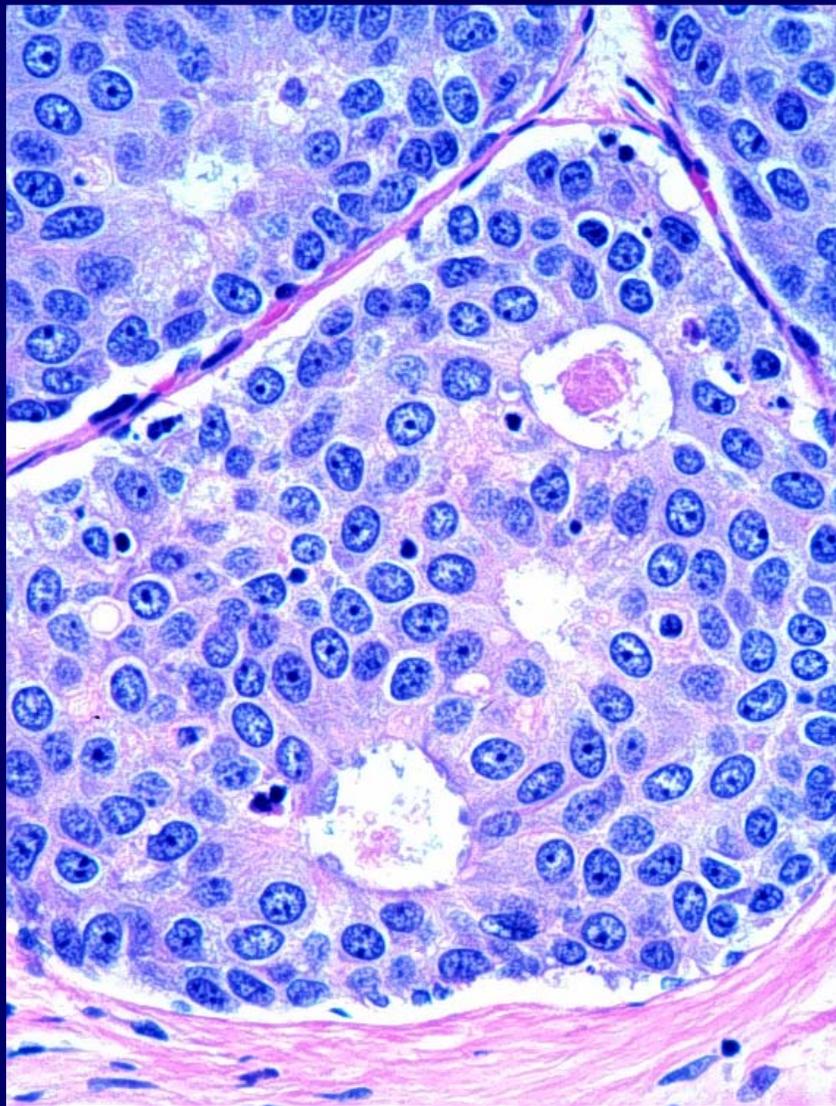
Practical Implications

- **Patients with large areas of DCIS with and without microinvasion should probably be managed similarly**
- **SLN biopsy**

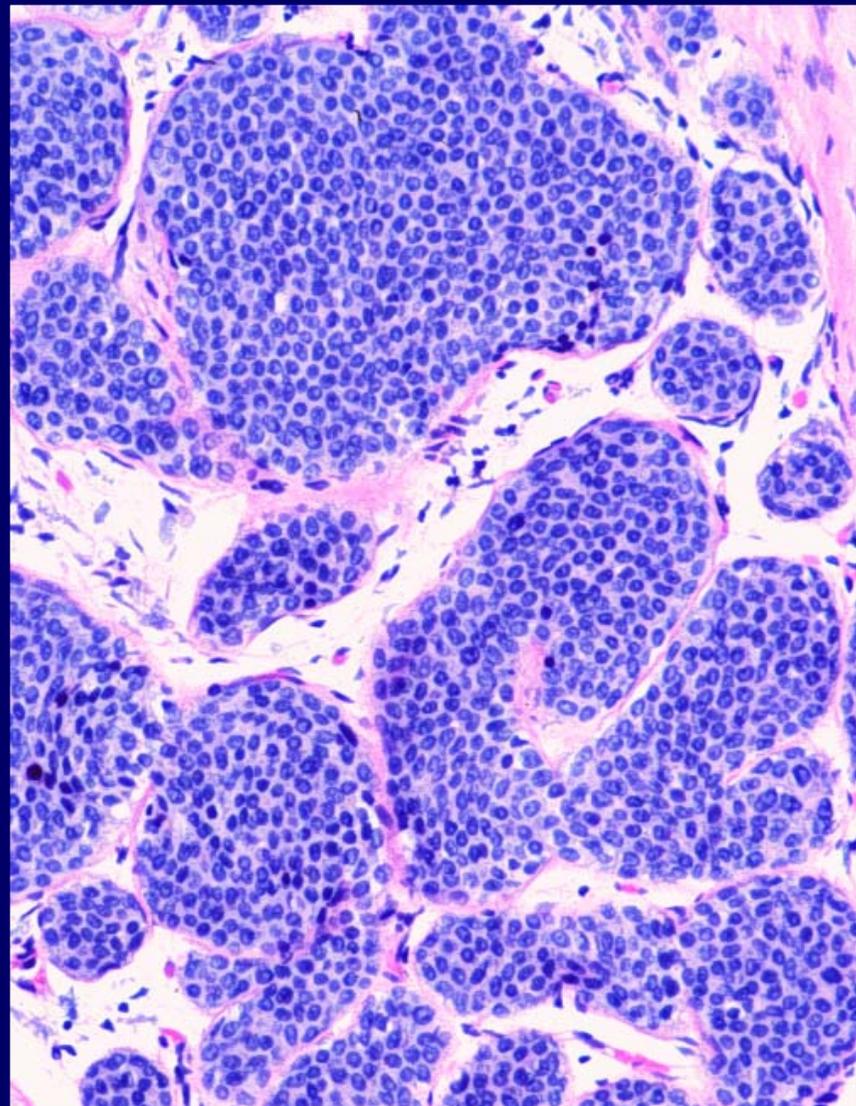
Problems in the Diagnosis of DCIS



DCIS



LCIS



DCIS vs LCIS

- **Some cases are diagnostic problems**
- **Problematic lesions increasingly common in breast biopsies performed because of mammographic microcalcifications**

DCIS vs LCIS

Why Do We Care?

Differences in management

DCIS

Viewed as precursor

- Complete eradication
- Margin evaluation

LCIS

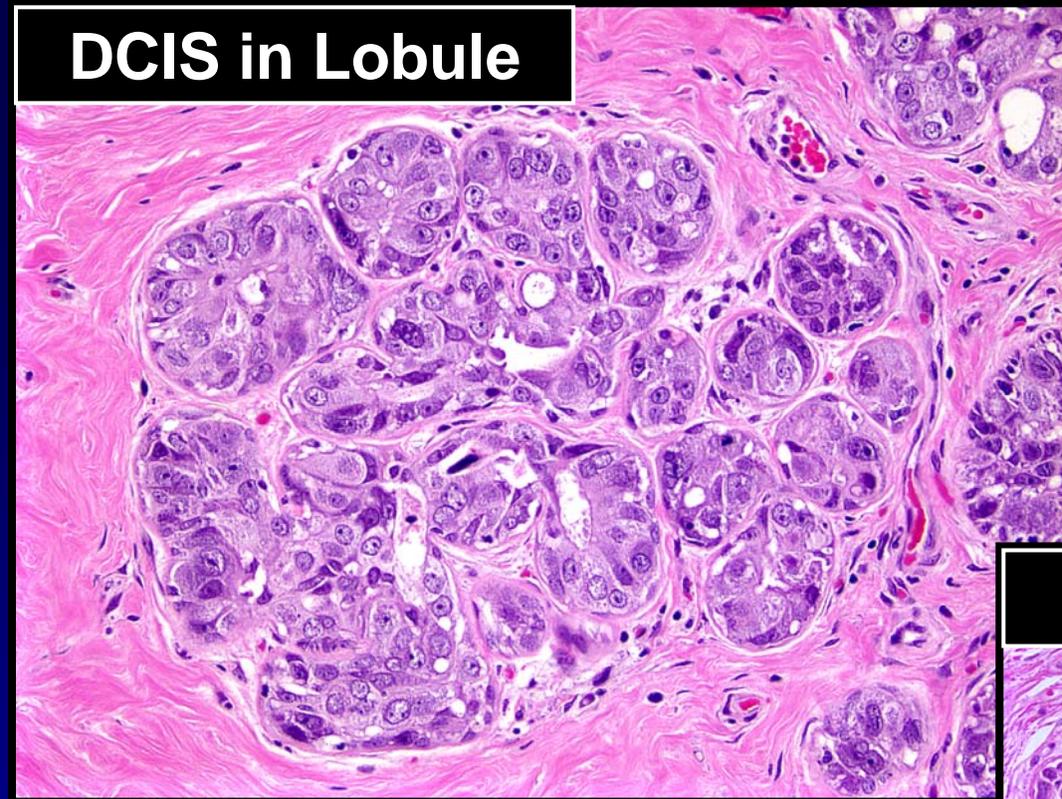
Viewed as risk factor

- Observation \pm tam
- No margin evaluation

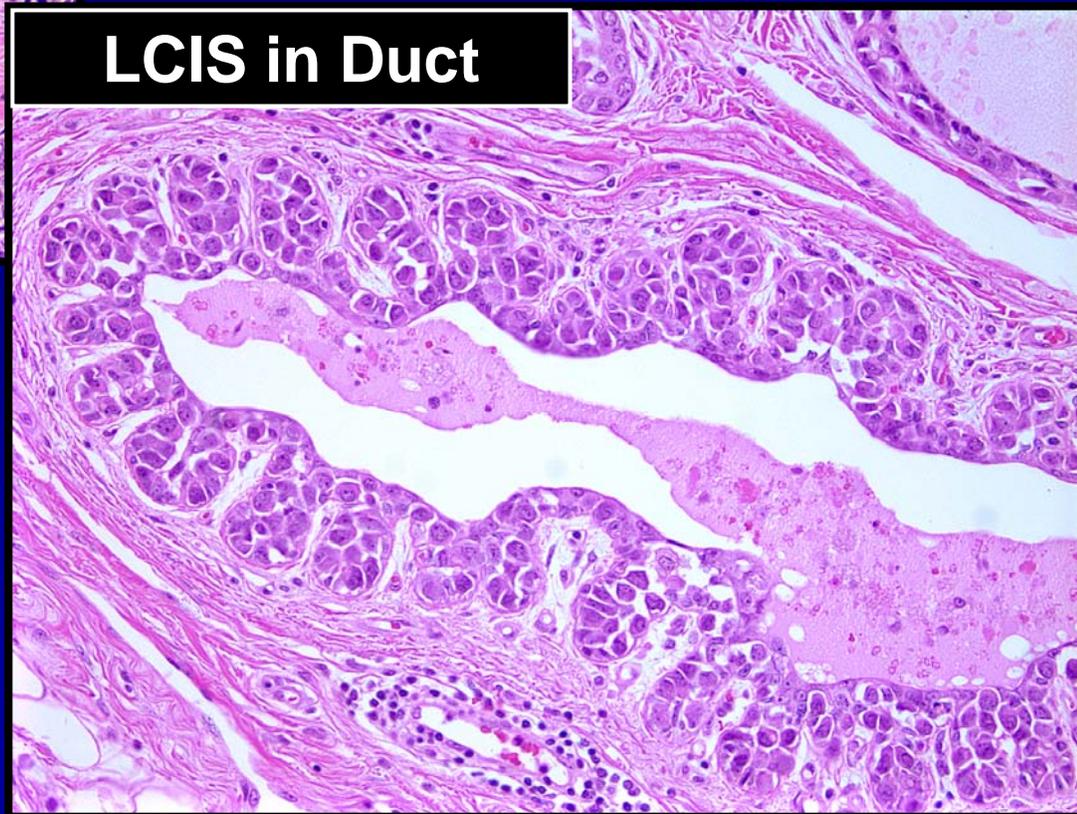
Problems in Distinguishing DCIS from LCIS

- **Overlap in distribution within ductal-lobular system**
 - DCIS can involve identifiable lobules
 - LCIS can involve ducts
- **Some LCIS lesions have features more commonly associated with DCIS**
- **Some DCIS lesions have features more commonly associated with LCIS**

DCIS in Lobule

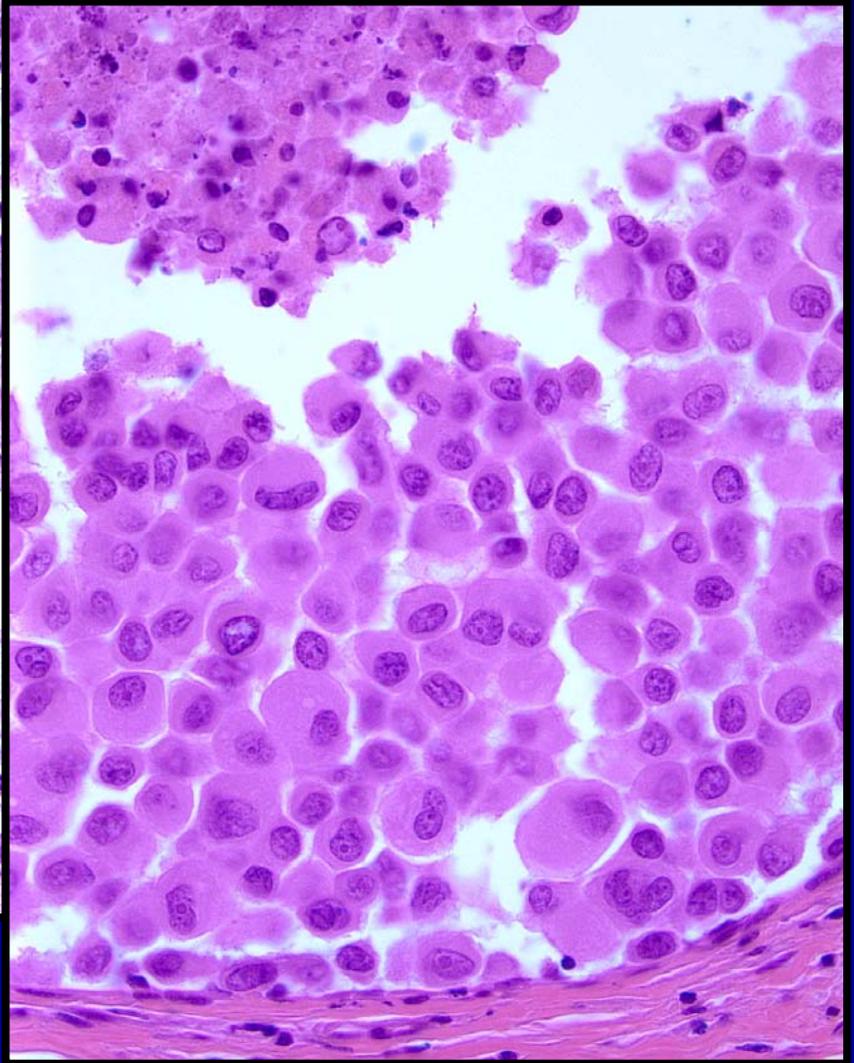
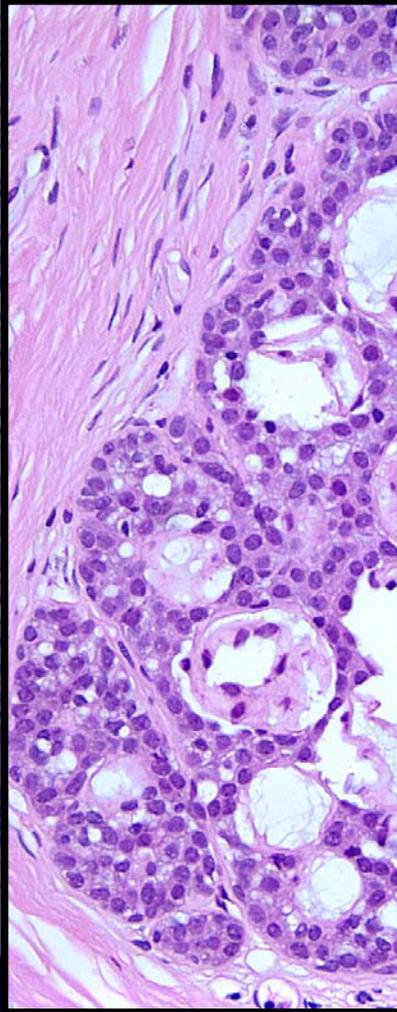
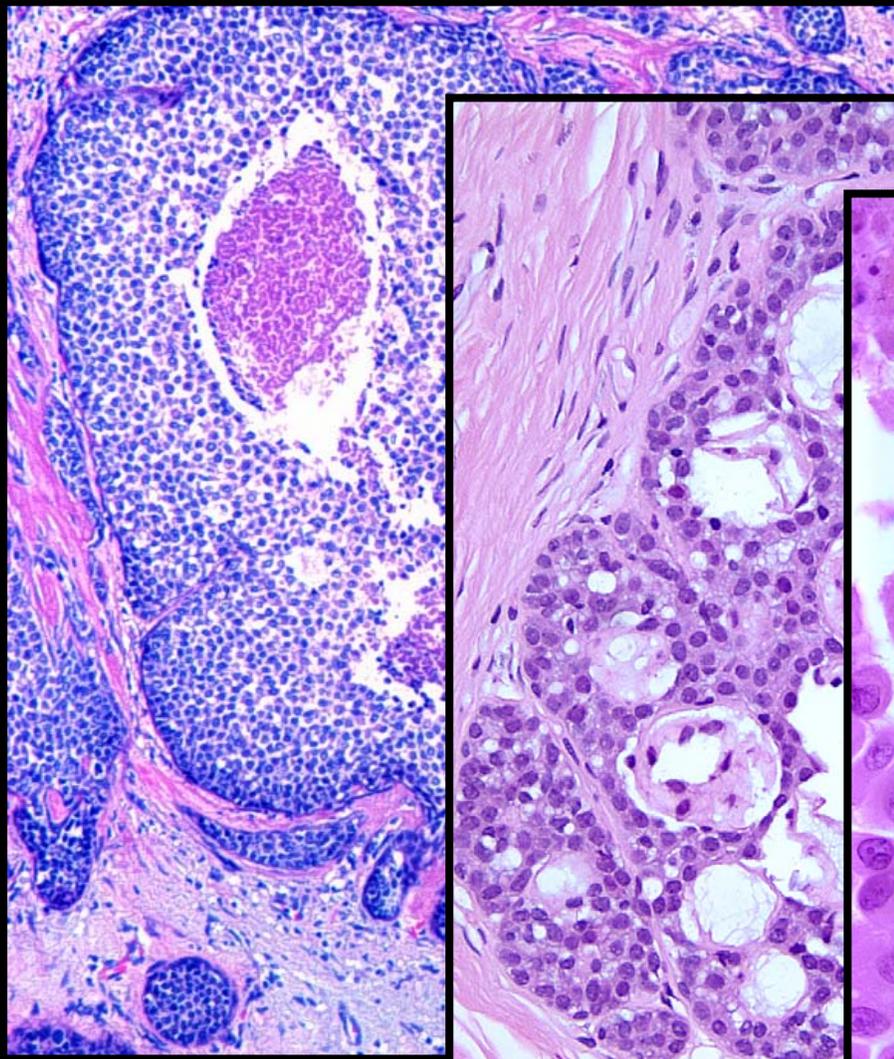
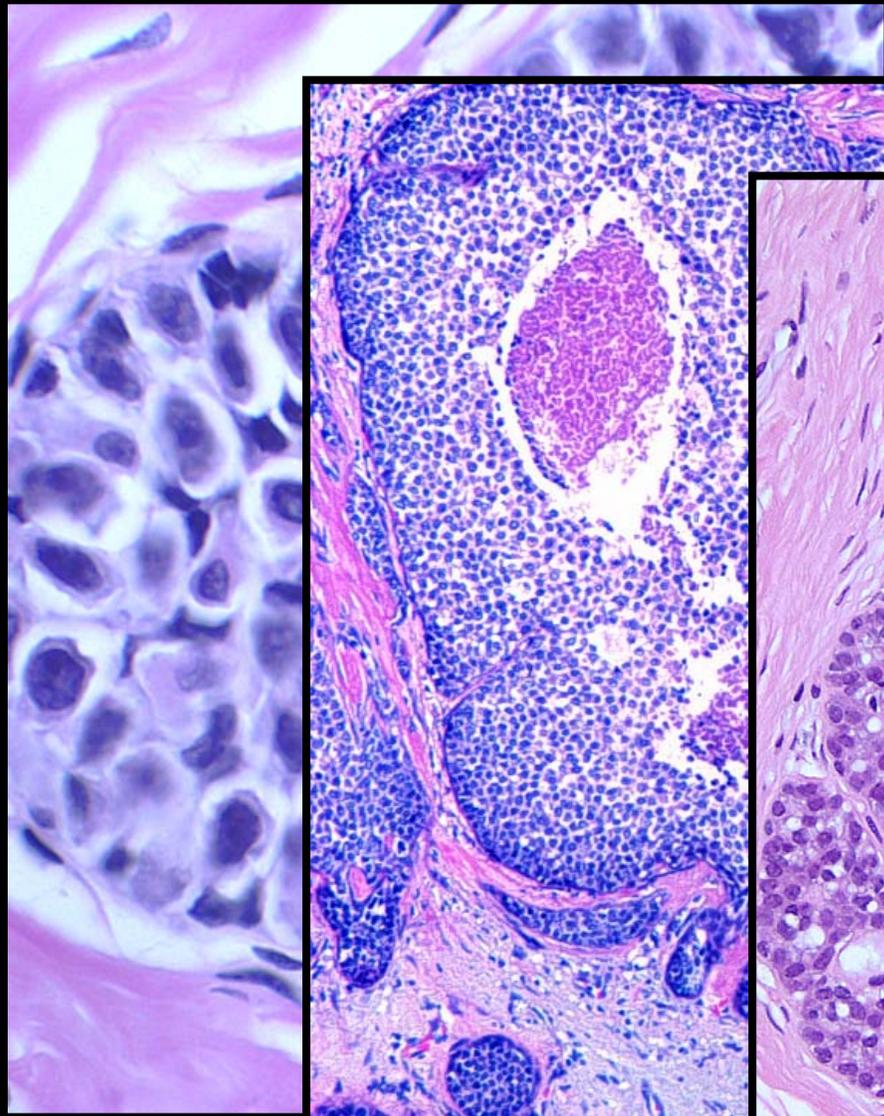


LCIS in Duct



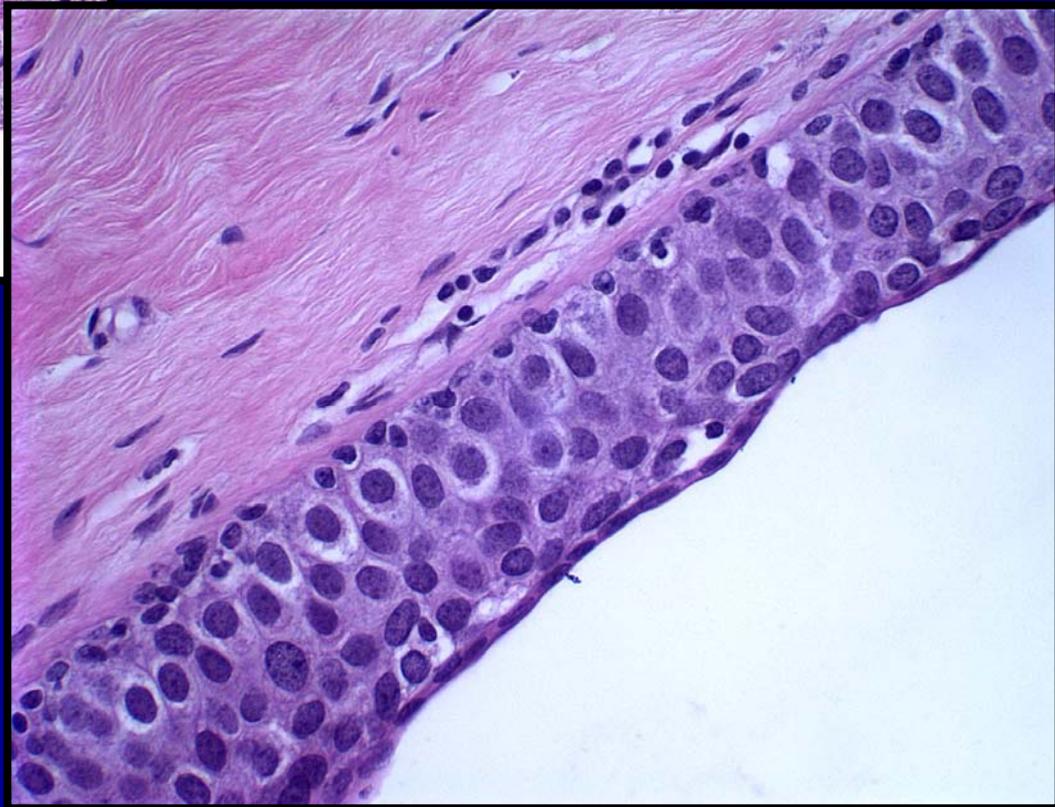
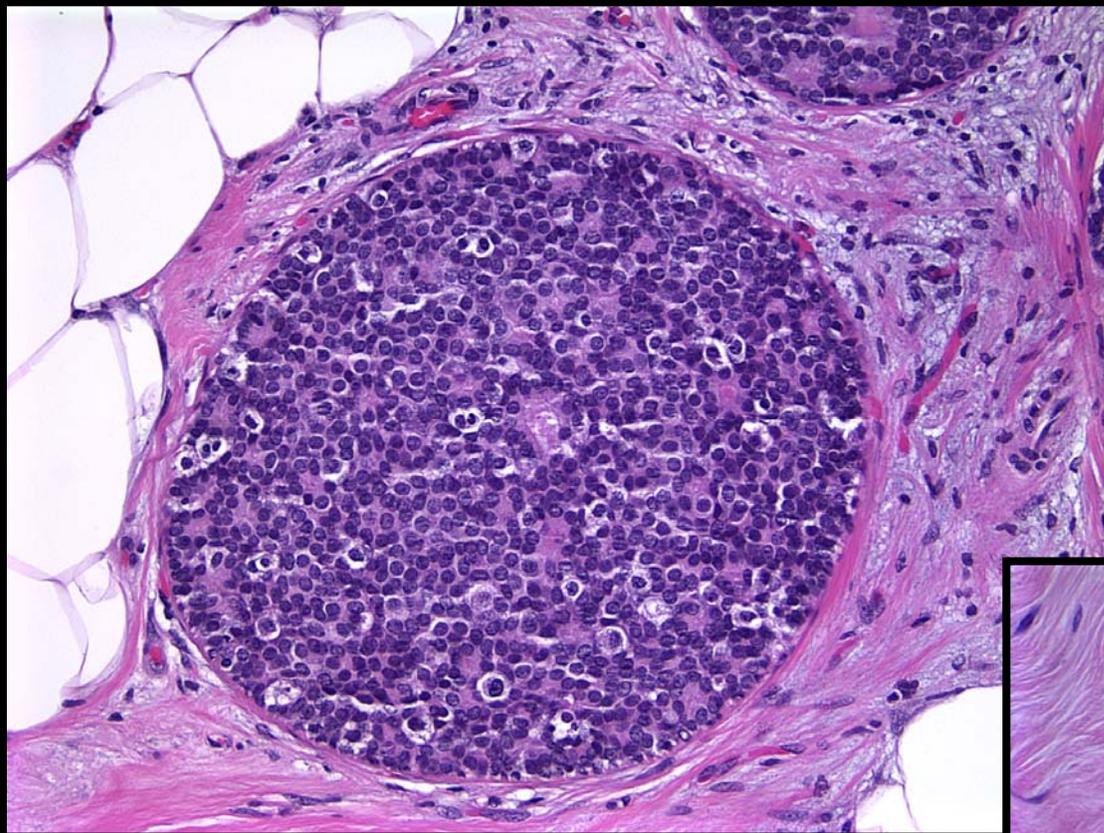
Features Usually Associated with DCIS That May Be Seen in LCIS

- Nuclear pleomorphism
- Comedo necrosis
- Cribriform-like pattern
- Prominent apocrine differentiation



Features Usually Associated with LCIS That May Be Seen in DCIS

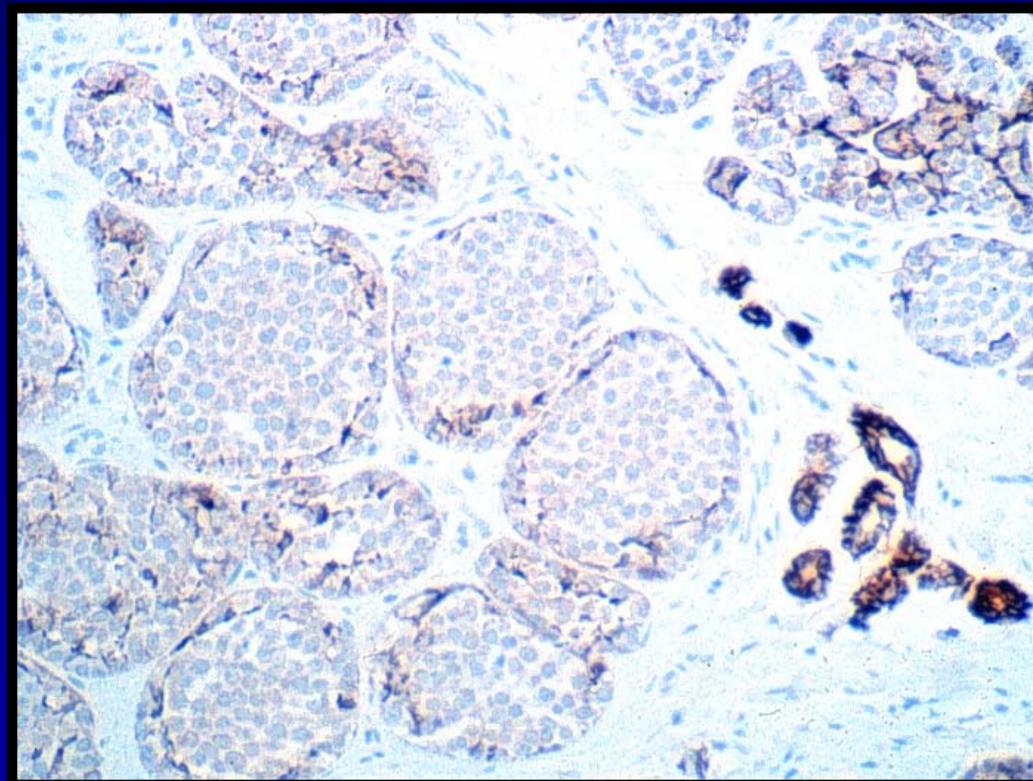
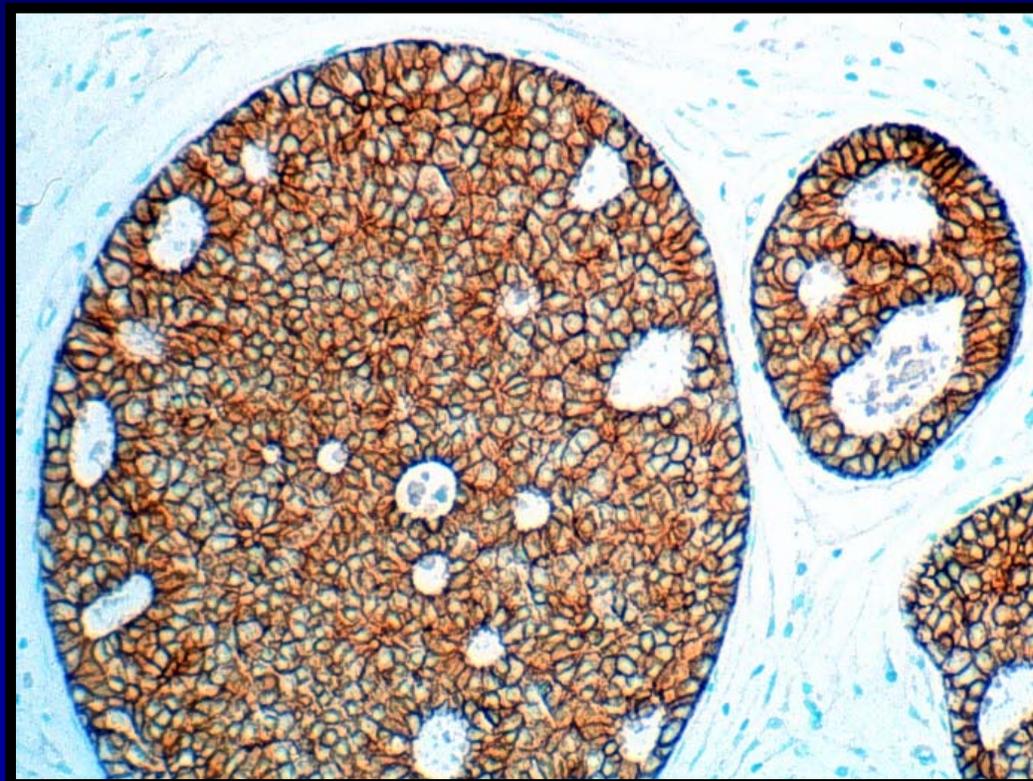
- **Small monomorphic cells**
- **Solid growth pattern**
- **Intracytoplasmic vacuoles**
- **Pagetoid involvement of ducts**



E-cadherin Staining May Be of Help in Problematic Cases

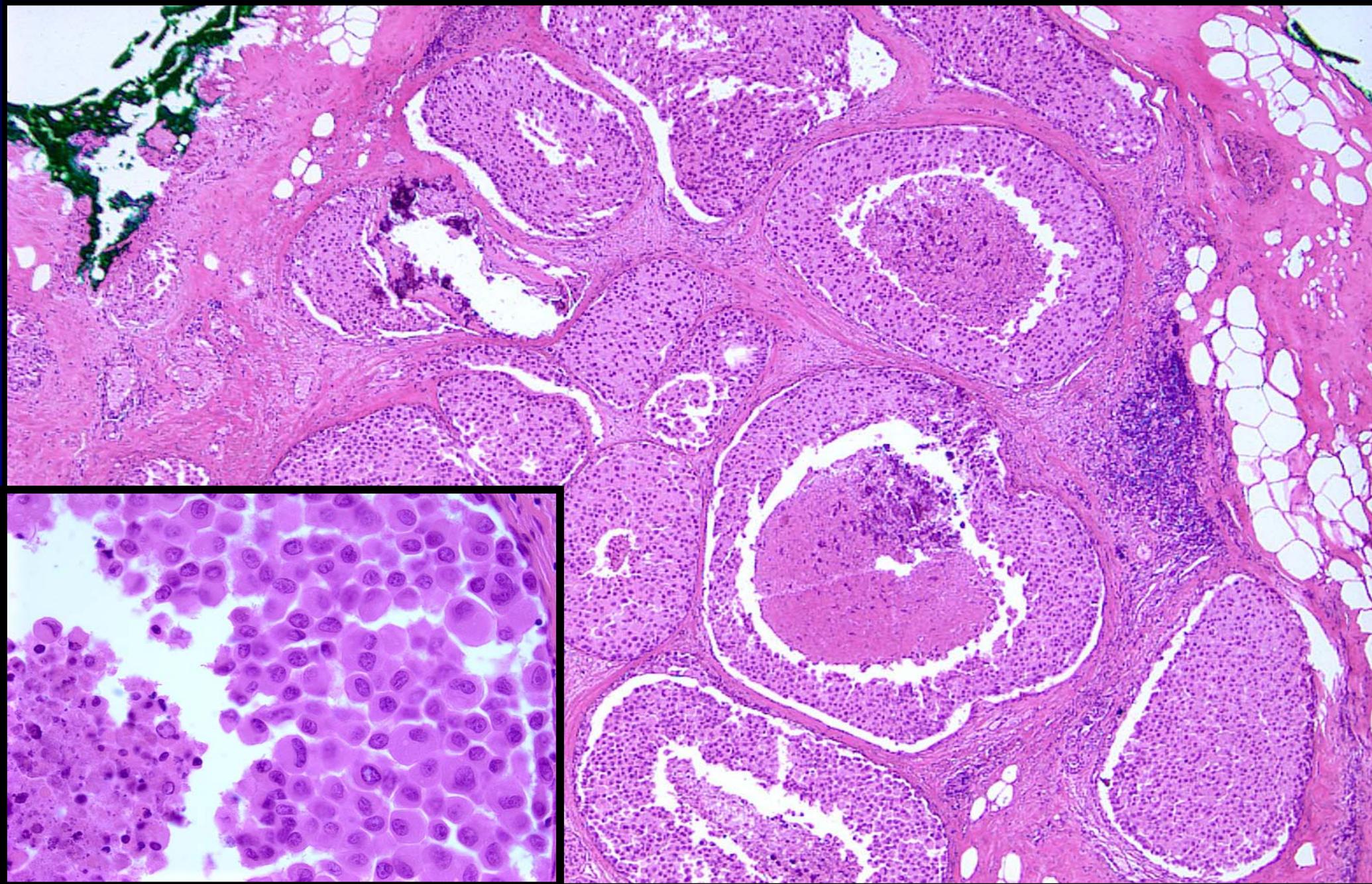
DCIS: positive

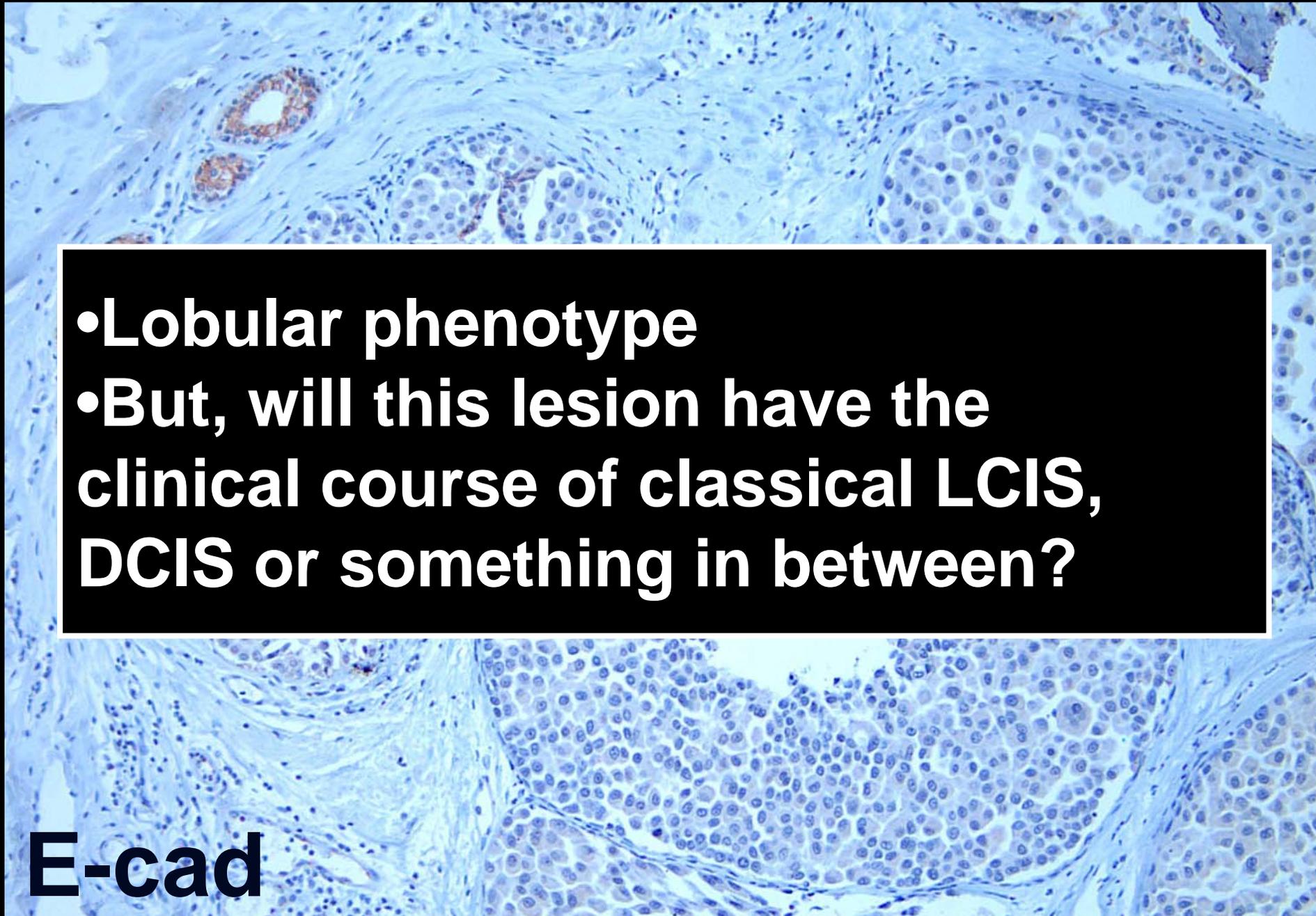
LCIS: negative



Practical Considerations

- **Current understanding of clinical behavior of DCIS and LCIS based on follow-up studies of lesions classified according to histologic features alone (“classical” forms of disease)**
- **Not clear that these results can be extrapolated to lesions that are histologically indeterminate but defined as either DCIS or LCIS by E-cadherin staining**
- **The most appropriate management of patients with histologically ambiguous in situ lesions currently not known**



- 
- Lobular phenotype
 - But, will this lesion have the clinical course of classical LCIS, DCIS or something in between?

E-cad

Conclusions

- Diagnosis of DCIS straightforward in most cases
- DCIS has many faces
- Problems with both under-diagnosis and over-diagnosis
- In order to properly study DCIS, we need to be sure that what we are studying is DCIS

Is This DCIS?

