

**Urothelial Neoplasms of the
Bladder, Renal Pelvis and Ureter:
Histologic, Molecular and Clinical
Correlates**

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Objectives

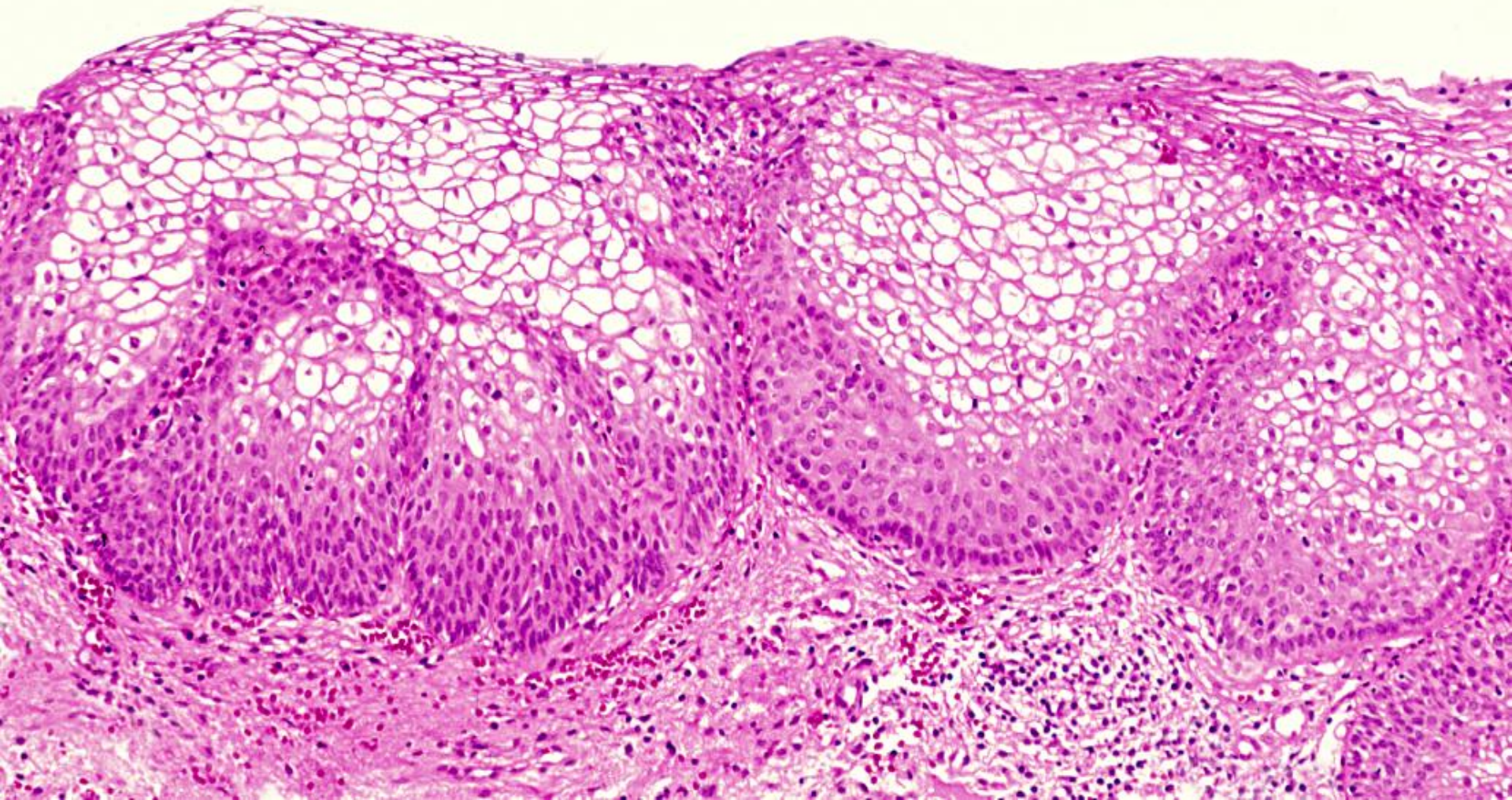
1. Review few important not tumor lesions.
 2. Establish criteria for diagnostic classification of pre invasive neoplasia of the urinary bladder.
 3. Discuss criteria for invasion and emphasize few relevant variants.
-
1. Provide a quick glimpse into the proposed molecular markers.

NON-NEOPLASTIC TUMOROUS CONDITIONS

**METAPLASIA
SQUAMOUS
INTESTINAL
“NEPHROGENIC”**

**CYSTITIS -
GLANDULARIS, CYSTICA**

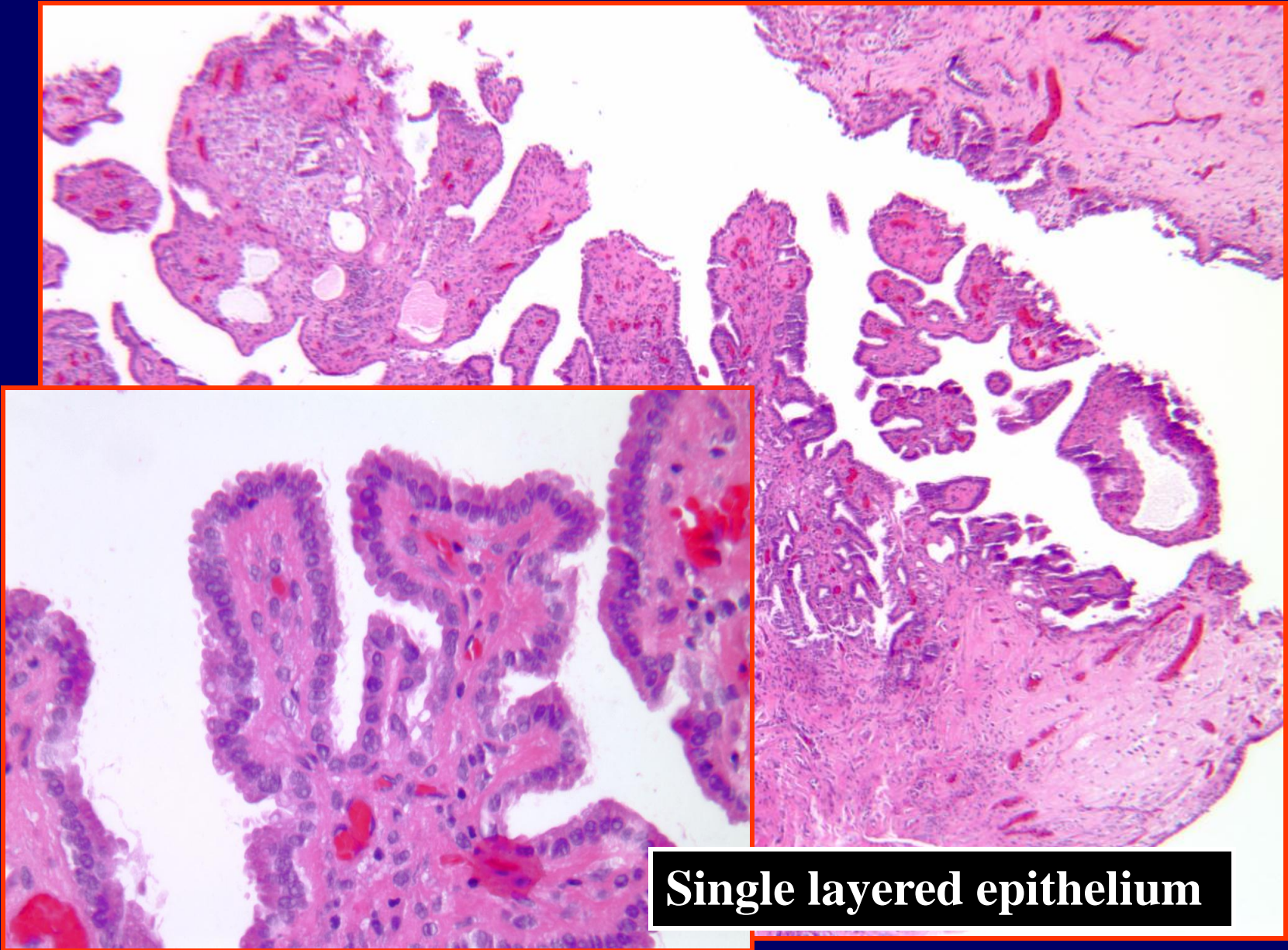
ENDOMETRIOSIS, ENDOCERVICOSI



NEPHROGENIC ADENOMA (METAPLASIA)

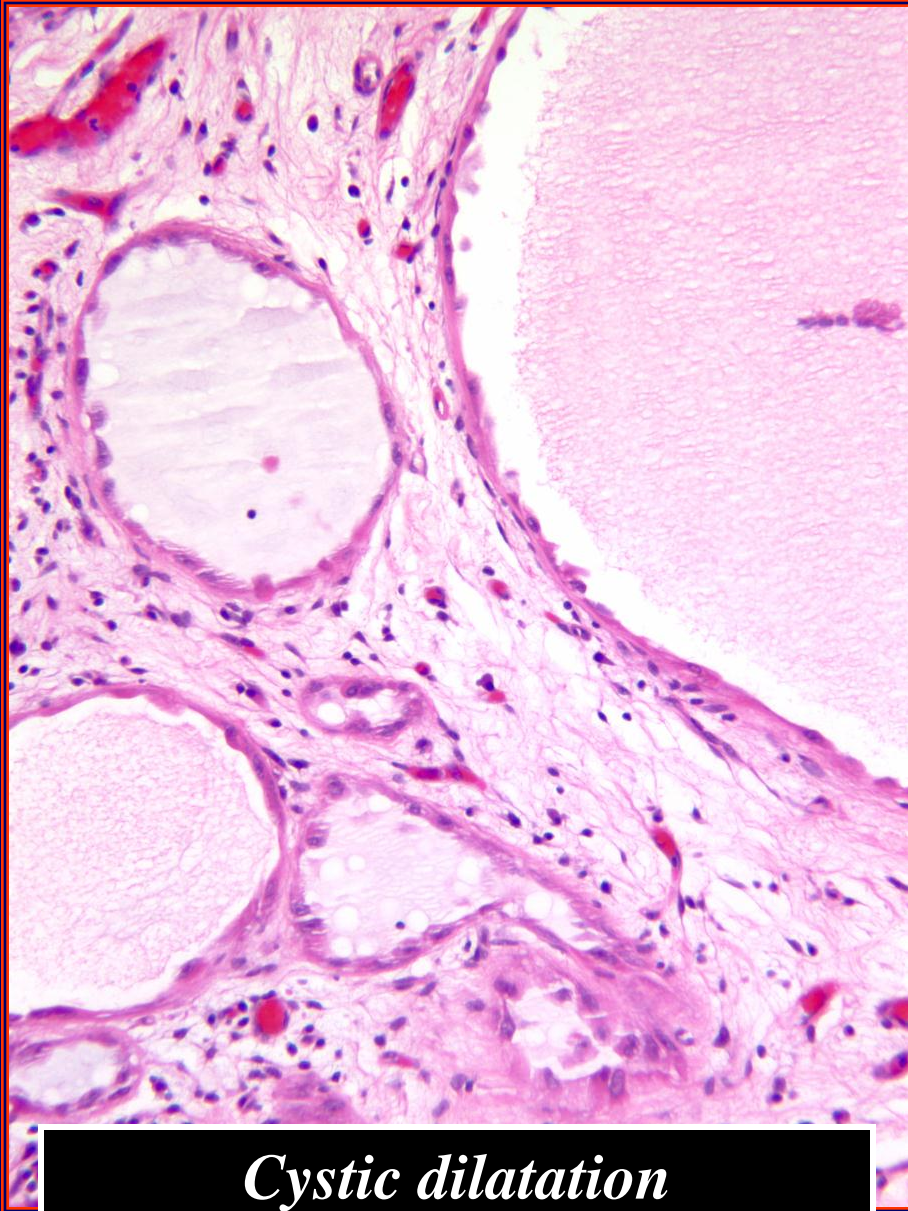
- **Most common in the setting of prior surgery or trauma (cystoscopy)**
- **Chronic irritation**
- **Renal transplantation**
- **Urinary bladder most common**
- **Single or multiple**
- **Papillary lesions at cystoscopy**

NEPHROGENIC ADENOMA

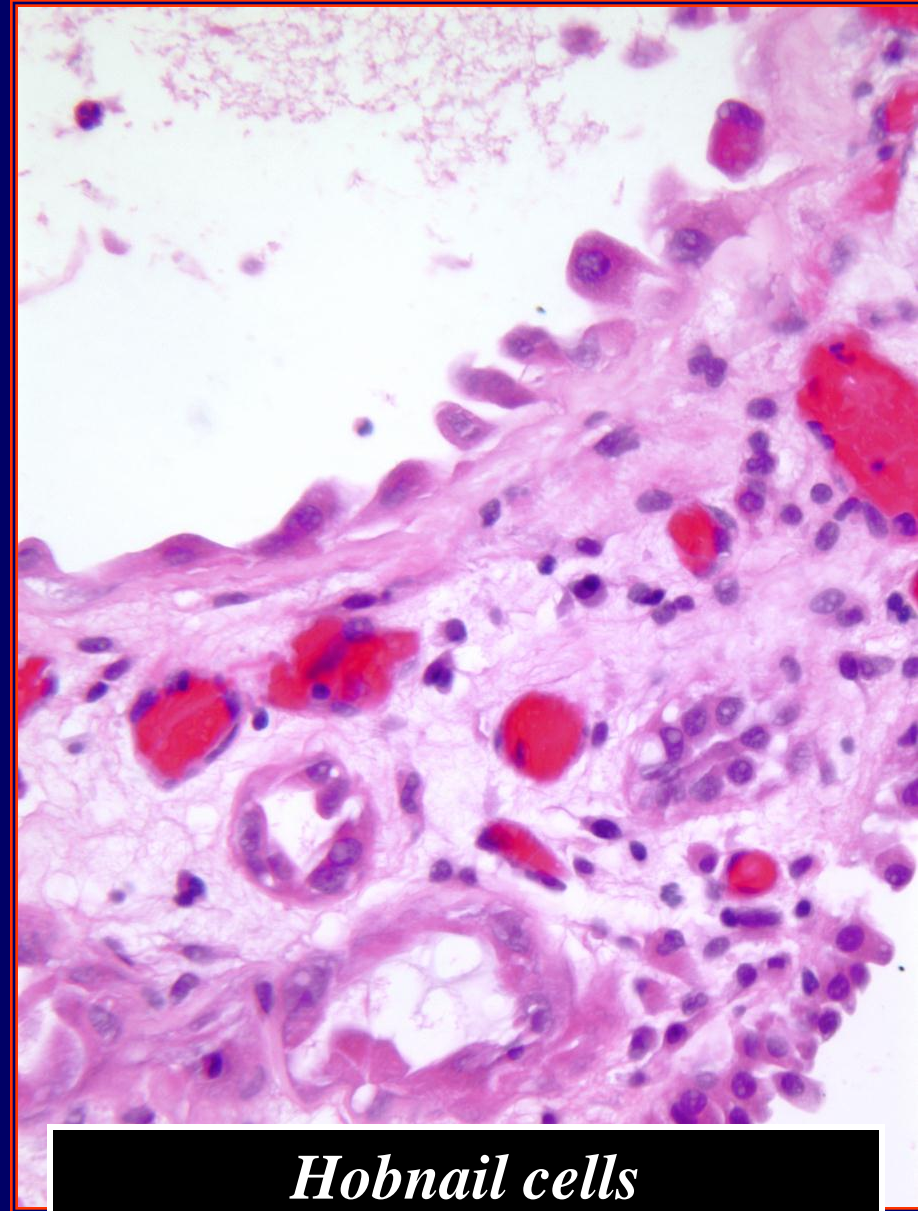


Single layered epithelium

NEPHROGENIC ADENOMA

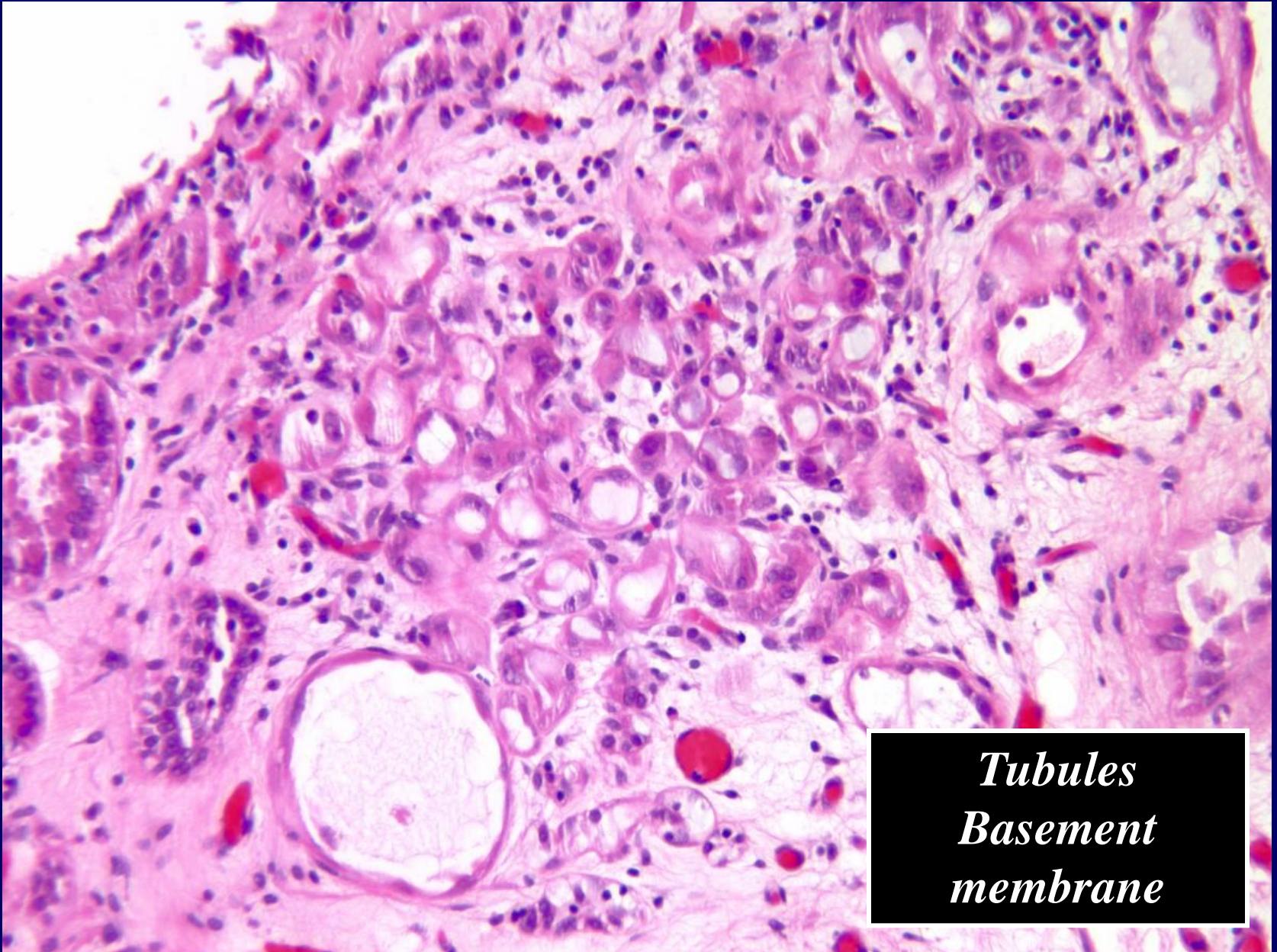


Cystic dilatation



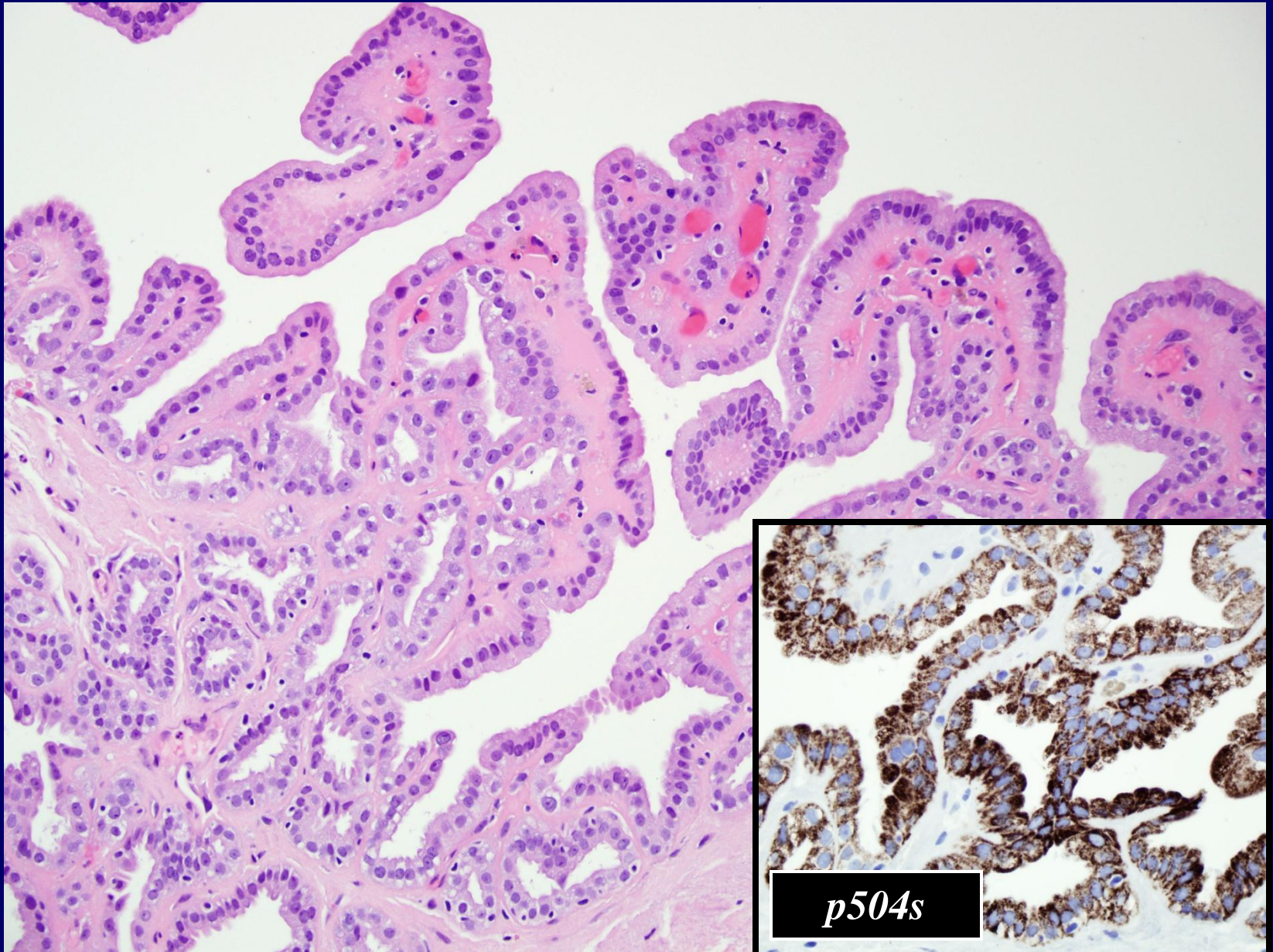
Hobnail cells

NEPHROGENIC ADENOMA



Tubules
Basement
membrane

NEPHROGENIC ADENOMA

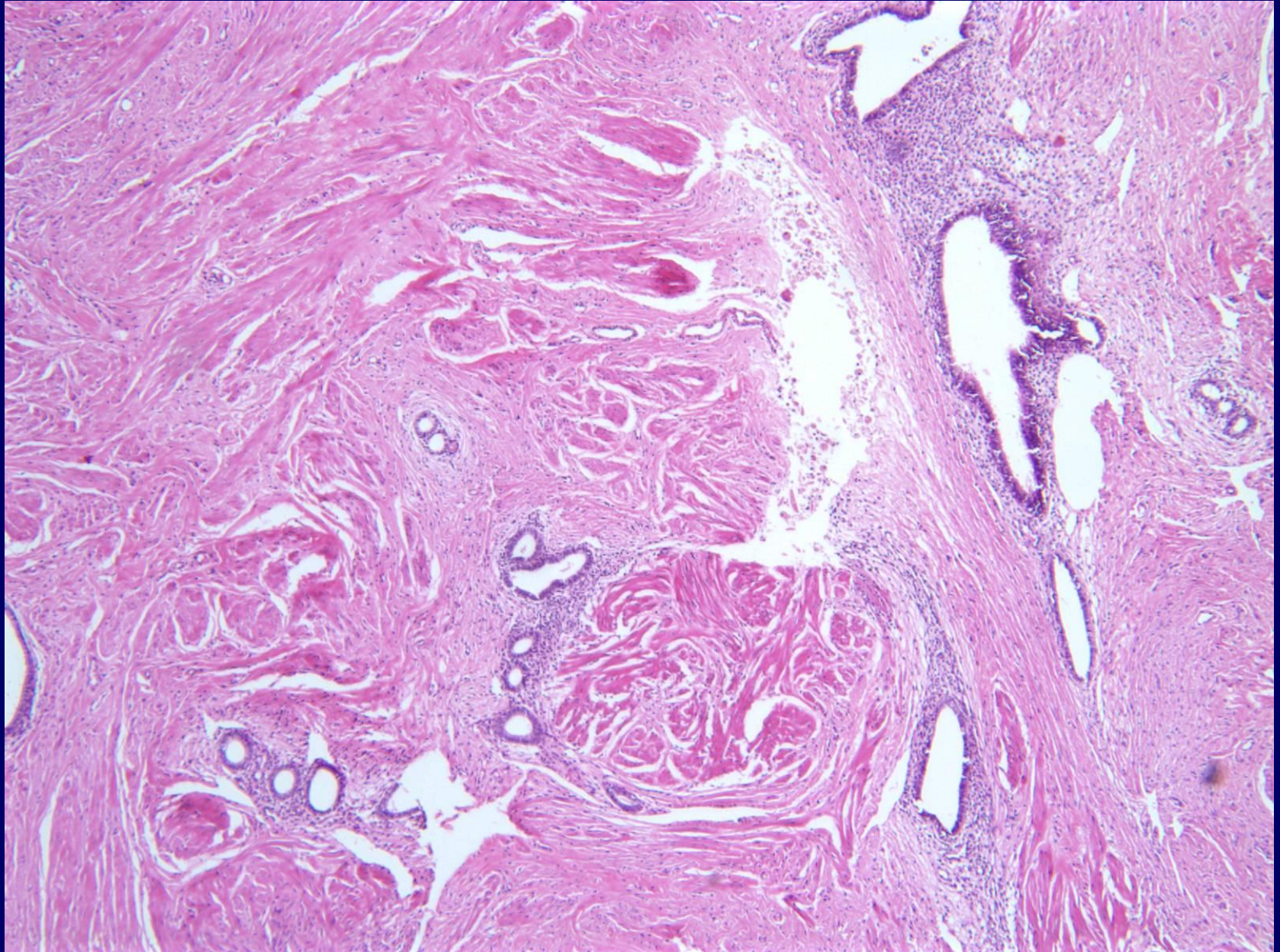


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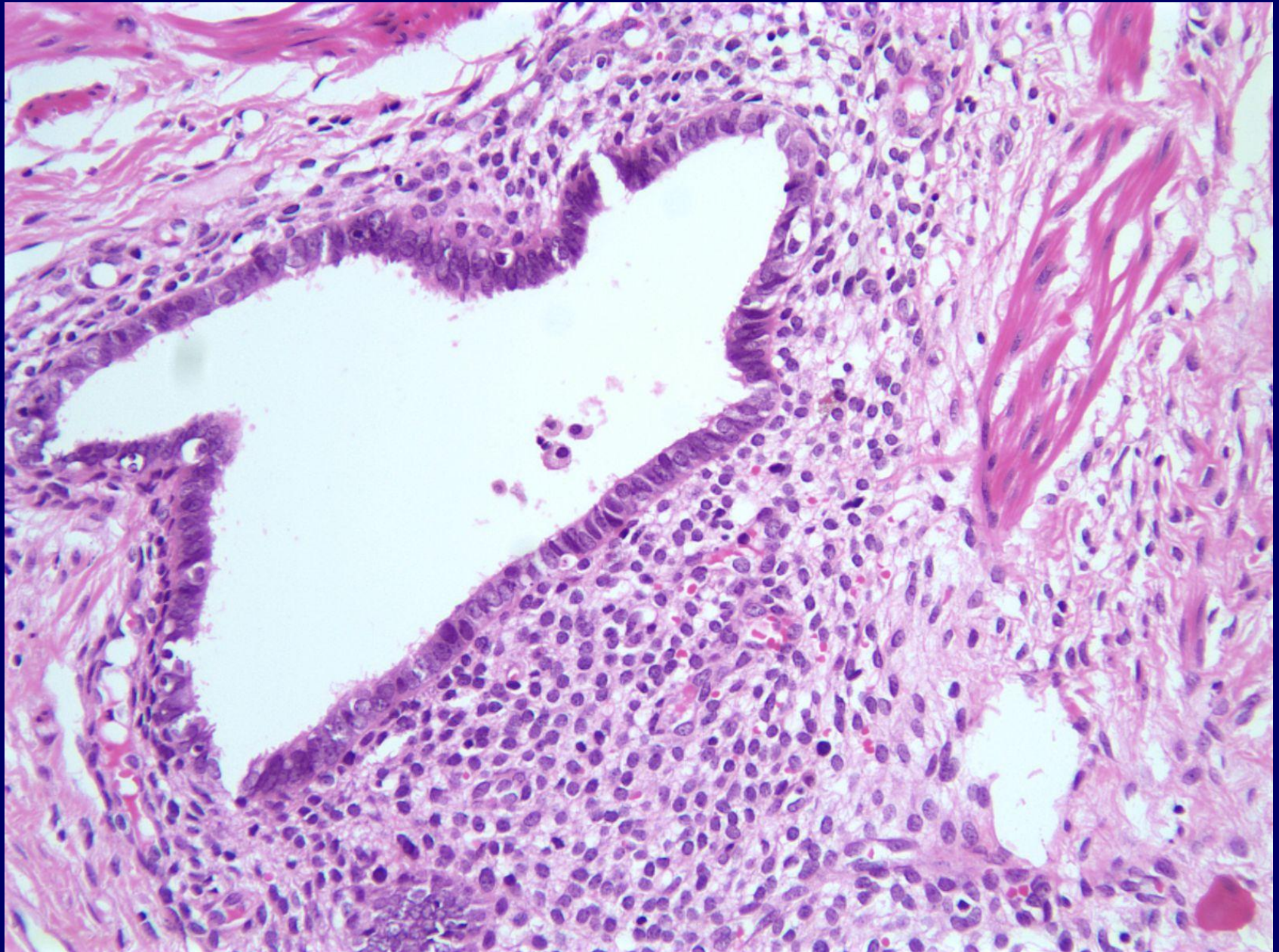
MÜLLERIAN LESIONS

- **Endometriosis**
 - 1% of women with endometriosis
 - Dark blue mucosal lesions
 - Glands, stroma, hemosiderin
- **Endocervicosis**
 - Masses up to 5 cm
 - Endocervical type glands
 - Haphazard distribution
- **Müllerianosis**
 - When endometriosis, endocervicosis or endosalpingiosis coexist

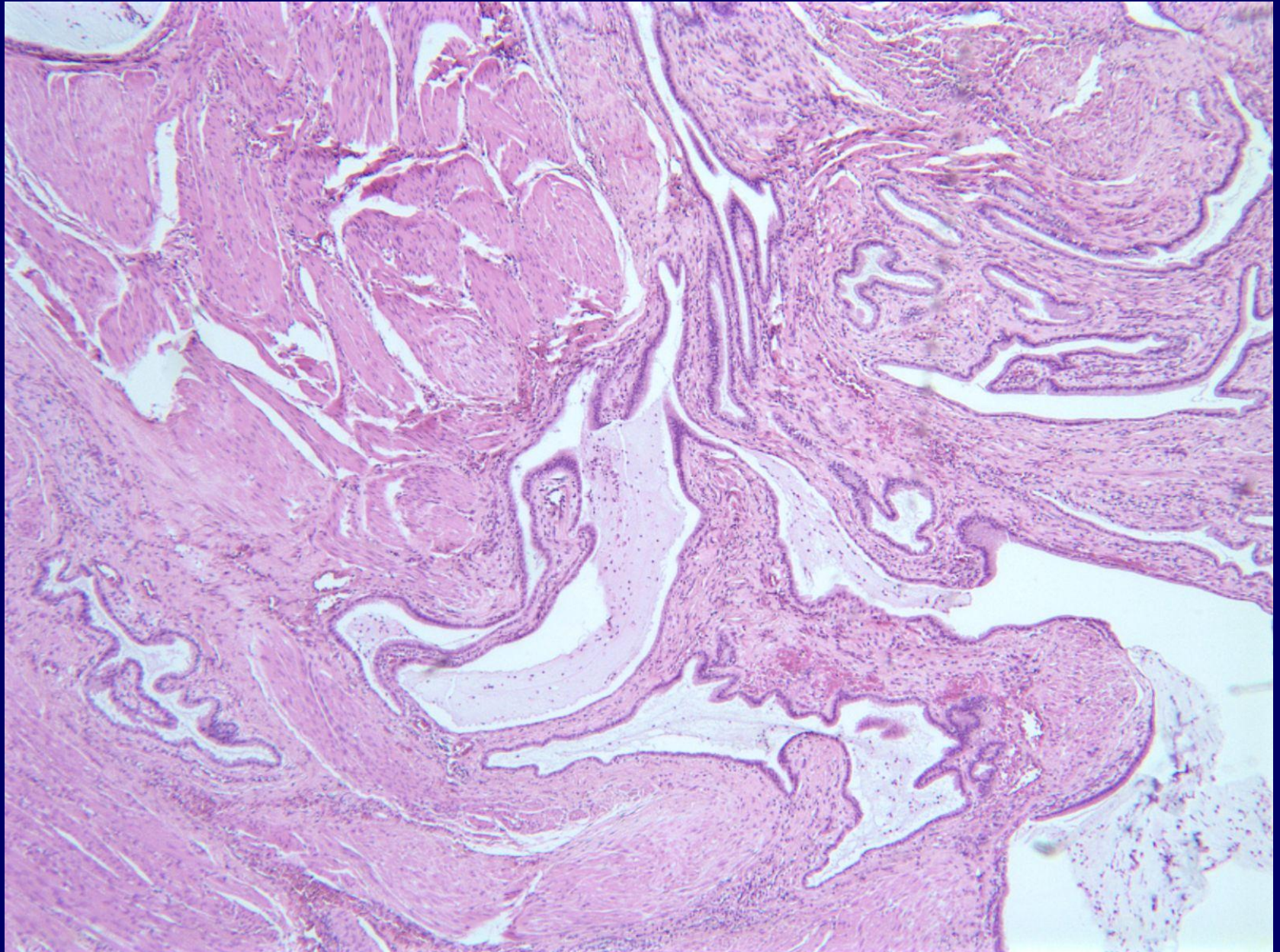
ENDOMETRIOSIS



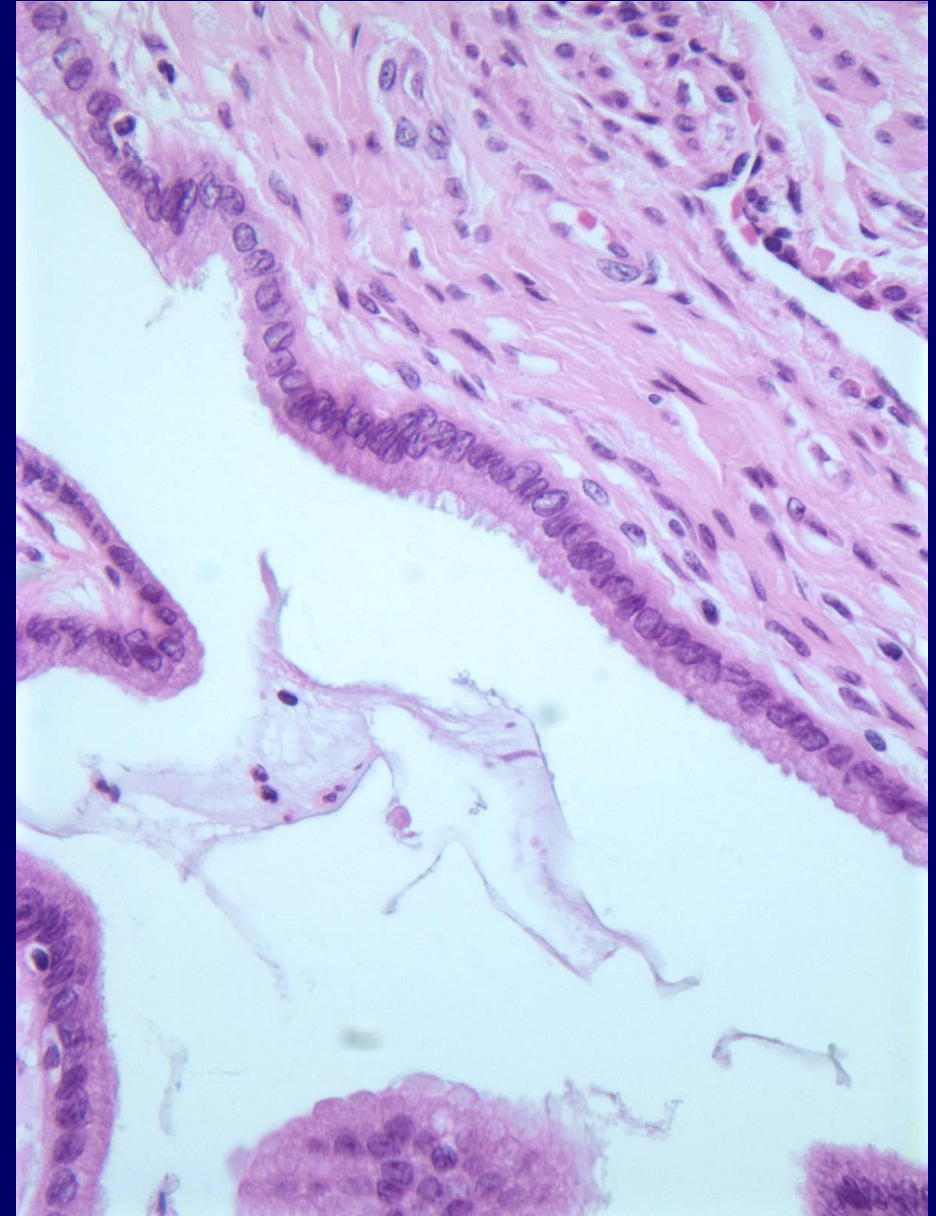
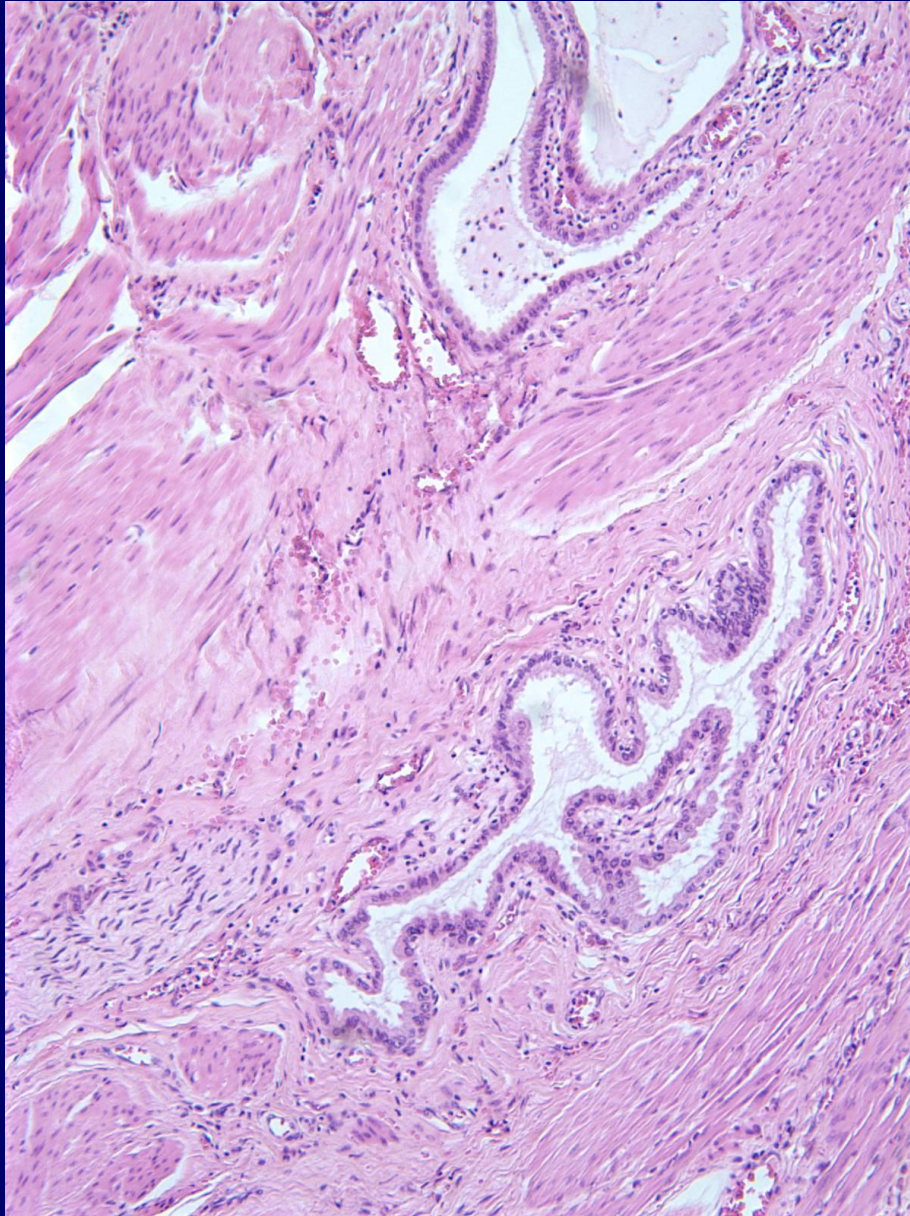
ENDOMETRIOSIS



ENDOCERVICOSIS



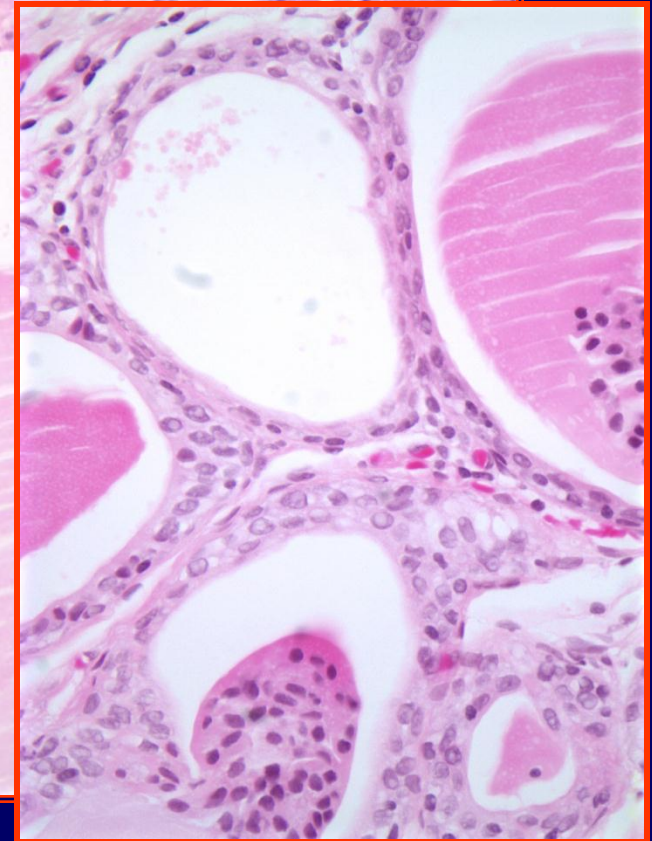
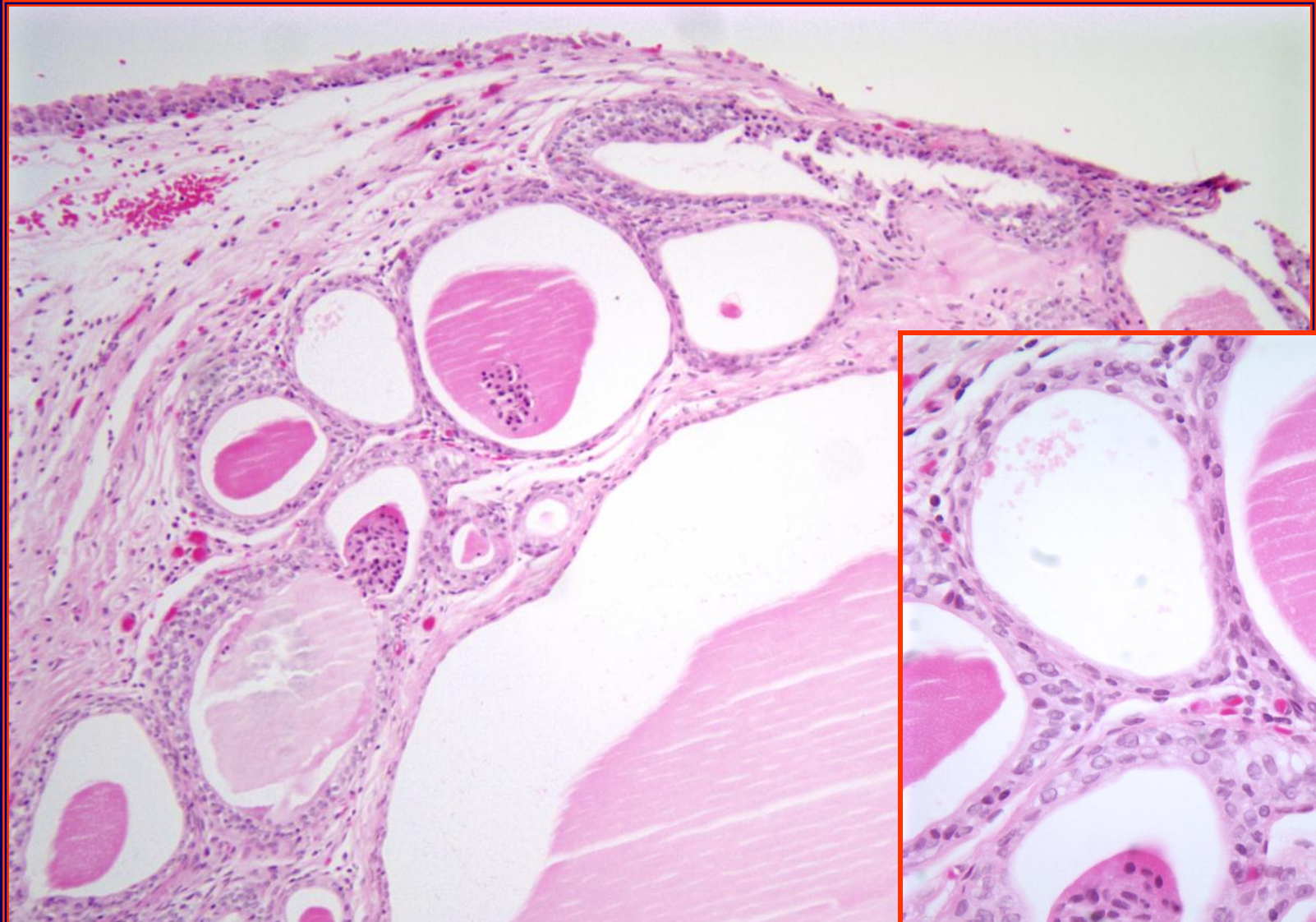
ENDOCERVICOSIS



CYSTITIS CYSTICA AND GLANDULARIS

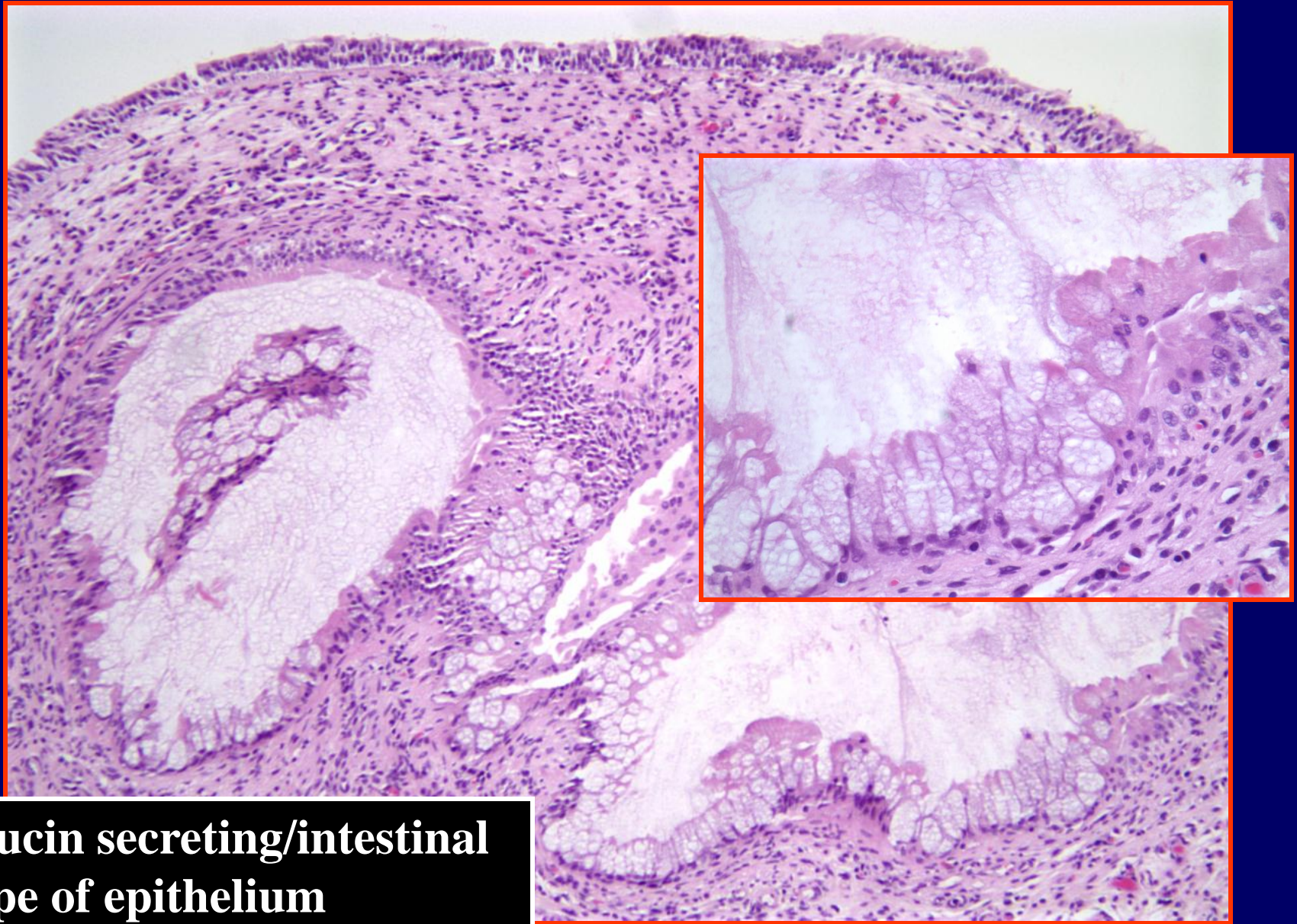
- **Cystic dilatation of von Brunn' s nests**
- **+/- intestinal metaplasia**
- **Cobblestone appearance
cystoscopically**
- **Can produce small mass lesions**
- **Extravasation of mucin into stroma**

CYSTITIS CYSTICA



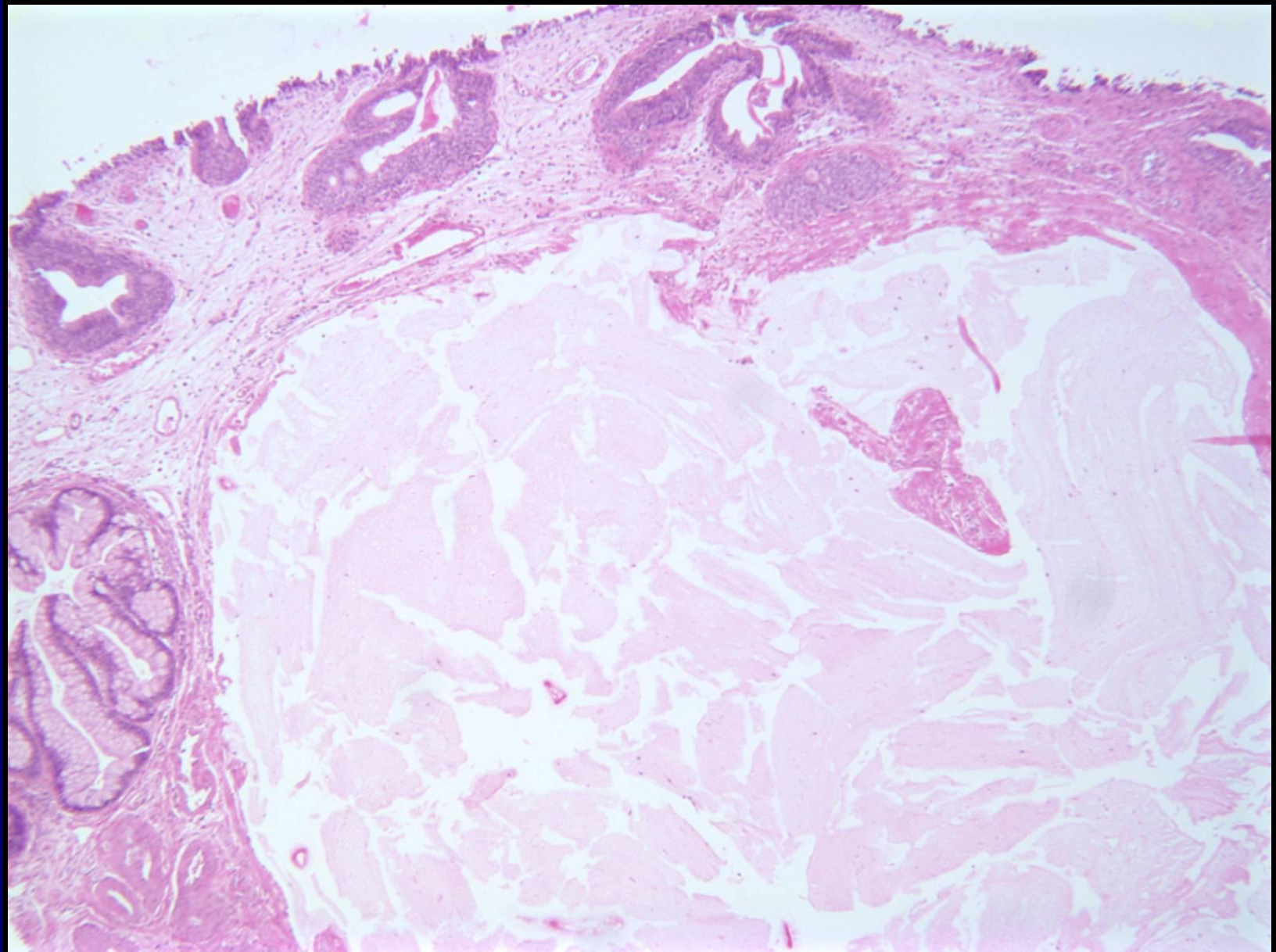
Dilated spaces lined by urothelium

CYSTITIS GLANDULARIS

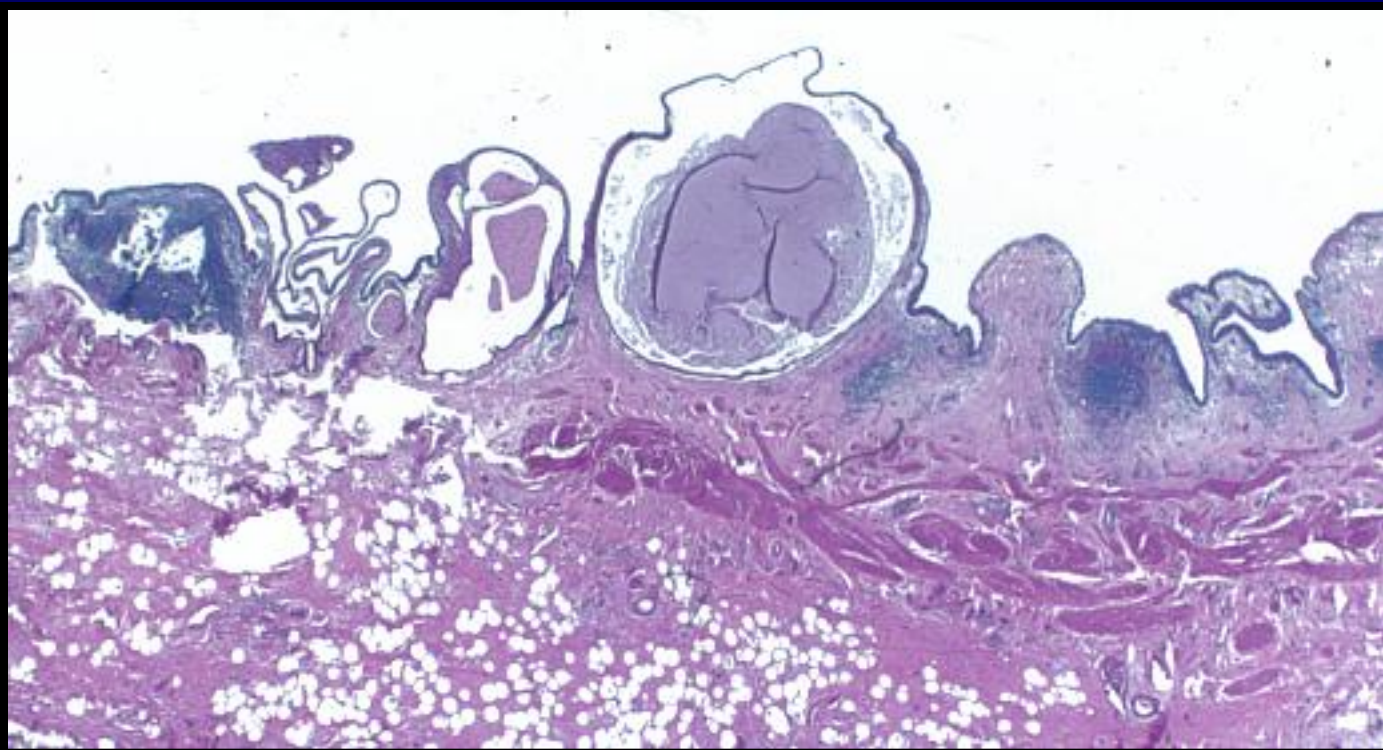


**Mucin secreting/intestinal
type of epithelium**

MUCIN EXTRAVASATION



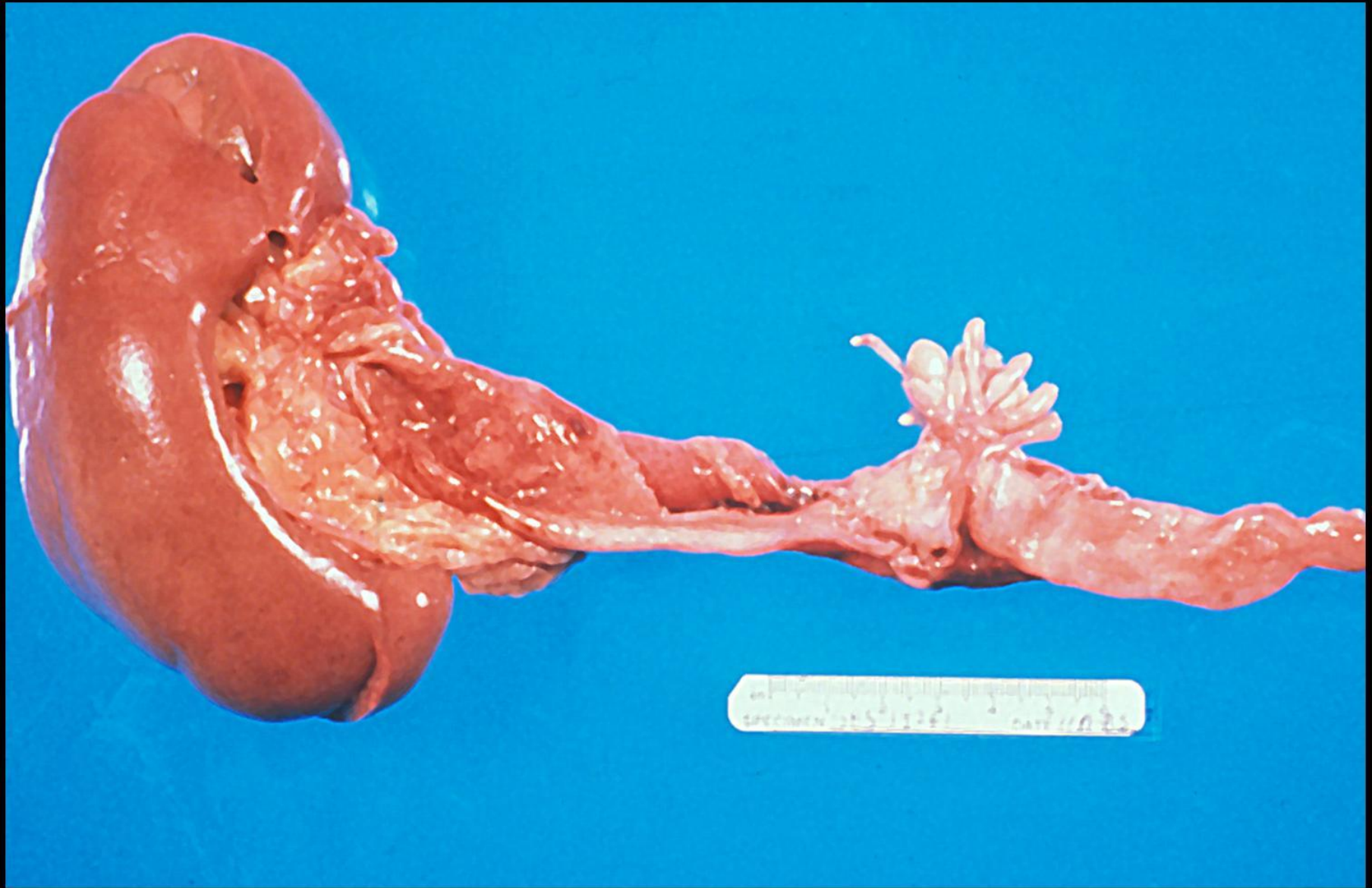
URETERITIS CYSTICA



FIBROEPITHELIAL POLYP

- **Occur throughout the urinary tract**
- **Proximal ureter/renal pelvis most common**
- **Young men most commonly affected**
- **Considered by many to be a benign neoplasm**
- **Often pedunculated with finger like projections**
- **Diagnosis can be suspected clinically**

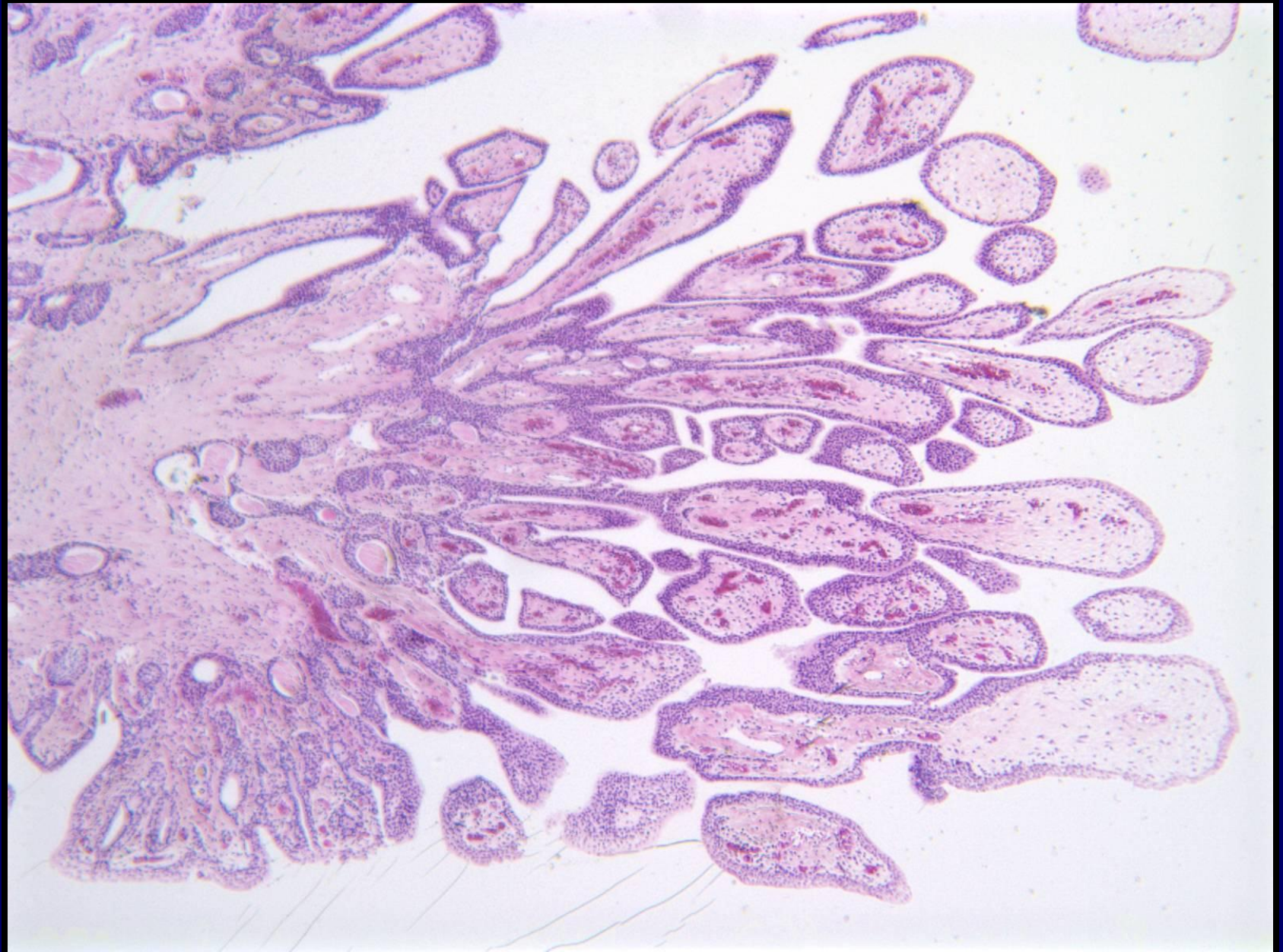
FIBROEPITHELIAL POLYP



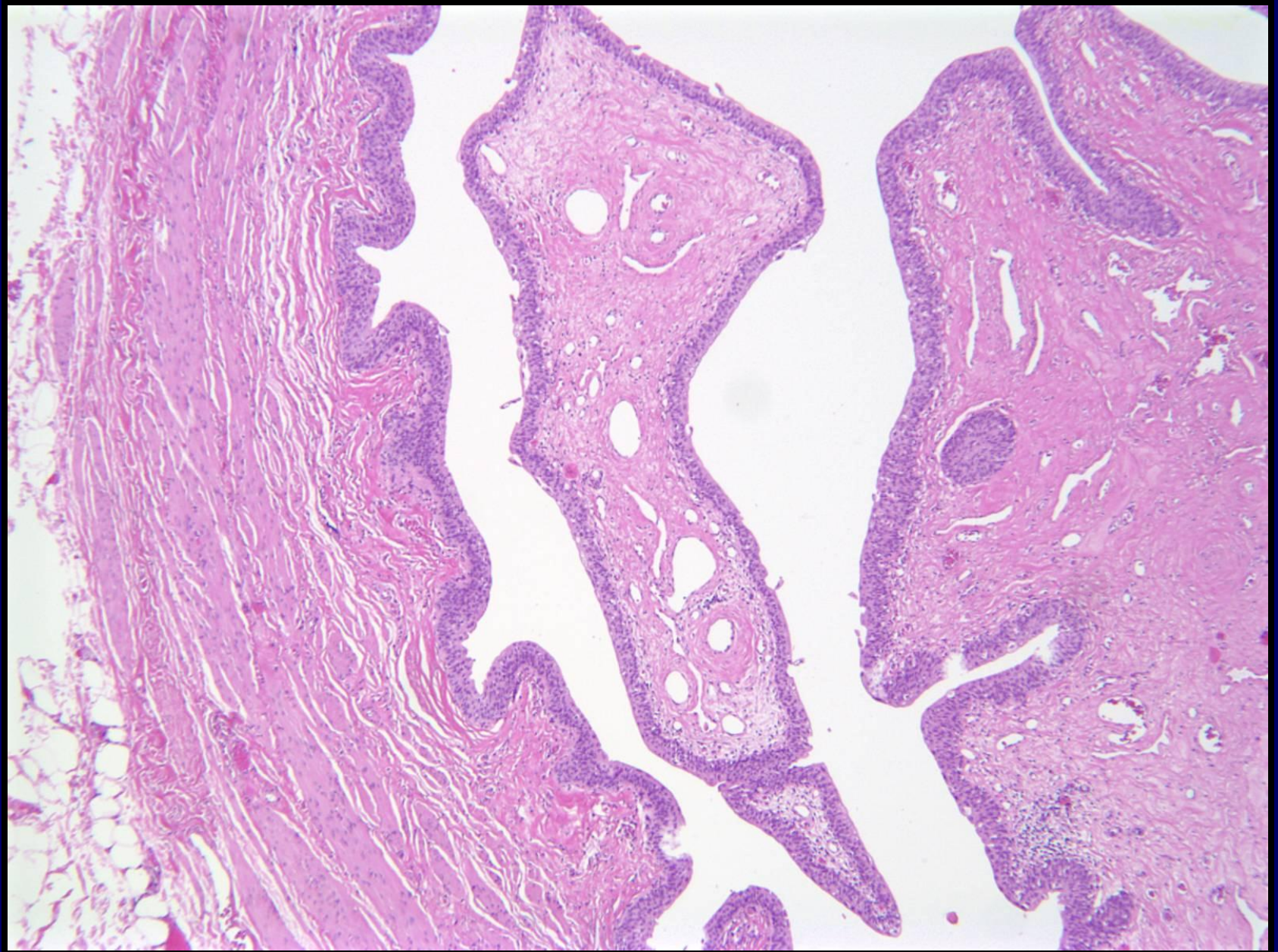
FIBROEPITHELIAL POLYP



FIBROEPITHELIAL POLYP

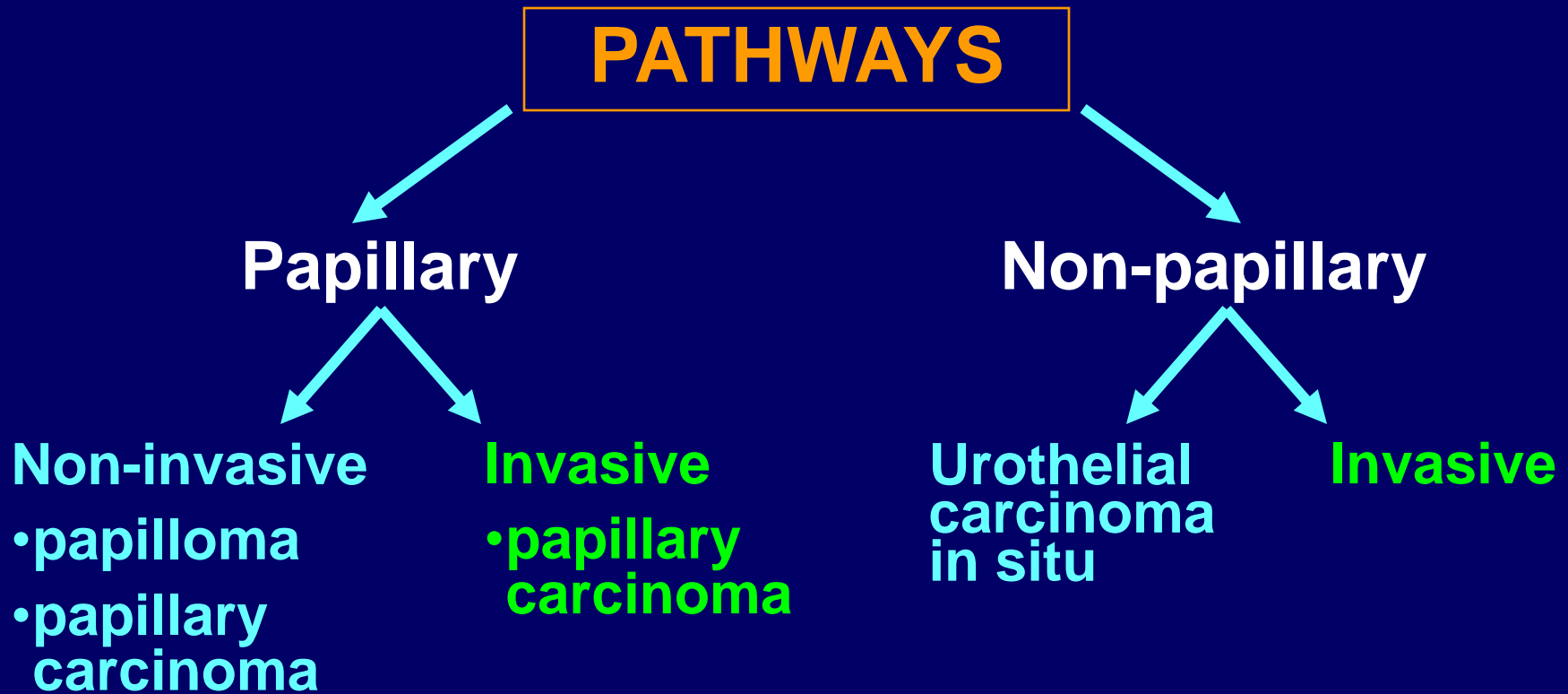


FIBROEPITHELIAL POLYP

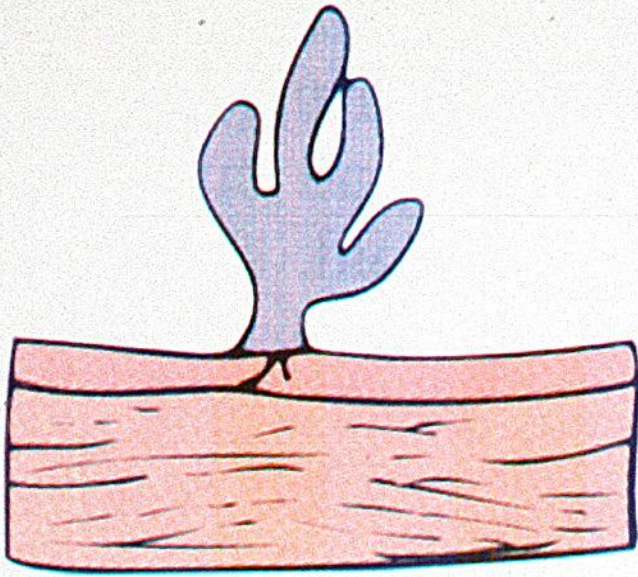




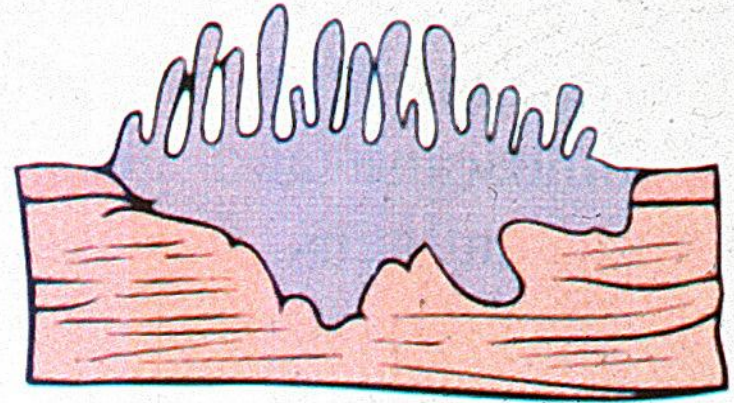
UROTHELIAL NEOPLASMS OF THE BLADDER



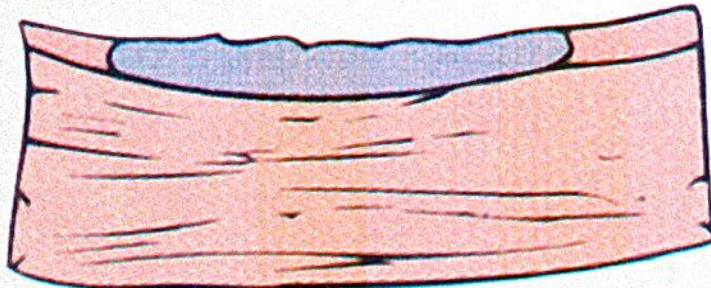
Pathways may be distinct or interrelated



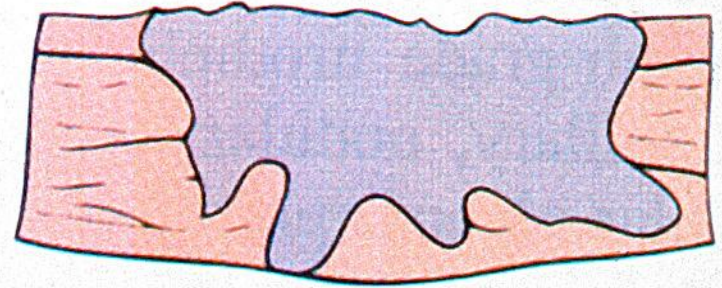
Papilloma-
papillary carcinoma



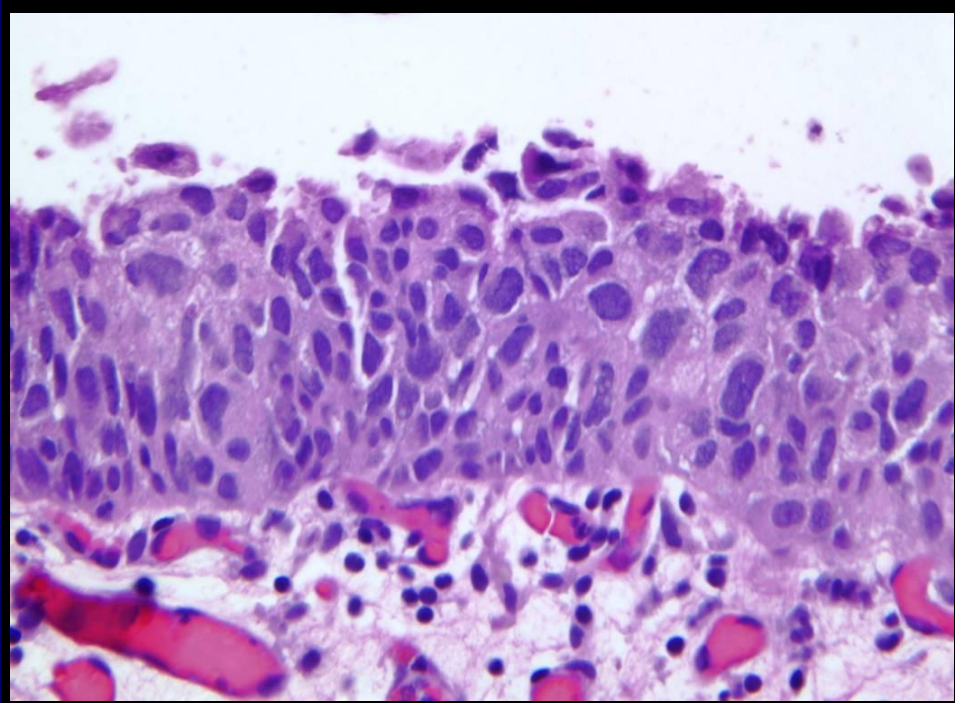
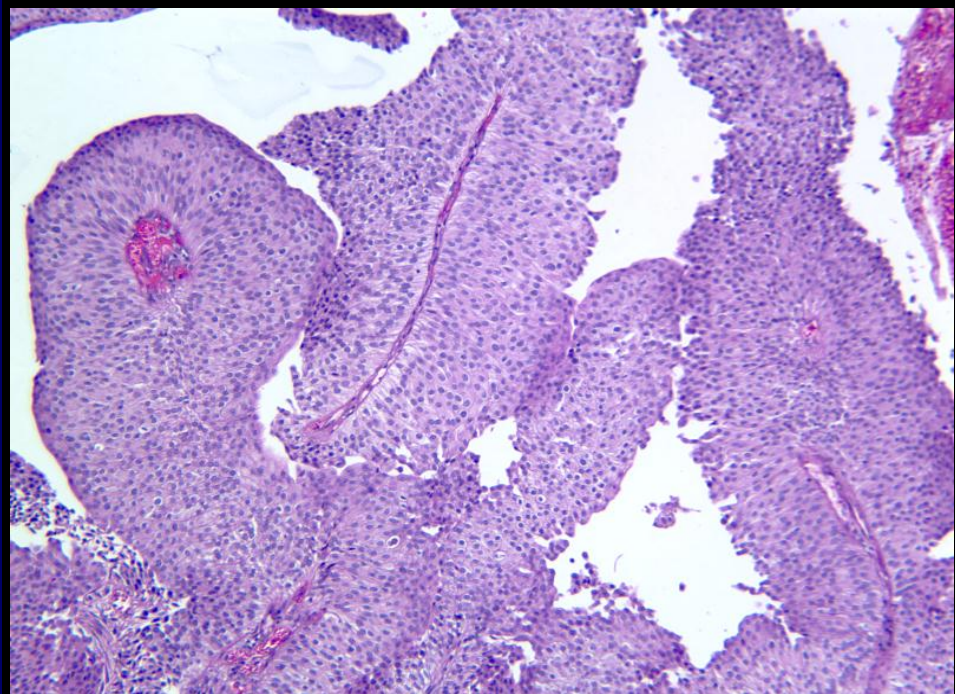
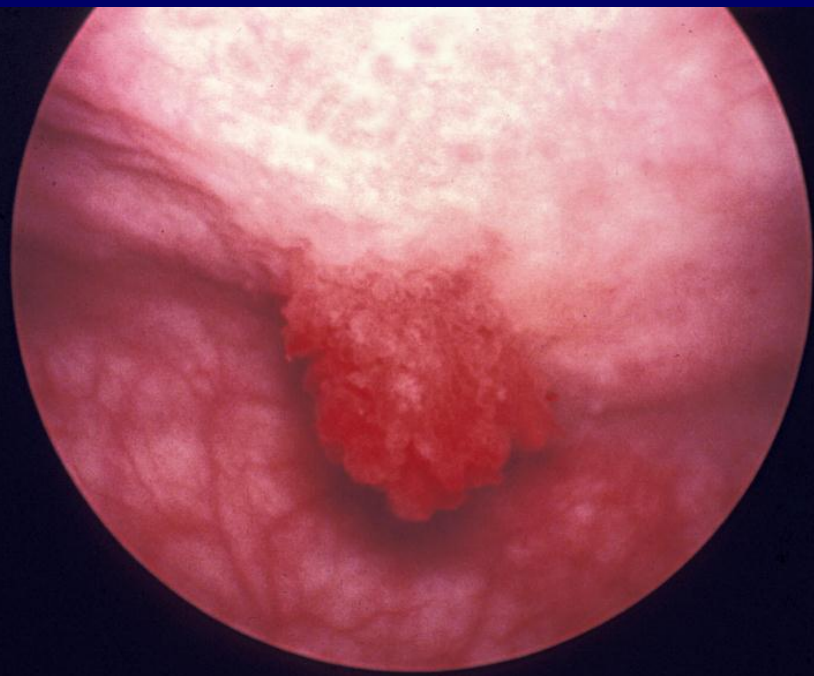
Invasive
papillary carcinoma



Flat noninvasive
carcinoma

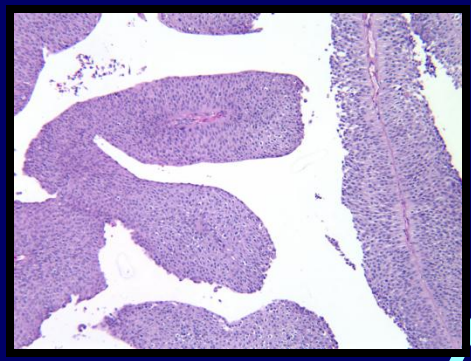


Flat invasive
carcinoma

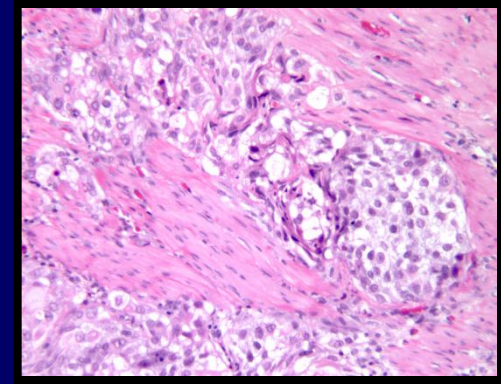


Historical Perspective of “staging” Bladder Ca

Discrepant Clinical VS Pathological



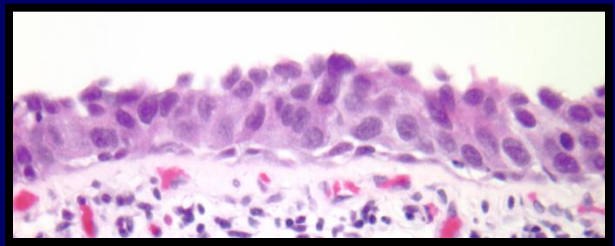
Non-invasive papillary Ca



Ca into muscularis propria

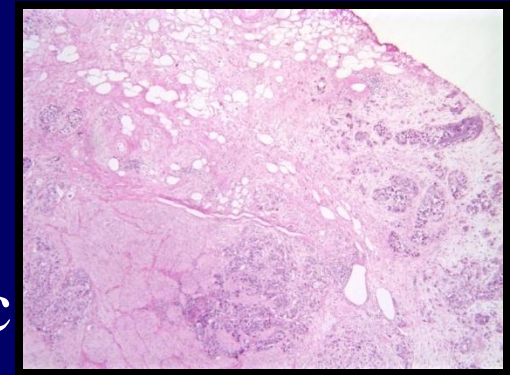
Superficial

Flat CIS

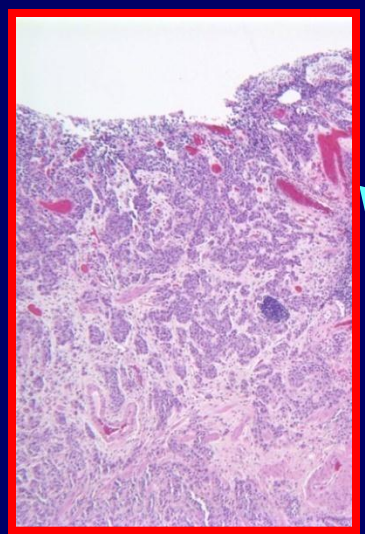


Ca invasive into lamina propria, muscularis mucosa & sub mucosa

Invasive



Ca into pericycstic fat



15-YEAR FOLLOW UP OF “SUPERFICIAL” BLADDER CA

Category	Progression free survival	Disease specific surv.
pTa – LG	95%	100%
pTa – HG	61%	74%
pT1	44%	62%

Herr HW, J Urol 163:60, 2000

1973 WHO GRADING CRITERIA

Mostofi, 1973

Grade 1	Tumors with the least degree of cellular anaplasia compatible with a diagnosis of malignancy
Grade 2	Histologic features between grades 1 and 2
Grade 3	Tumors with the most severe degrees of cellular anaplasia

1973 WHO GRADING

Application by many pathologists

Grade 1	Tumors with the least degree of cellular anaplasia compatible with a diagnosis of malignancy
Grade 1-2	?
Grade 2	Histologic features between grades 1 and 2
Grade 2-3	?
Grade 3	Tumors with the most severe degrees of cellular anaplasia

WHO/ISUP 2004 CLASSIFICATION

- **NORMAL**
- **HYPERPLASIA**
- **FLAT LESIONS WITH ATYPIA**
 - Reactive (inflammatory) atypia
 - Atypia of unknown significance
 - Dysplasia (low grade intraurothelial neoplasia)
 - Carcinoma in situ (high grade intraurothelial neoplasia)
- **PAPILLARY NEOPLASMS**
 - Papilloma
 - Inverted papilloma
 - Papillary neoplasm of low malignant potential
 - Papillary carcinoma, low grade
 - Papillary carcinoma, high grade
- **INVASIVE NEOPLASMS**

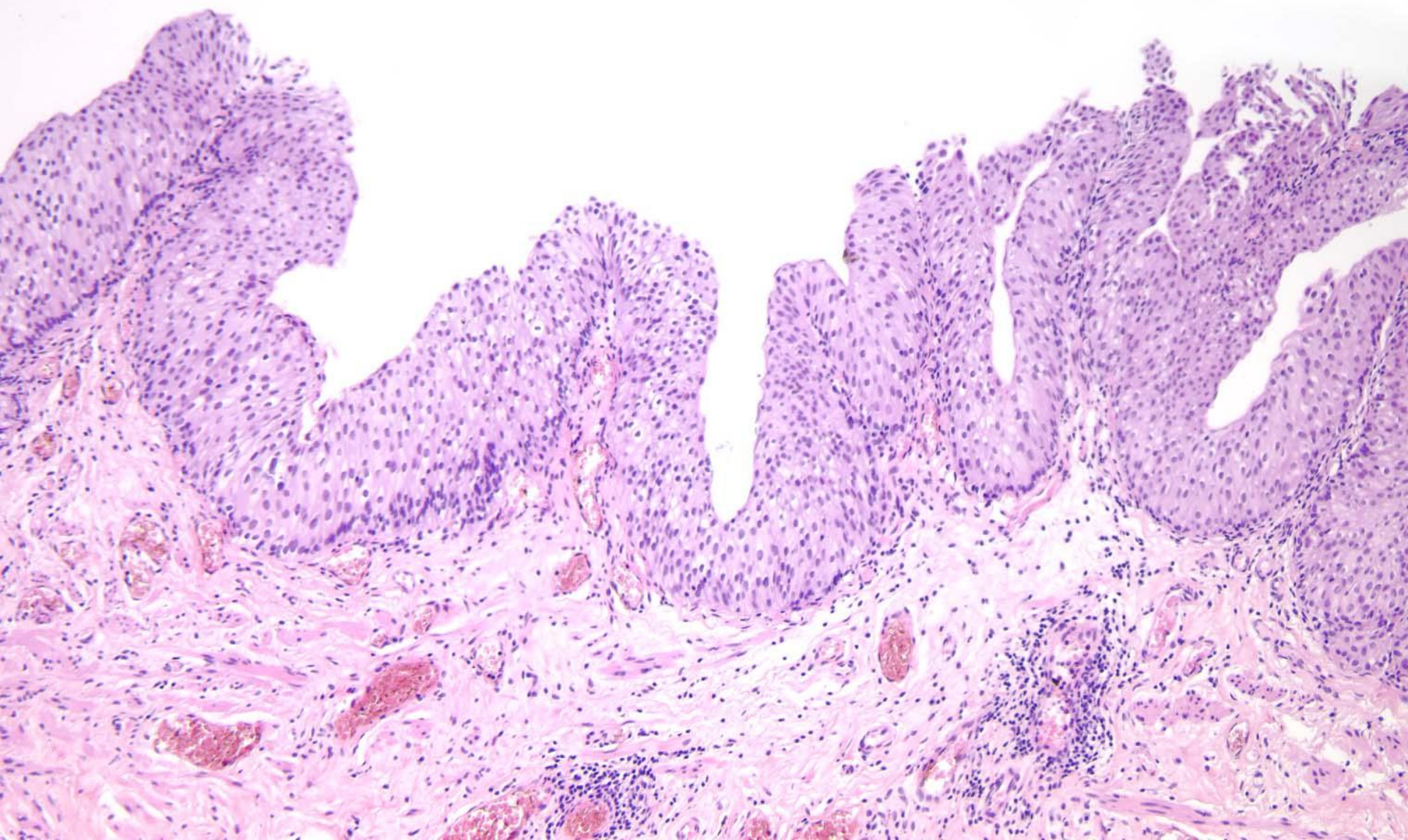
WHO 2004 CLASSIFICATION HYPERPLASIA WITH PSEUDOPAPILLARY ARCHITECTURE

HISTOLOGY

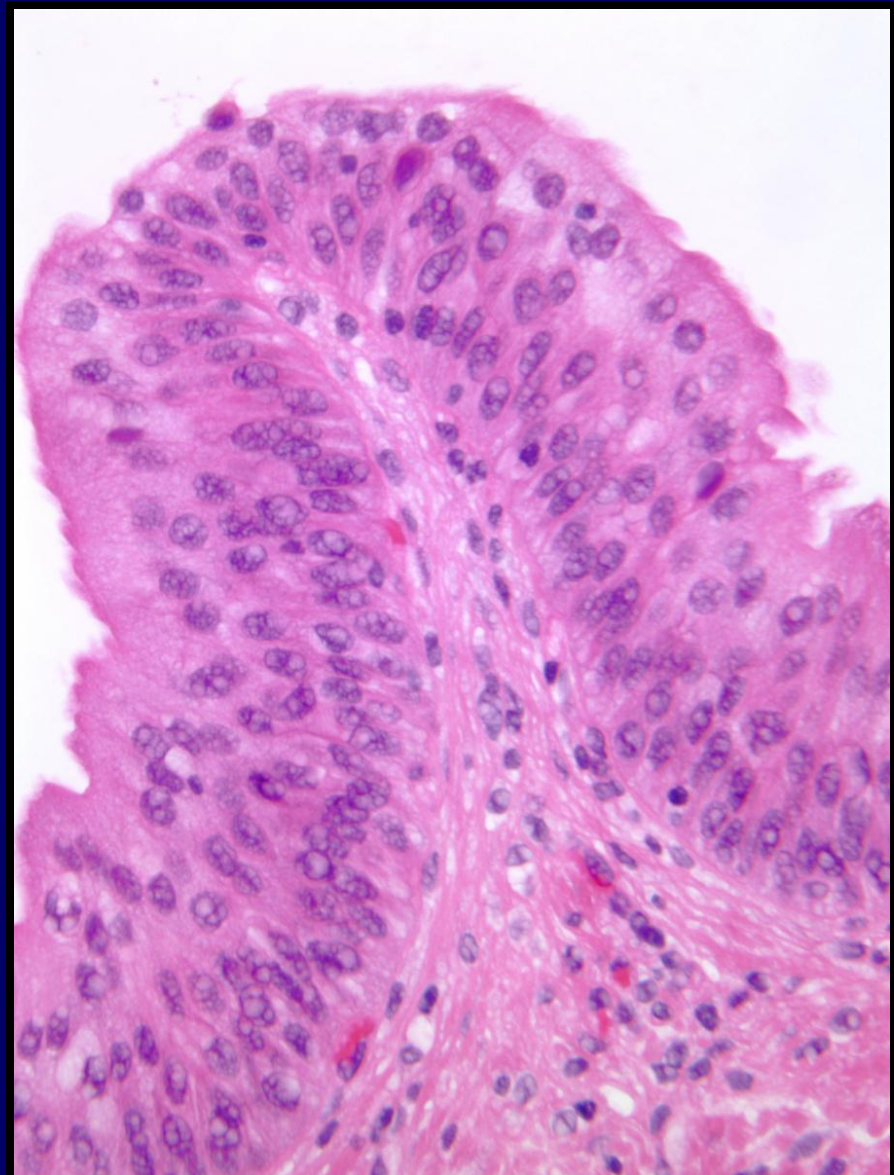
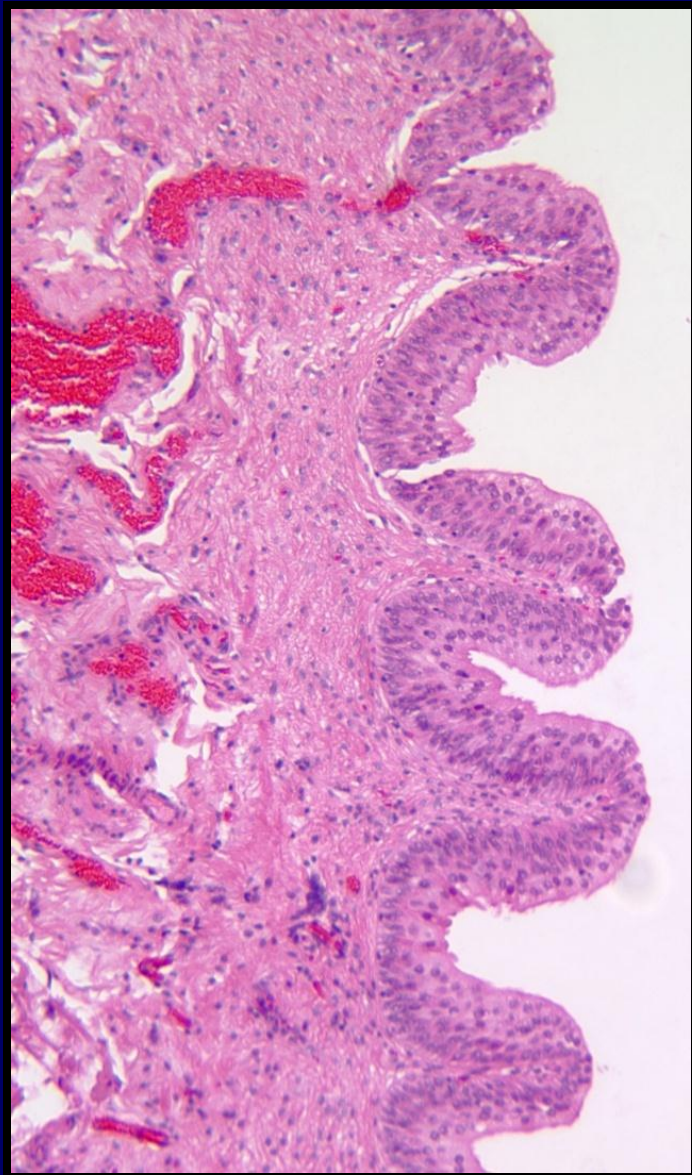
- **Slight tenting or undulating pattern of urothelium**
- **May see dilated capillaries at base but well developed vascular cores absent**
- **Urothelium of varying thickness**
- **No significant cytologic atypia**

Papillary Urothelial Hyperplasia

- **Tented or undulated thickened urothelium.**
- **Base with dilated capillaries, yet no discrete papillary fronds.**
- **Normal appearing urothelium.**



“PAPILLARY HYPERPLASIA”

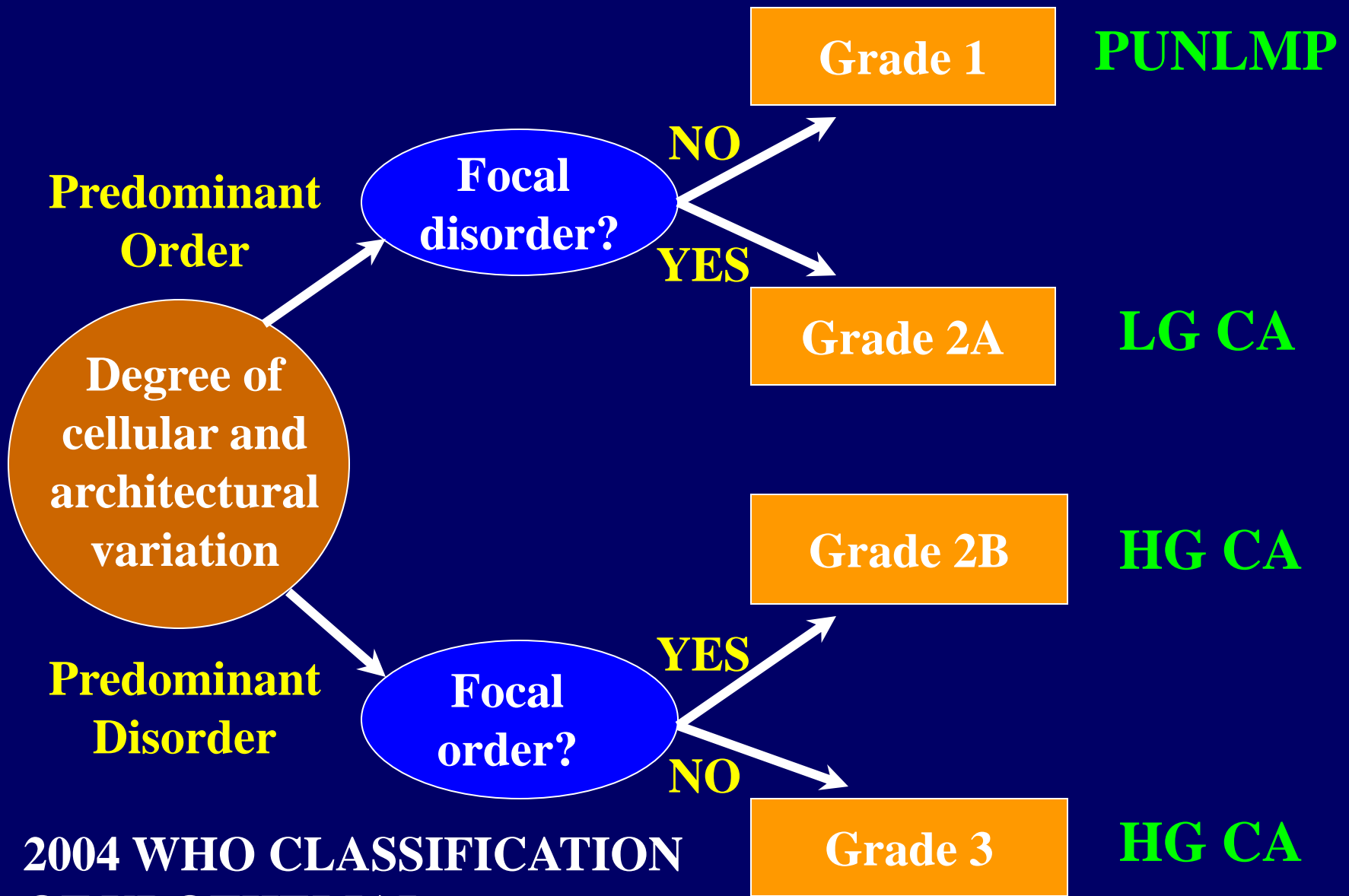


WHO 2004 CLASSIFICATION PAPILLARY NEOPLASMS

- ❖ Papilloma
- ❖ Inverted papilloma
- ❖ Papillary neoplasm of low malignant potential
- ❖ Papillary carcinoma (low grade)
- ❖ Papillary carcinoma (high grade)

HISTOLOGIC FEATURES OF PAPILLARY UROTHELIAL LESIONS

	Papilloma	Papillary neoplasm of low malignant potential	Low-grade papillary carcinoma	High-grade papillary carcinoma
Architecture				
Papillae	Delicate.	Delicate. Occasionally fused.	Fused, branching, and delicate.	Fused, branching and delicate.
Organization of cells	Identical to normal.	Polarity identical to normal. Any thickness. Cohesive.	Predominantly ordered, yet minimal crowding and minimal loss of polarity. Any thickness. Cohesive.	Predominantly disordered with frequent loss of polarity. Any thickness. Often dyscohesive.
Cytology				
Nuclear size	Identical to normal.	May be uniformly enlarged.	Enlarged with variation in size.	Enlarged with variation in size.
Nuclear shape	Identical to normal.	Elongated, round-oval, uniform.	Round-oval. Slight variation in shape and contour.	Moderate-marked pleomorphism.
Nuclear chromatin	Fine.	Fine.	Mild variation within and between cells.	Moderate-marked variation both within and between cells with hyperchromasia.
Nucleoli	Absent.	Absent to inconspicuous.	Usually inconspicuous.	Multiple prominent nucleoli may be present.
Mitoses	Absent	Rare, basal.	Occasional, at any level.	Usually frequent, at any level. May be atypical
Umbrella cells	Uniformly present.	Present.	Usually present.	May be absent.

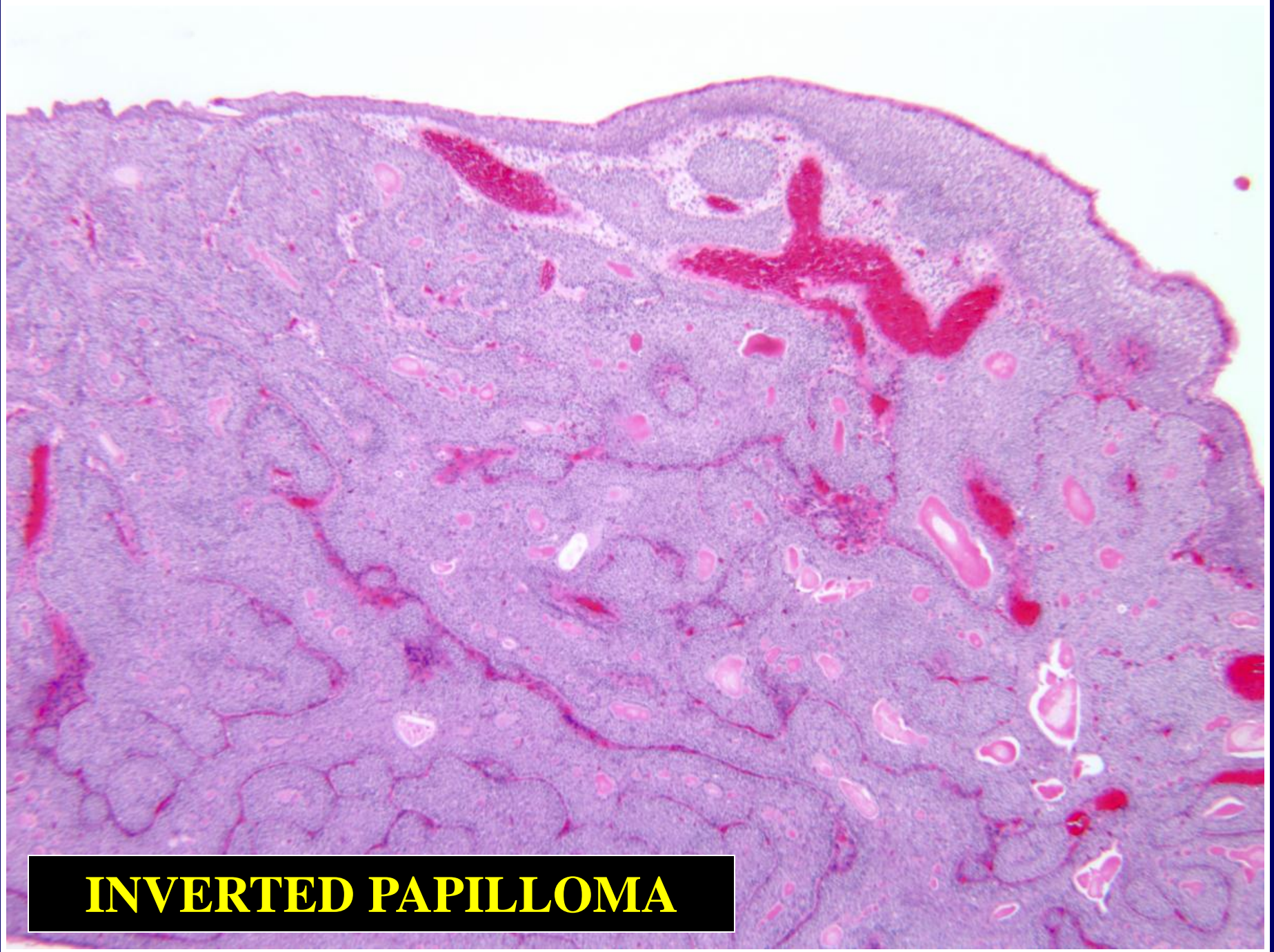


**2004 WHO CLASSIFICATION
OF UROTHELIAL
NEOPLASMS**

WHO 2004 CLASSIFICATION

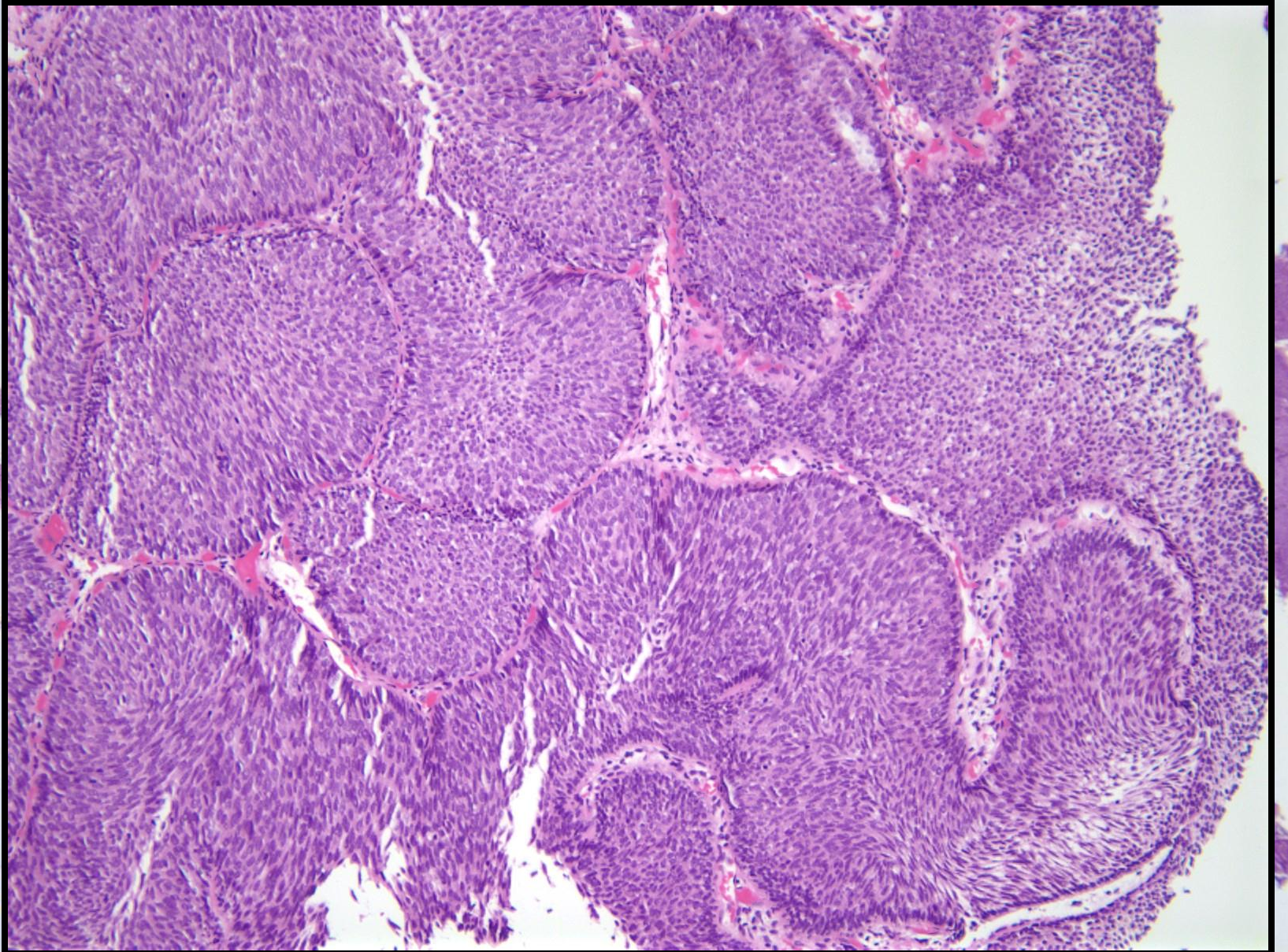
INVERTED PAPILLOMA

- **Younger men – trigone region**
- **Low recurrence rate**
- **Often polypoid architecture**
- **Covered by normal or attenuated urothelium with anastamosing cords arising from surface at multiple sites**



INVERTED PAPILOMA

INVERTED PAPILLOMA

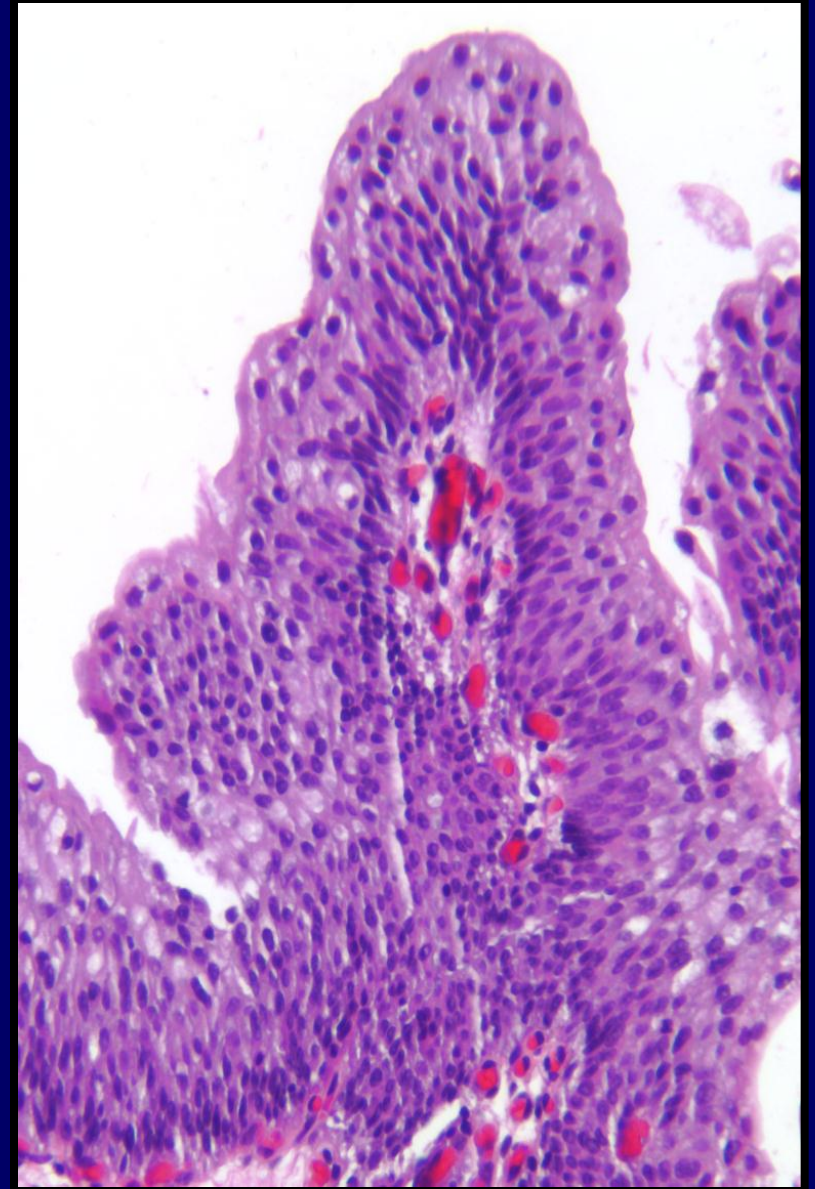
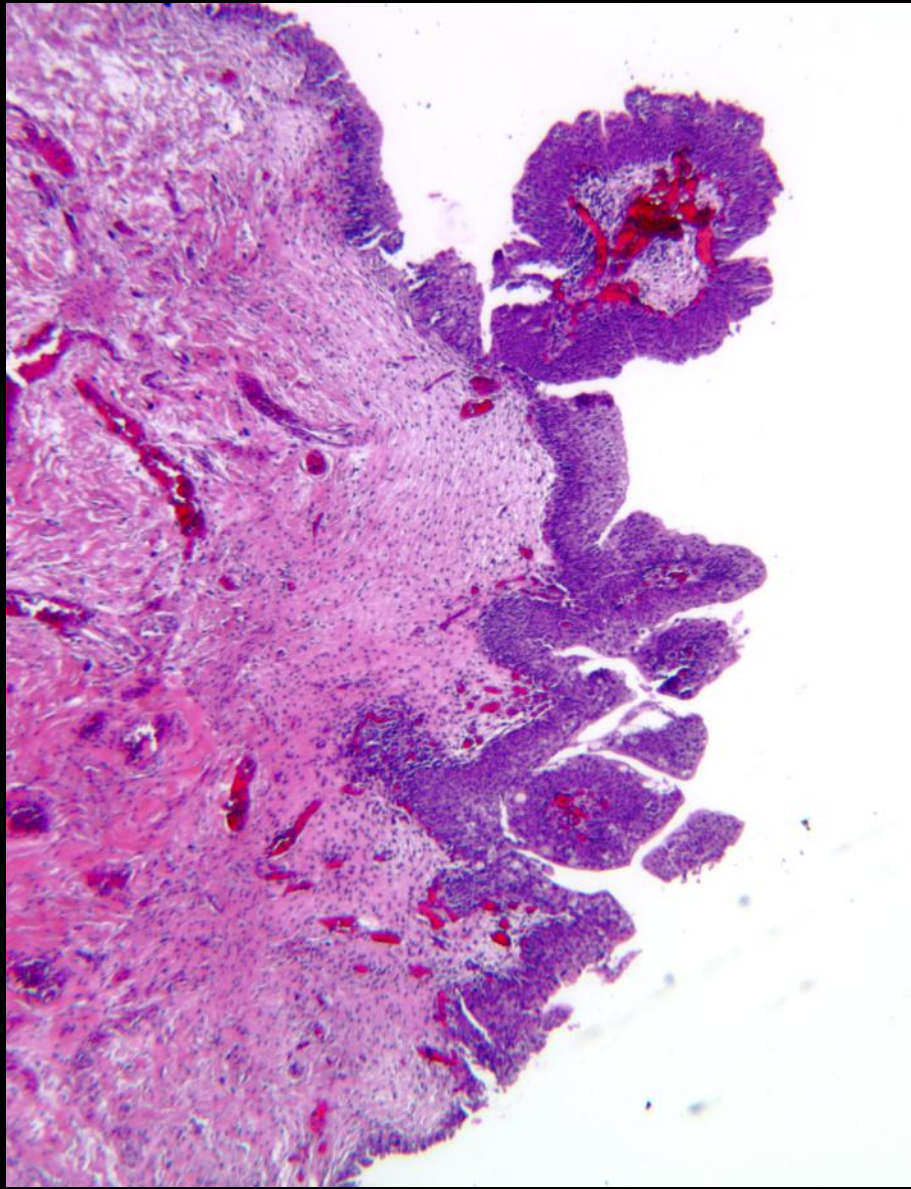


WHO 2004 CLASSIFICATION

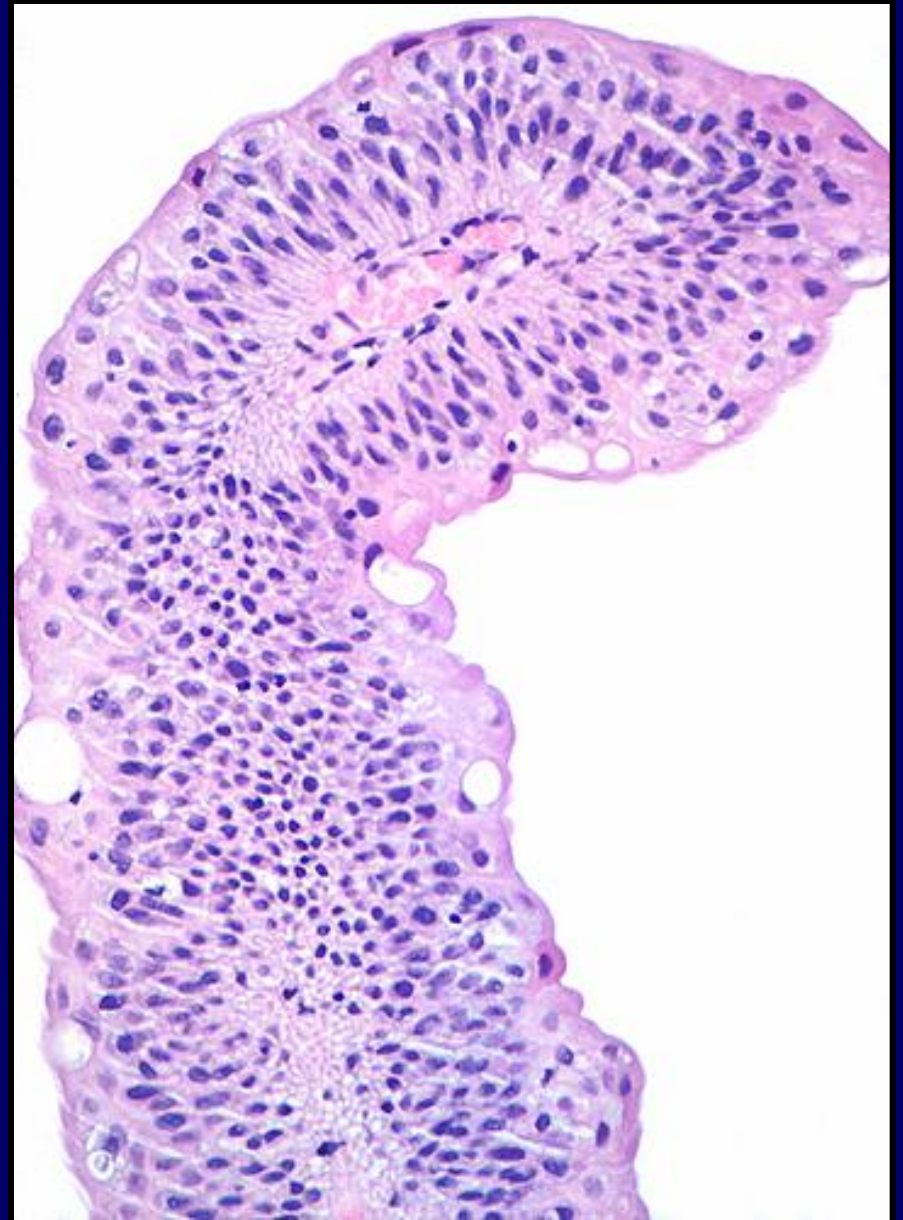
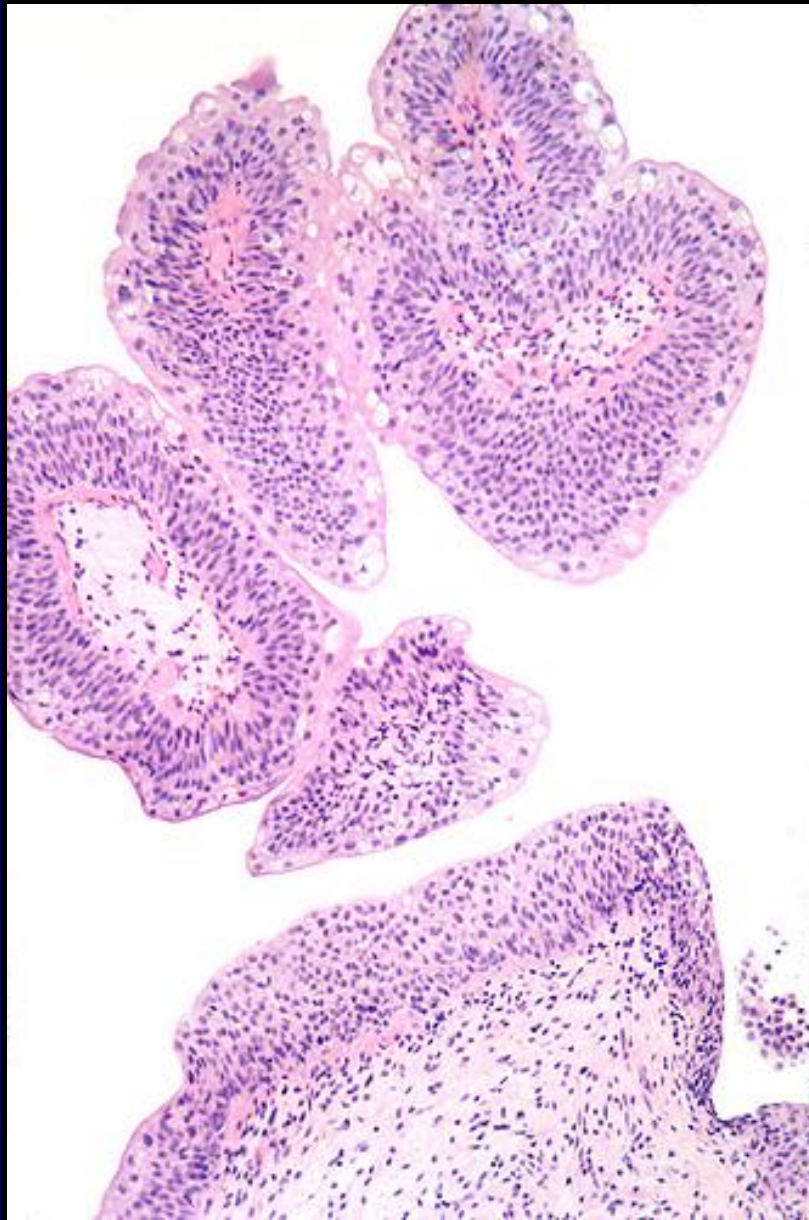
UROTHELIAL PAPILLOMA

- **Restrictive criteria of 1973 WHO and 1998 WHO/ISUP continue**
- **Generally applied to small isolated lesions in younger patients**
- **Few fine papillary fronds**
- **Covered by essentially normal appearing urothelium with no atypia**

PAPILLOMA



PAPILLOMA

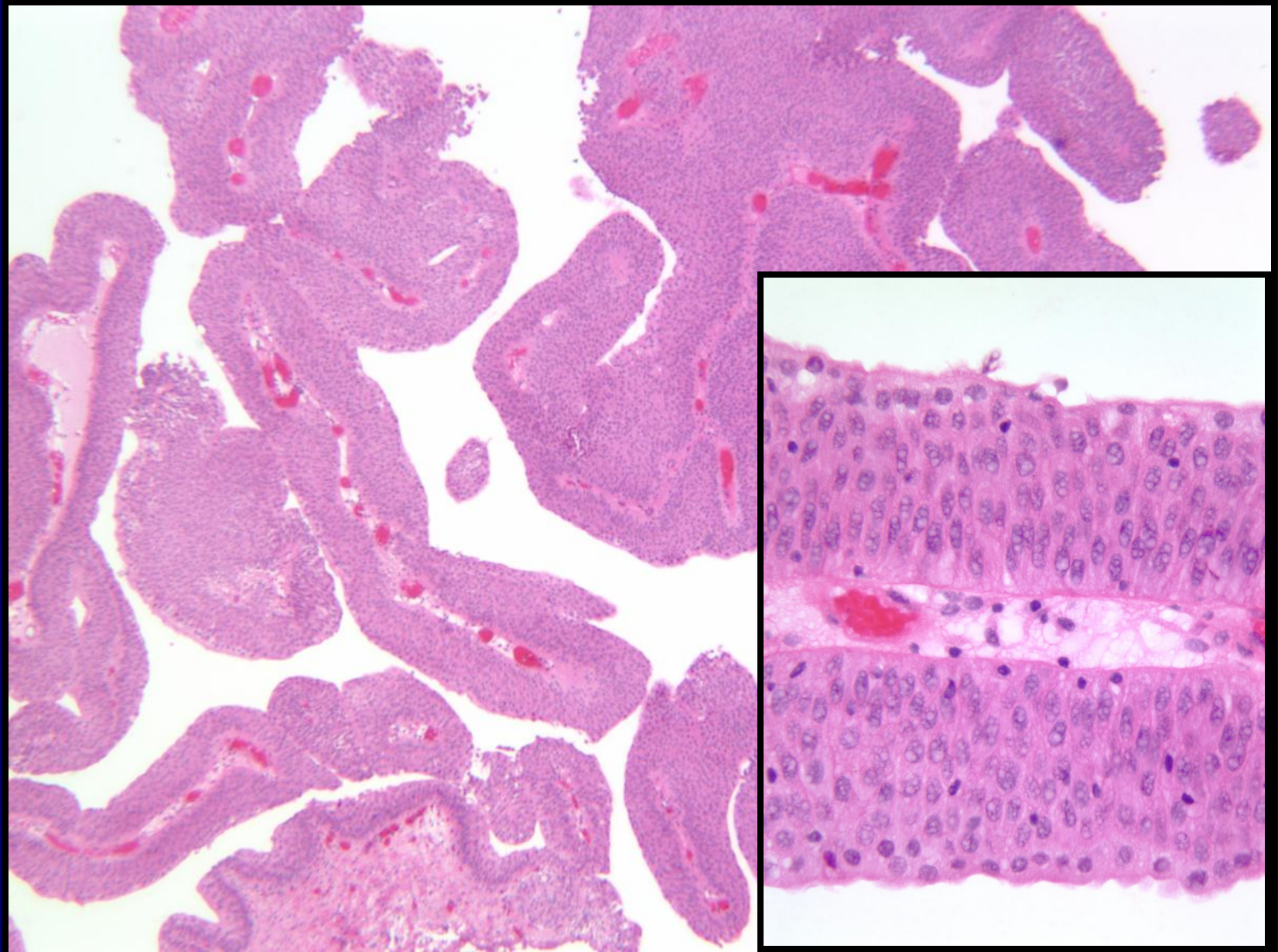


WHO 2004 CLASSIFICATION

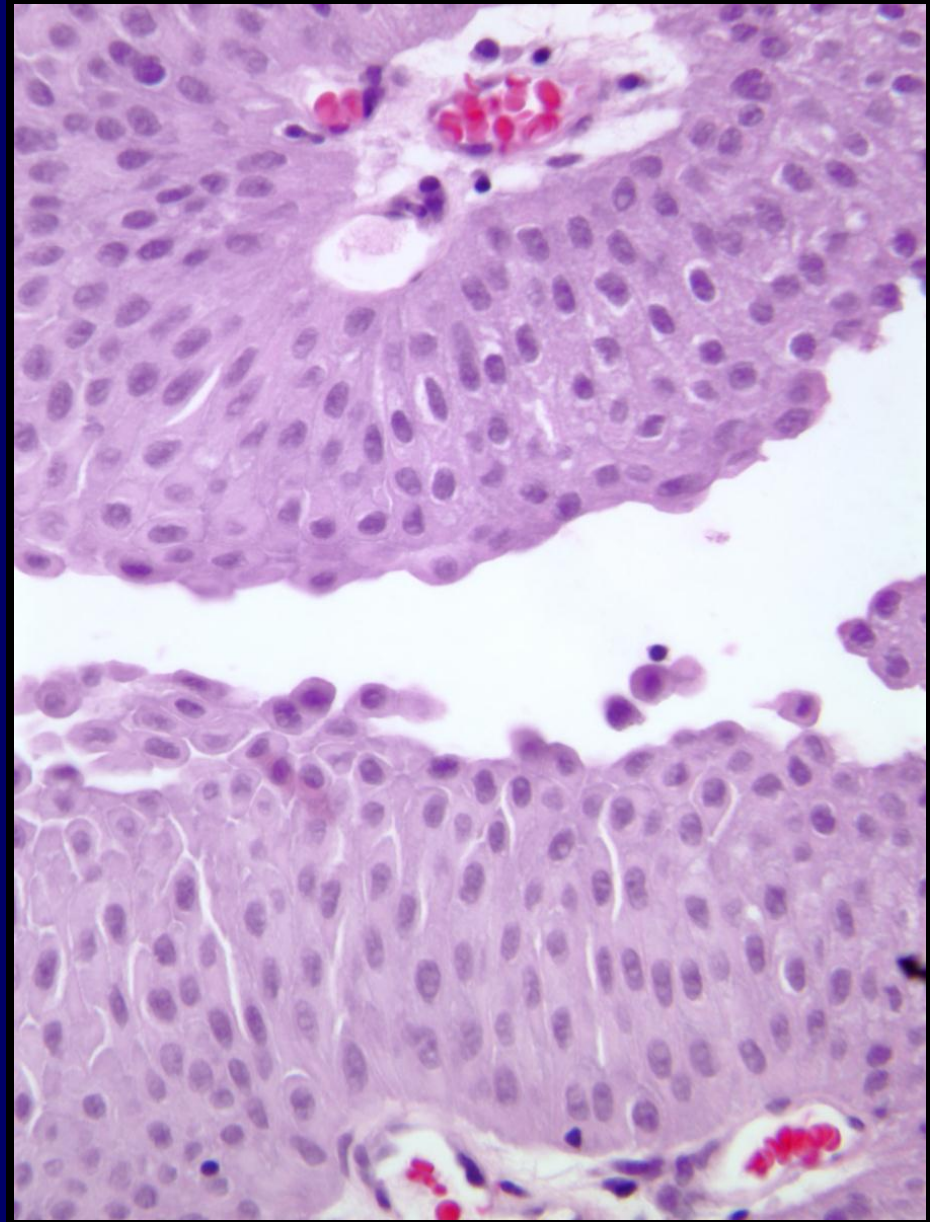
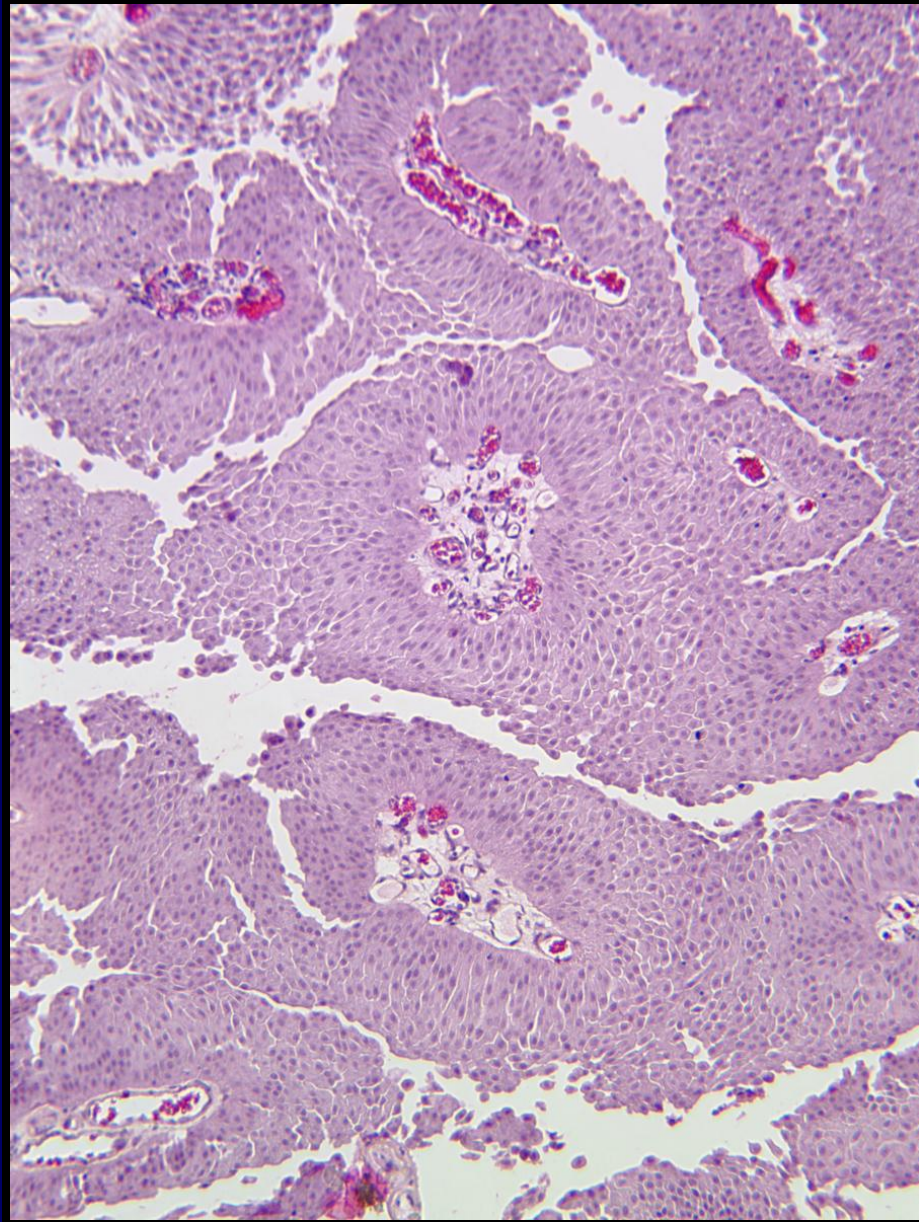
PAPILLARY UROTHELIAL NEOPLASM OF LOW MALIGNANT POTENTIAL

- **Compromise terminology to recognize neoplastic nature but avoid “carcinoma”**
- **Exophytic papillary growth**
- **Delicate papillae**
- **Covering urothelium with little to no architectural or cytologic abnormalities**

PUNLMP



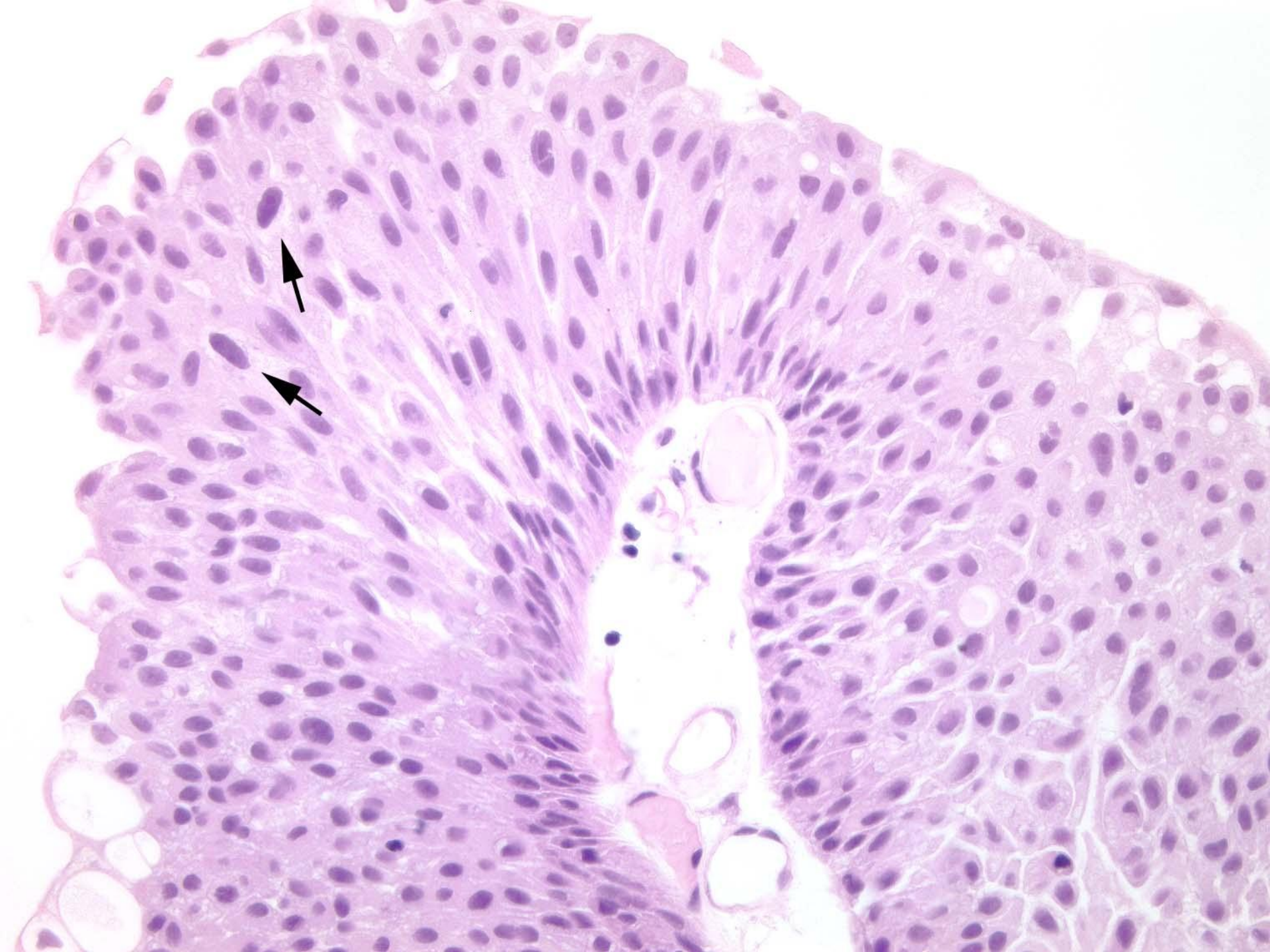
PUNLMP

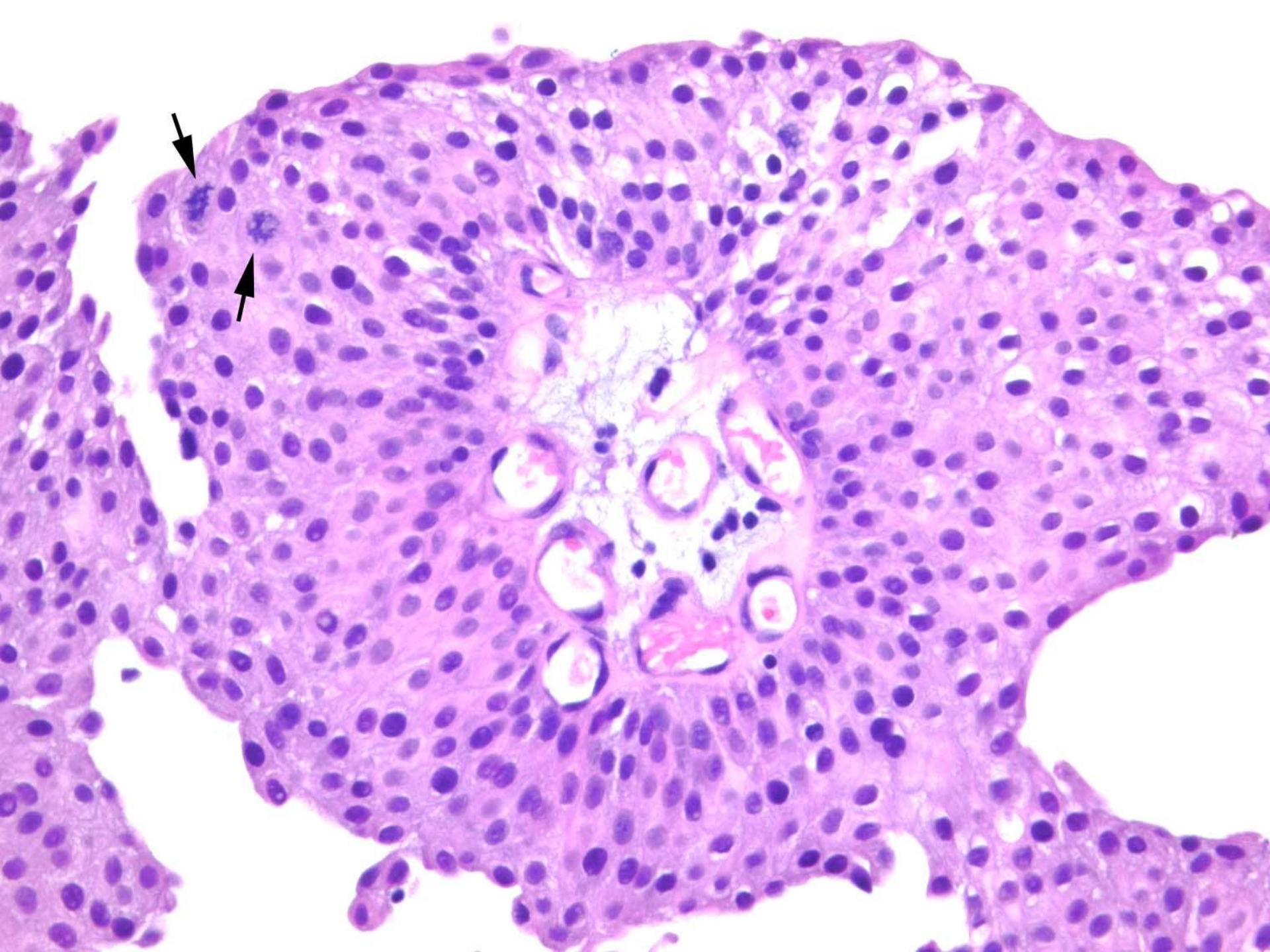


WHO 2004 CLASSIFICATION

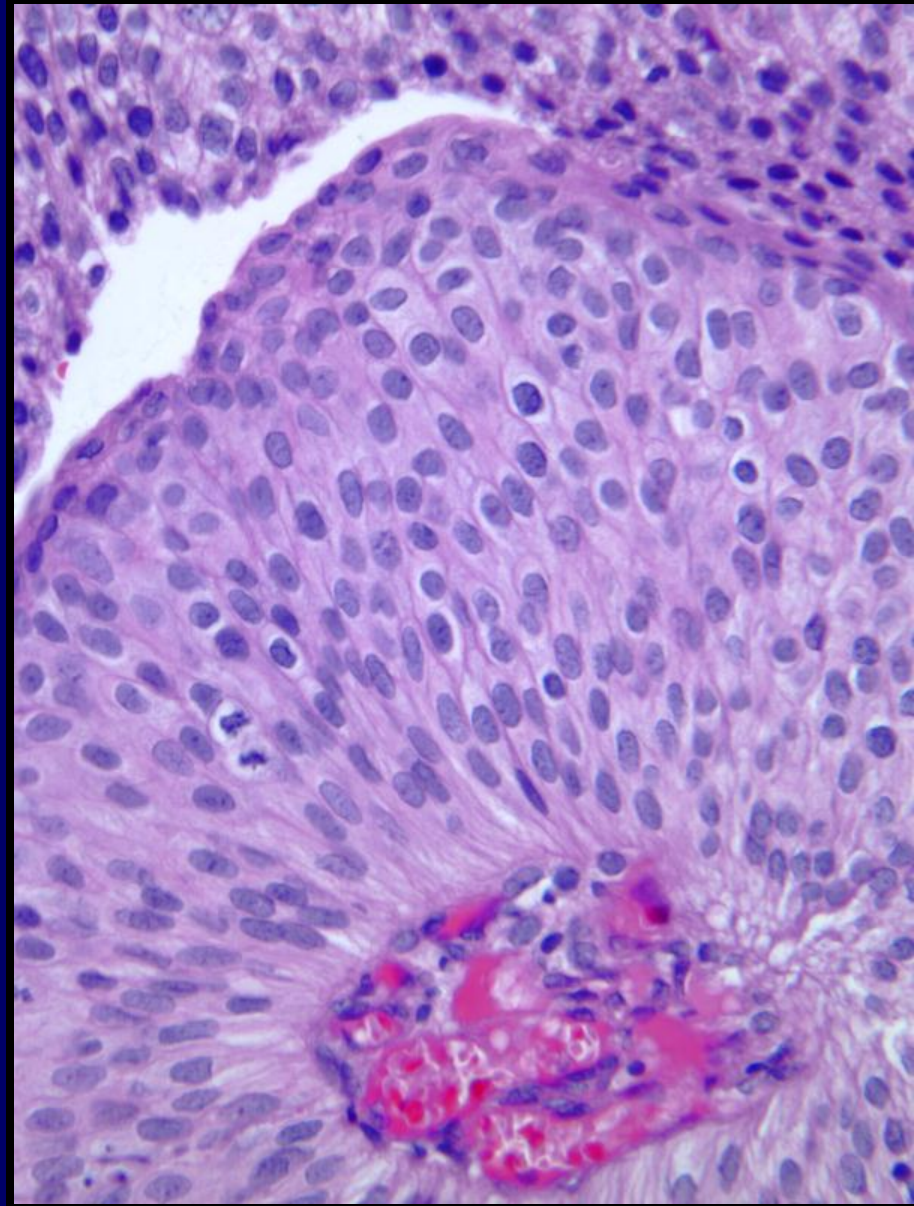
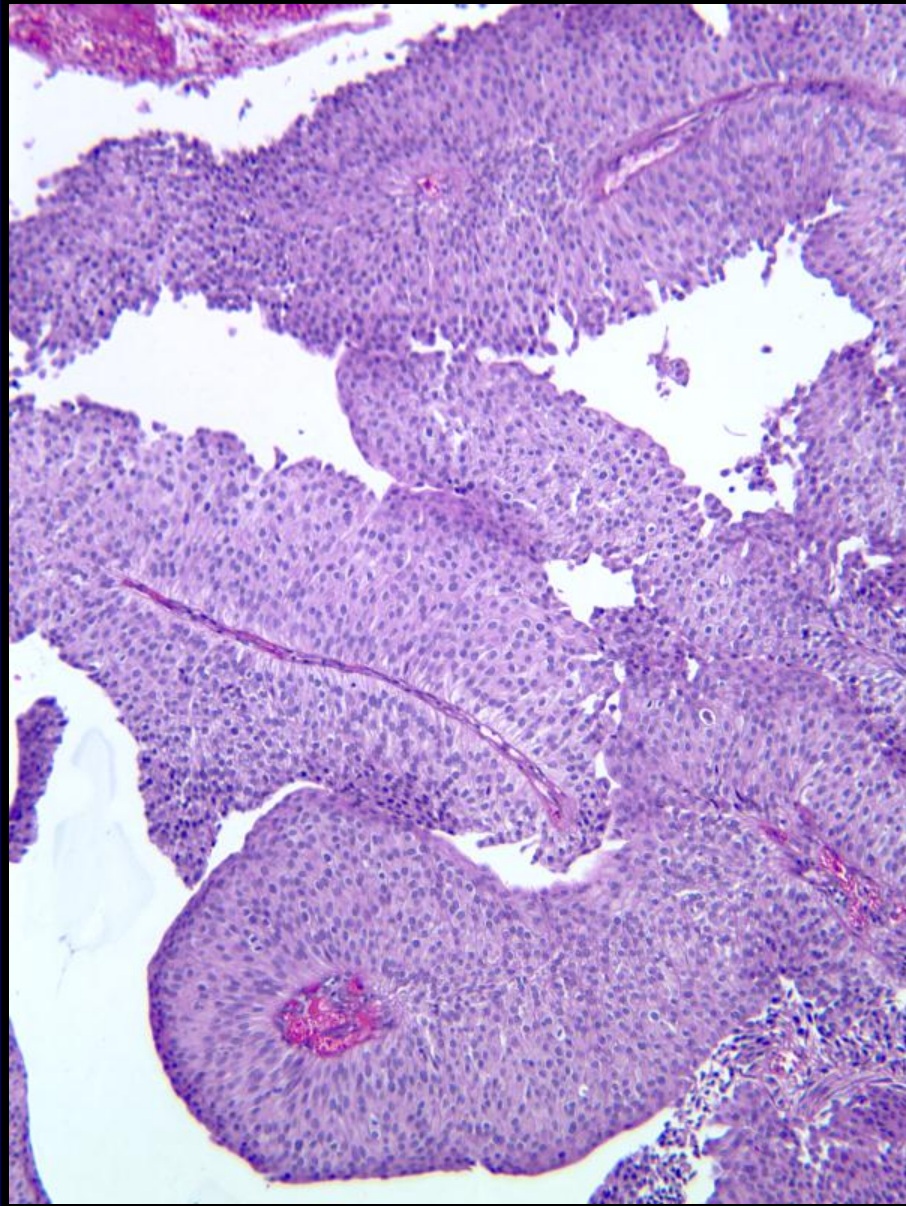
PAPILLARY CARCINOMA, LOW GRADE

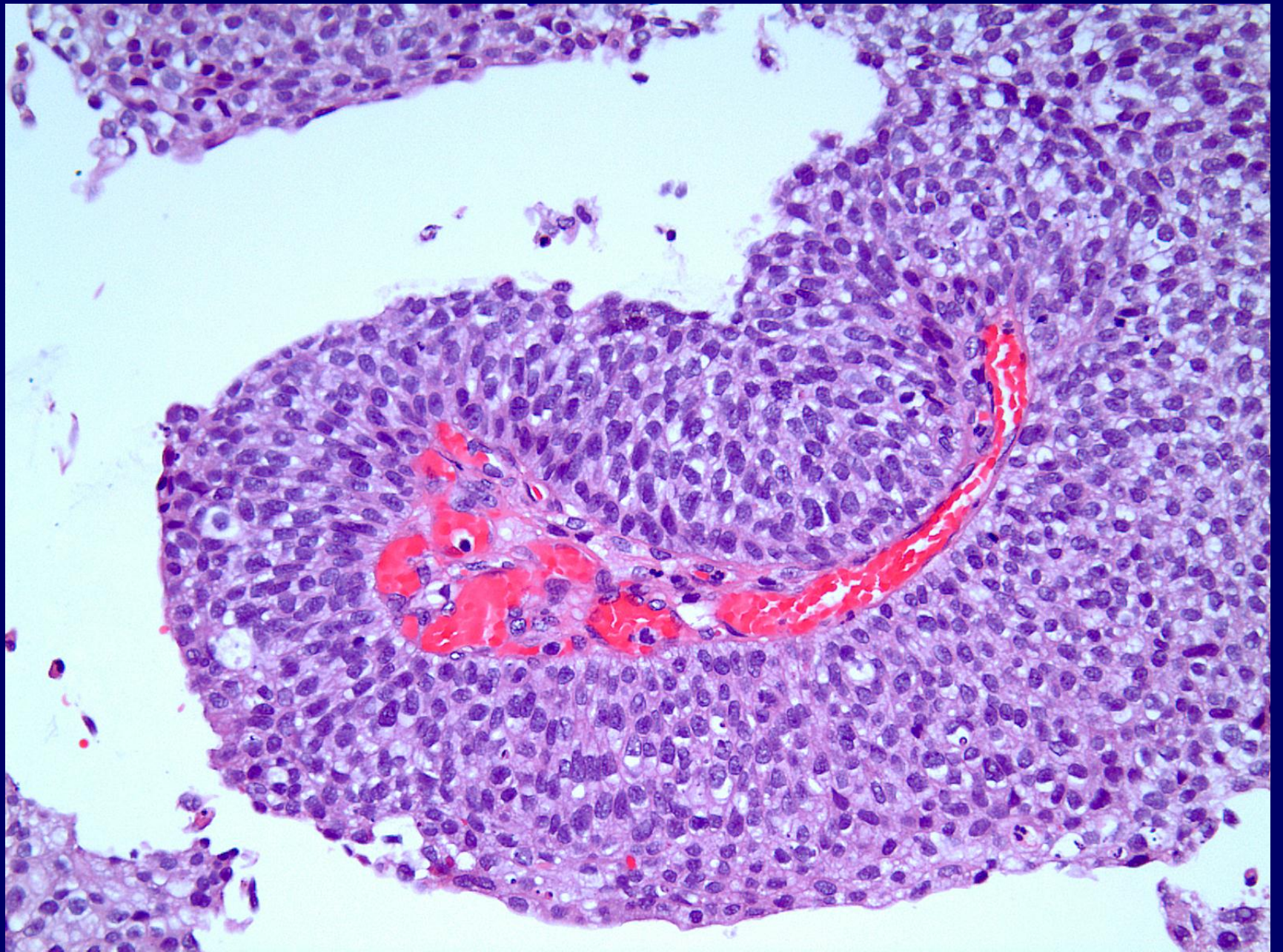
- **Largely made up lower half of WHO grade 2 (1973)**
- **Significant risk of recurrence but low risk of invasion**
- **Delicate, occasionally fused papillae**
- **Characterized by an overall orderly appearance but shows definite though mild cytologic abnormalities**





LOW GRADE

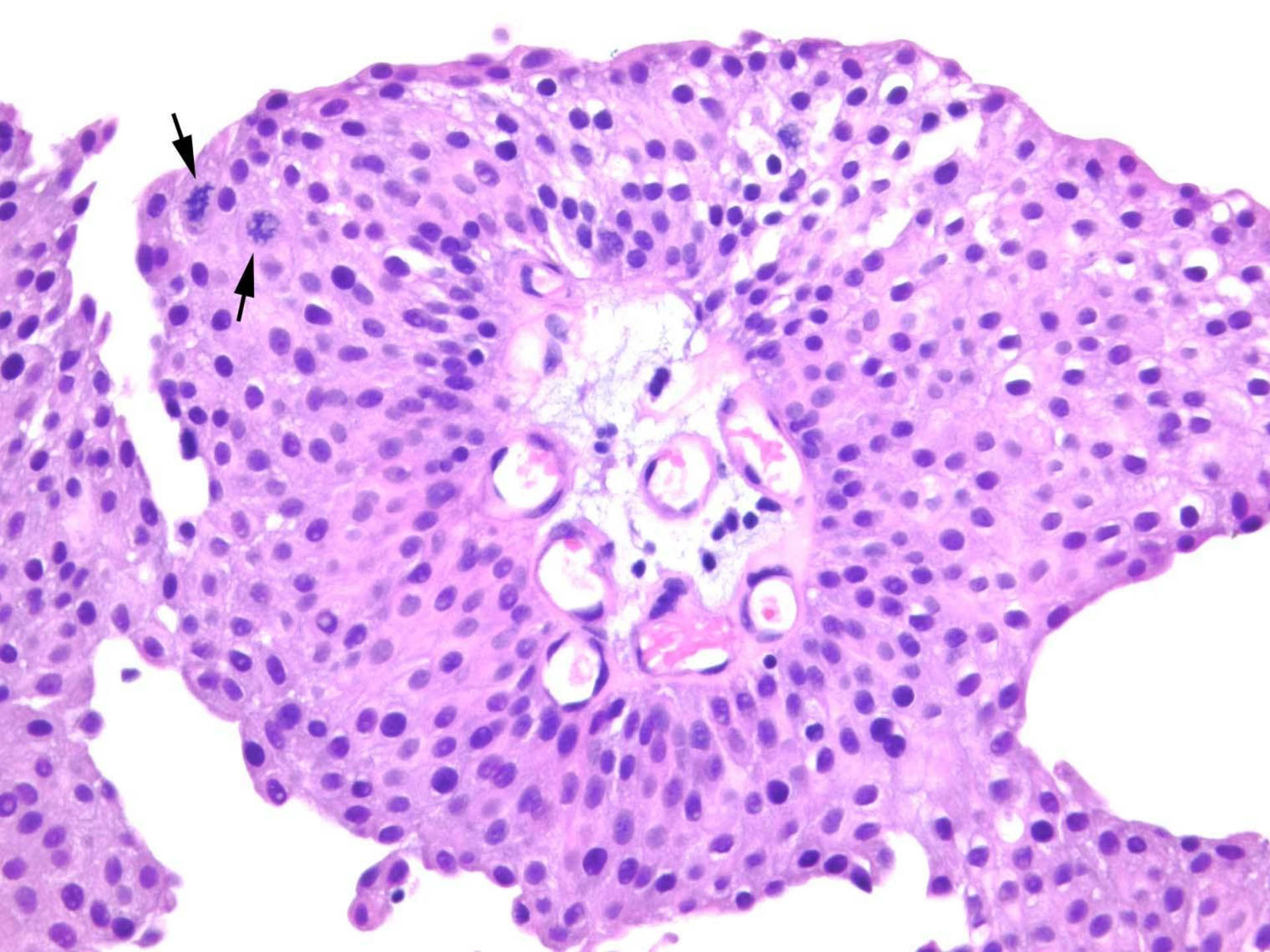


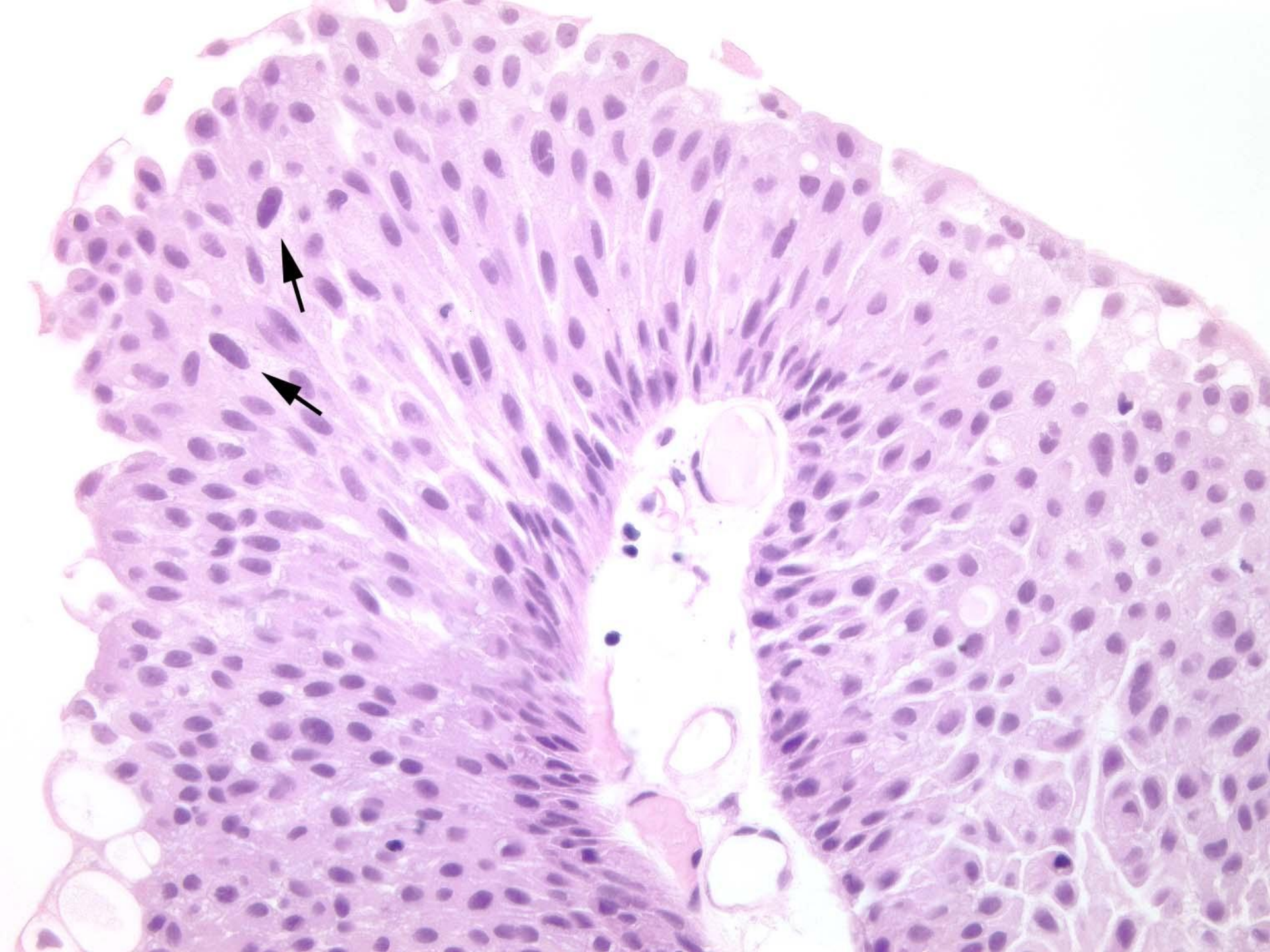


WHO 2004 CLASSIFICATION

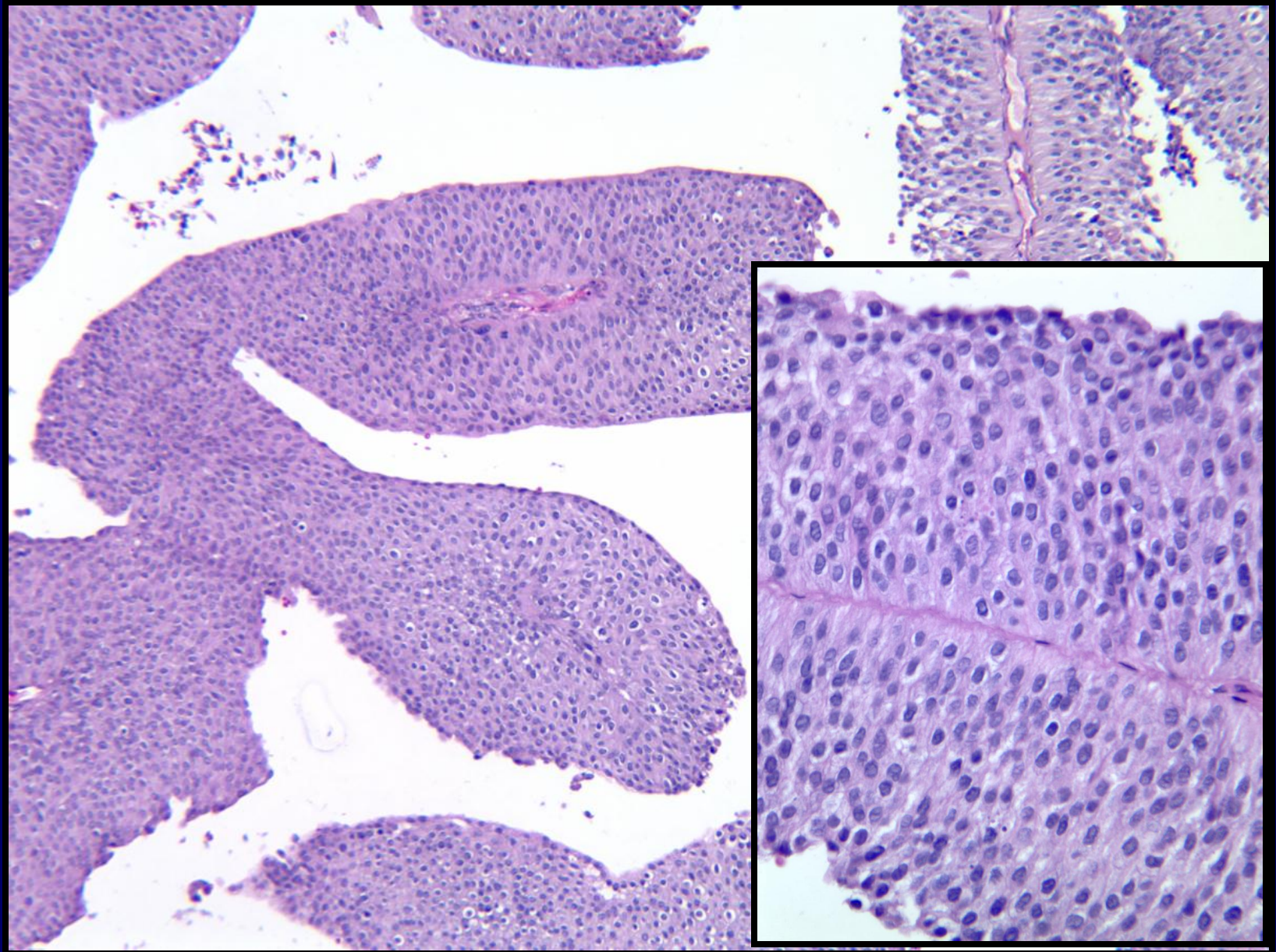
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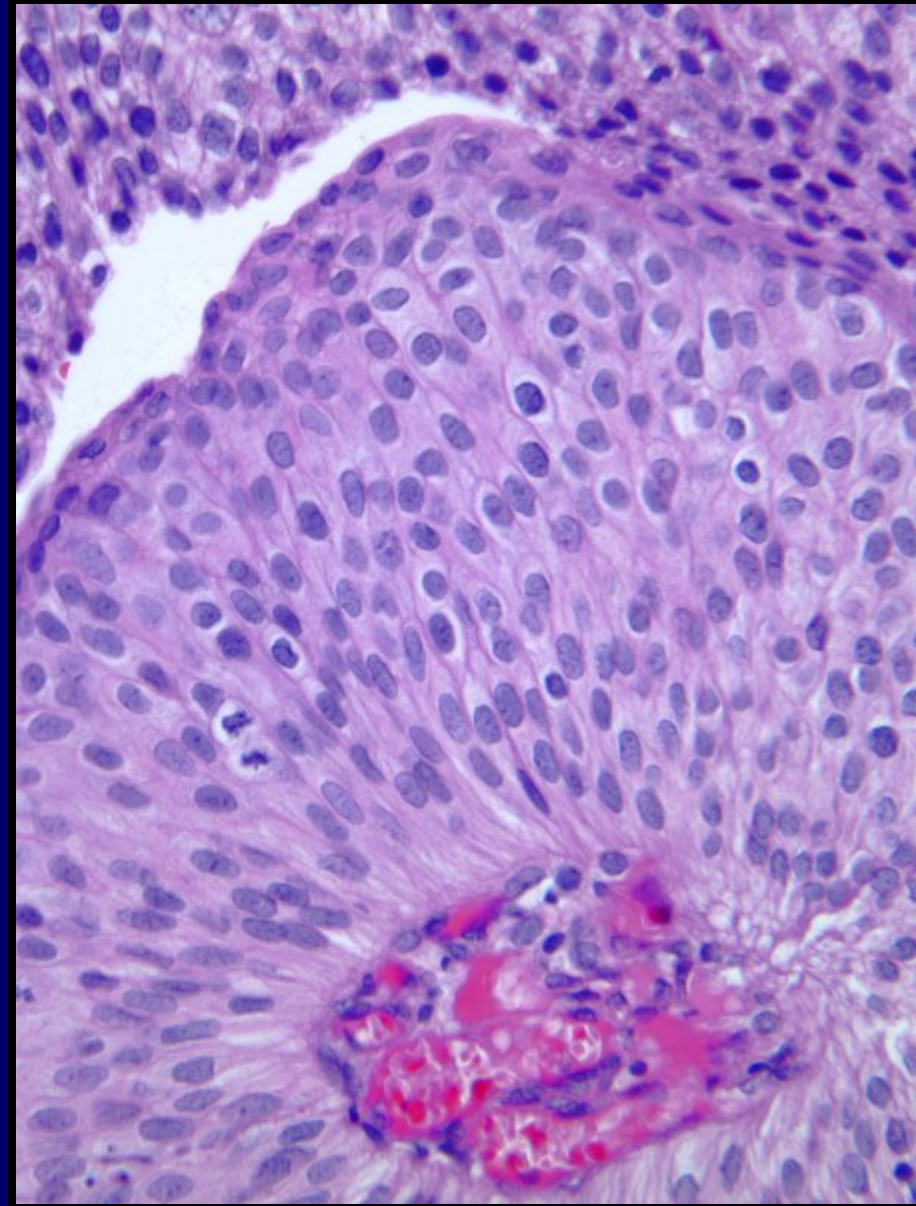
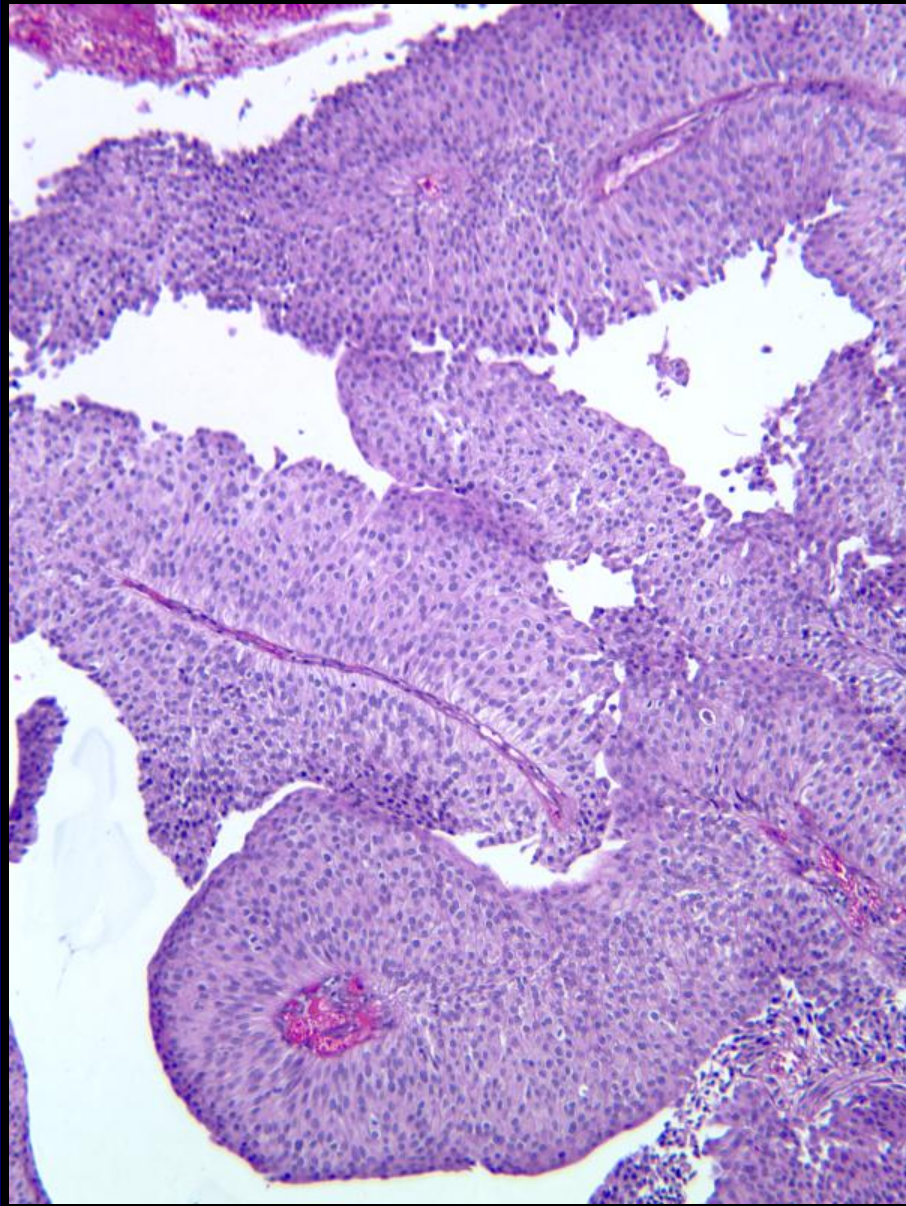




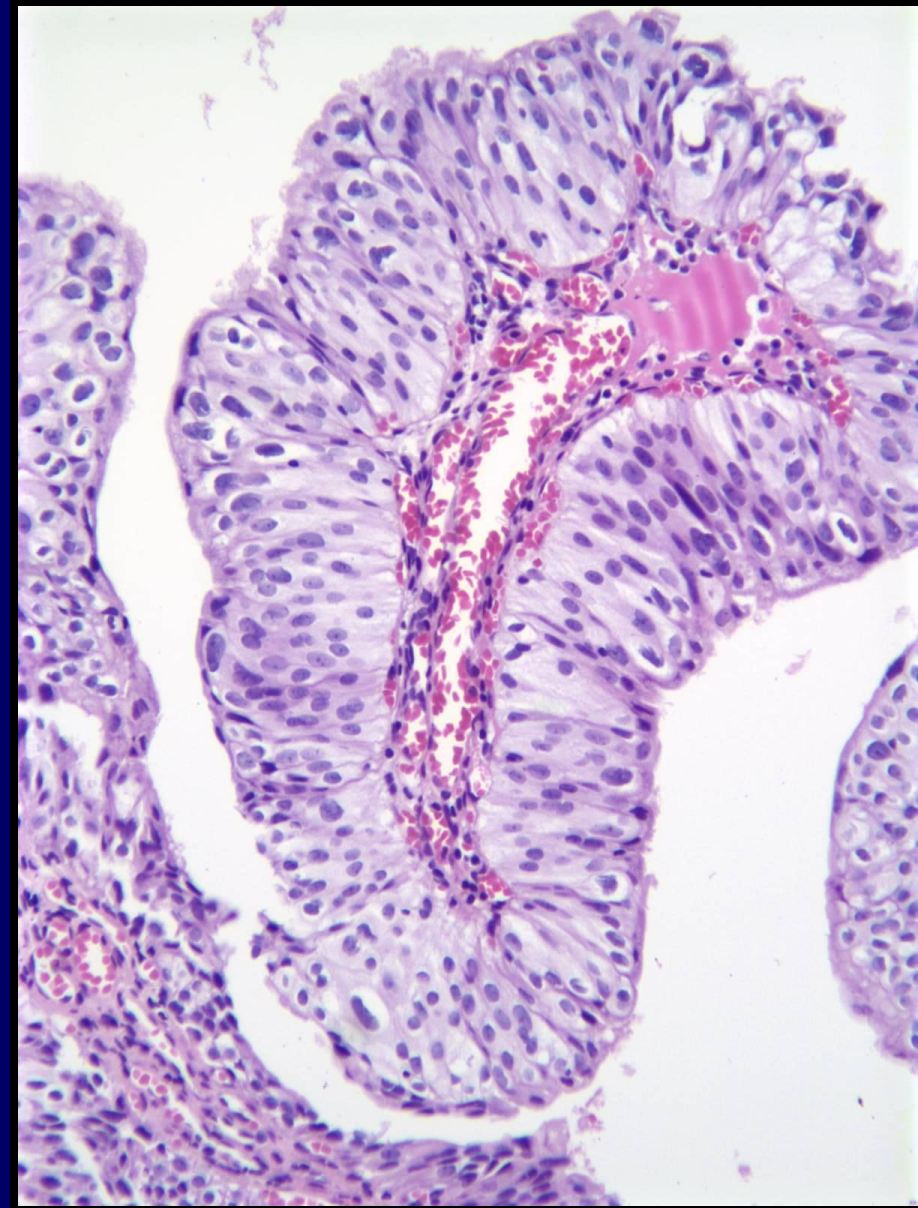
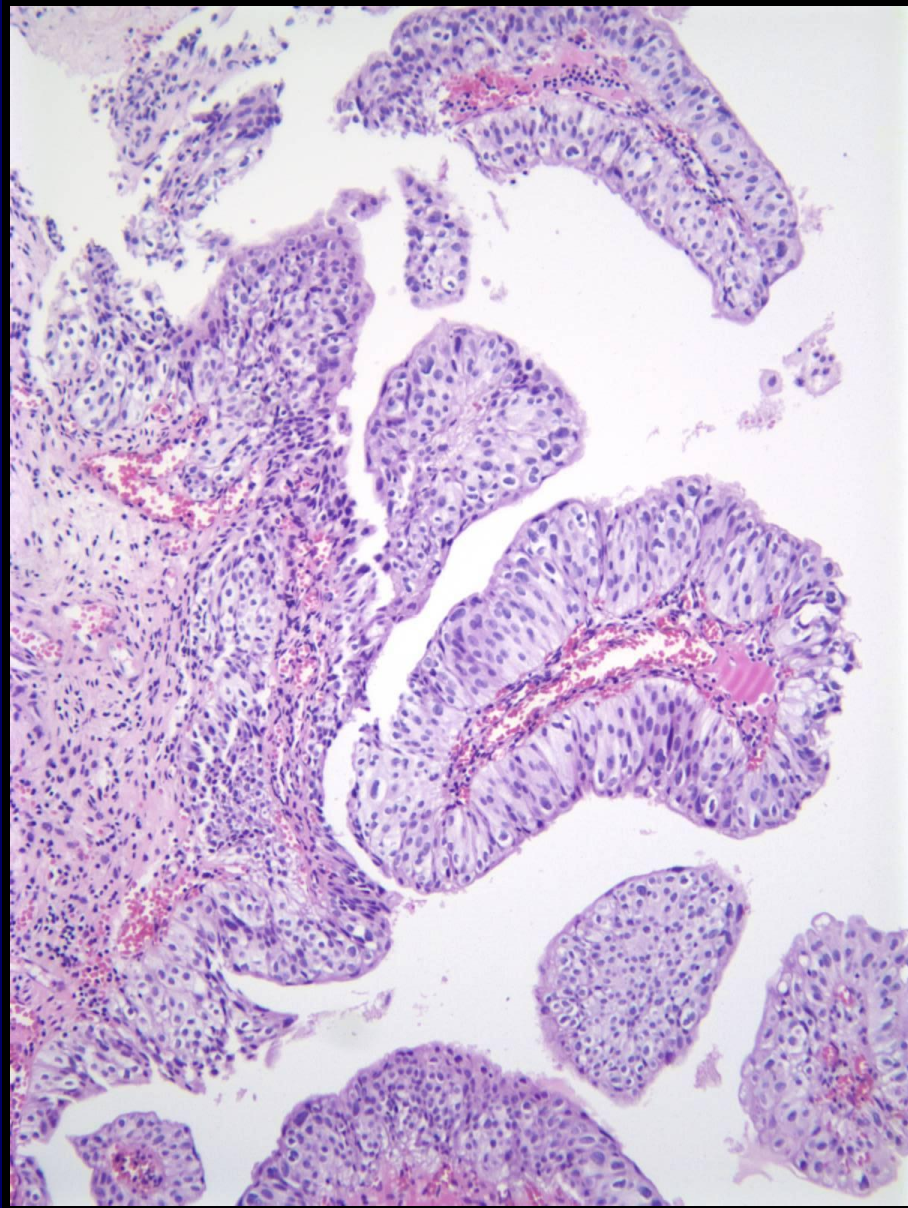
LOW GRADE

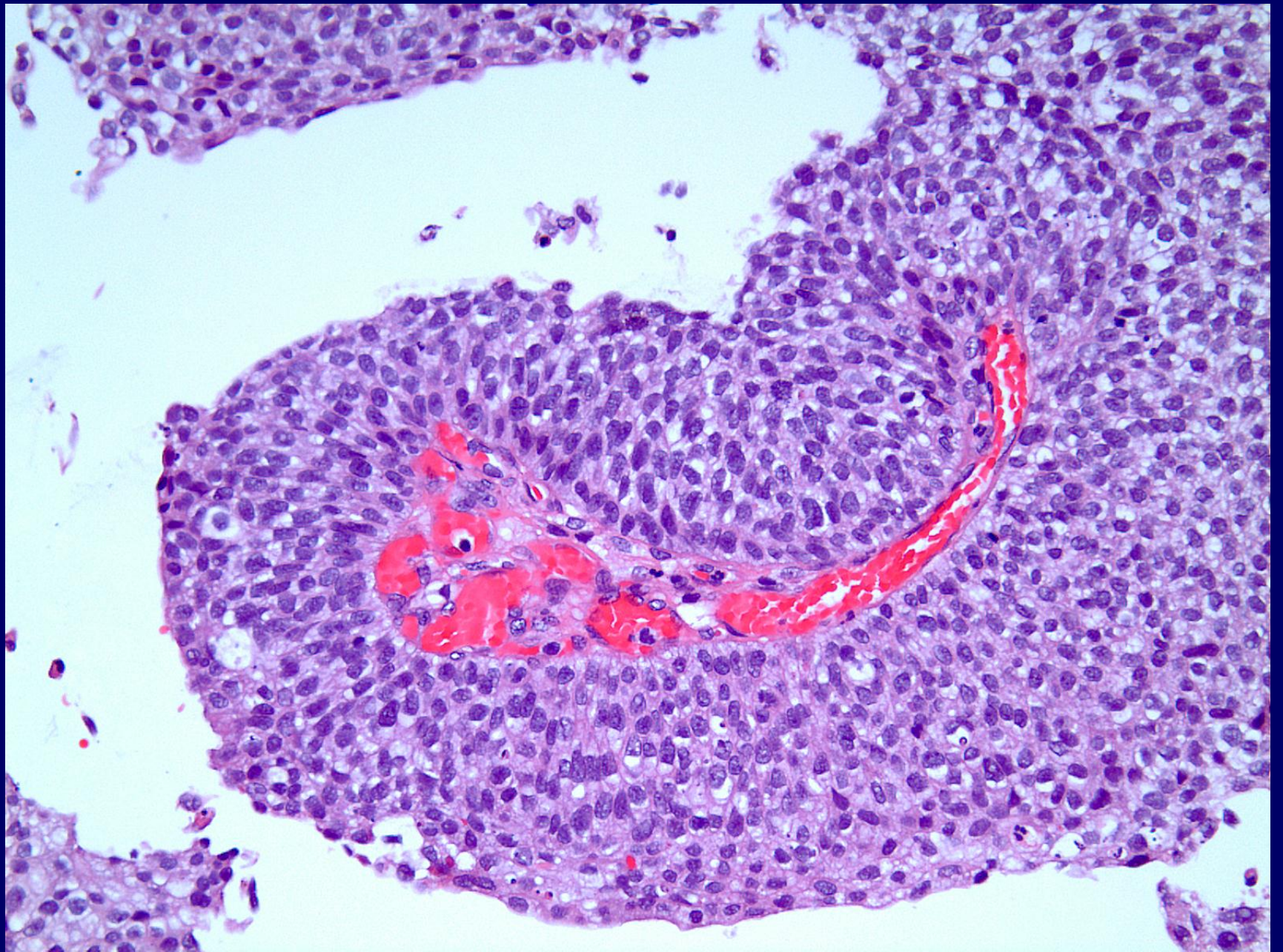


LOW GRADE



LOW GRADE



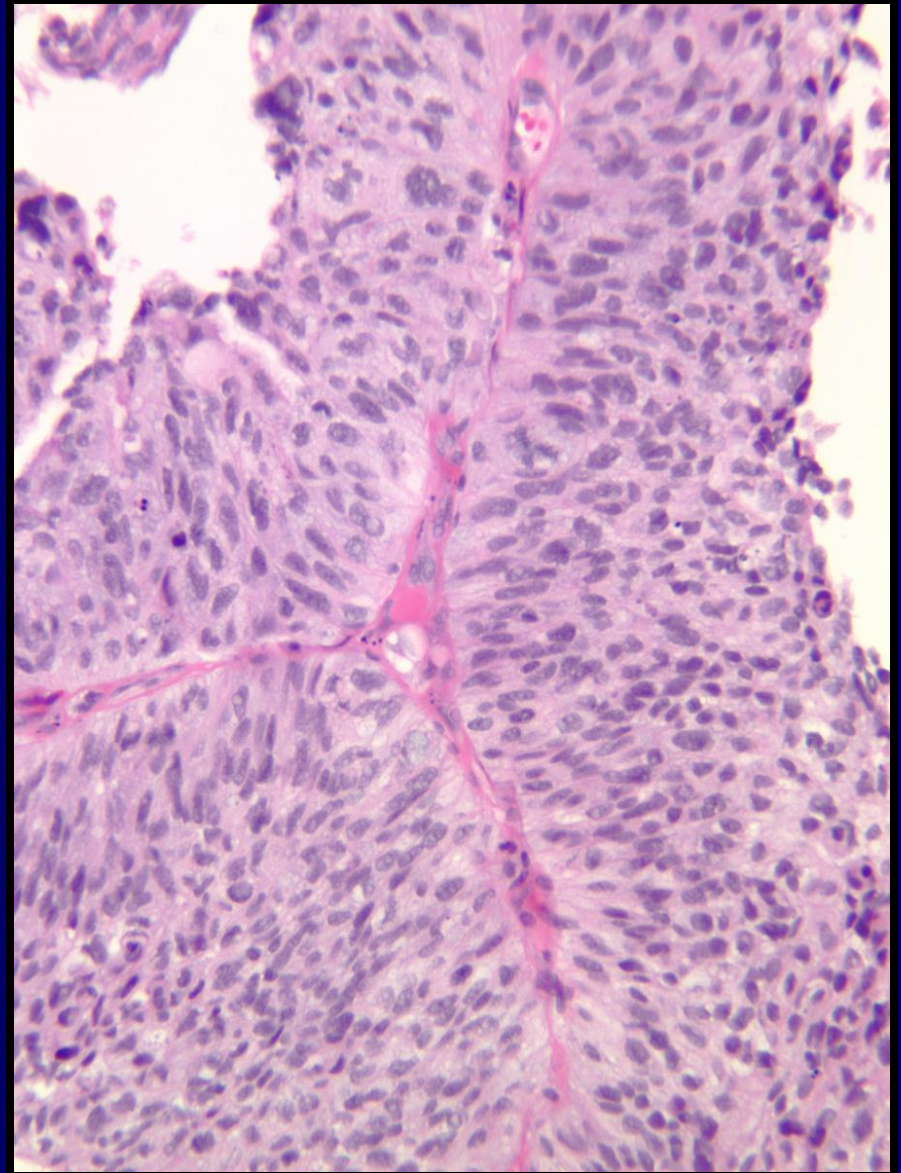
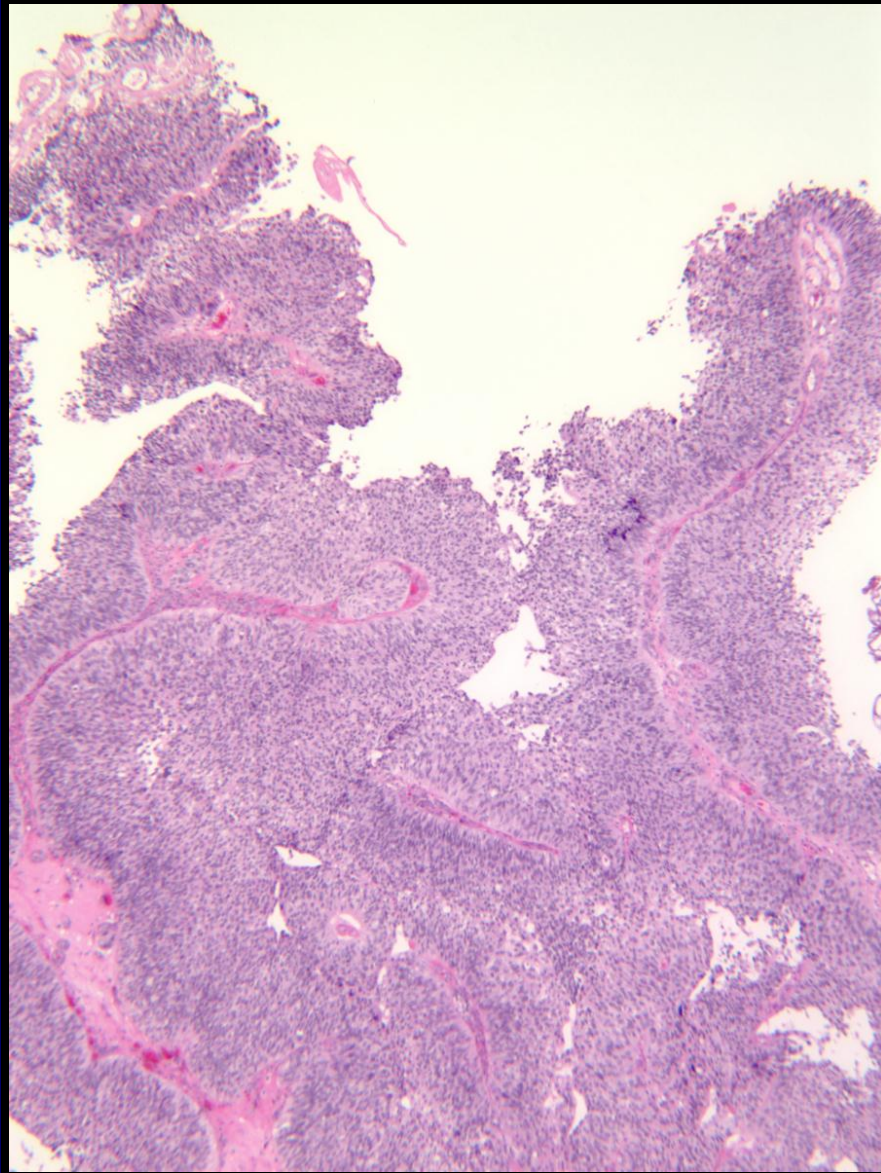


WHO 2004 CLASSIFICATION

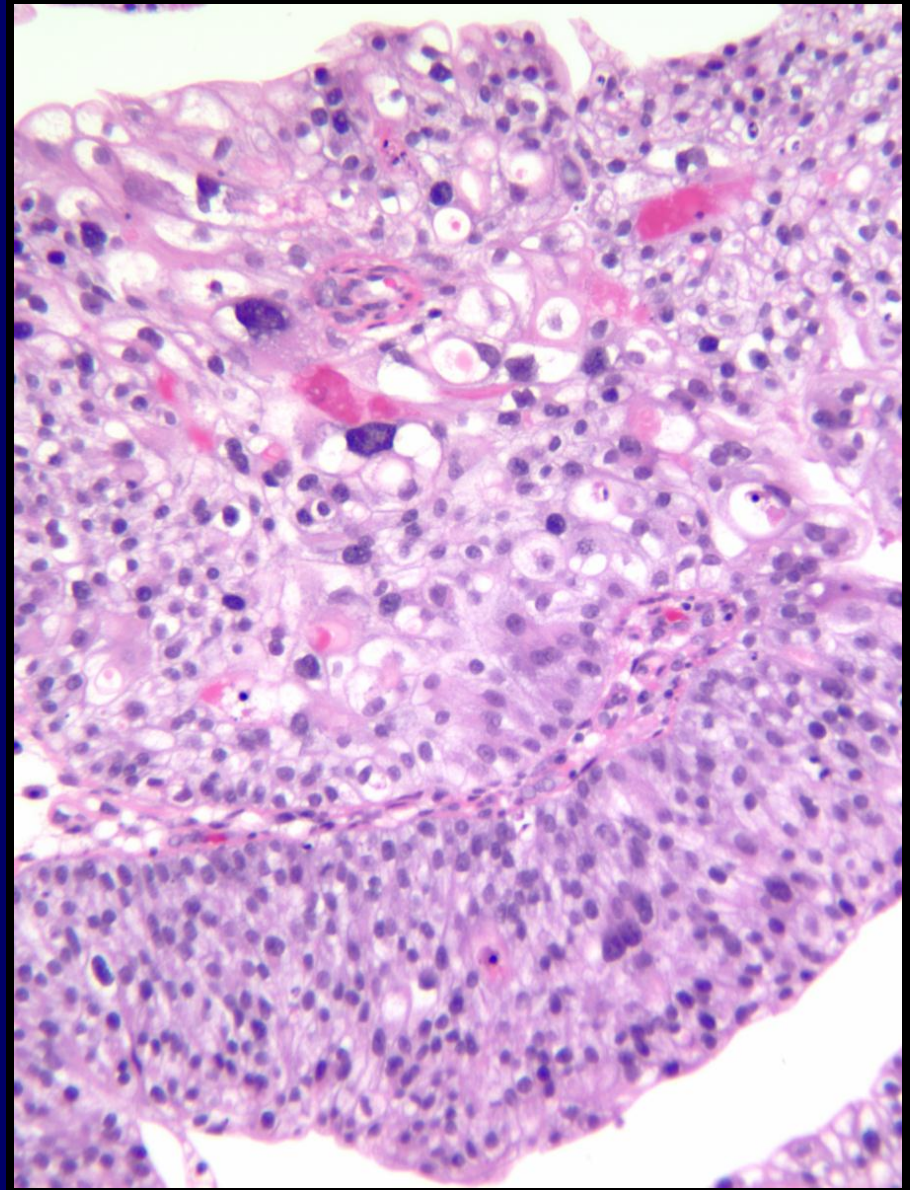
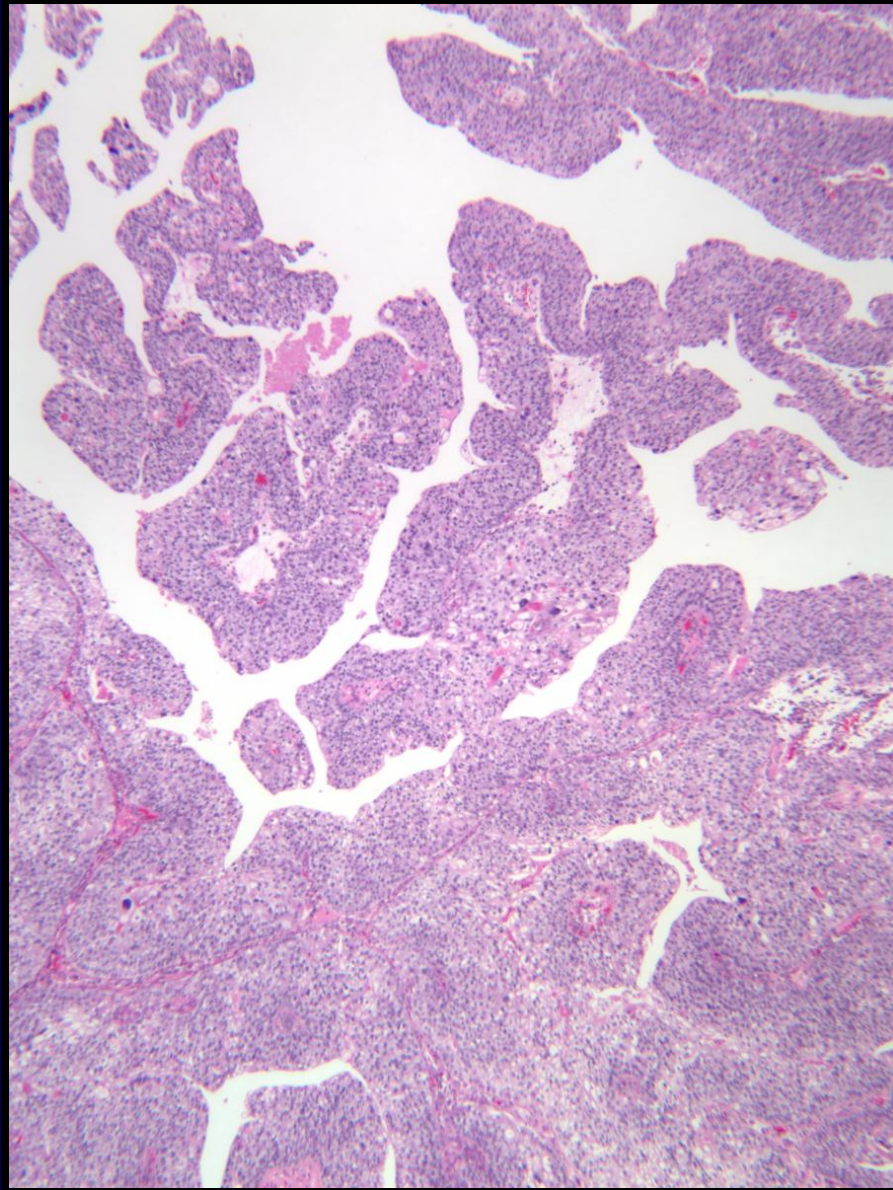
PAPILLARY CARCINOMA, HIGH GRADE

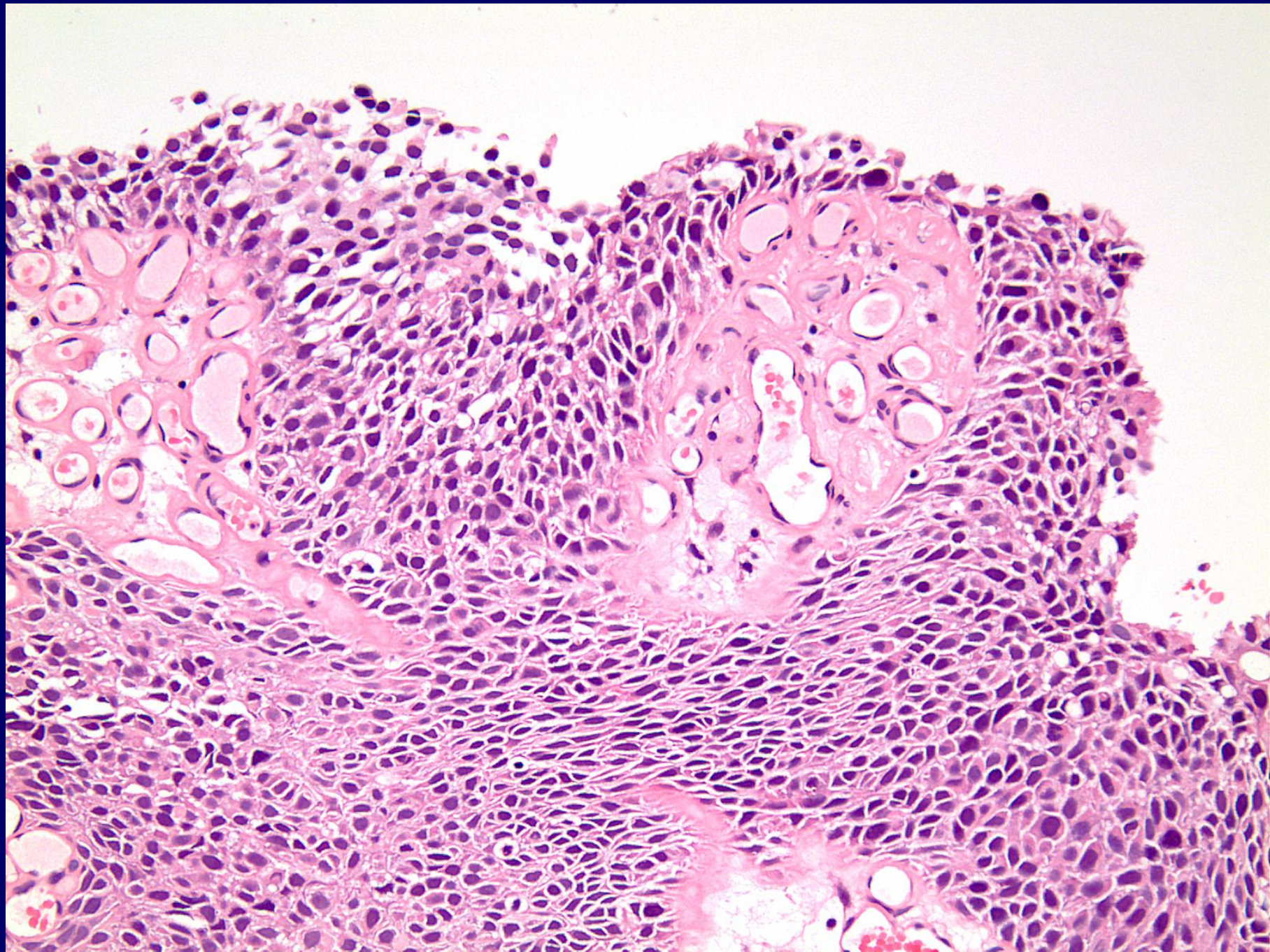
- **Significant risk of progression**
- **Generally requires intravesical therapy**
- **Overall impression is one of disorder**
- **Irregular, often fused papillae**
- **Significant cytologic atypia is characteristic**

HIGH GRADE

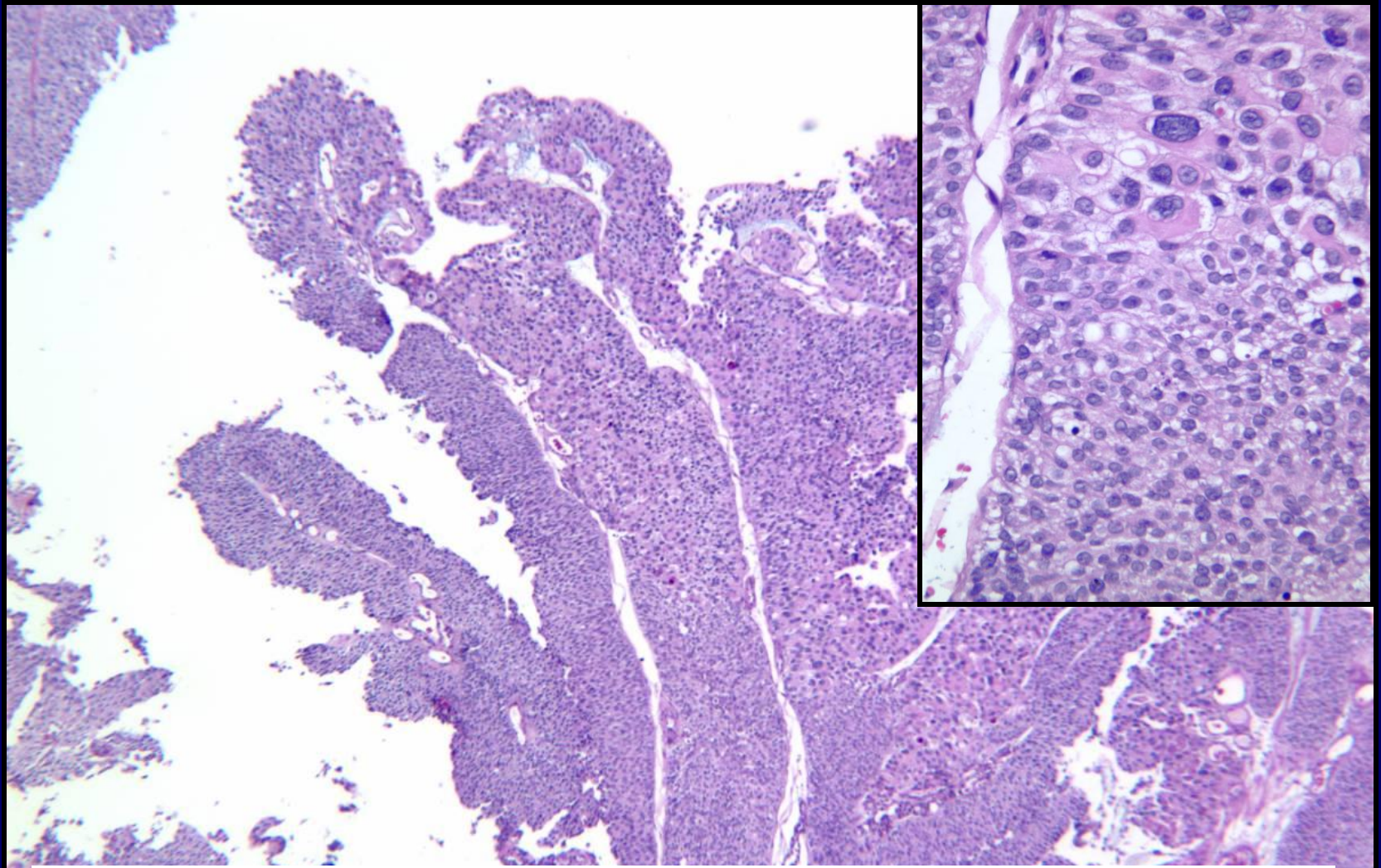


HIGH GRADE





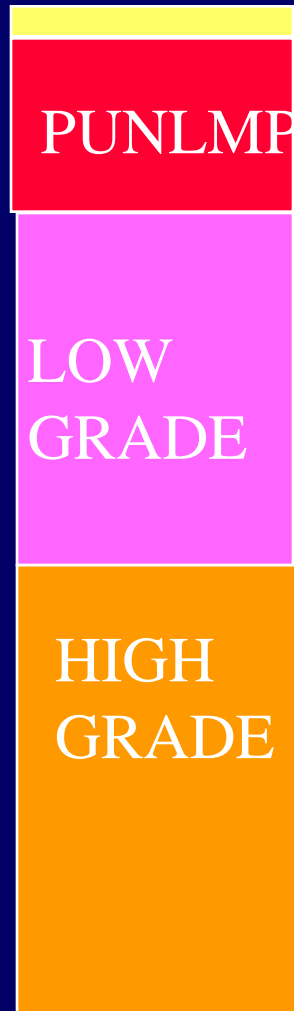
BLADDER – PAPILLARY UC



**52/164 (32%) papillary UC were grade heterogeneous,
*Cheng et al. Cancer 88:1663-1670, 2000***

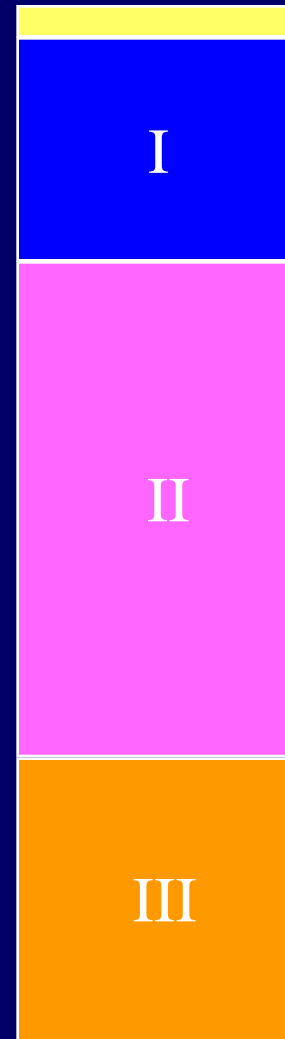
CORRELATIONS OF WHO CLASSIFICATIONS

1998/ISUP

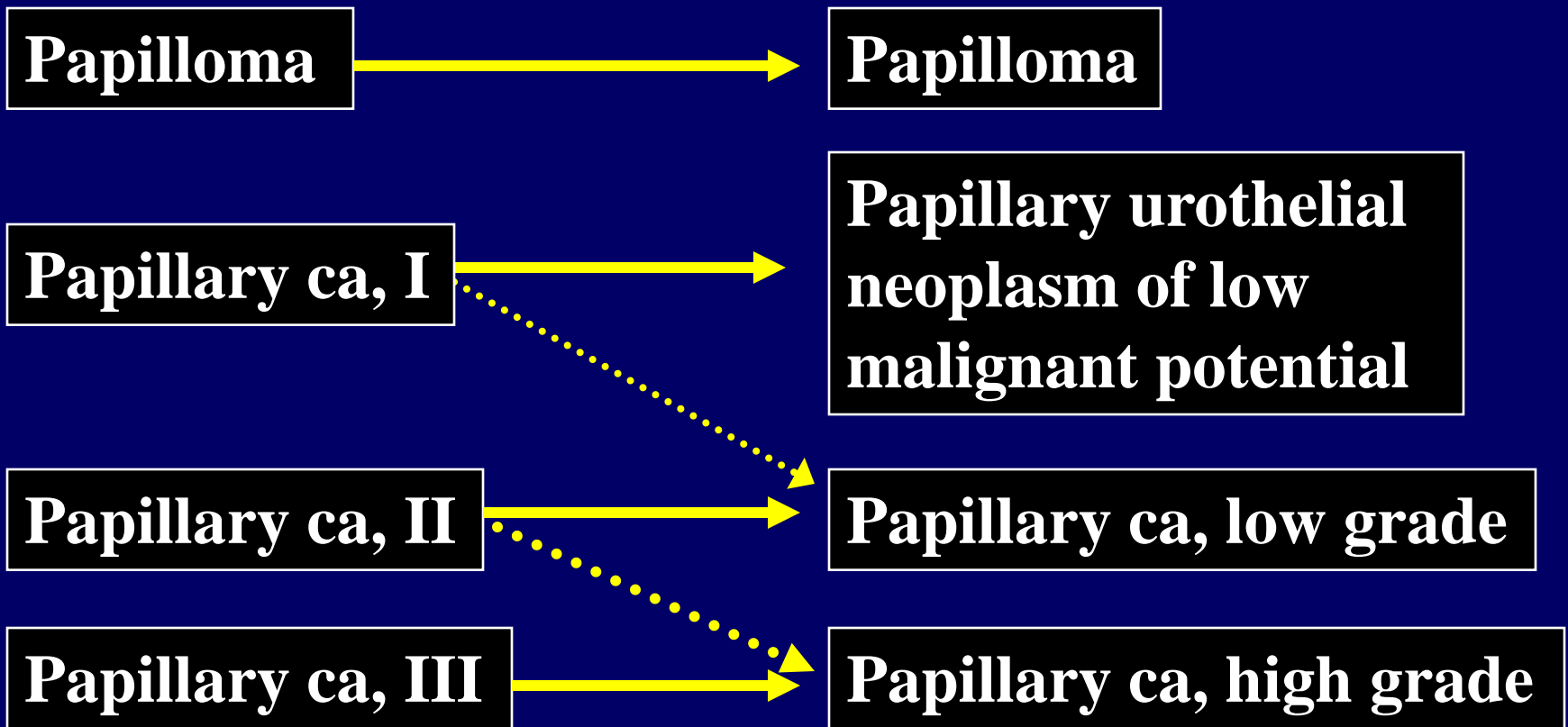


PAPILLOMA

1973



WHO 1973 vs WHO 2004



Relationship Between 1973 WHO and 1998/2004 WHO/ISUP Classification

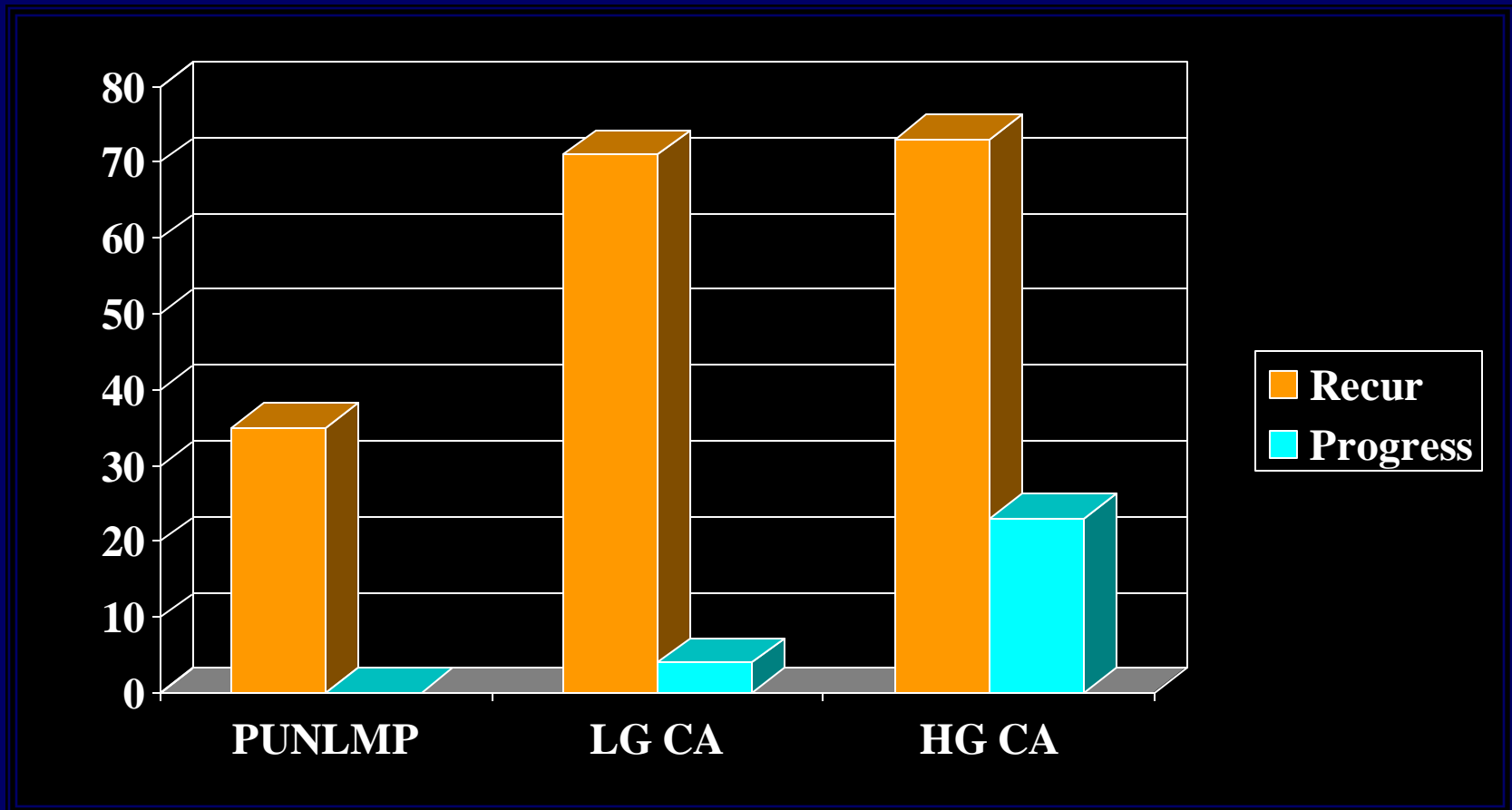
WHO 1973	#	PAP	LMP	LG	HG
G 1	42	2	13	26	1
G 2	79	0	13	64	22
G 3	6	0	0	0	6

Samaratunga et al. Urology 60:315, 2002

WHO/ISUP GRADING IN pTa UROTHELIAL CARCINOMA

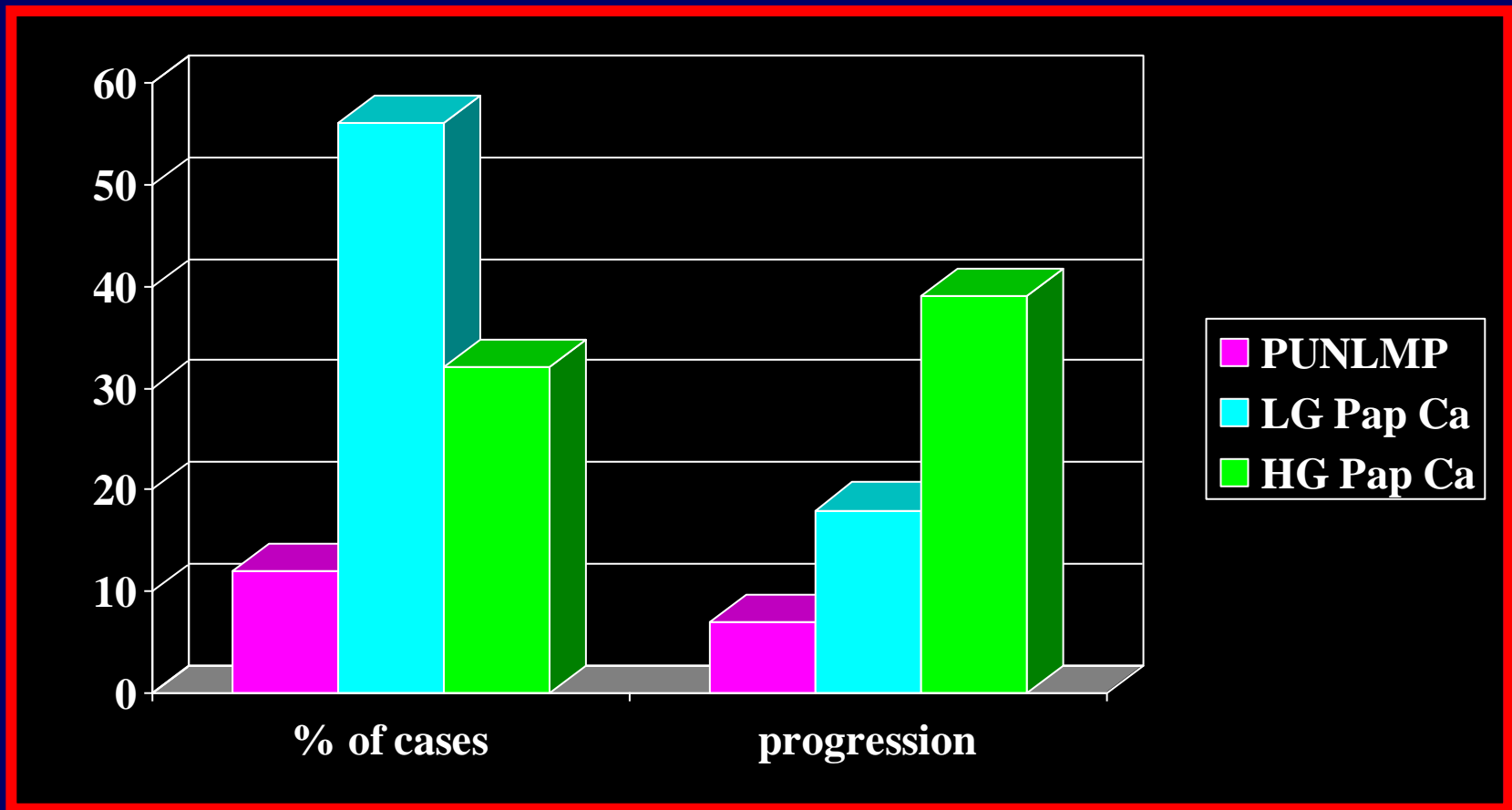
- **680 new cases, 363 (53%) pTa**
- **Grade distribution:**
 - **PUNLMP** **95 (26%)**
 - **Low grade** **160 (44%)**
 - **High grade** **108 (30%)**
- **Treatment:**
 - **TURBT alone** **358 (98.6%)**
- **Follow up: minimum 5-years**

WHO/ISUP GRADING IN pTa UROTHELIAL CARCINOMA



Holmäng et al, J Urol 165:1124-1130, 2001

WHO/ISUP (1998) OUTCOME DATA



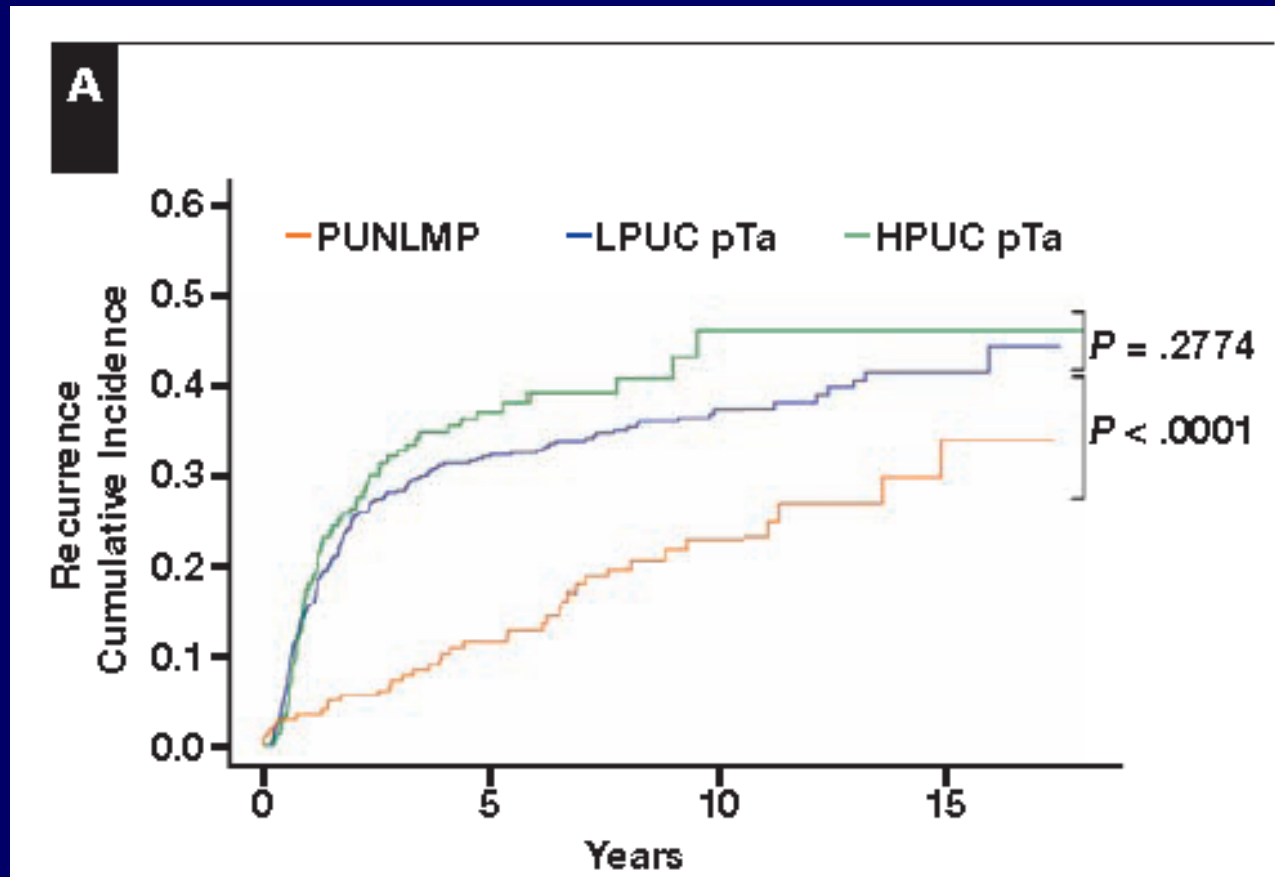
Cheng et al, Cancer 88:1663, 2000

**Prognostic Significance of the 2004
WHO/ISUP Classification for Prediction of
Recurrence, Progression, and Cancer-
Specific Mortality of Non–Muscle-Invasive
Urothelial Tumors of the Urinary Bladder:
A Clinicopathologic Study of 1,515 Cases**

Chen Pan et al: Am J Clin Pathol. 2010;133:788-95

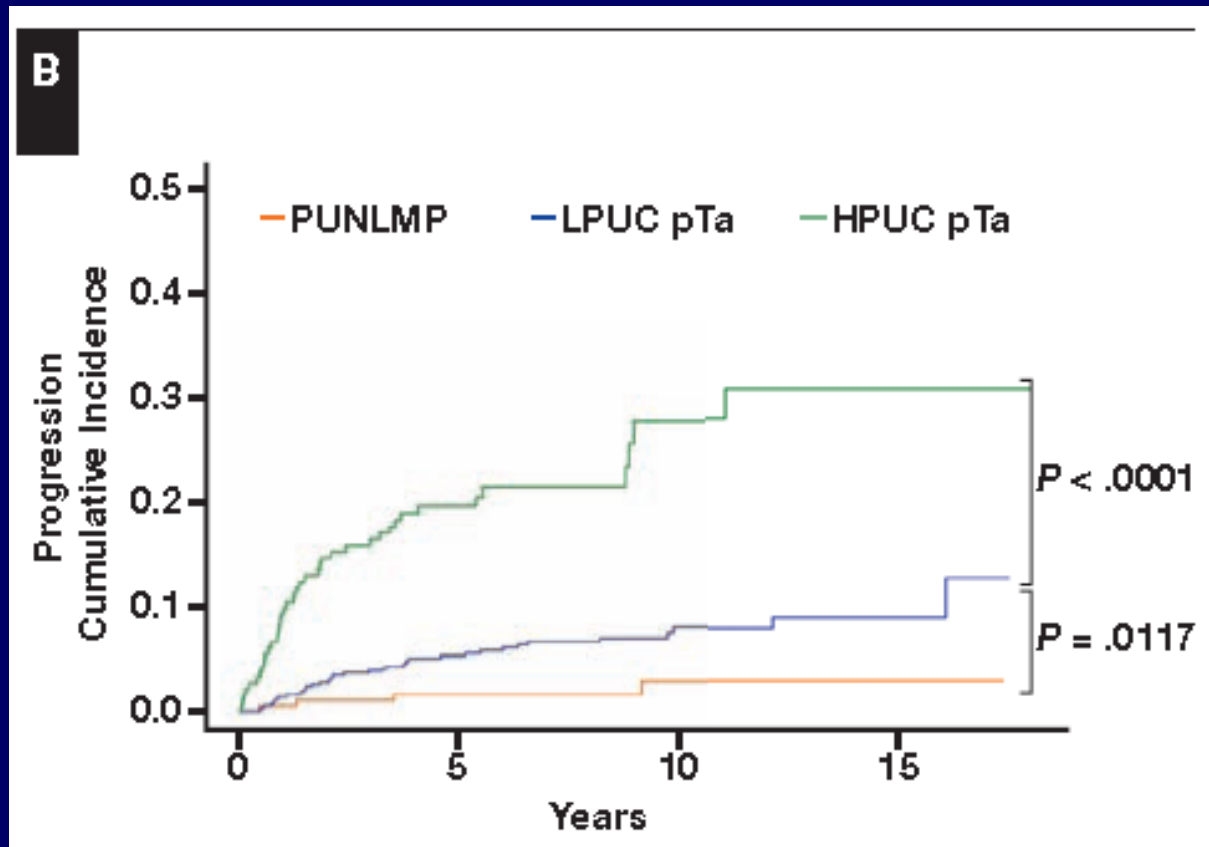
Taipei Veterans General Hospital, Taiwan

Chen Pan et al: Am J Clin Pathol. 2010;133:788-95

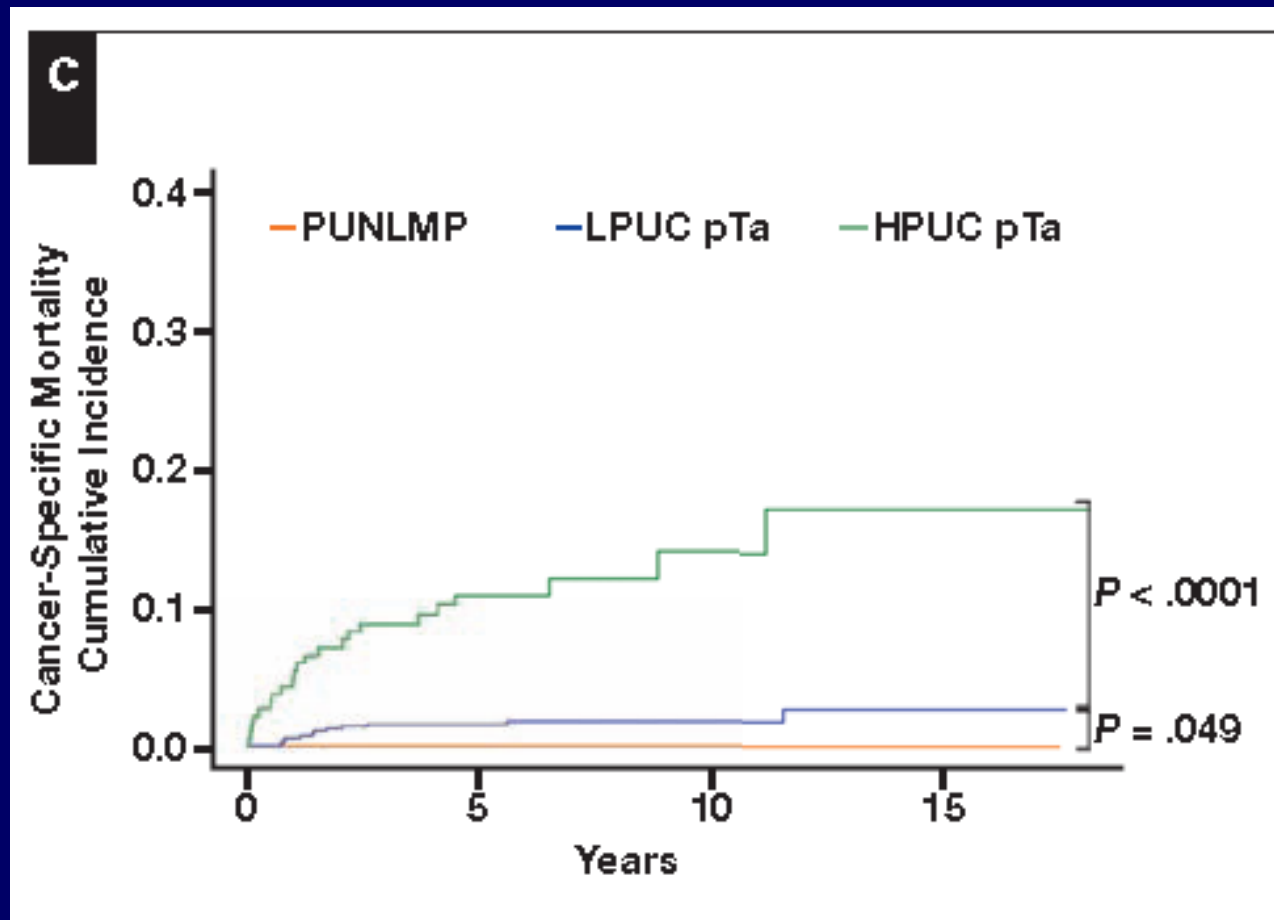


Cumulative incidence plots of recurrence for patients with pTa bladder tumors of different grades

Chen Pan et al: Am J Clin Pathol. 2010;133:788-95



Cumulative incidence plots of progression for patients with pTa bladder tumors of different grades



Cumulative incidence plots of cancer-specific mortality for patients with pTa bladder tumors of different grades.

Flat Urothelium

NORMAL

HYPERPLASIA

FLAT LESIONS WITH ATYPIA

Reactive (inflammatory) atypia

Atypia of unknown significance

**Dysplasia (low grade
intraurothelial neoplasia)**

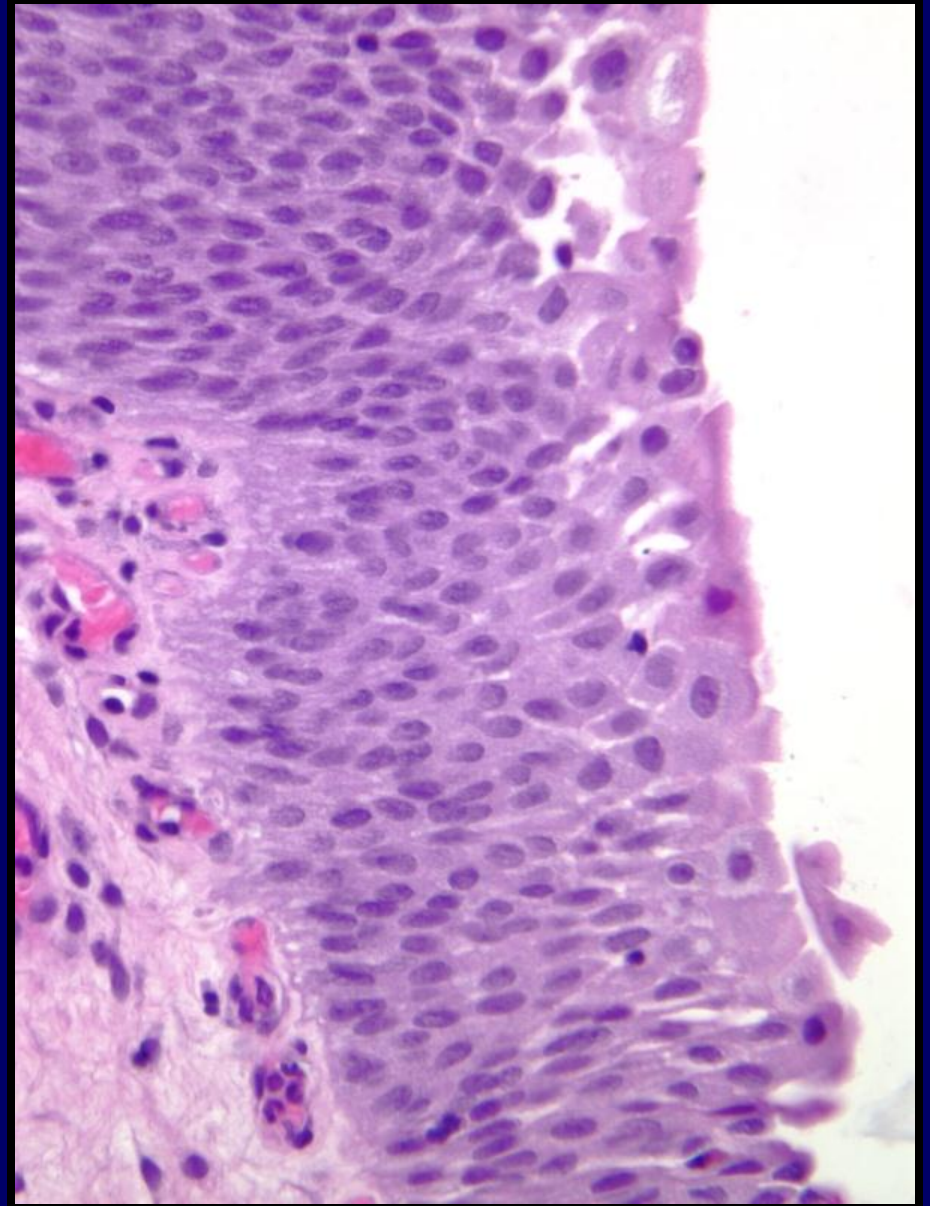
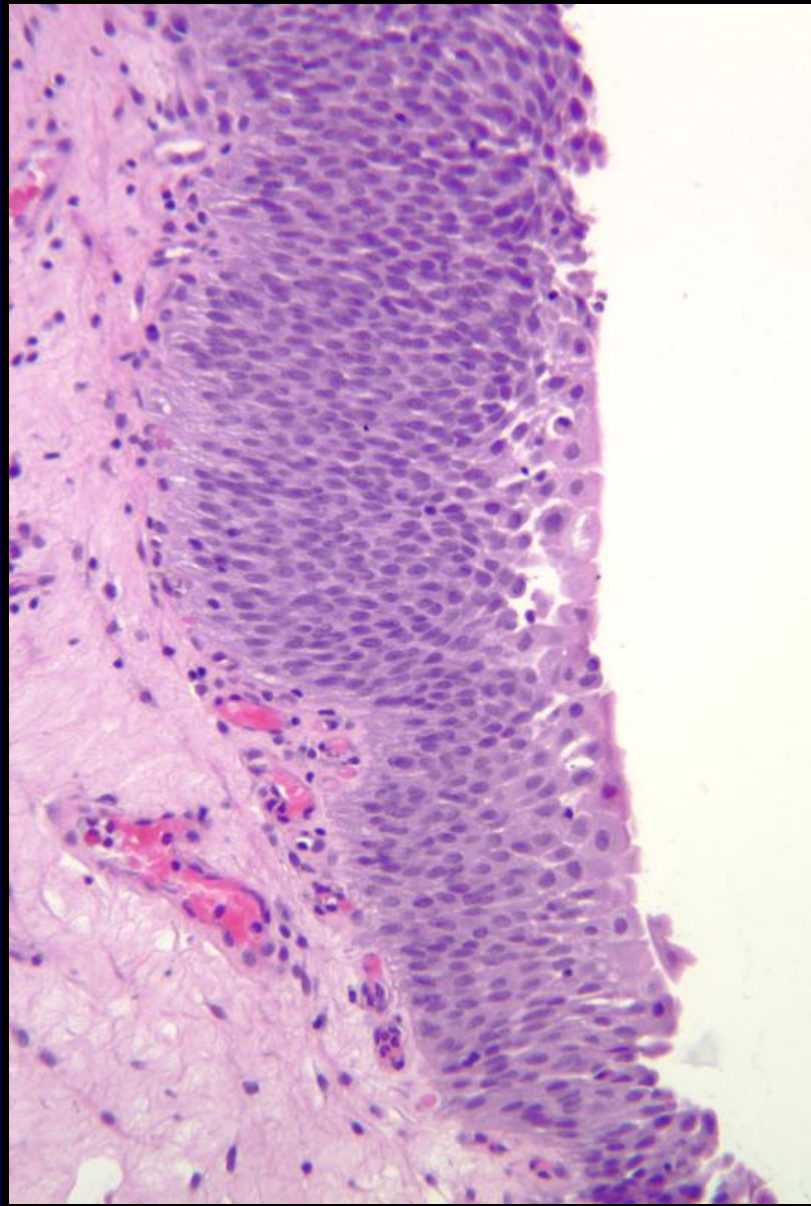
**Carcinoma in situ (high grade
intraurothelial neoplasia)**

WHO 2004 CLASSIFICATION

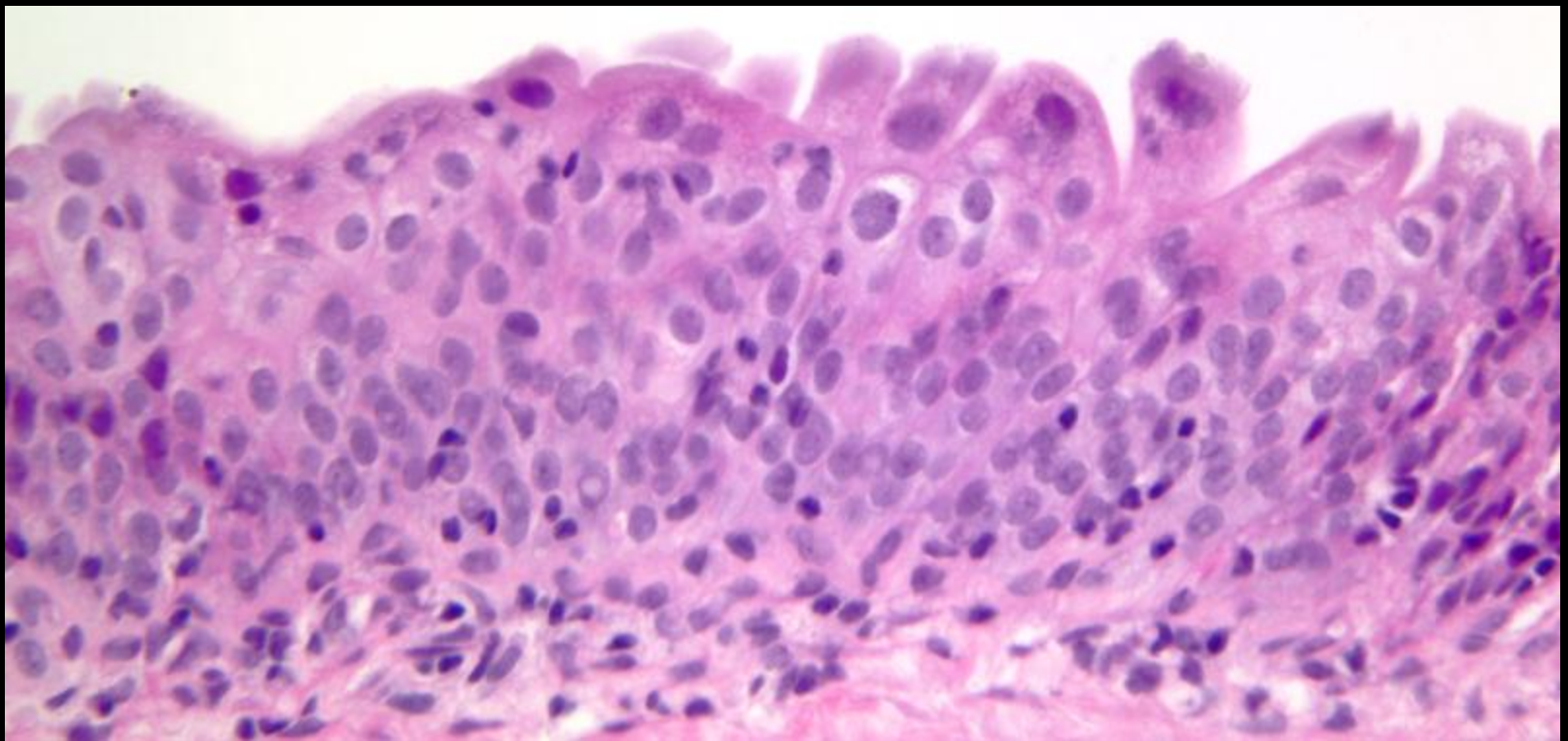
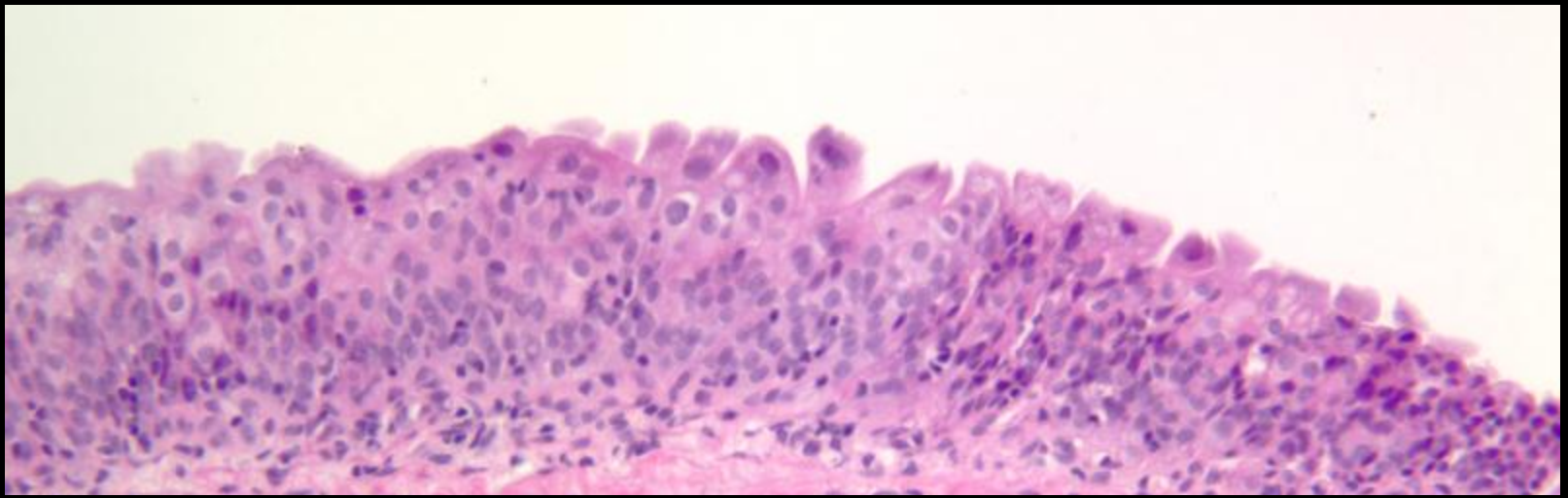
REACTIVE ATYPIA

- **Typically a history of recurrent infection, instrumentation or other**
- **Epithelium may or may not be thickened**
- **Nuclei uniformly enlarged and vesicular**
- **May be prominent centrally located nucleoli**
- **Mitotic figures may be frequent**
- **Acute and/or chronic inflammation**

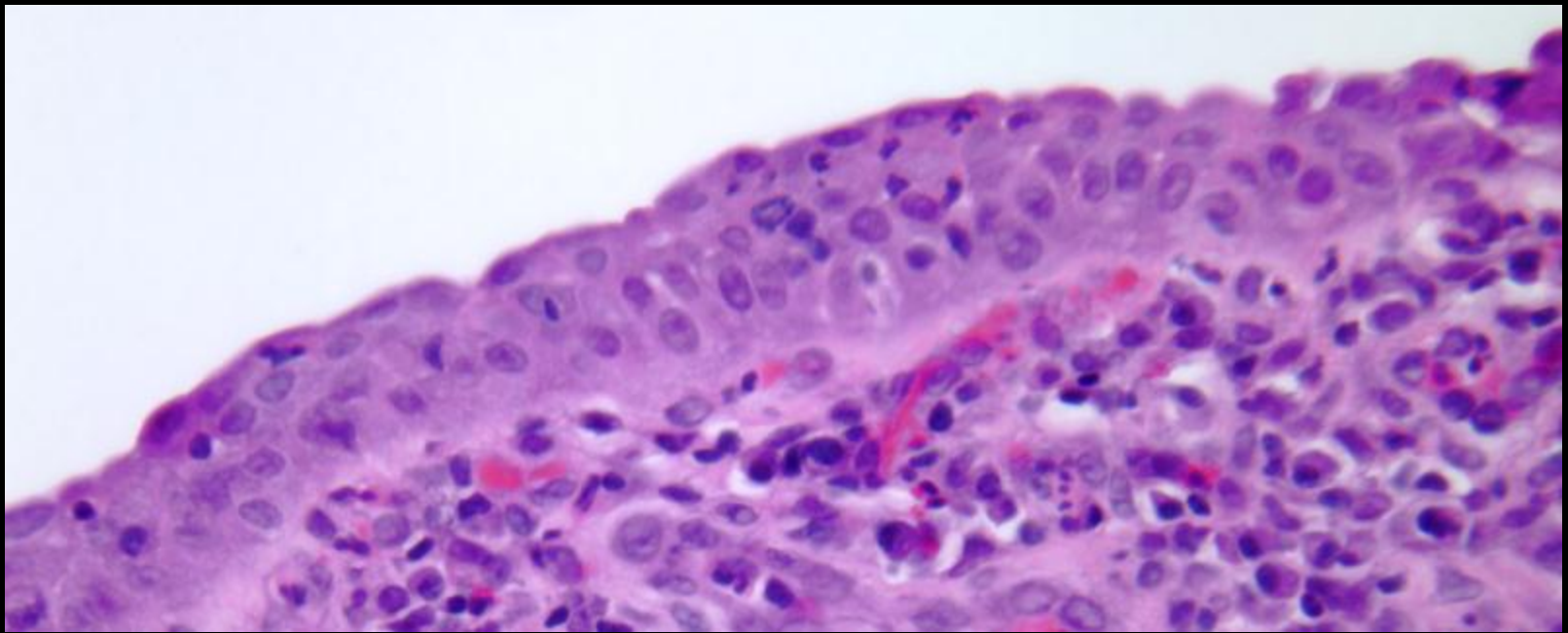
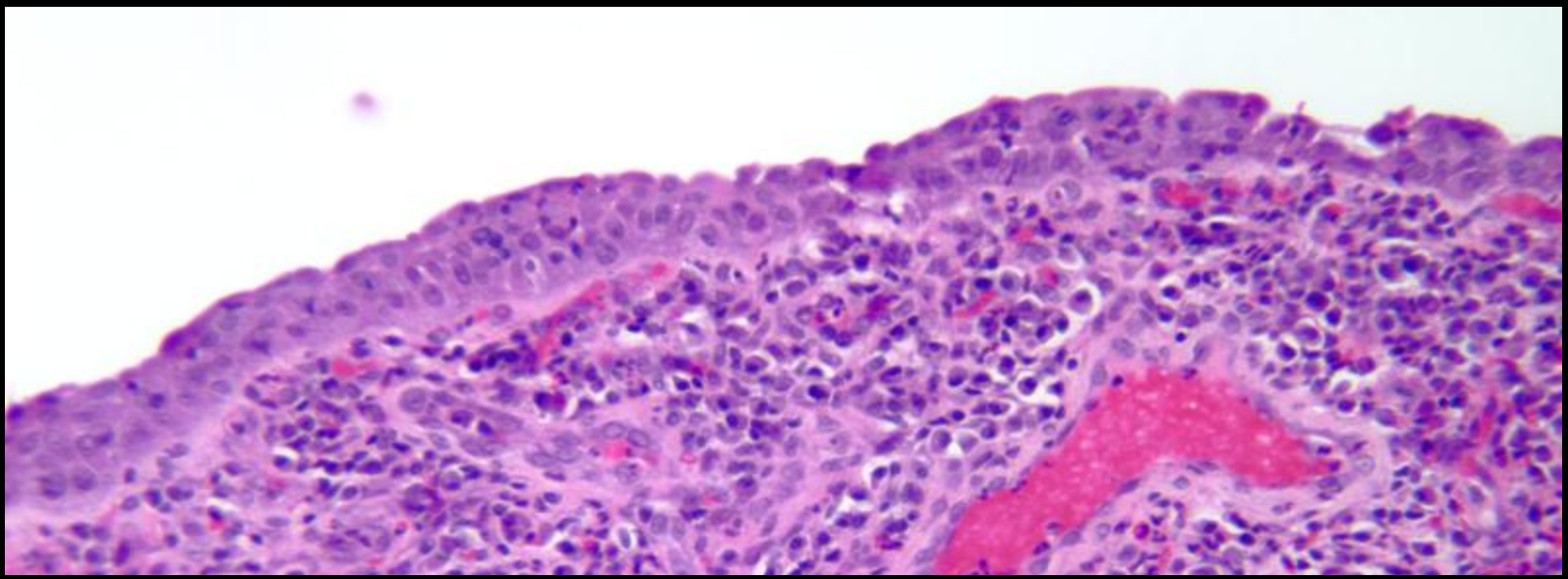
HYPERPLASIA



REACTIVE ATYPIA



REACTIVE ATYPIA

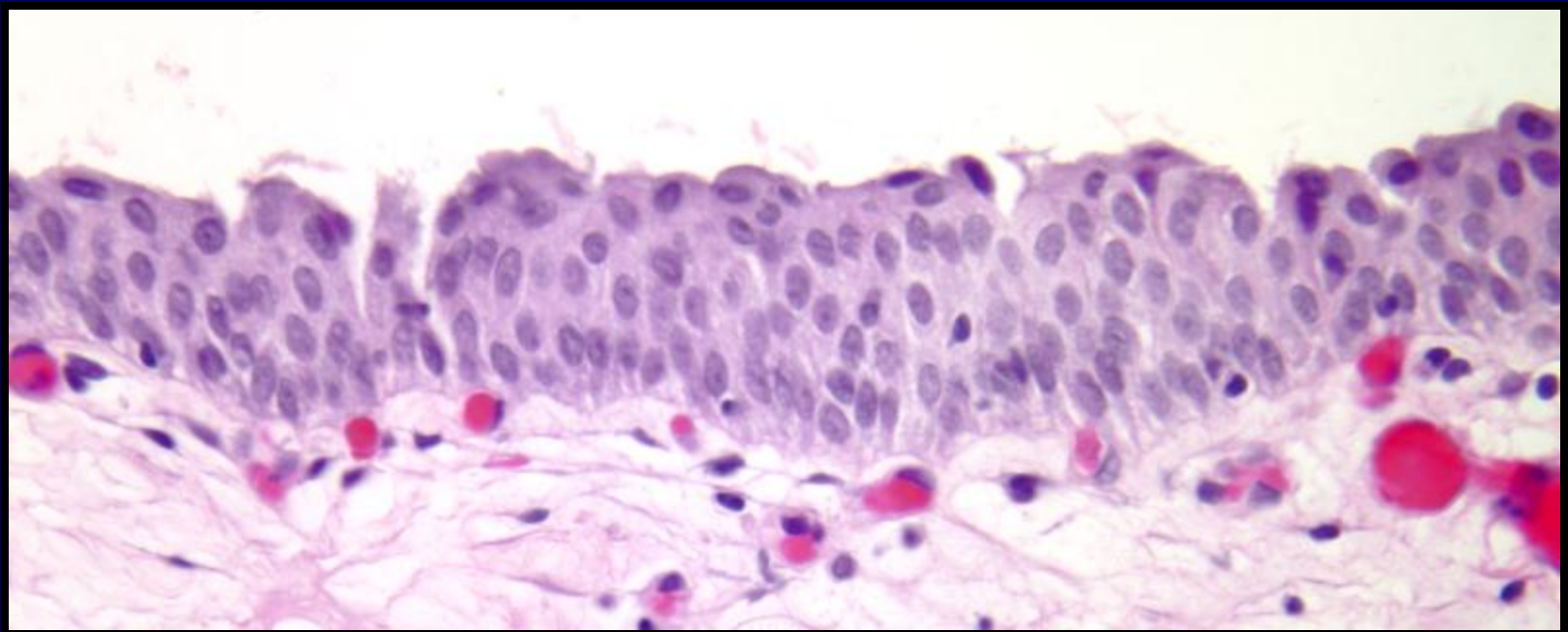
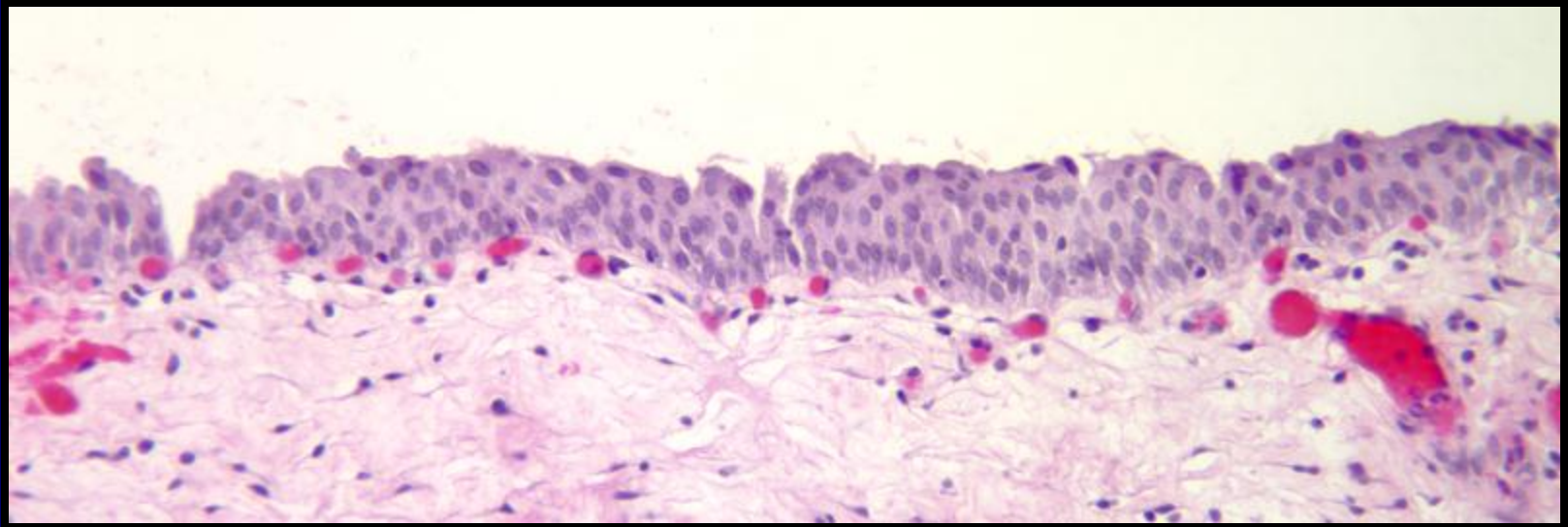


WHO 2004 CLASSIFICATION

ATYPIA OF UNKNOWN SIGNIFICANCE

- **Cases falling into gray zone between clearly reactive and clearly neoplastic**
- **Reserved for cases where dysplasia cannot be ruled out with certainty**
- **Usually inflammatory background**
- **Patients may be followed and reevaluated after inflammation subsides**

ATYPIA - UNKNOWN SIGNIFICANCE

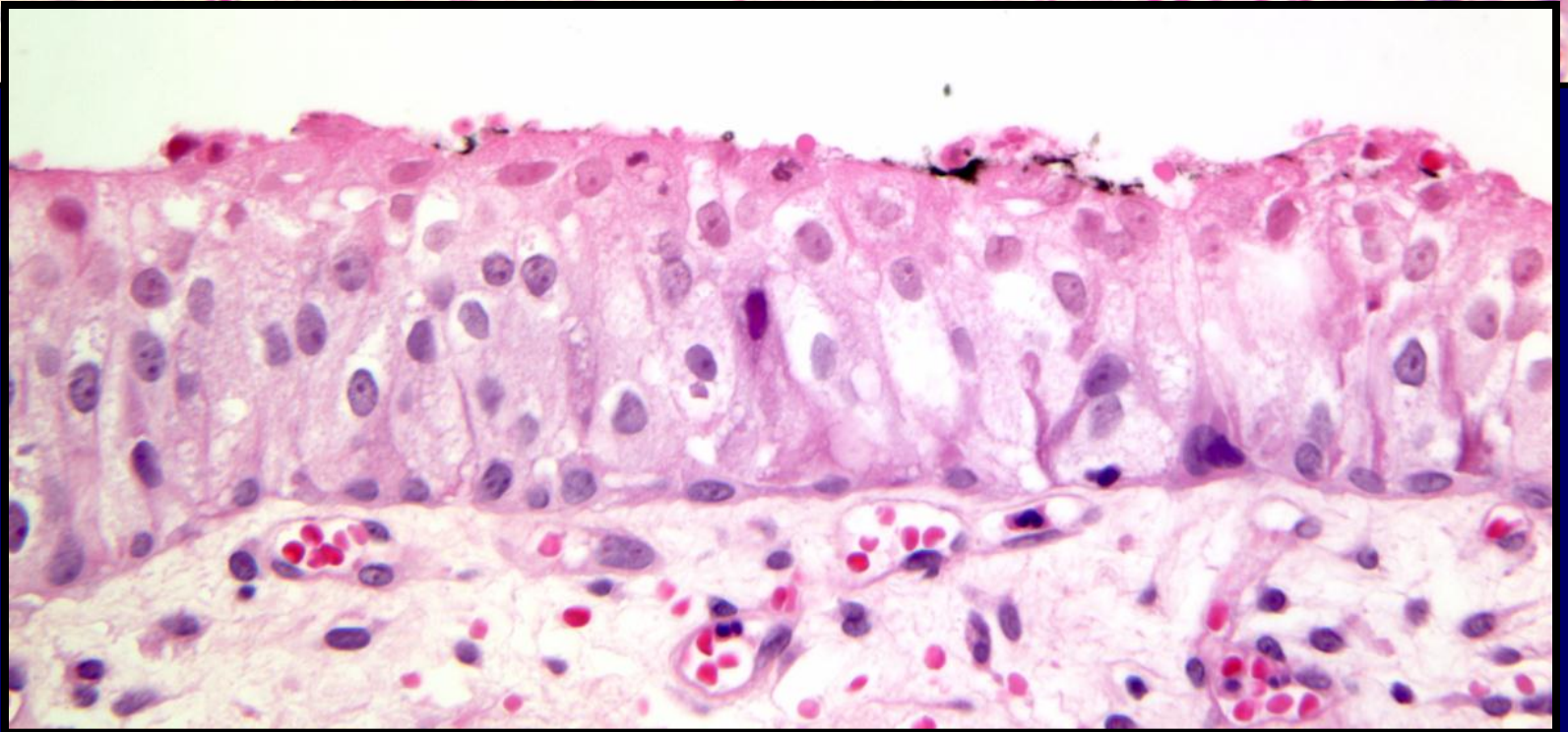
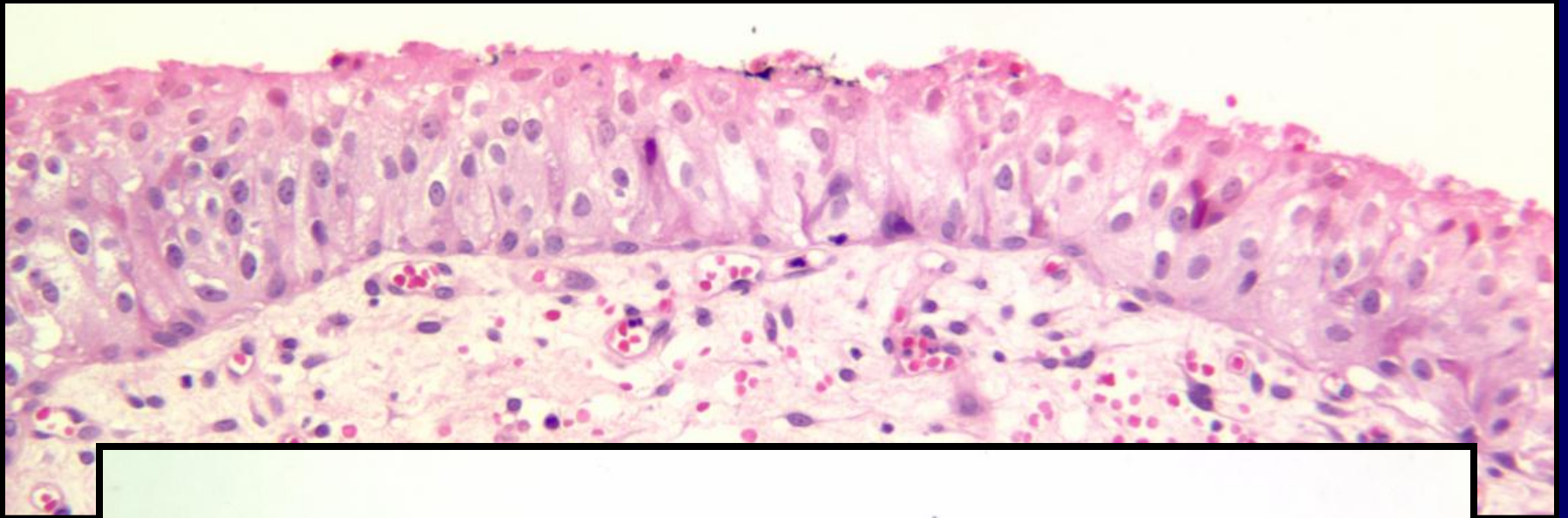


WHO 2004 CLASSIFICATION

DYSPLASIA (LOW GRADE INTRAUROTHELIAL NEOPLASIA)

- **Need to recognize a lesion with changes short of CIS**
- **Overall features strongly indicative of a neoplastic atypia but fall short of criteria for carcinoma in situ**
- **Significance and treatment to be determined**

DYSPLASIA



WHO 2004 CLASSIFICATION CARCINOMA IN SITU (HIGH GRADE INTRAUROTHELIAL NEOPLASIA)

- **Reproducibility of diagnosis best at high end of scale**
- **Documented precursor of invasive cancer**
- **Many cases with proven clinical significance under diagnosed**
- **Need for the category of CIS to be expanded to include lower grade lesions “moderate dysplasia”**

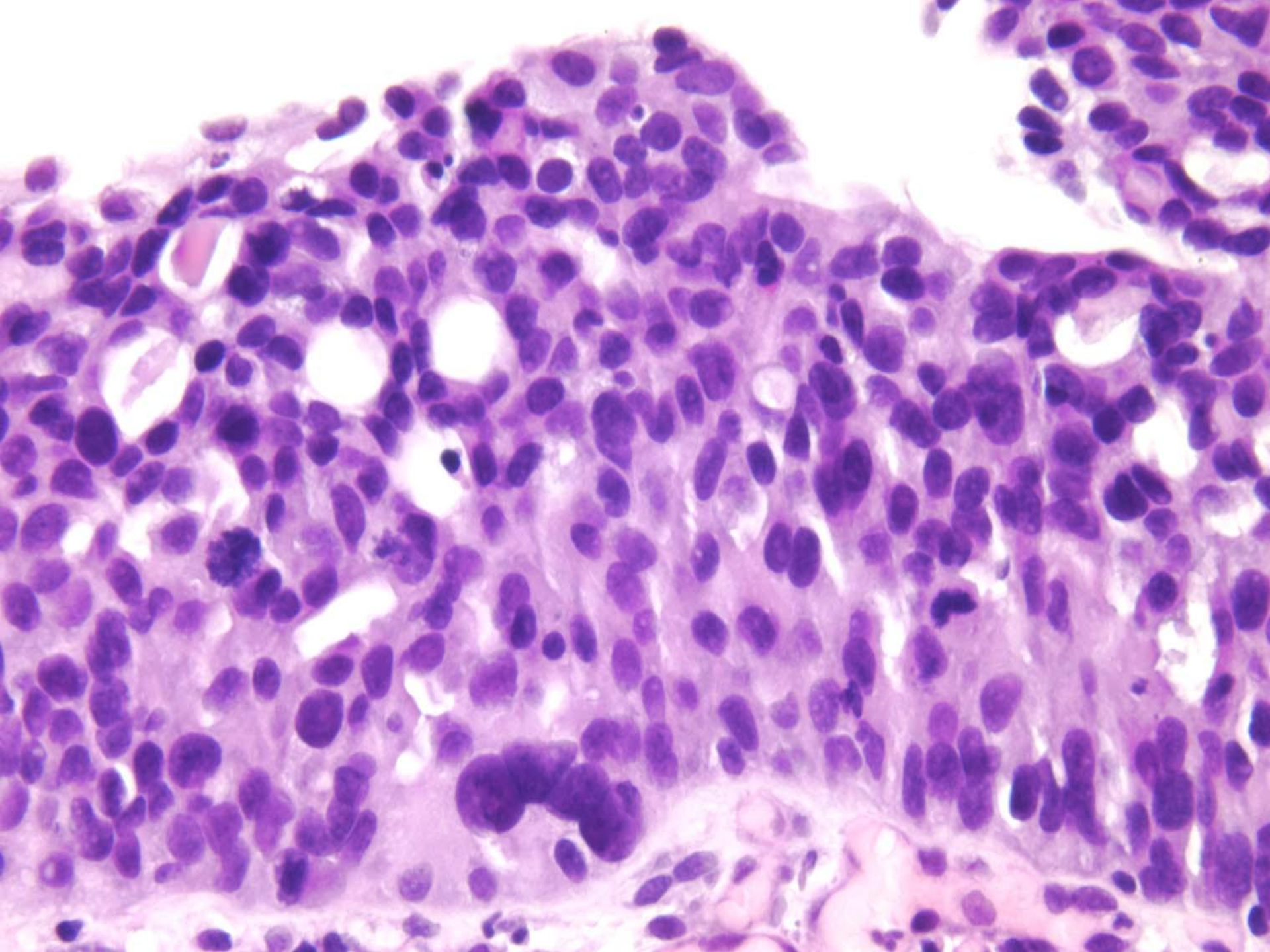
CIS: Histology

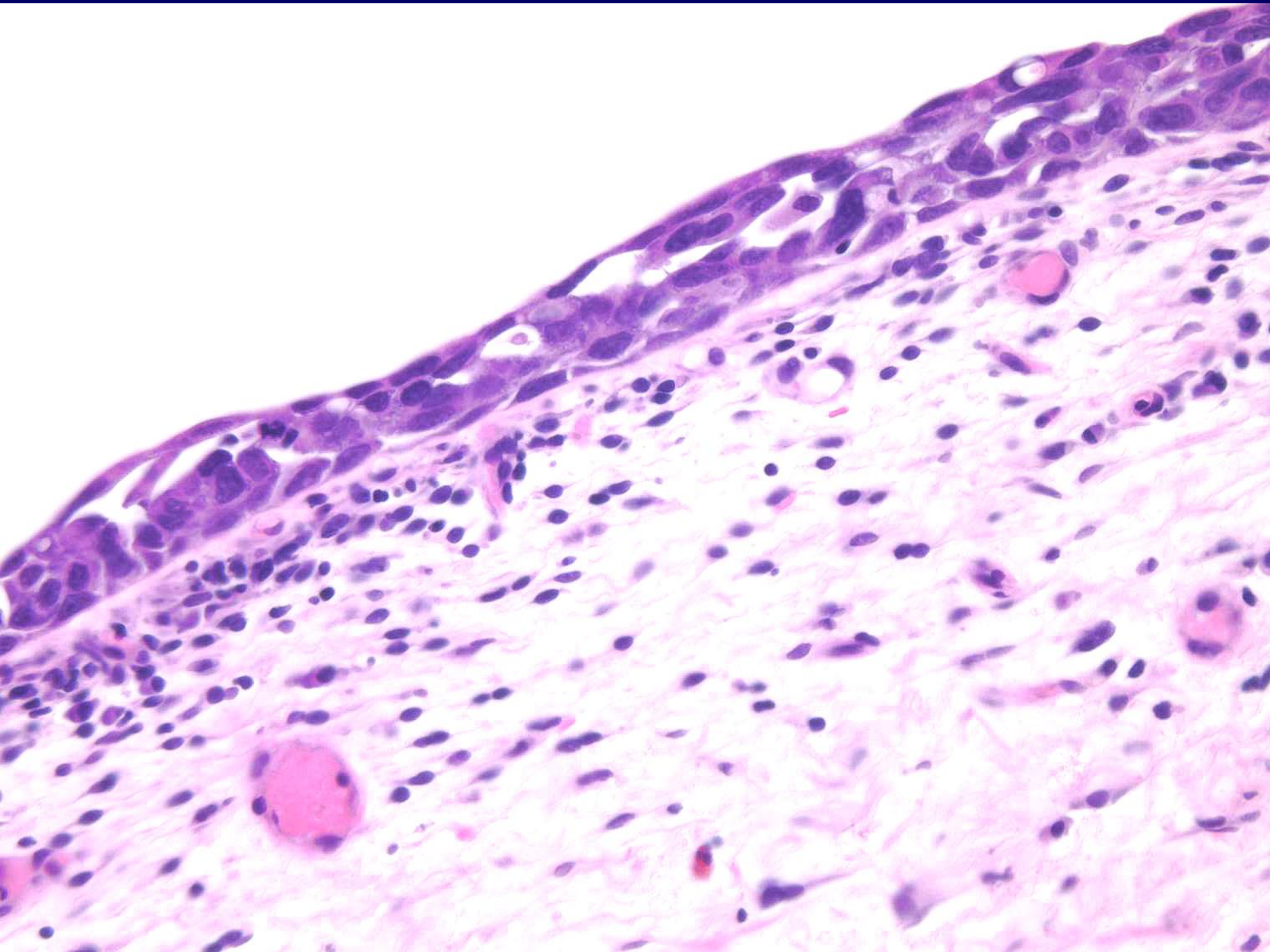
- **Presence of cytologically malignant cells regardless of quantity or location**

Does not require full thickness involvement, umbrella cell layer may be present

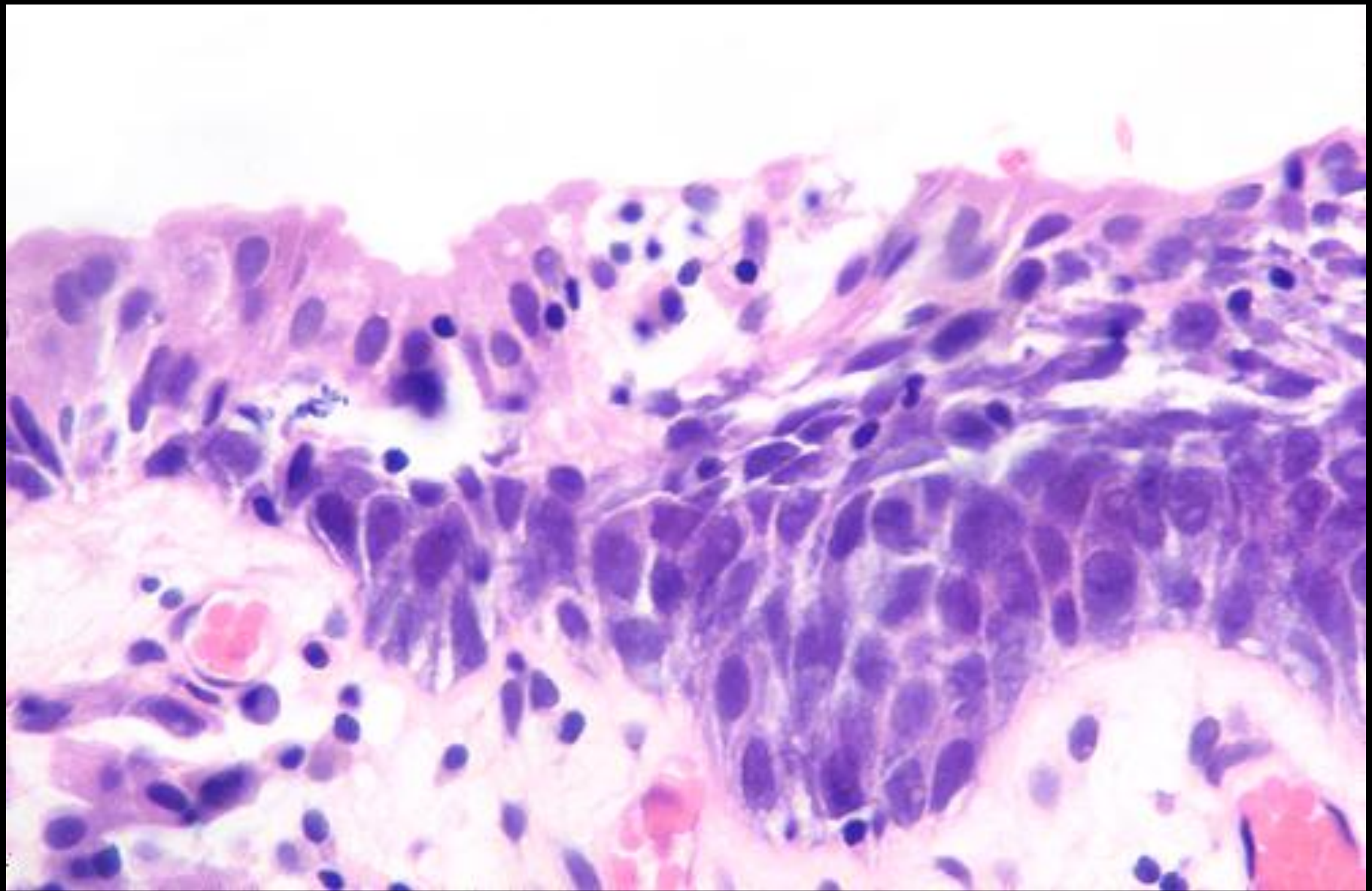
Pagetoid

- **Enlarged & hyperchromatic with variations in cell sizes**
- **Dyscohesive – “denuding cystitis”**

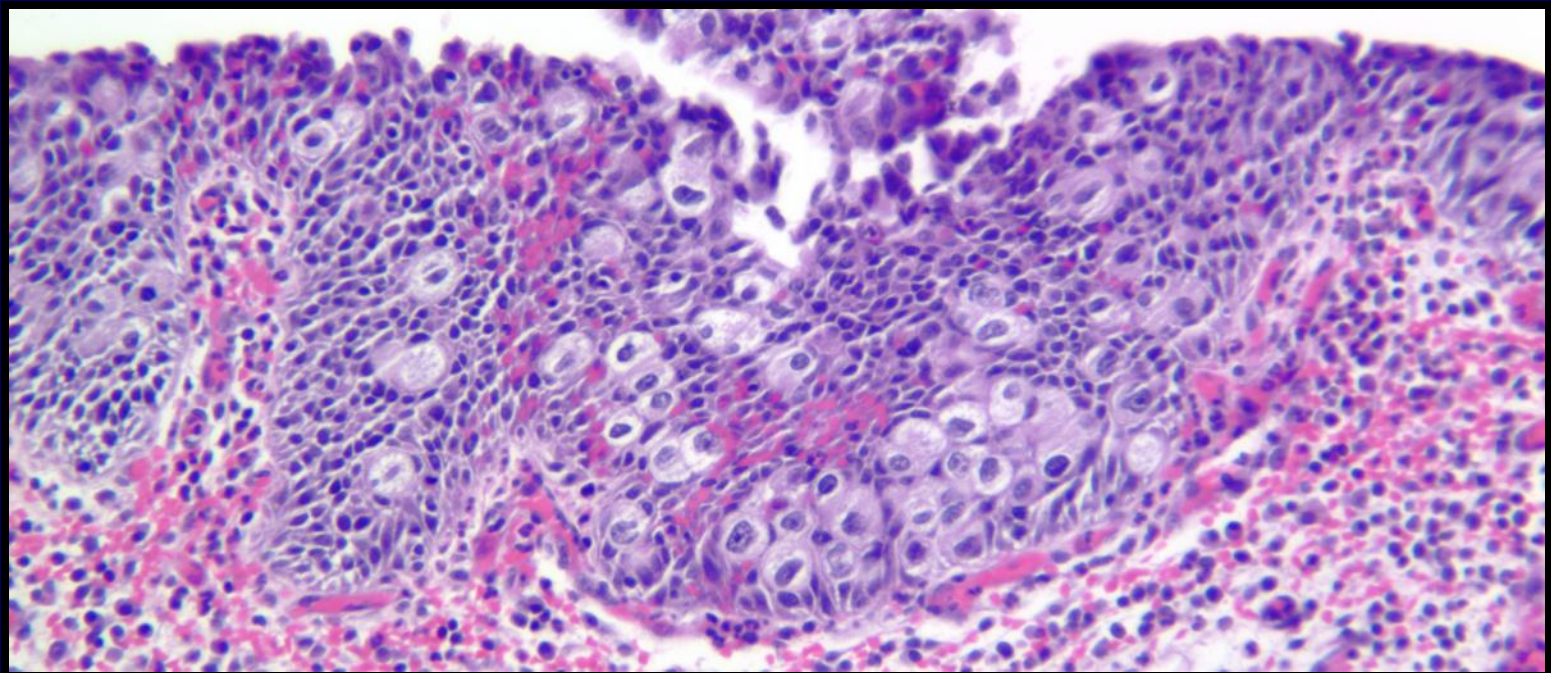
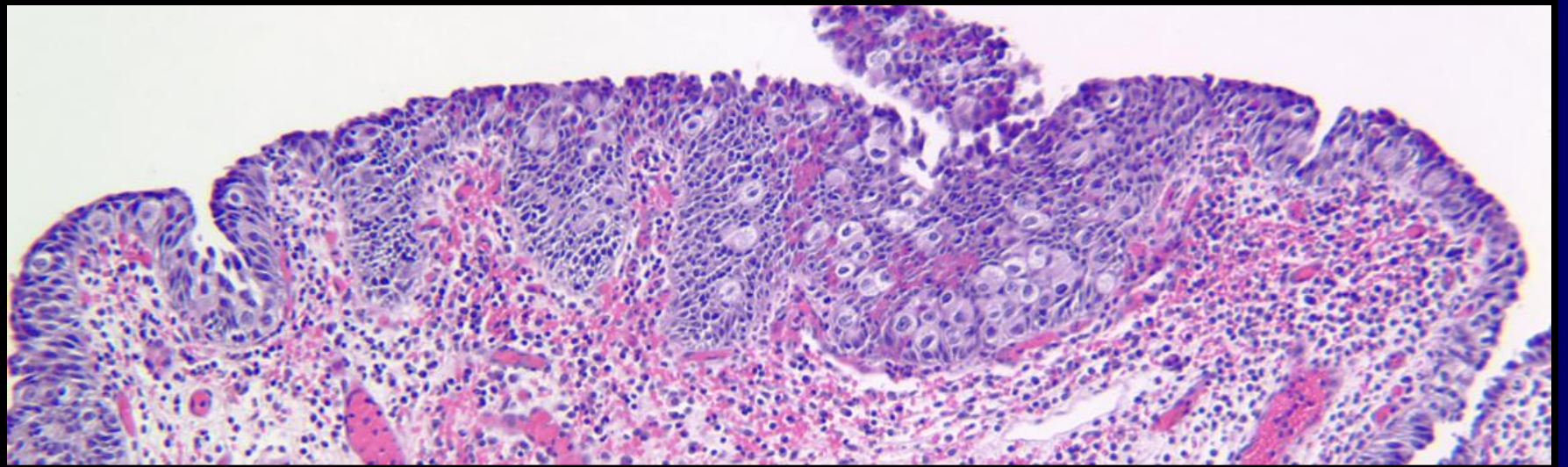


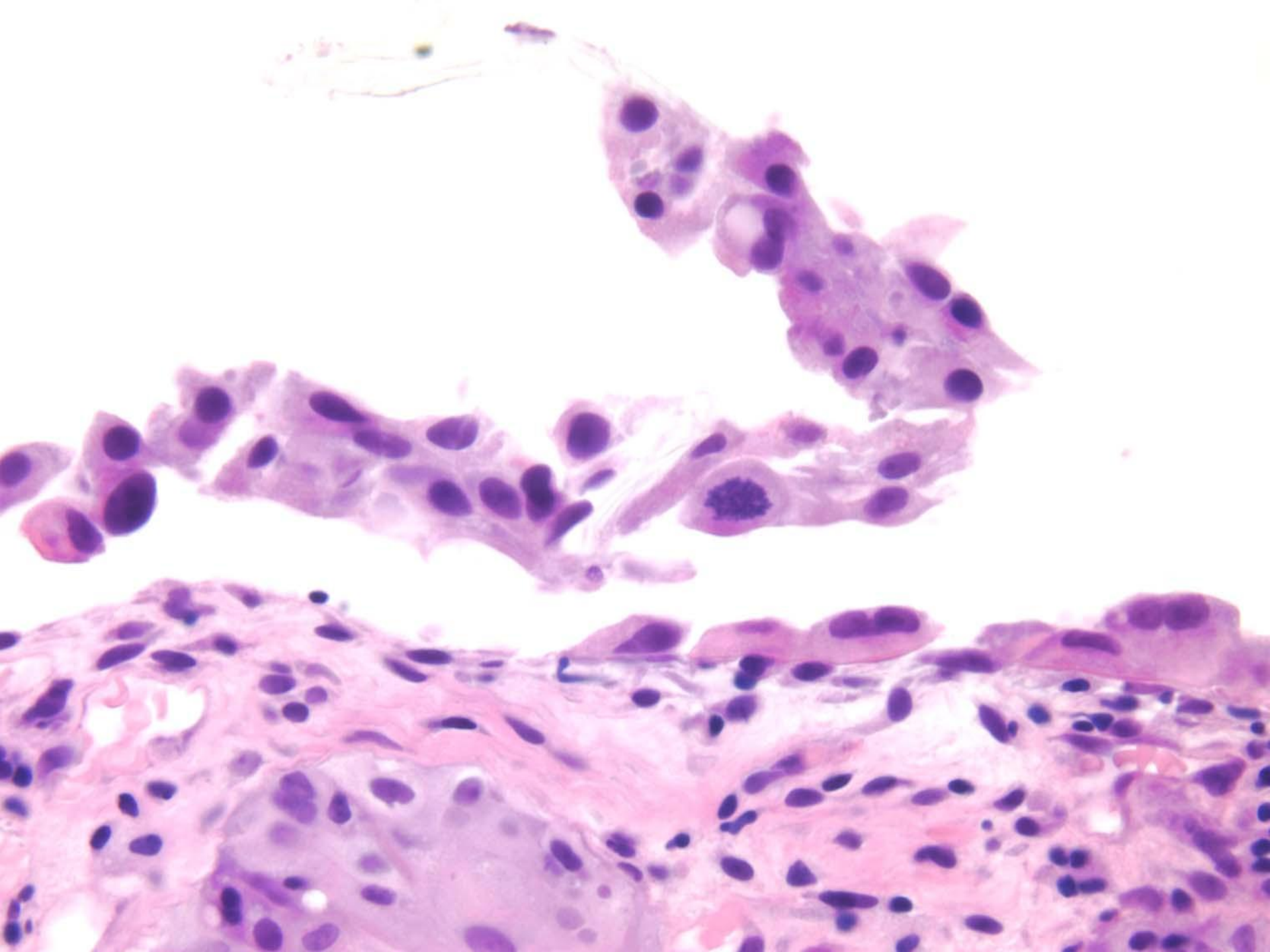


CIS - UNDERMINING

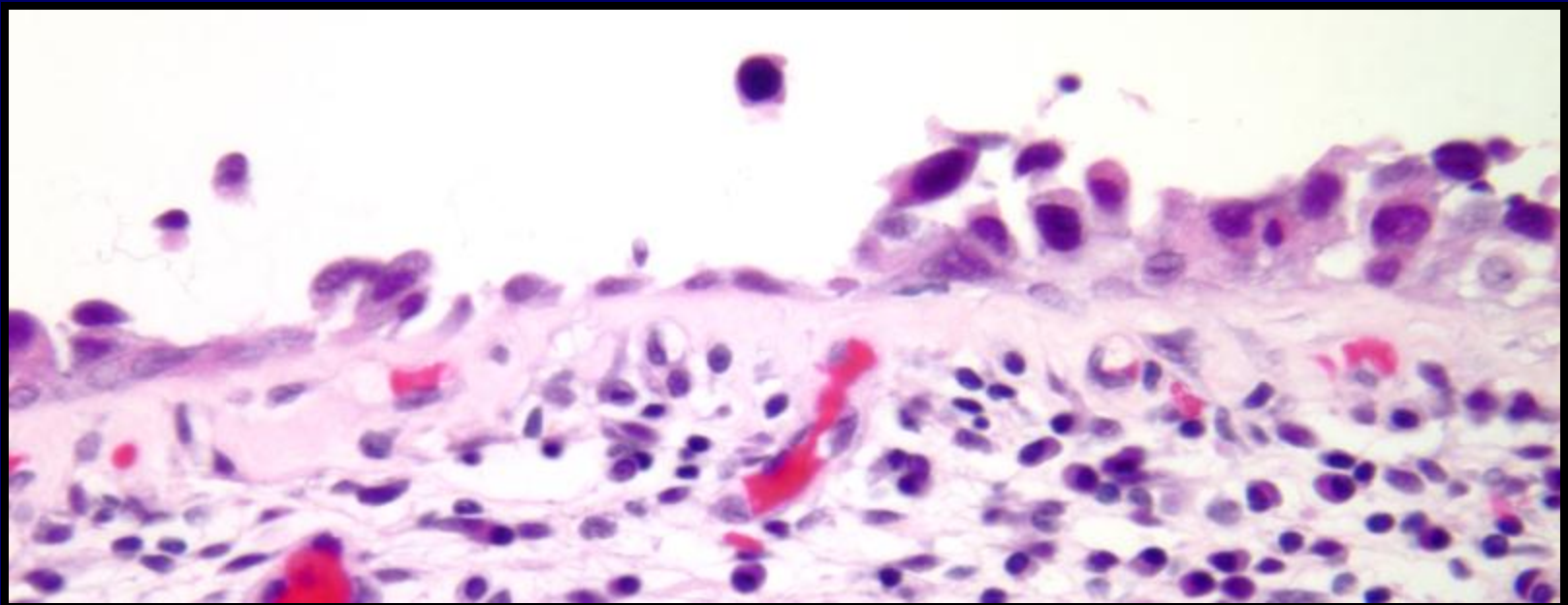
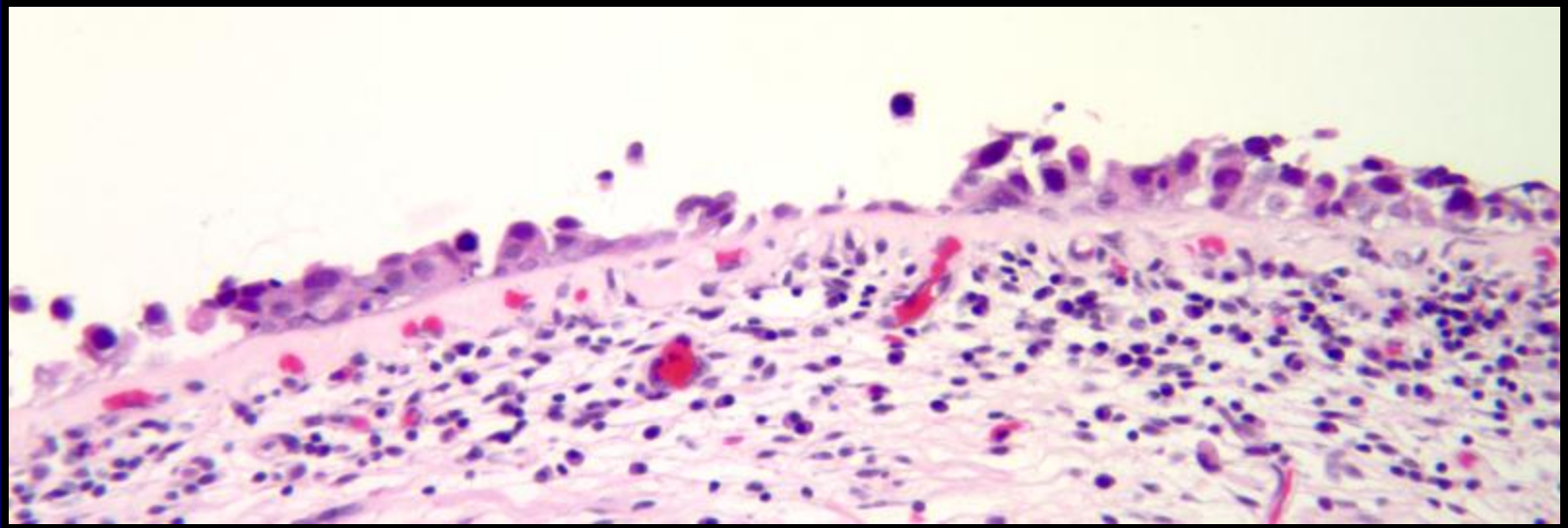


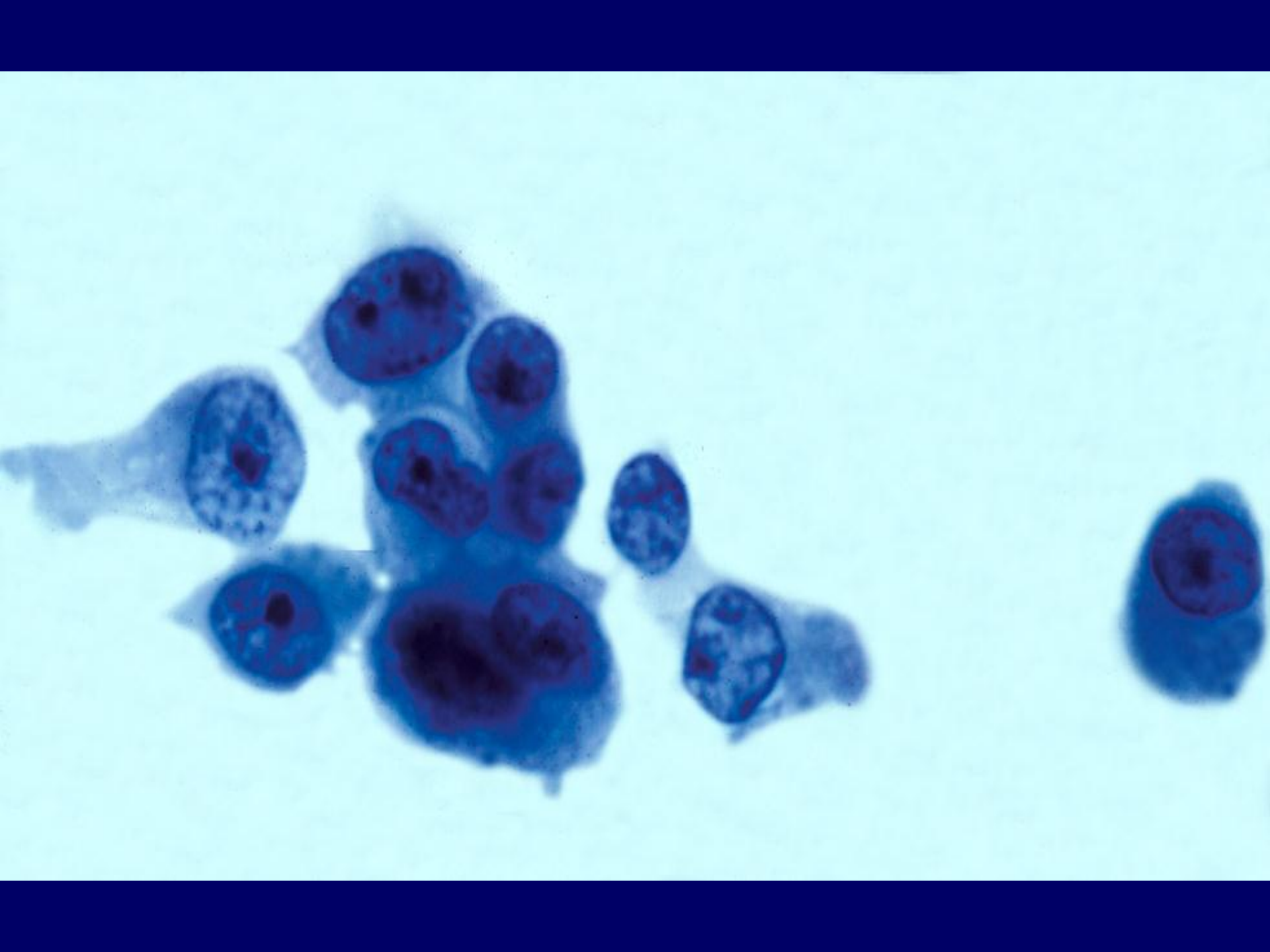
CIS - PAGETOID



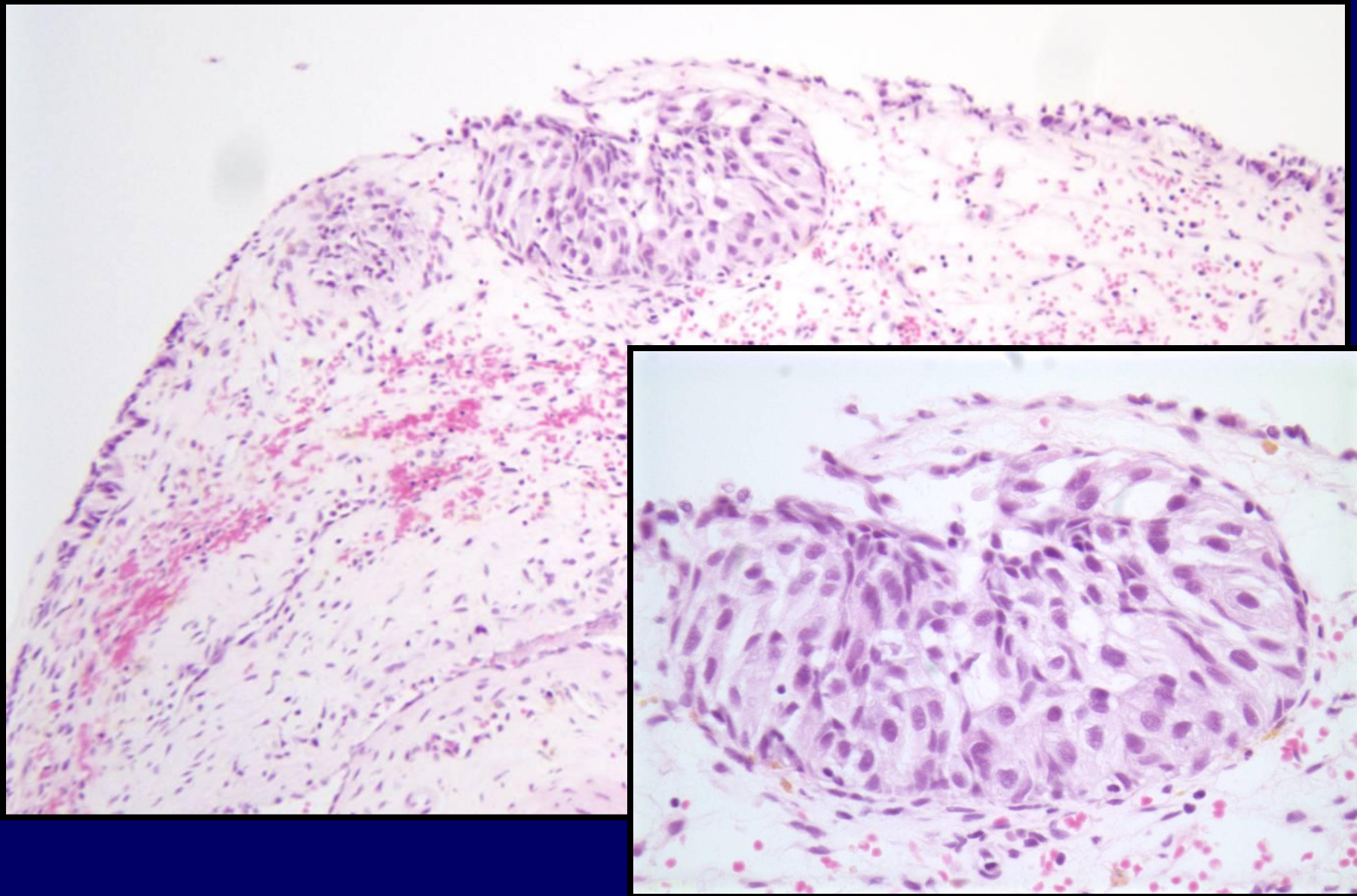


CIS - DENUDING





CIS - DENUDING



UROTHELIAL CARCINOMA IN SITU - LONG TERM OUTCOME

SURVIVAL-TYPE	10-Year	15-Year
Progression-free	63%	59%
Cancer-specific	79%	74%
All-cause	55%	40%

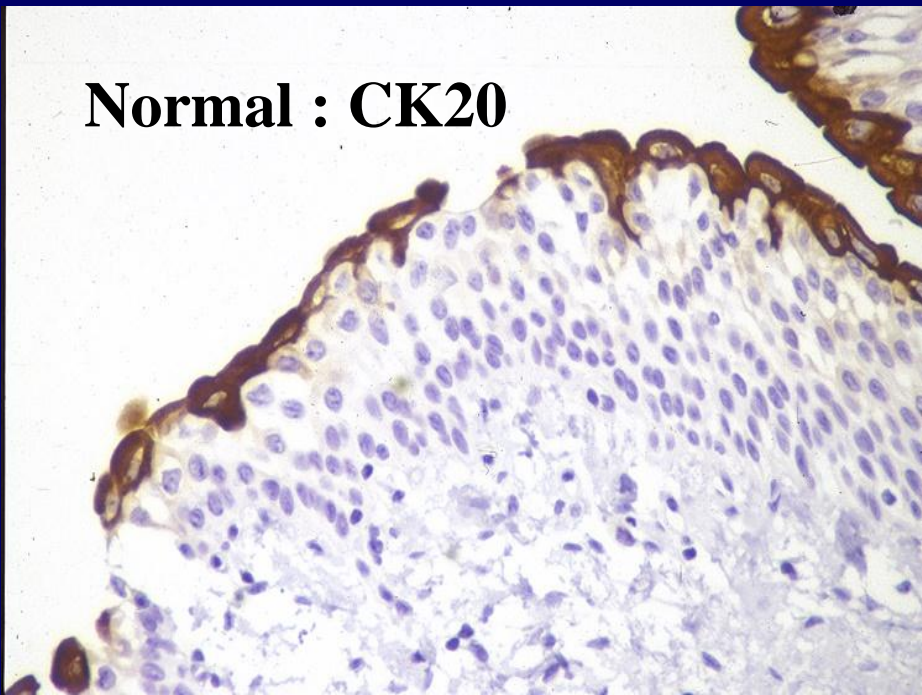
Cheng et al, Cancer 85:2469, 2000

UROTHELIAL FLAT LESIONS REPRODUCIBILITY STUDY

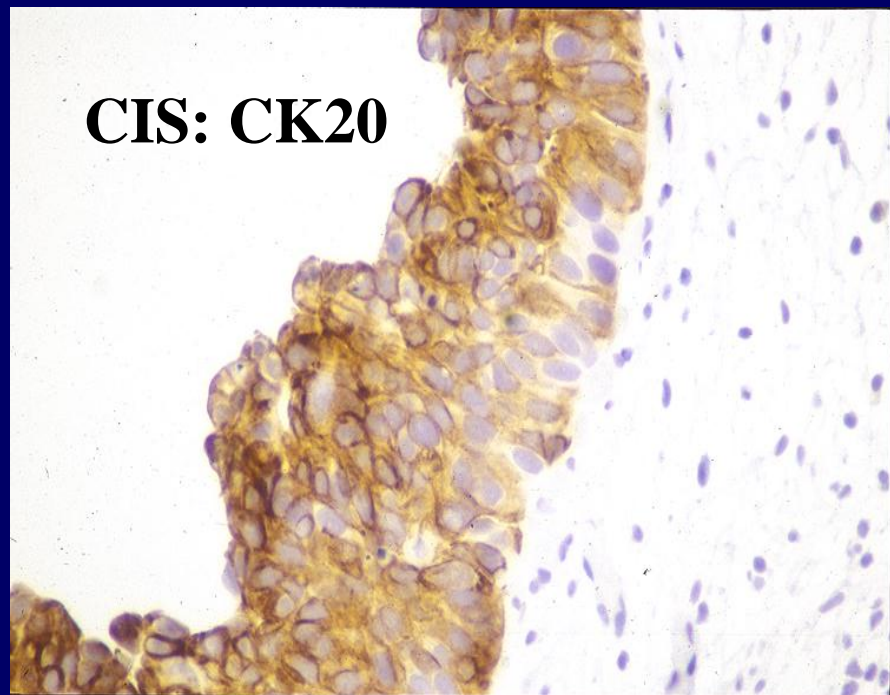
Category	Kappa	p-value	Agreement
Normal	0.484	<0.0001	Good
Reactive	0.361	<0.0001	Fair
Atypia ??	0.317	<0.0001	Fair
LGD	0.174	<0.0001	Poor
HGD/CIS	0.653	<0.0001	Excellent
Overall	0.453	<0.0001	Good

Amin et al, Modern Pathol, 1997

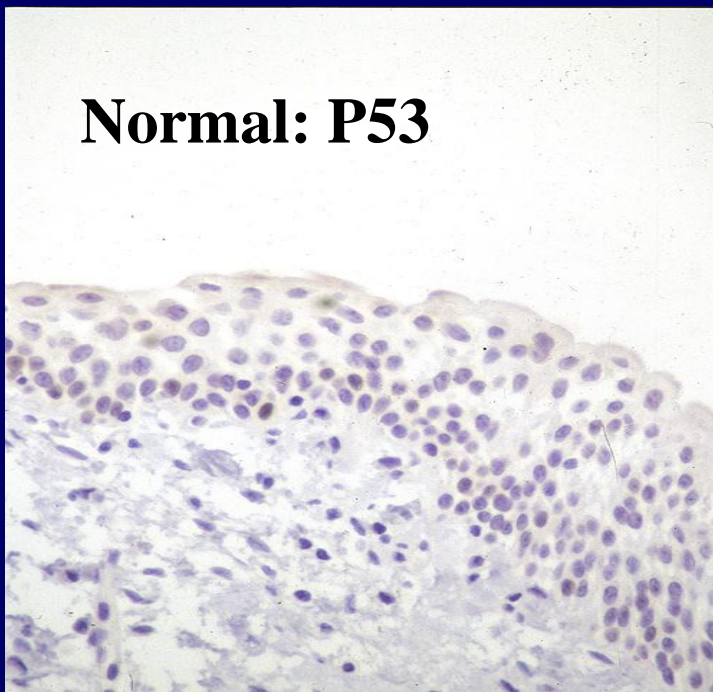
Normal : CK20



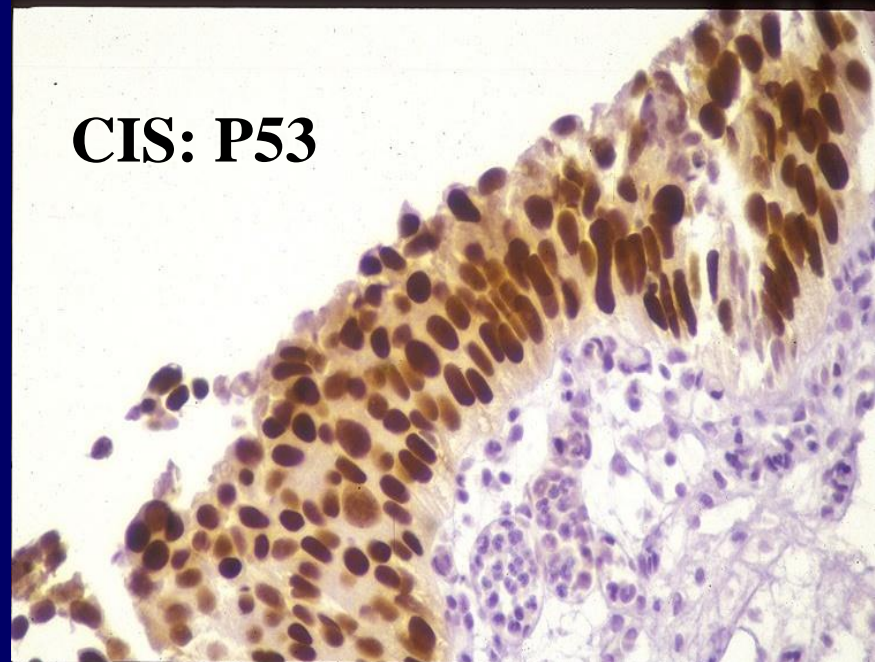
CIS: CK20



Normal: P53



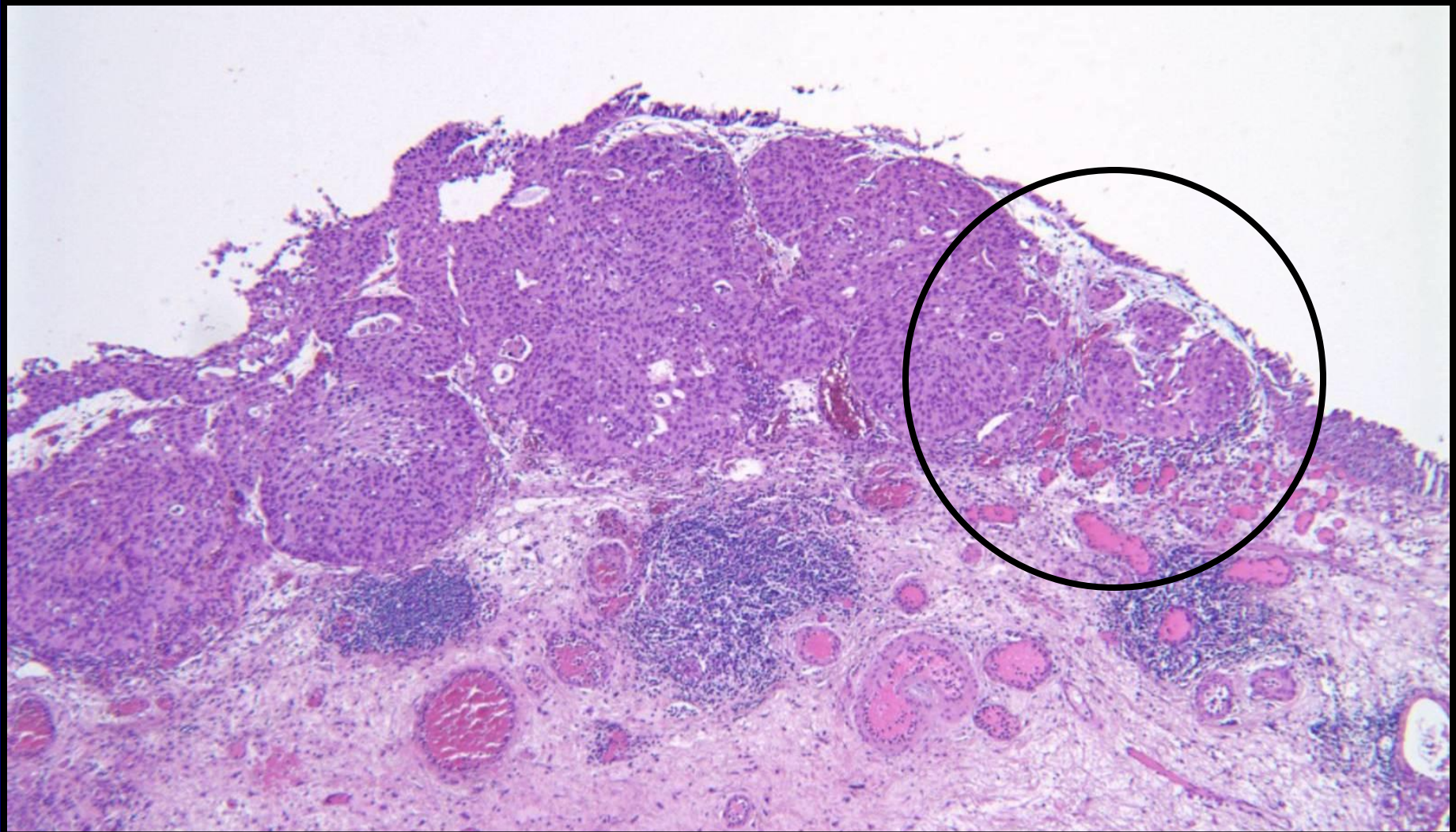
CIS: P53



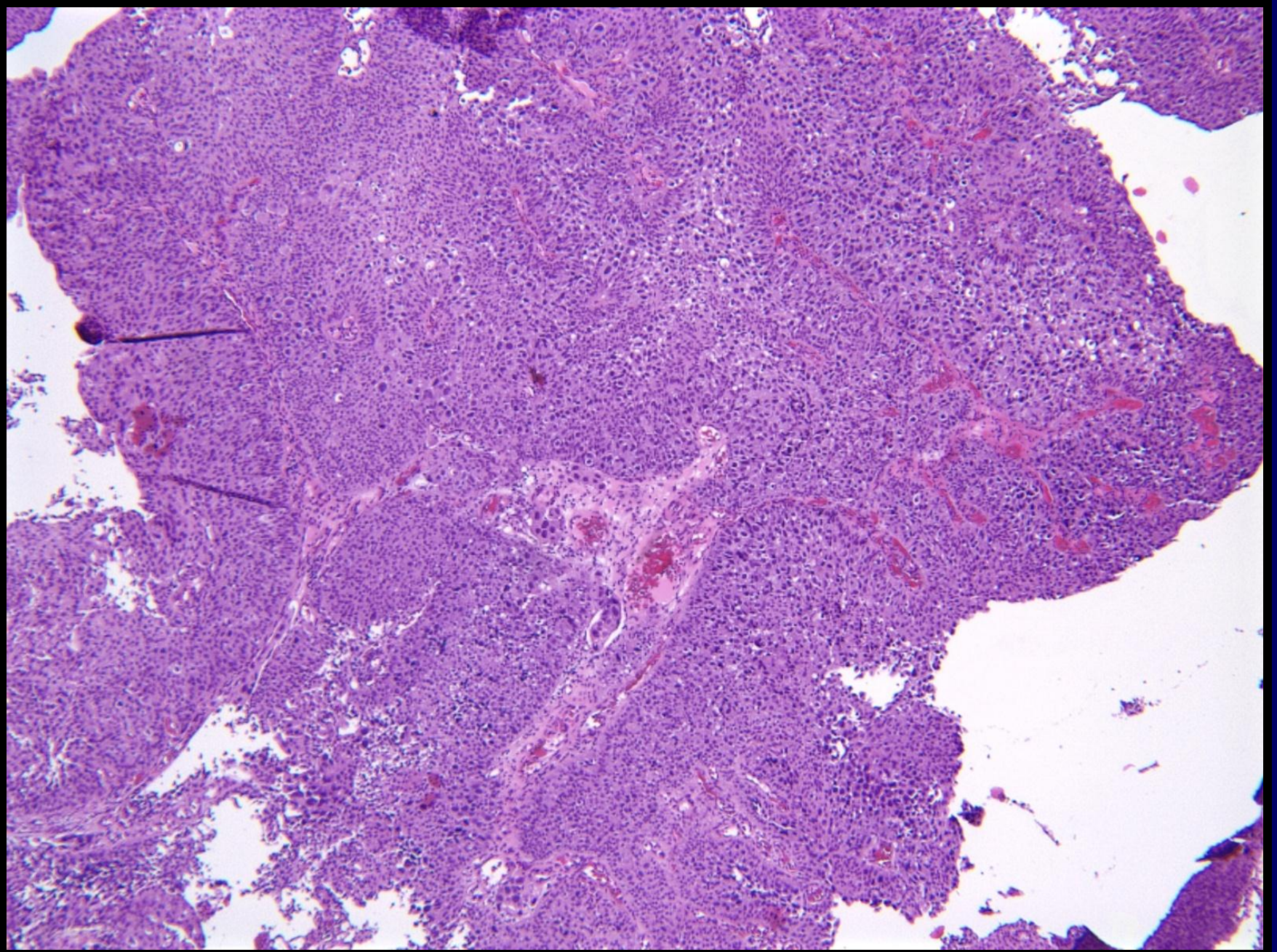
HISTOLOGIC FEATURES OF INVASION

- **Loss of smooth BM outline**
- **Single cells or irregular clusters of cells haphazardly extending from surface**
- **Invading cells with more abundant eosinophilic cytoplasm than non-invasive**
- **Retraction artifact**
- **Stromal edema - myxoid, desmoplasia or fibrosis**
- **Inflammation**

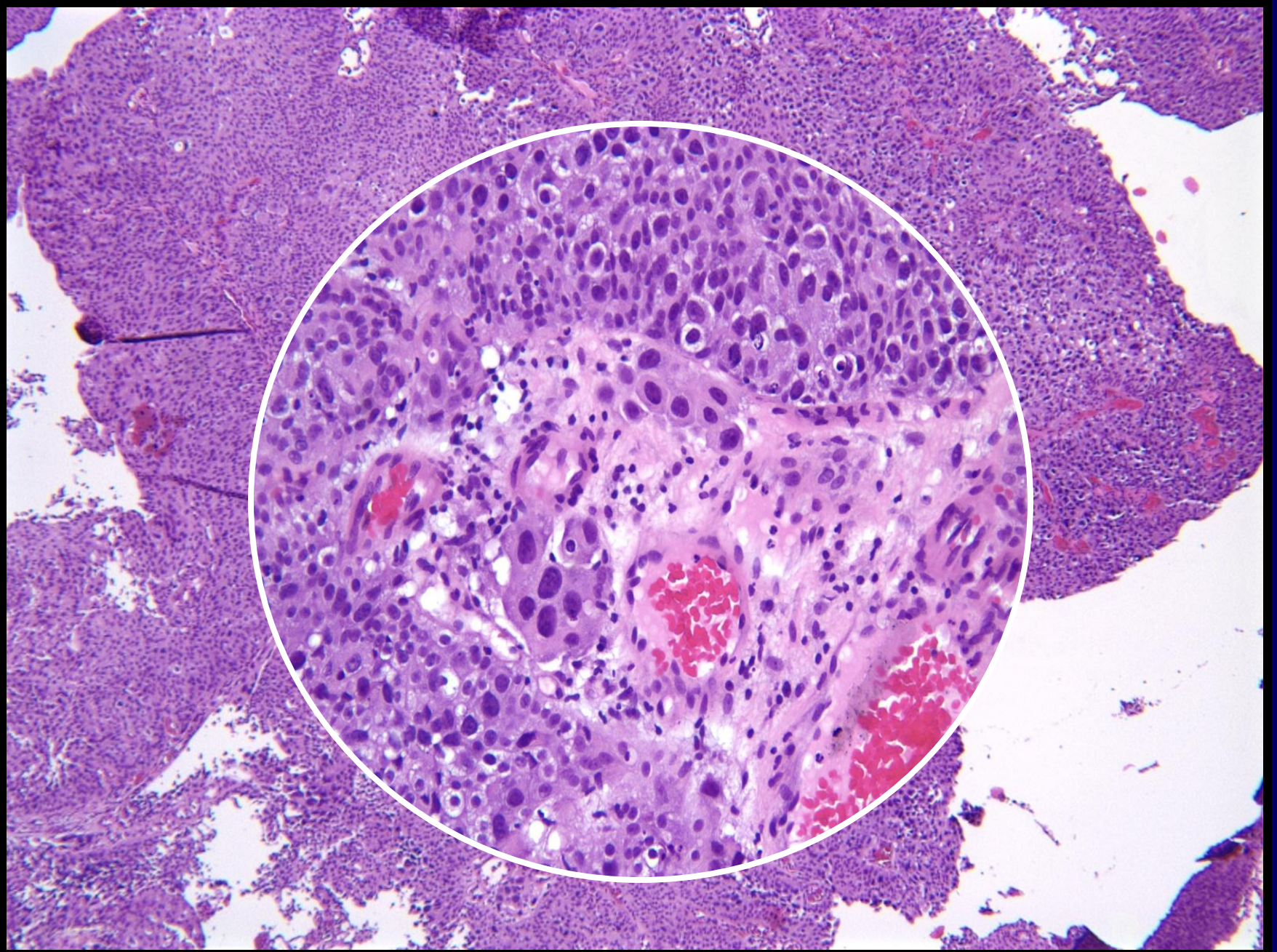
LAMINA PROPRIA INVASION



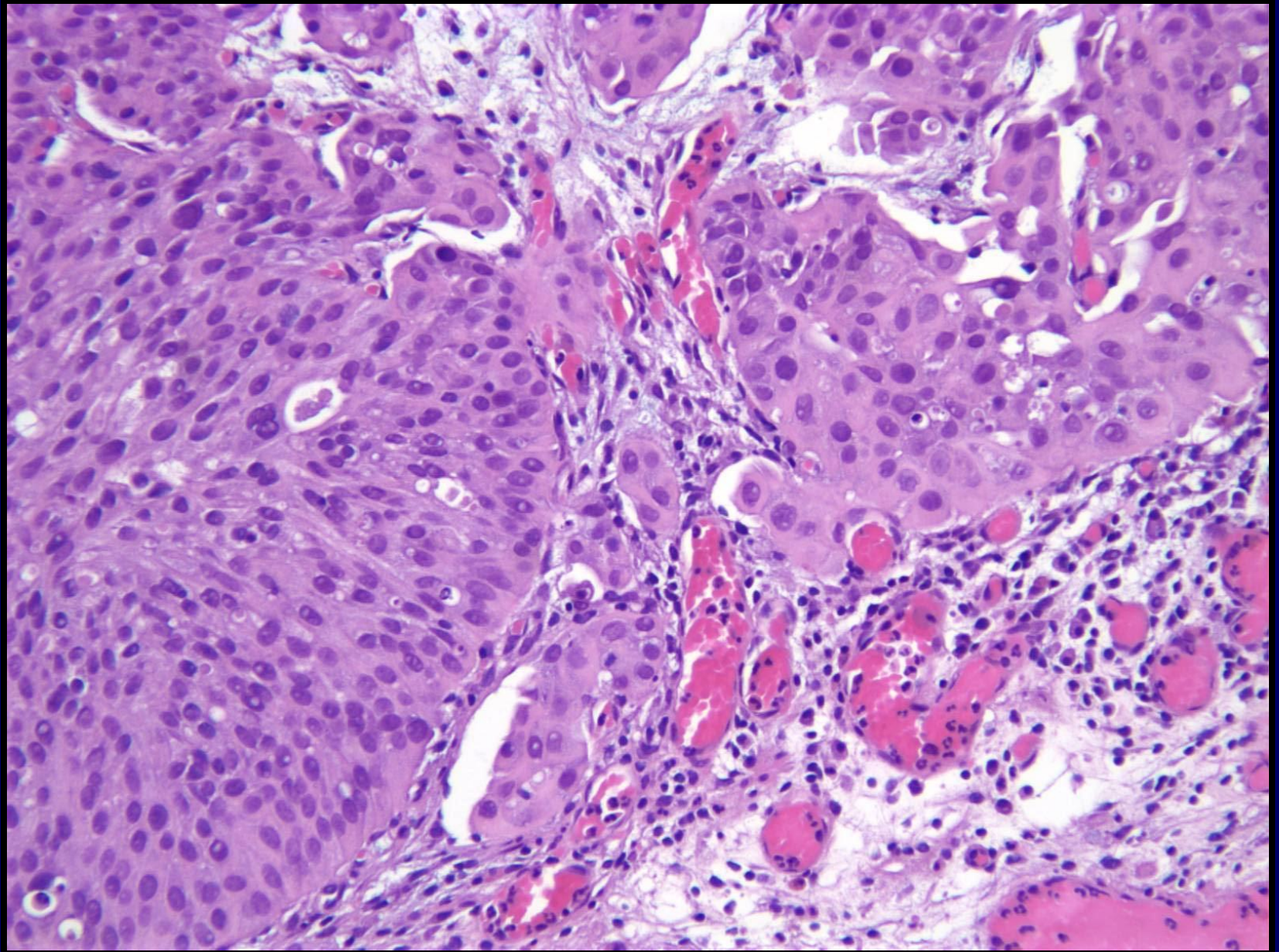
DIAGNOSIS OF INVASION

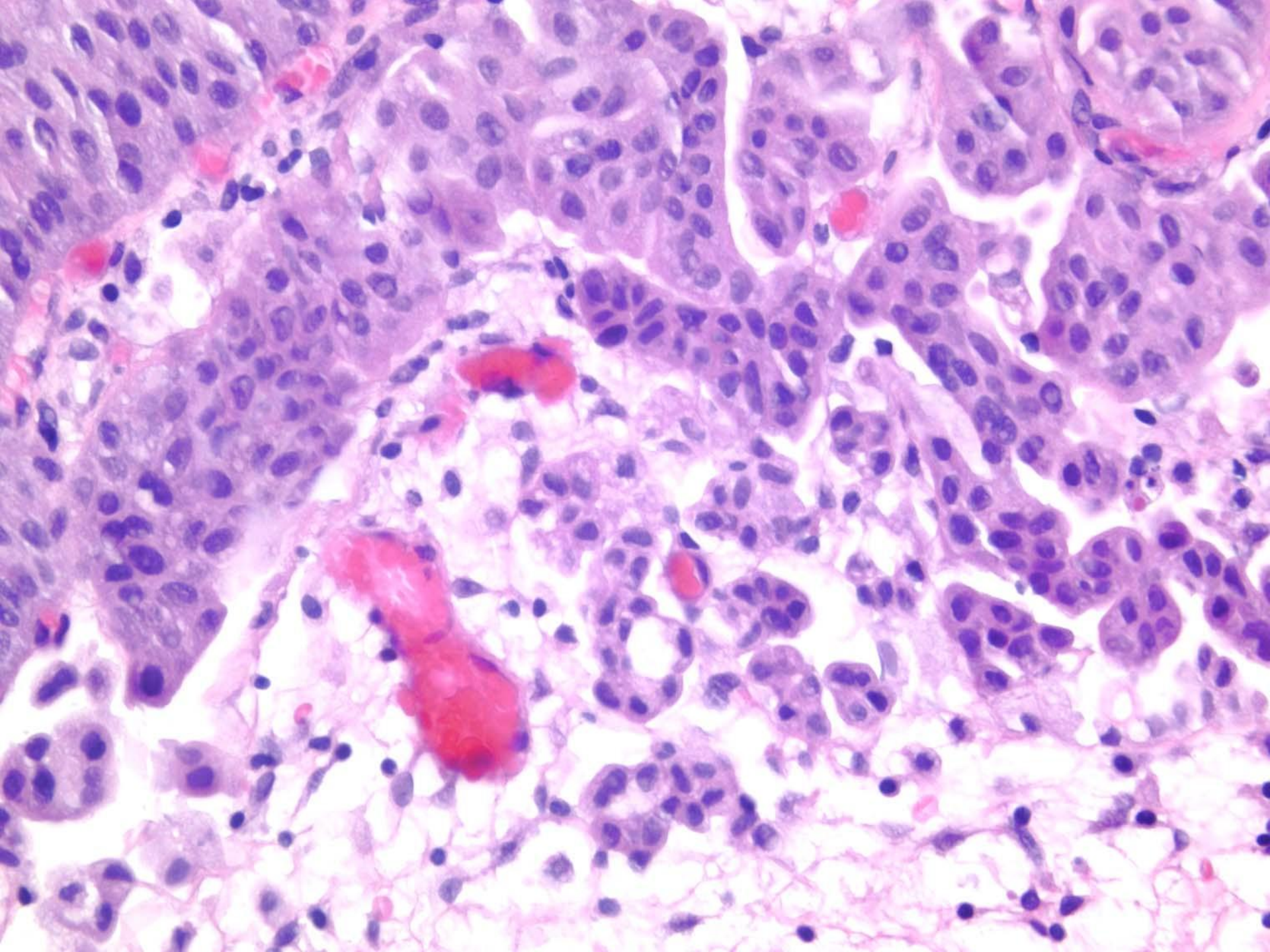


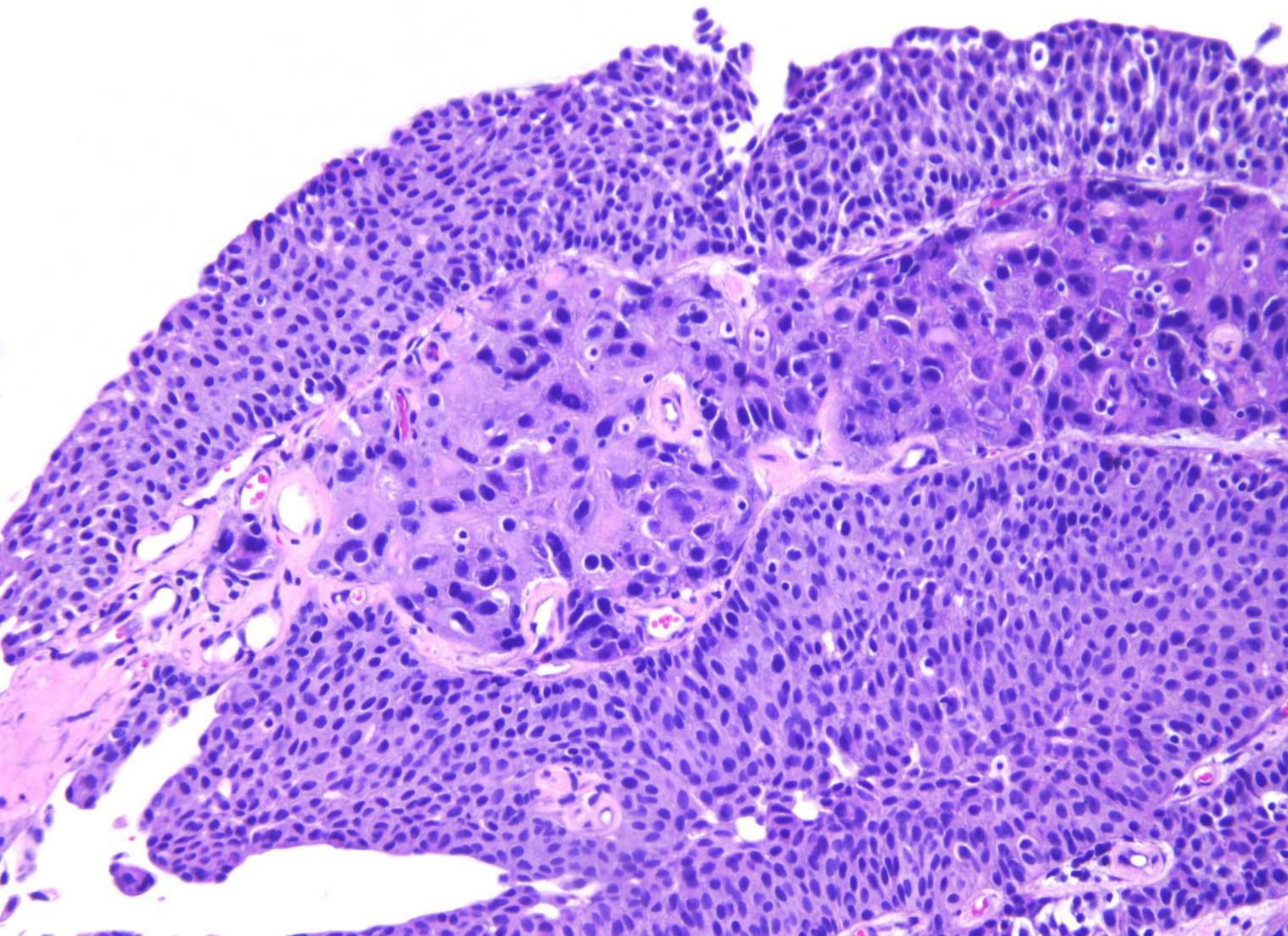
DIAGNOSIS OF INVASION



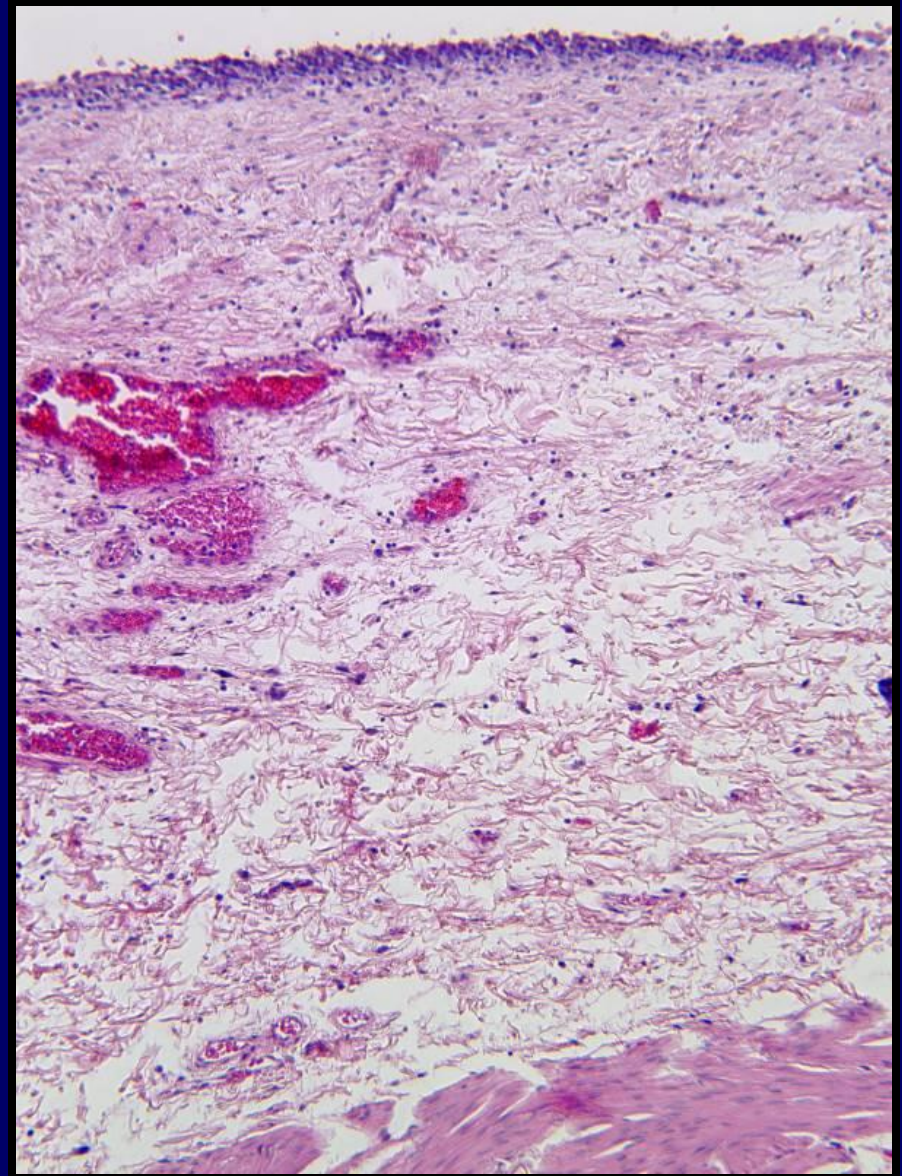
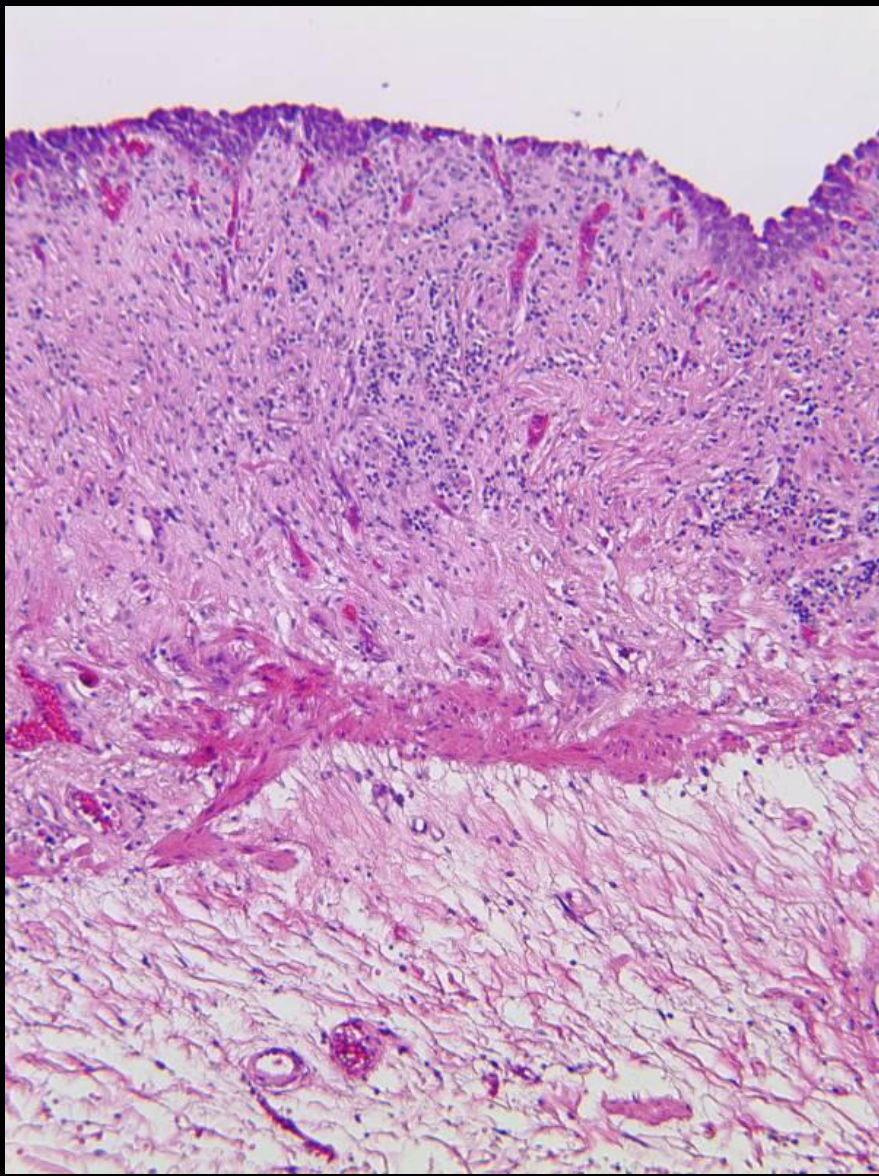
LAMINA PROPRIA INVASION



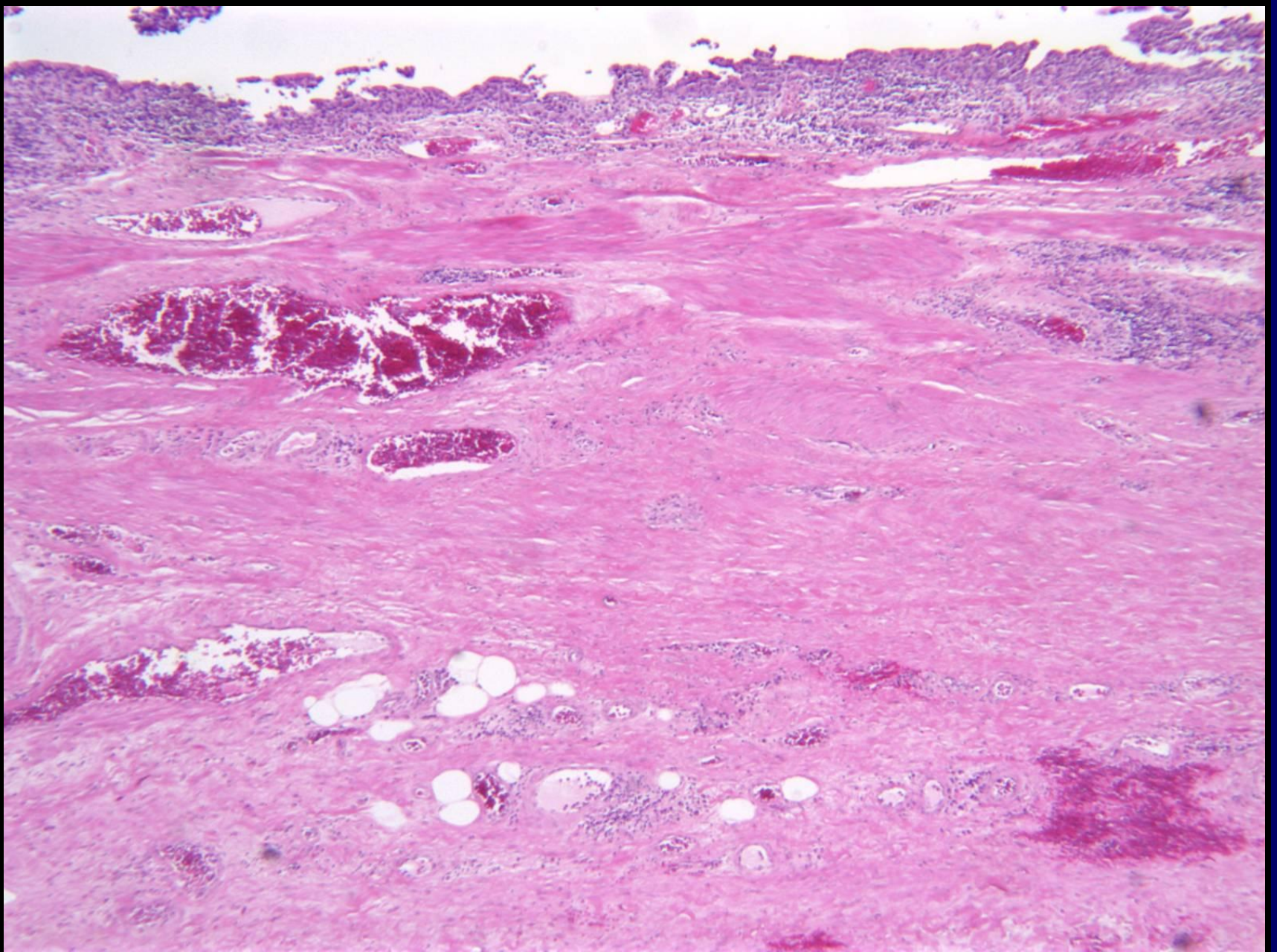




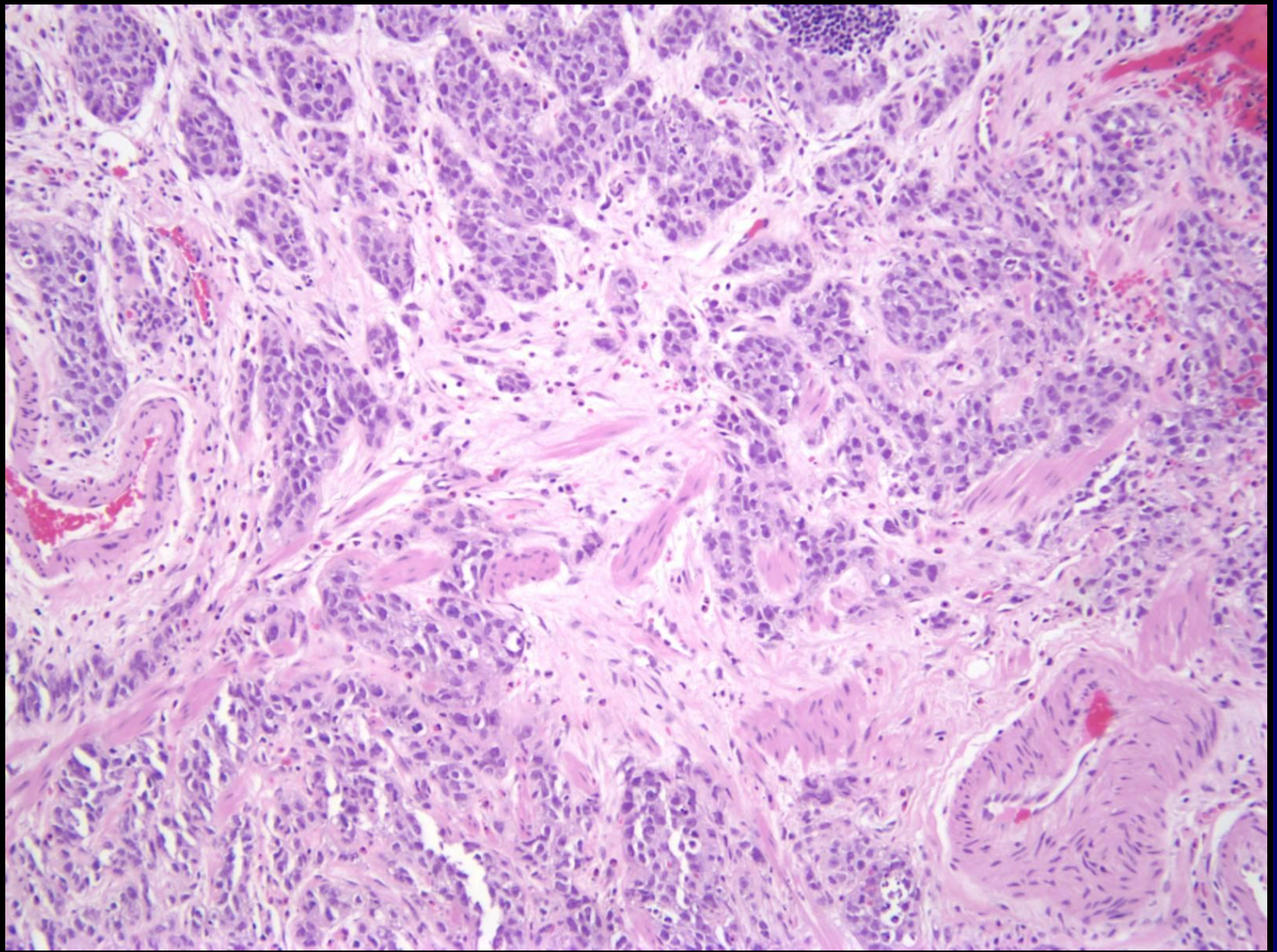
MUSCULARIS MUCOSAE



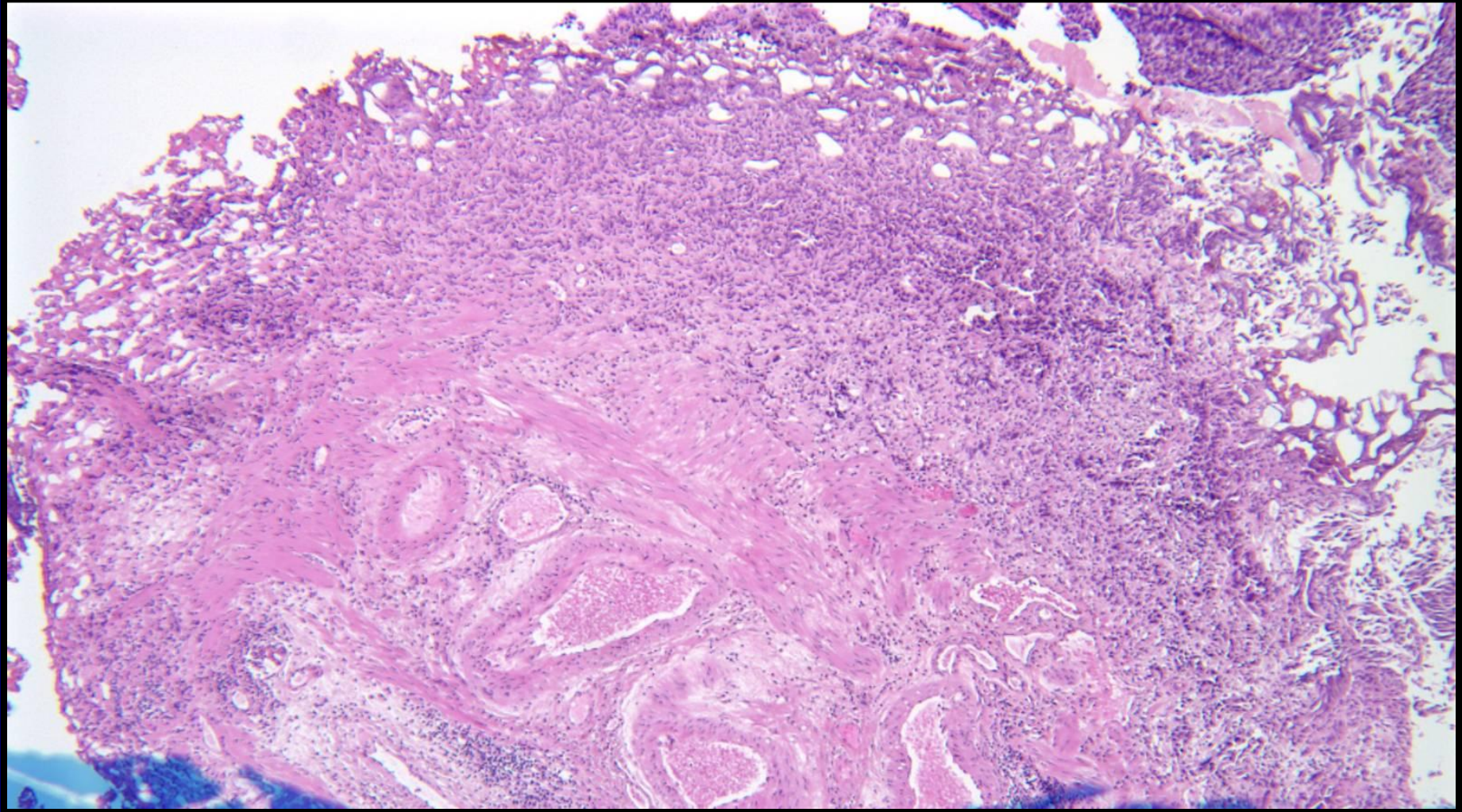
TRIGONE REGION



MUSCULARIS MUCOSAE INVASION

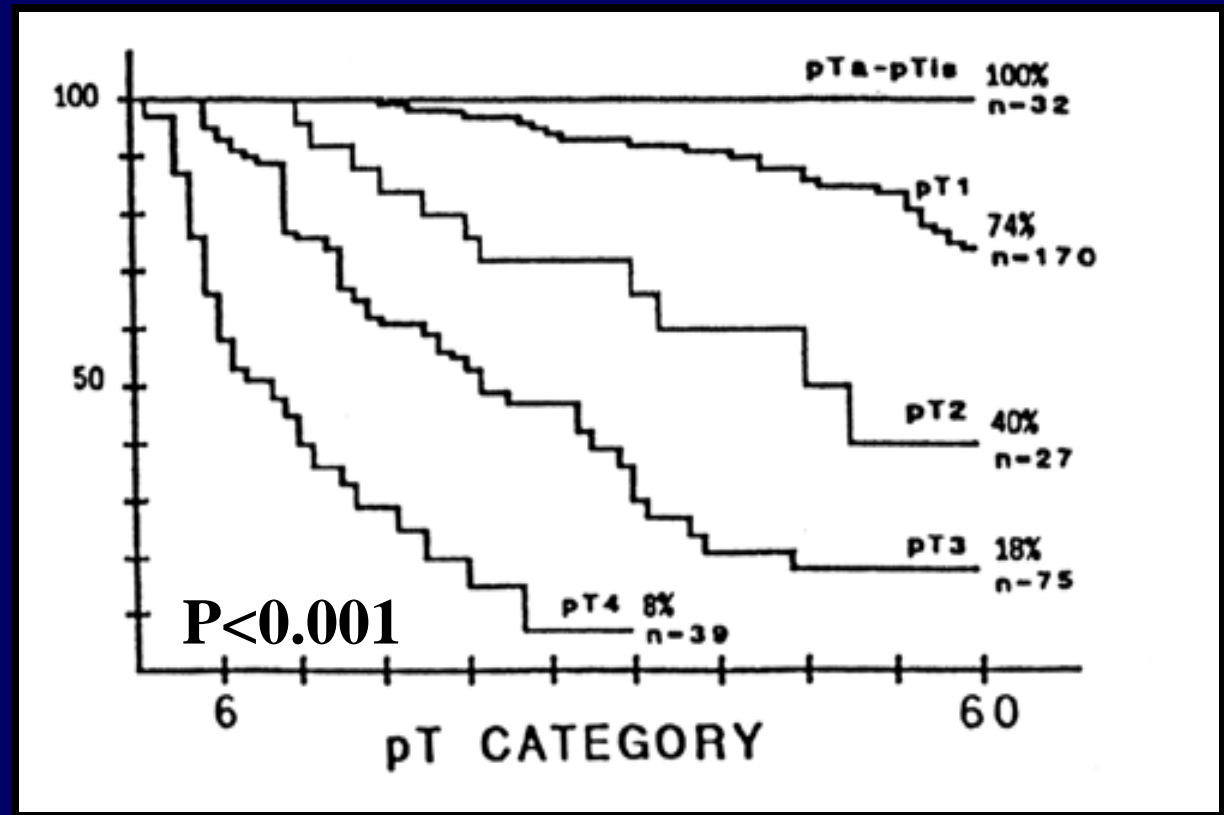


MUSCULARIS MUCOSAE INVASION



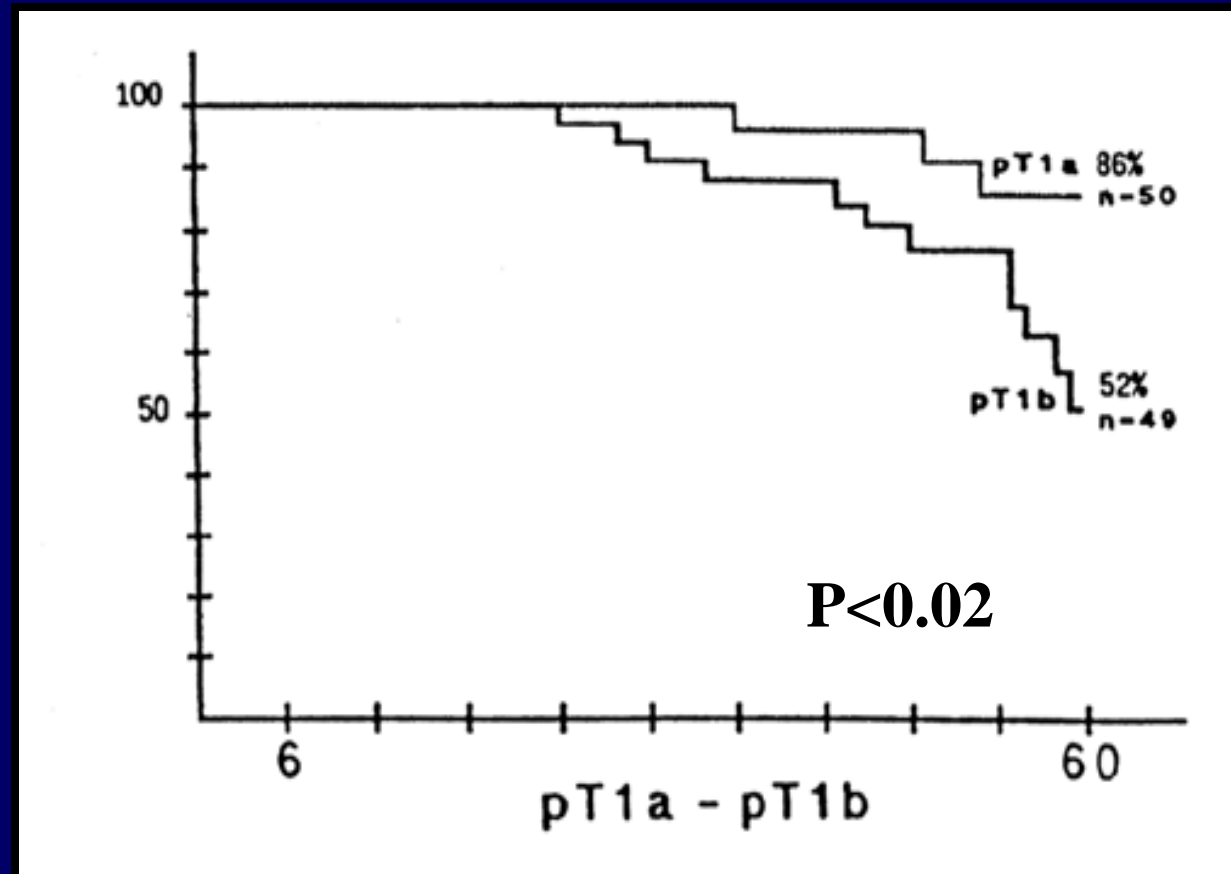
SURVIVAL ACCORDING TO PATHOLOGIC STAGE (AJCC - 1987)

- 343 patients - initial treatment
- M:F, 6.6:1
- Age, mean 66 yrs
- Treated by:
 - TUR (59%)
 - cyst (14%)
 - RT (15%)



SURVIVAL ACCORDING TO MUSCULARIS MUCOSAE INVASION

- 343 patients - initial treatment
 - 170 pT1
- Cases centrally reviewed
- **Substaging possible in 99 (58%)**
- Treated by:
 - TURBT with intravesical tx



SURVIVAL ACCORDING TO MUSCULARIS MUCOSAE INVASION

- 151 patients – pT1 on TUR
- Cases centrally reviewed
- 97 included in study
 - All high-grade with mp in specimen
- **Substaging possible in 85 (88%)**
- Treated by:
 - TURBT +/- intravesical BCG

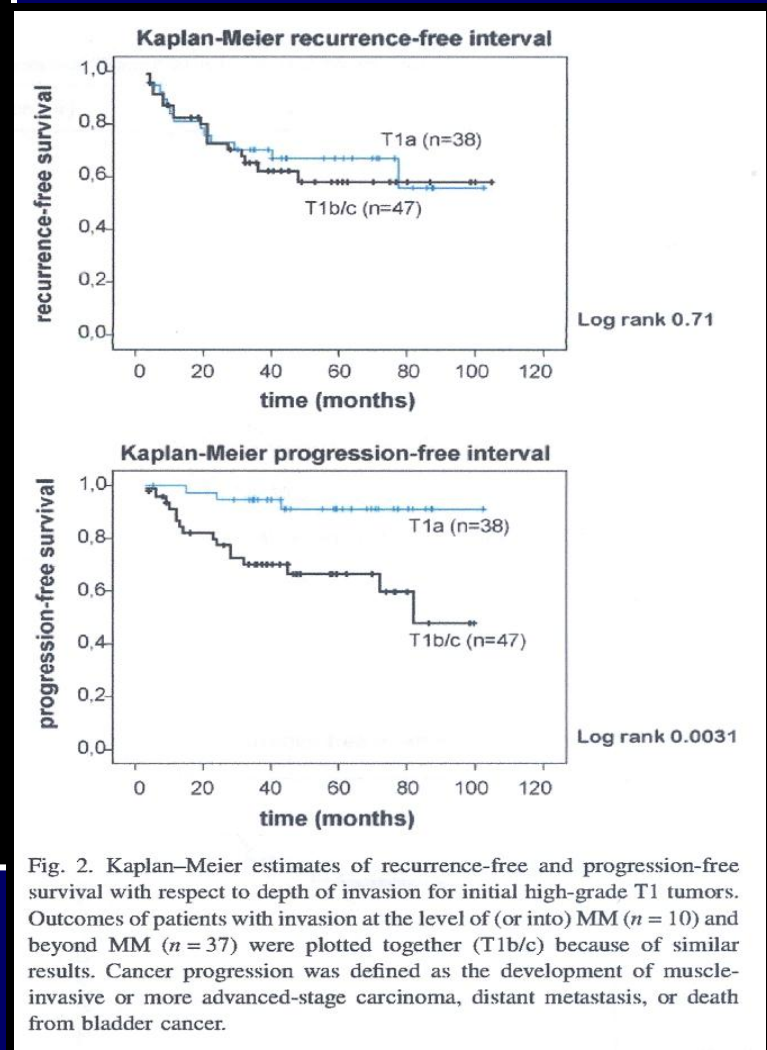


Fig. 2. Kaplan-Meier estimates of recurrence-free and progression-free survival with respect to depth of invasion for initial high-grade T1 tumors. Outcomes of patients with invasion at the level of (or into) MM ($n = 10$) and beyond MM ($n = 37$) were plotted together (T1b/c) because of similar results. Cancer progression was defined as the development of muscle-invasive or more advanced-stage carcinoma, distant metastasis, or death from bladder cancer.

NEOPLASMS OF THE RENAL PELVES AND URETERS

ESSENTIALLY SAME AS BLADDER EXCEPT:

LOWER FREQUENCY

STRONGER a/w CHEMICALS (PHENACETIN)

STRONGER a/w OUTFLOW OBSTRUCTION

DECREASED VALUE OF CYTOLOGY IN Dx

INCREASED FREQUENCY UC_a ELSEWHERE

NEOPLASMS OF THE URETHRA

LIKE BLADDER EXCEPT:

LOWER FREQUENCY

HIGHER INCIDENCE IN WOMEN

INCREASED SQUAMOUS TYPE

INCREASED CLEAR CELL TYPE

HIGHER STAGE AT DIAGNOSIS





UROTHELIAL CARCINOMA NESTED VARIANT

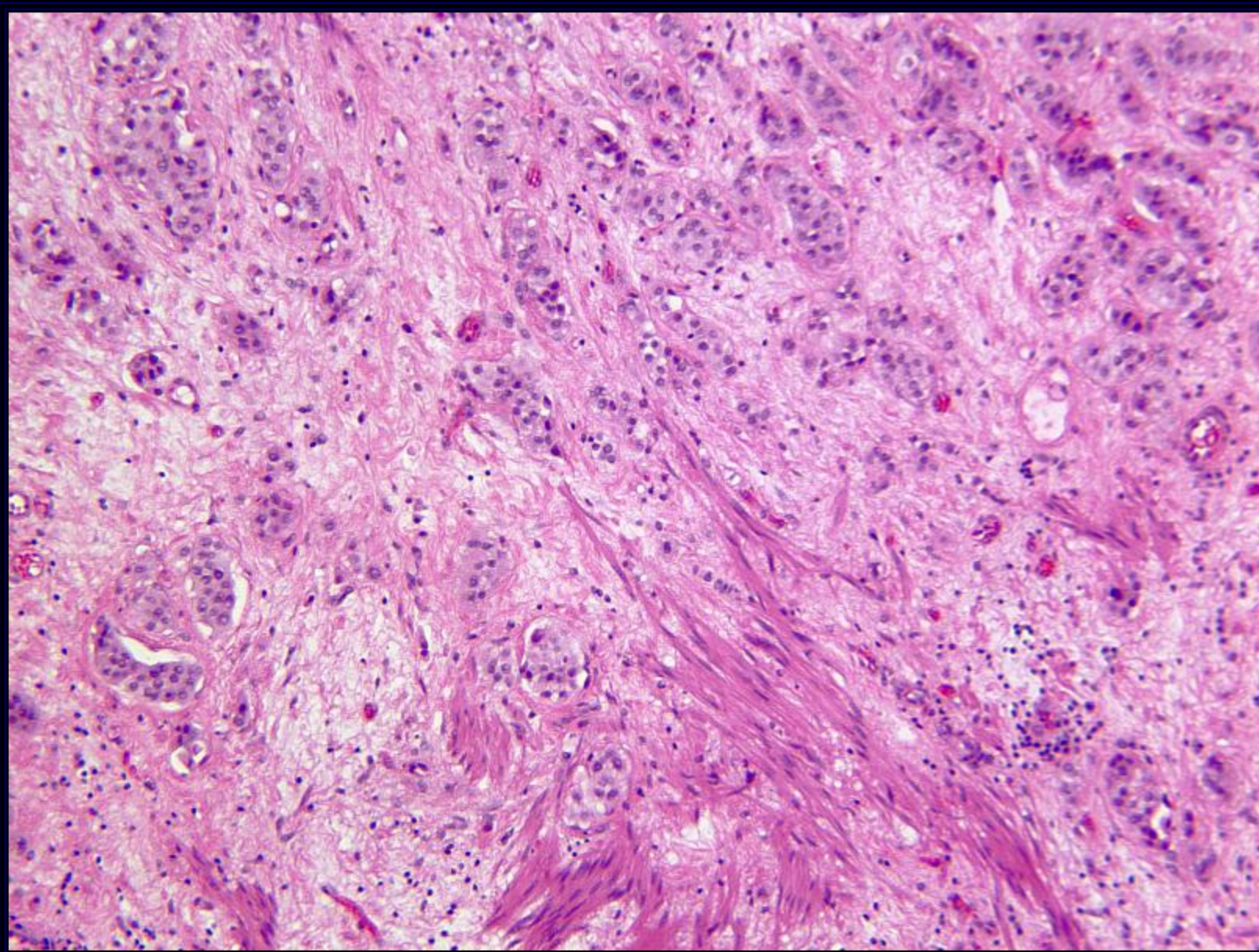
- **CLINICAL**

- Similar epidemiology to usual UC
- Similar biologic behavior

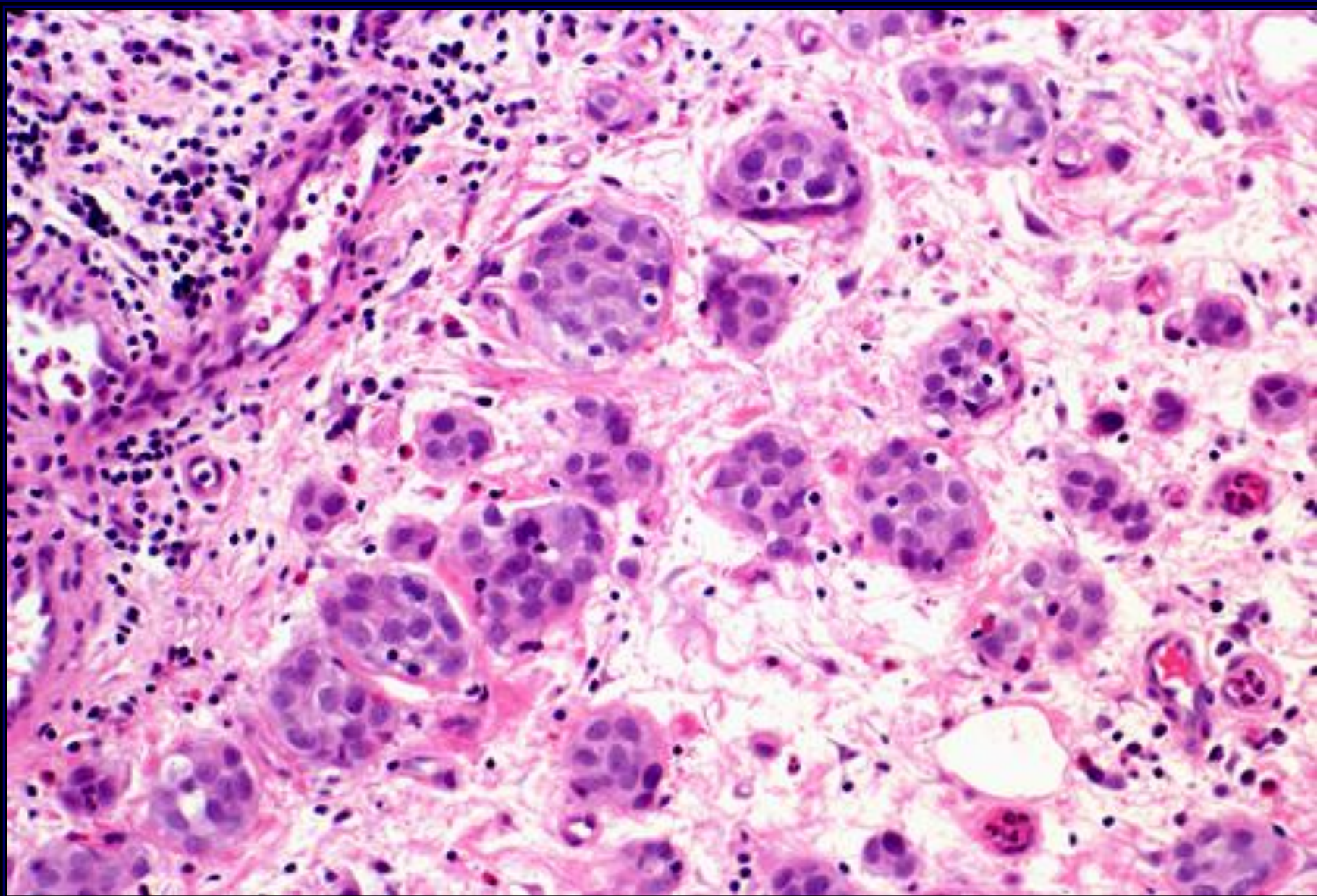
- **PATHOLOGY**

- Small solid nests, some with tubules
- Infiltrative growth pattern
- Low nuclear grade
- Typical UC component present in 50%

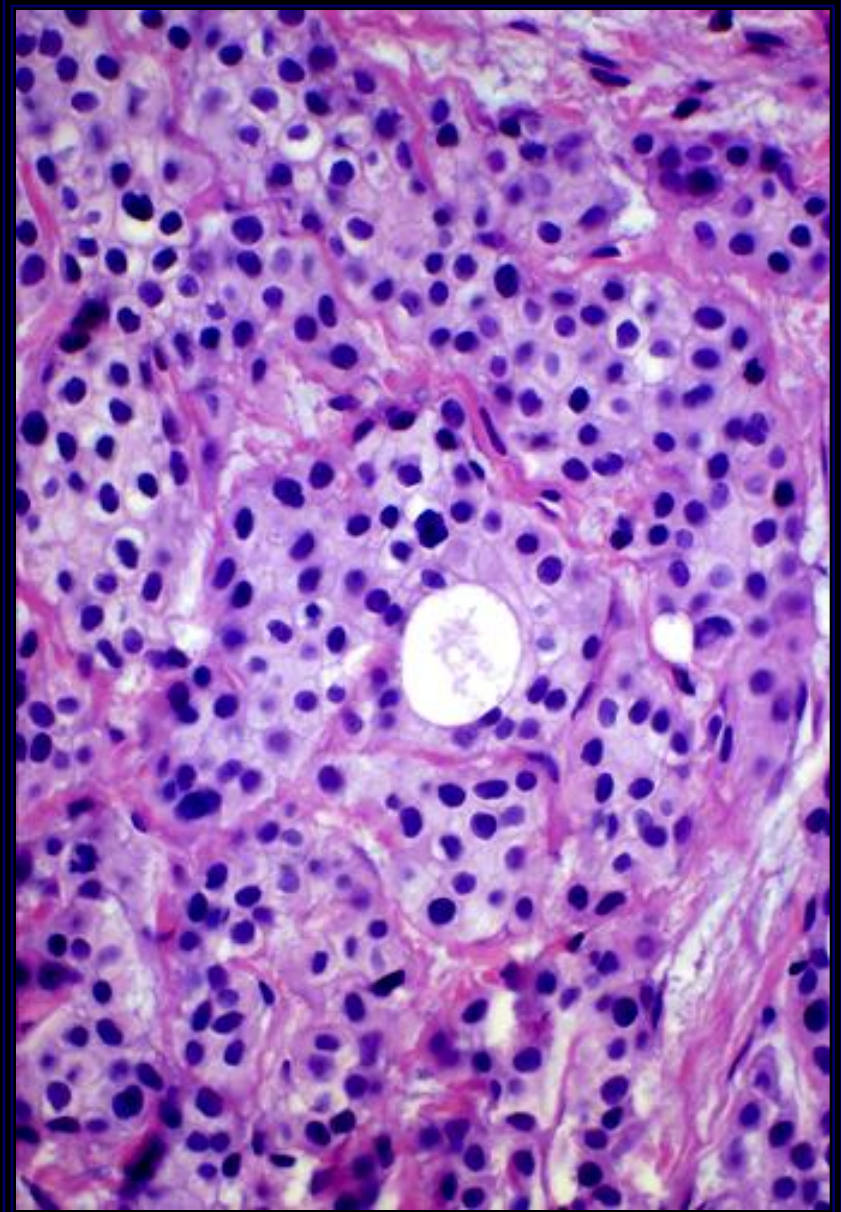
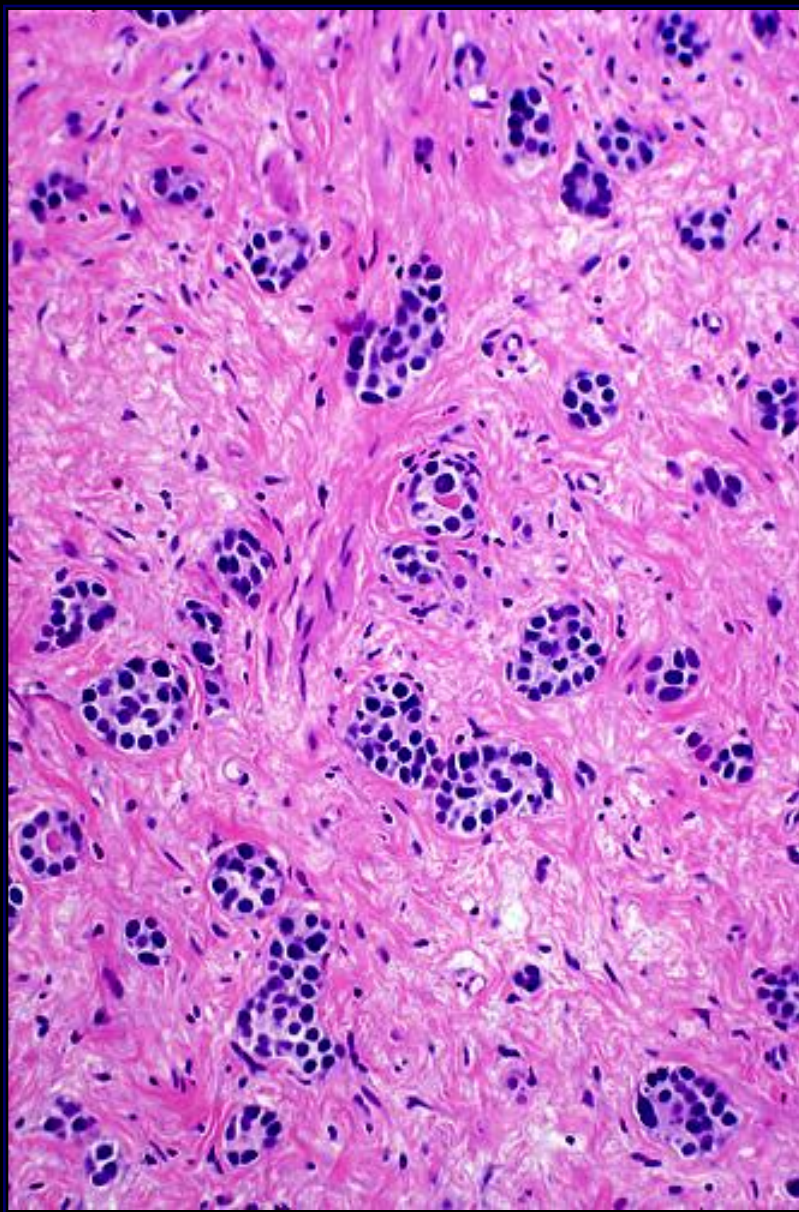
NESTED VARIANT



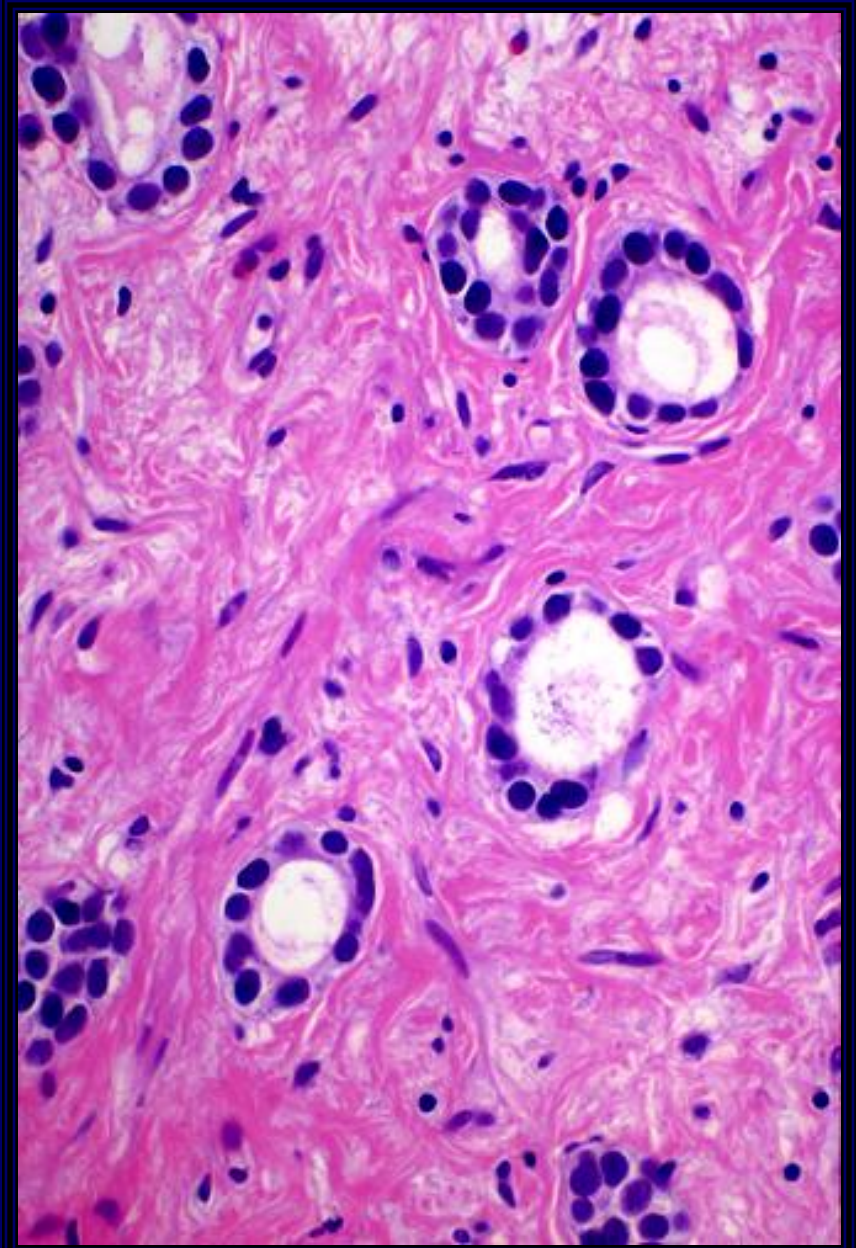
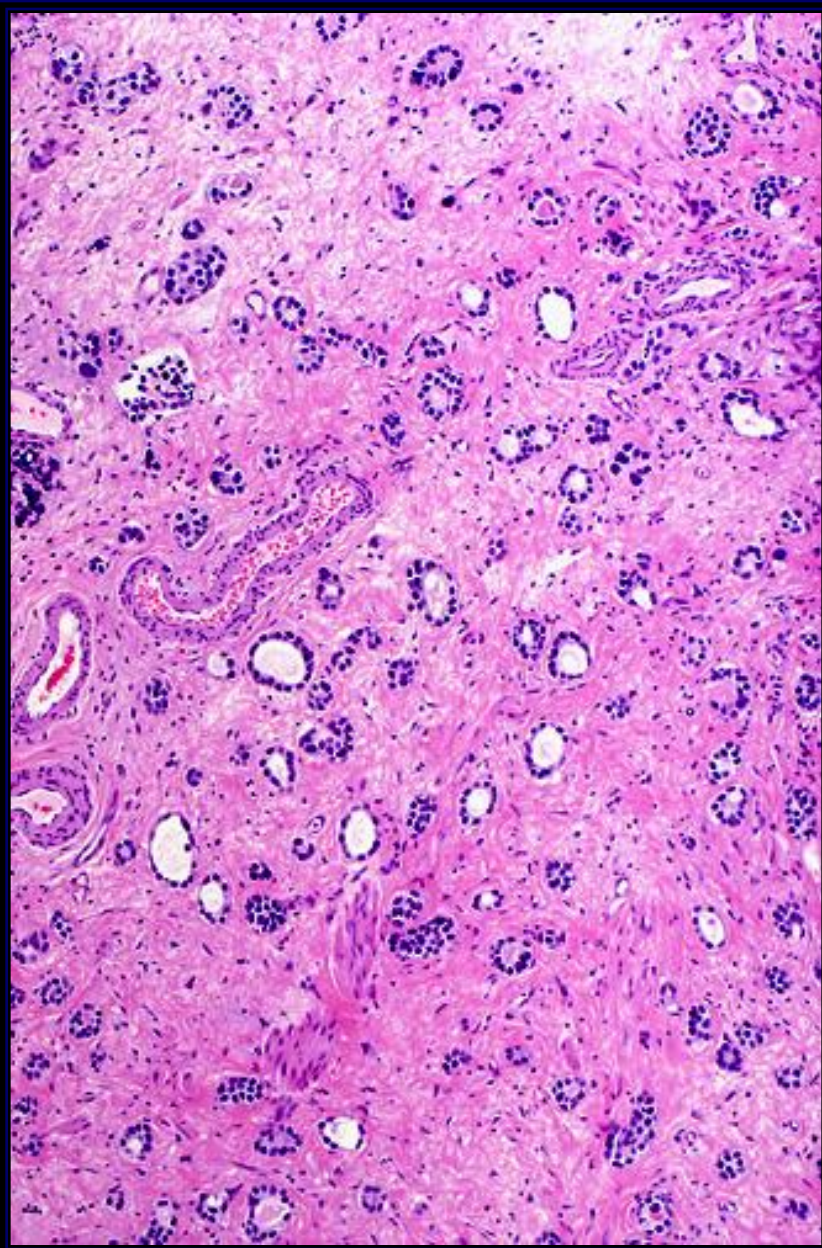
NESTED VARIANT



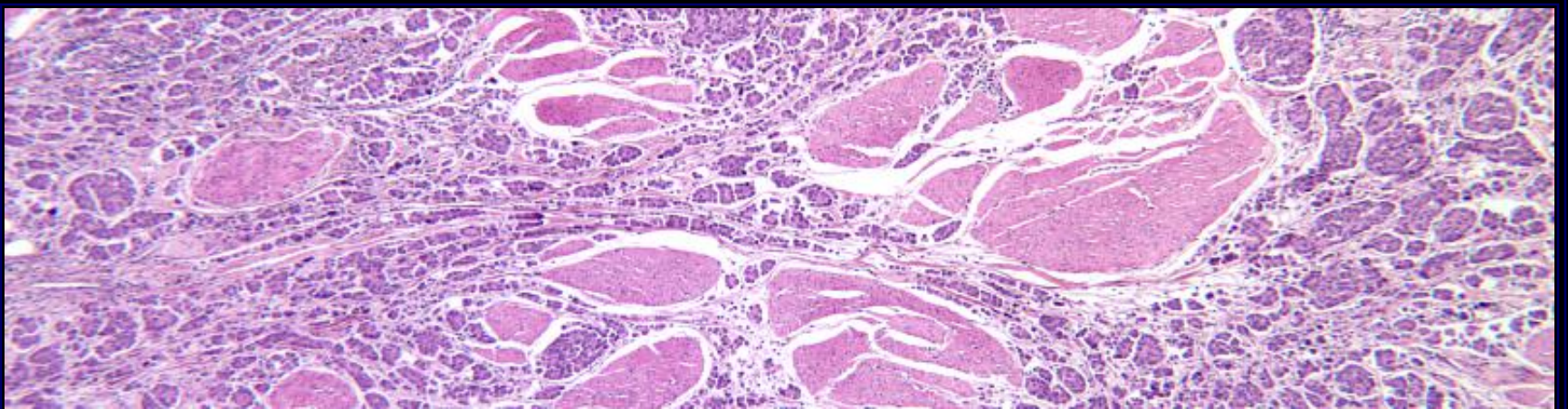
NESTED VARIANT



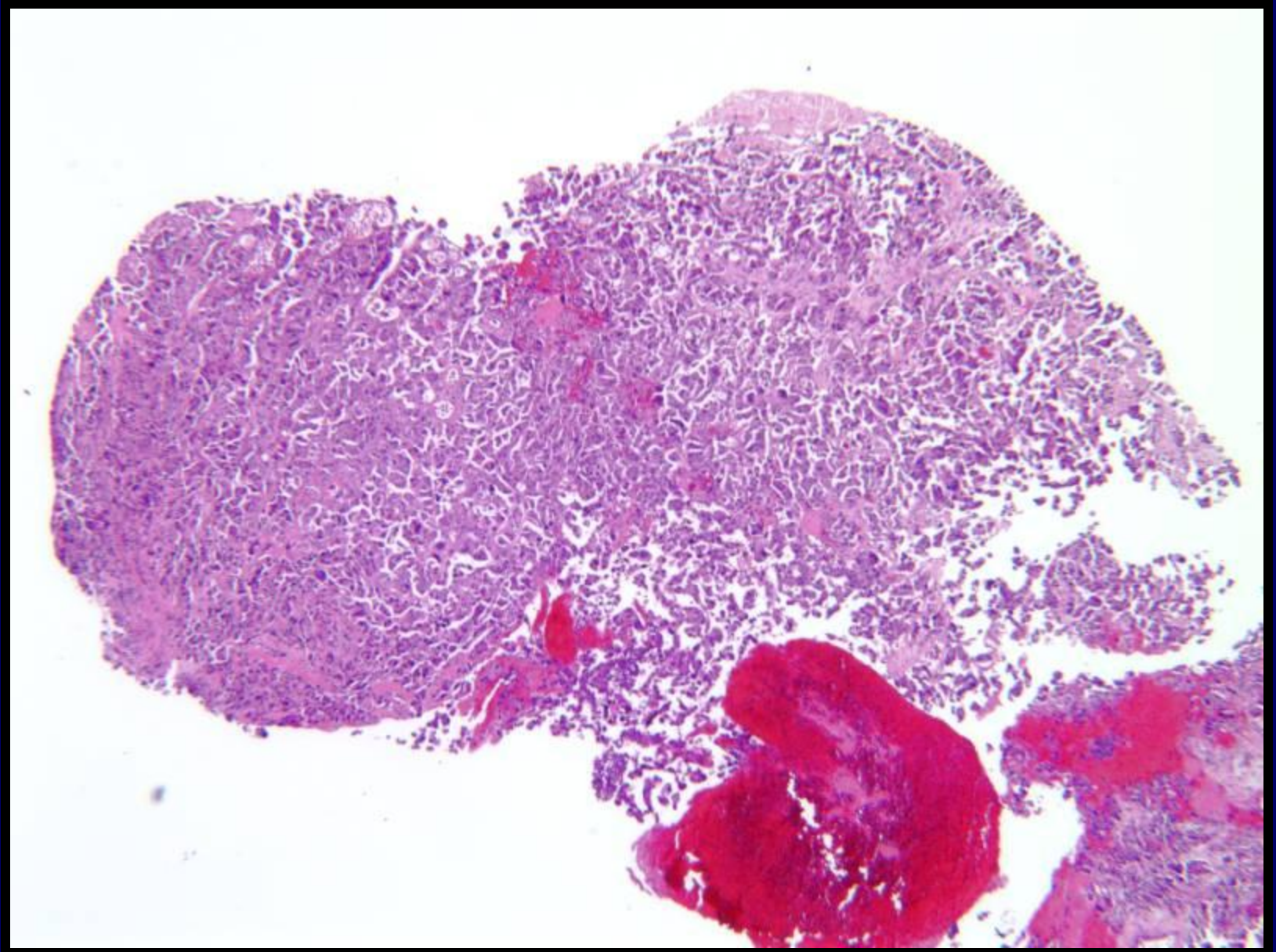
MICROCYSTIC VARIANT



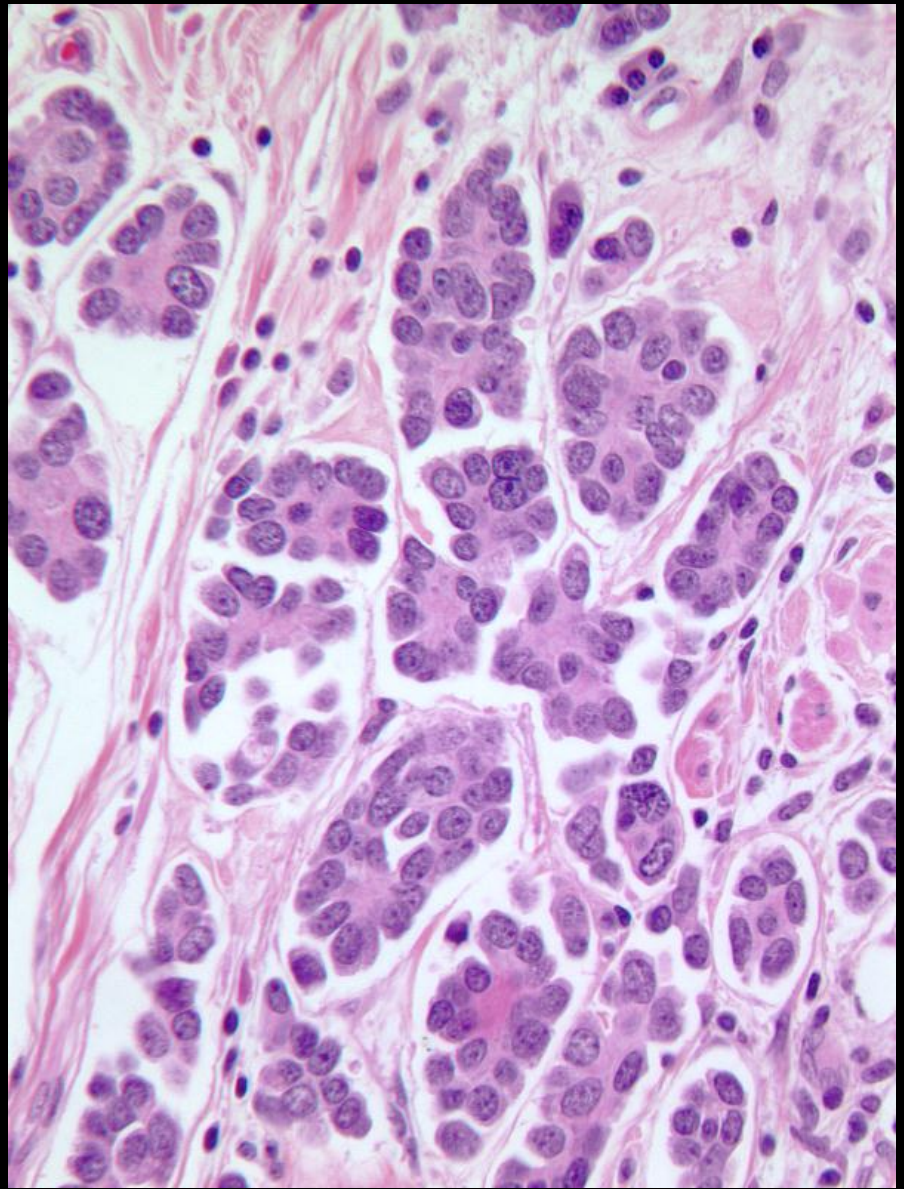
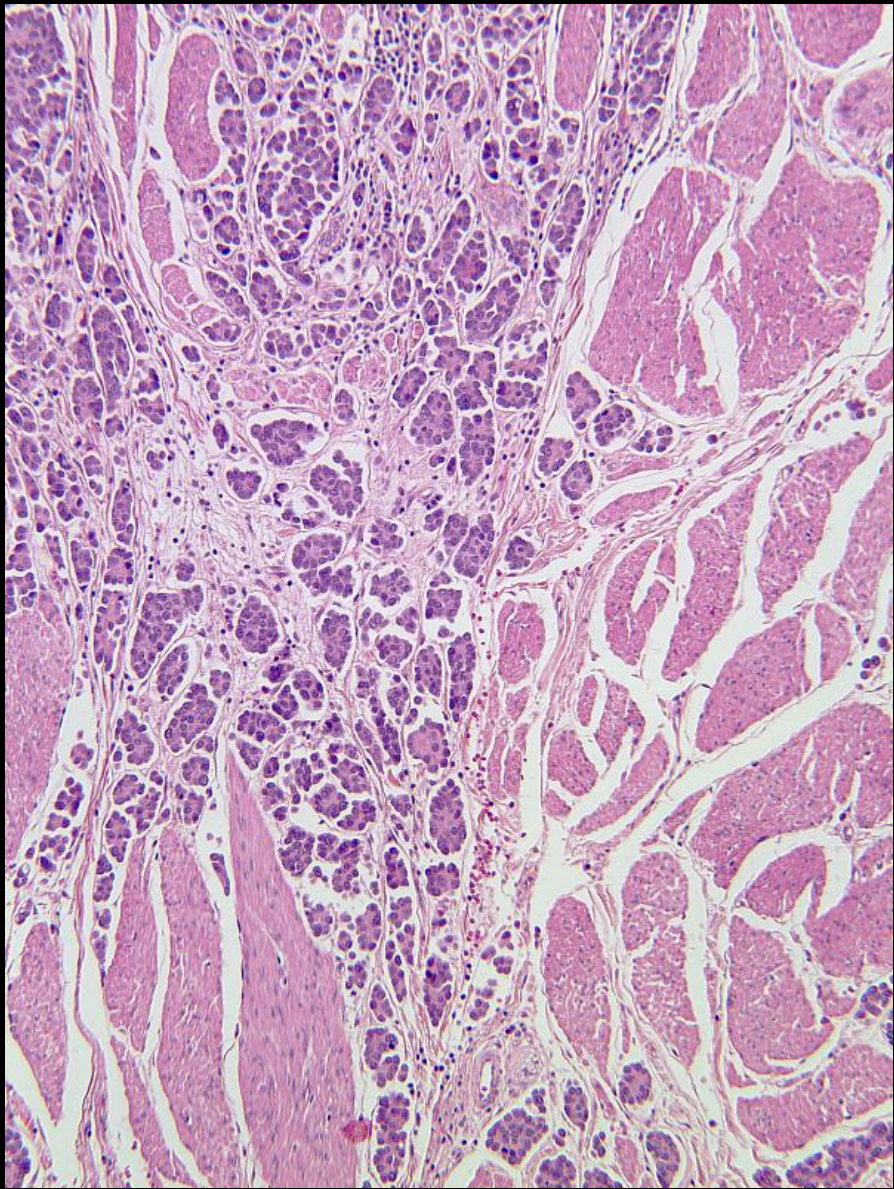
MICROPAPILLARY VARIANT



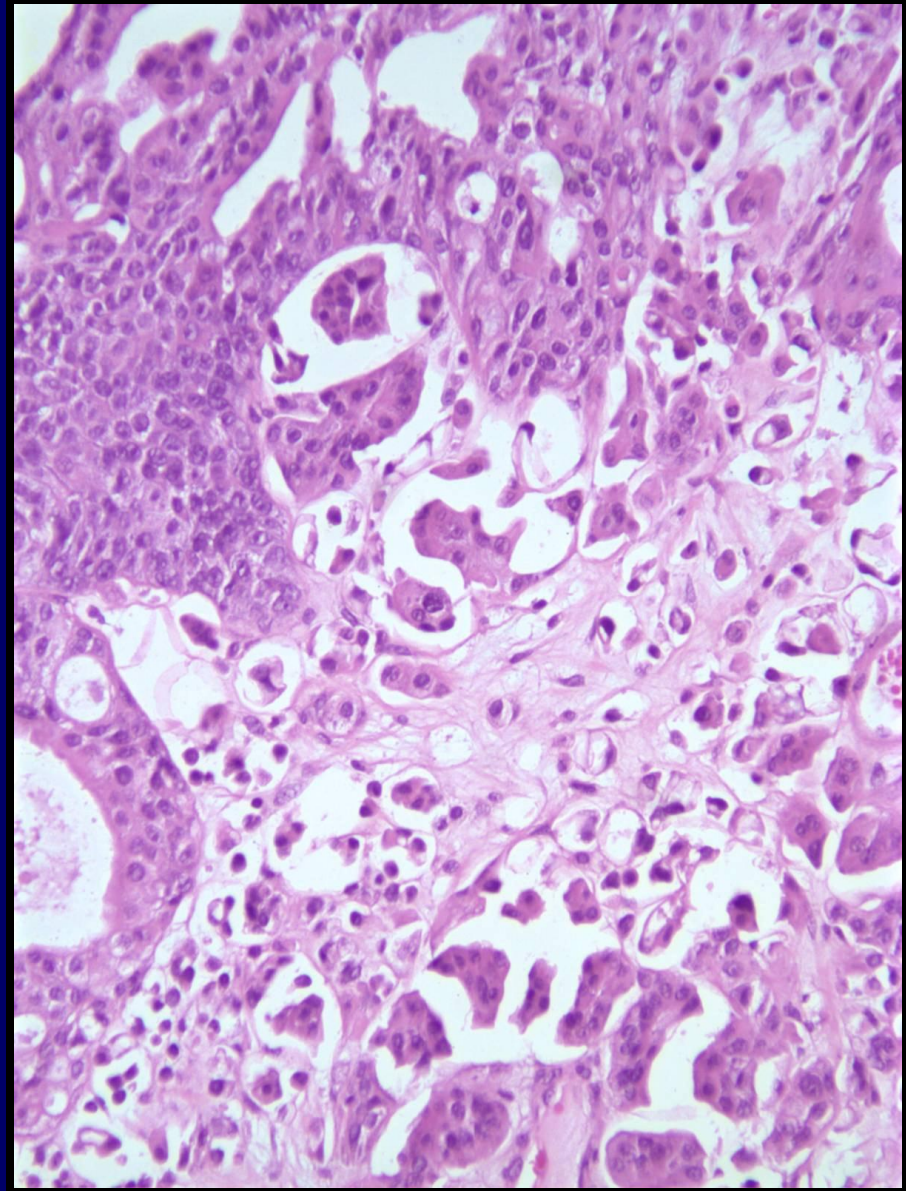
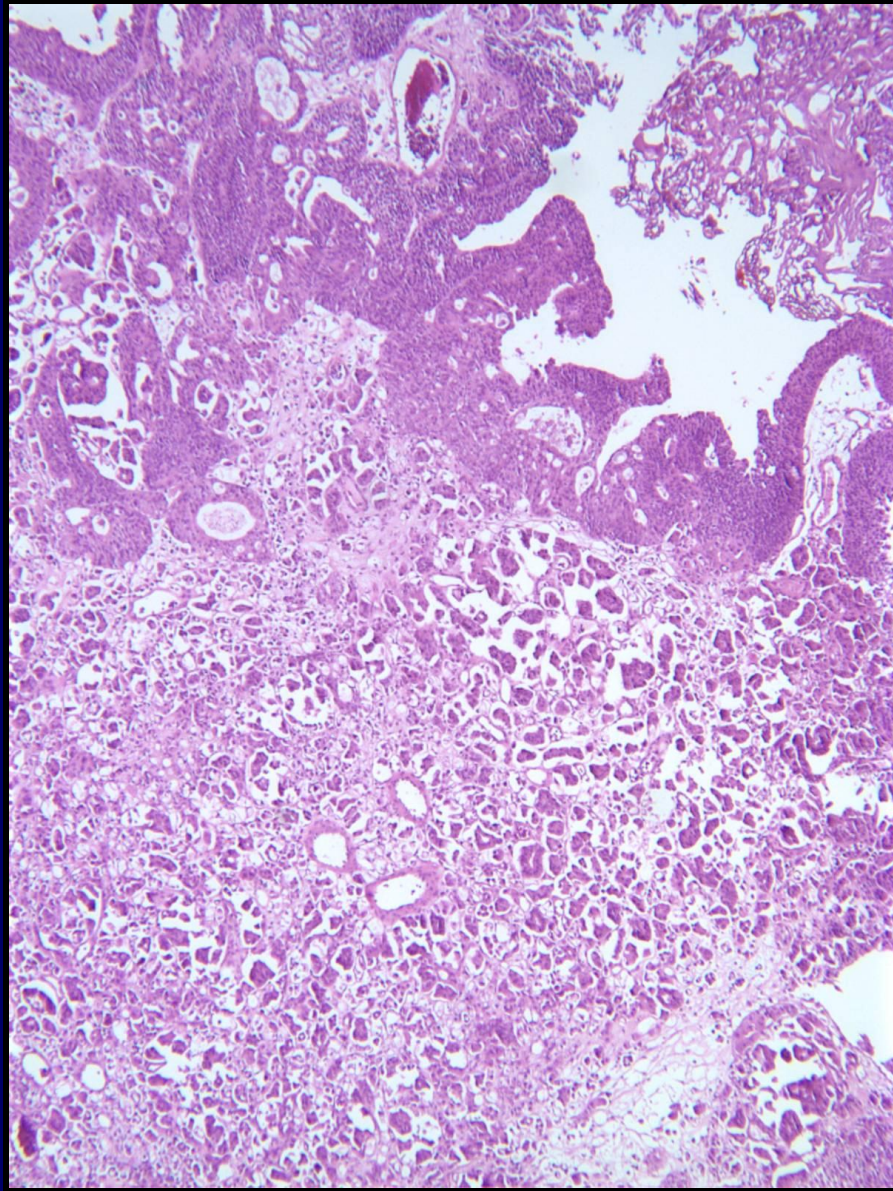
UC - MICROPAPILLARY VARIANT



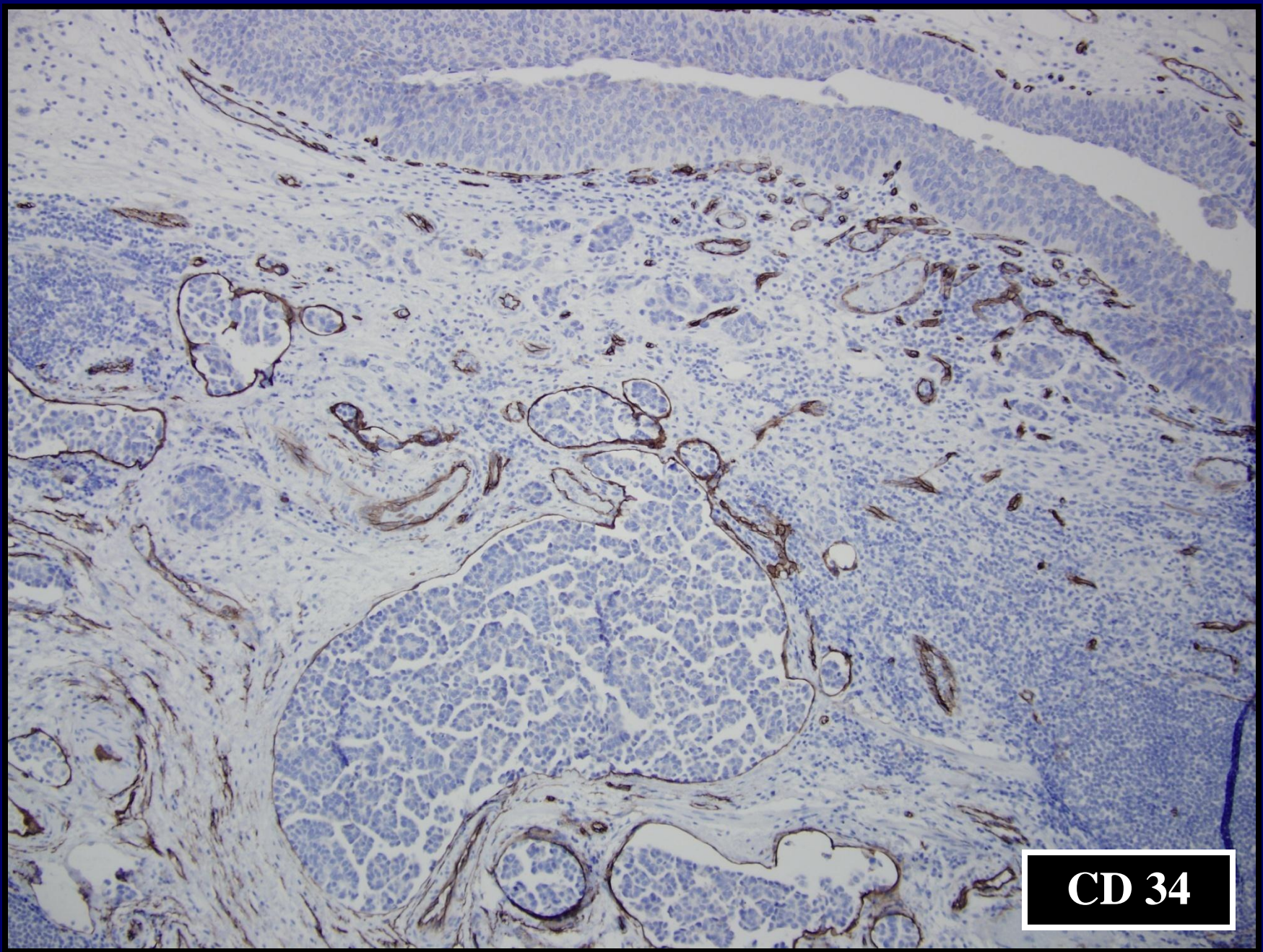
MICROPAPILLARY VARIANT



UC - MICROPAPILLARY VARIANT



UC - MICROPAPILLARY VARIANT



CD 34

UC - MICROPAPILLARY VARIANT

