Biopsies of the Urinary Bladder and the Prostate

Practical Diagnostic Considerations

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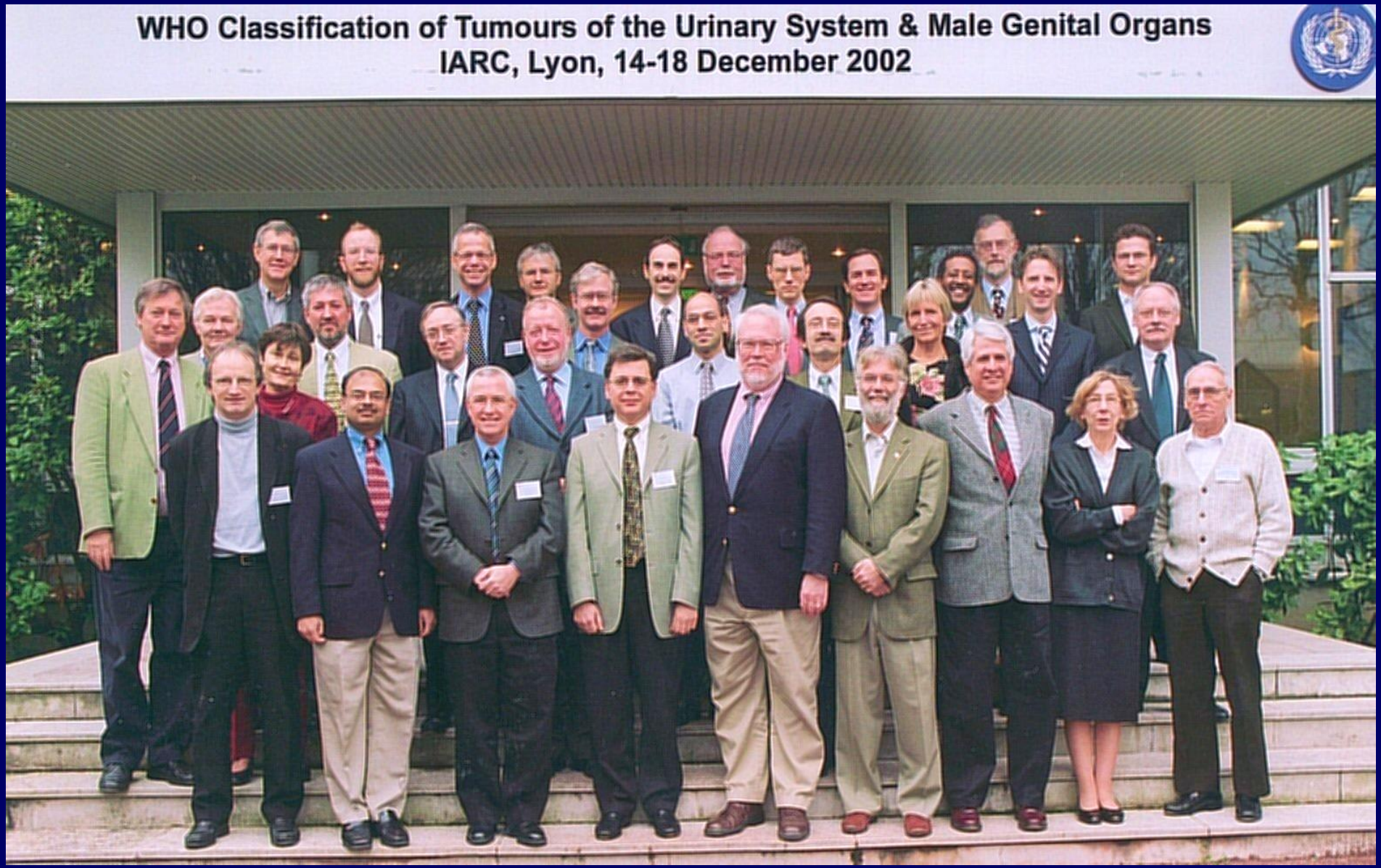
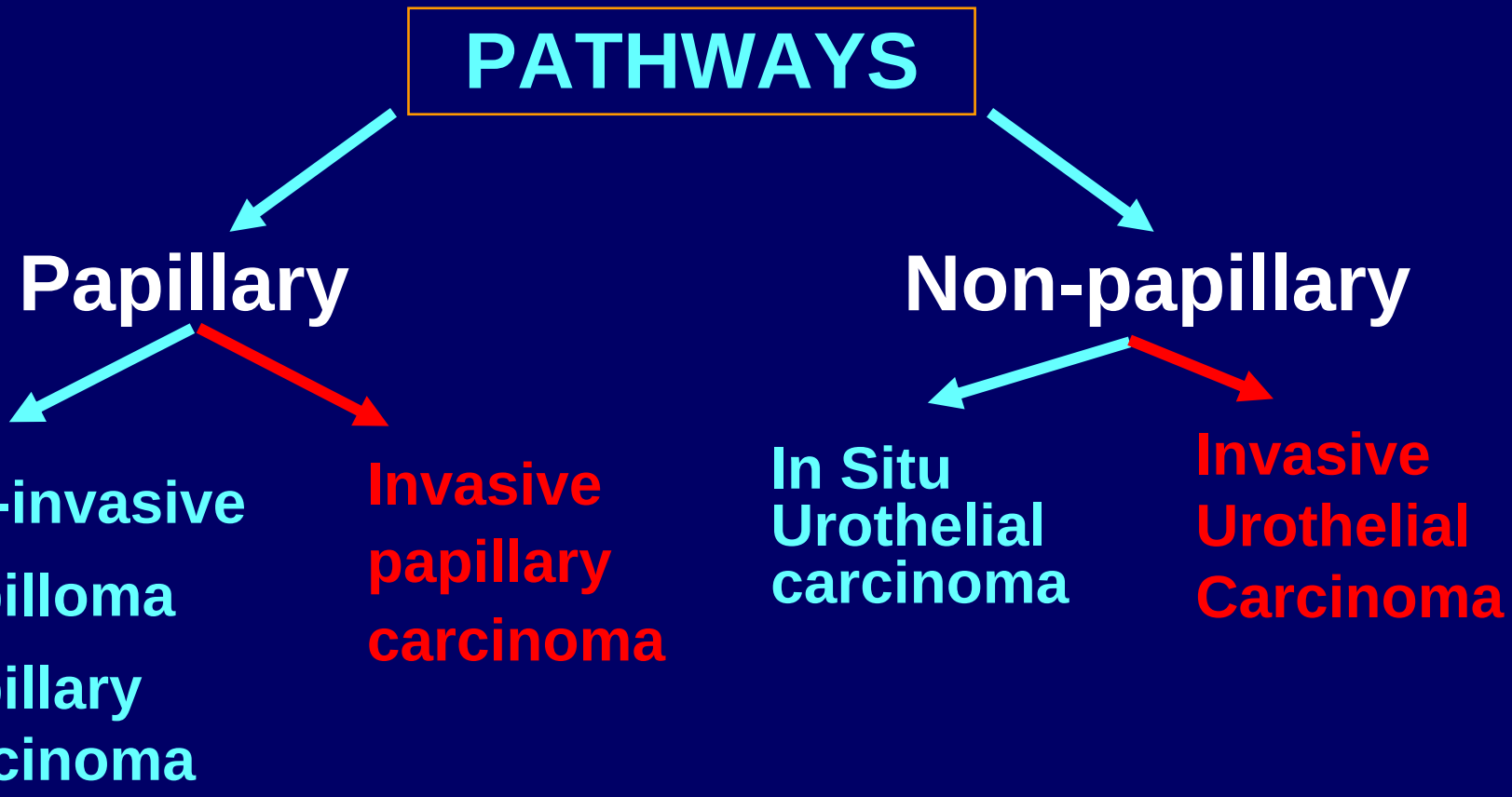
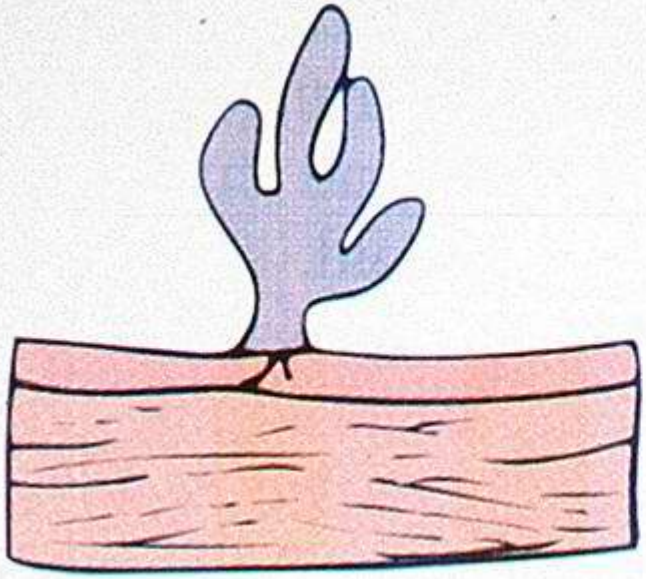
WHO Classification of Bladder Tumors


WHO Classification of Tumours of the Urinary System & Male Genital Organs
IARC, Lyon, 14-18 December 2002

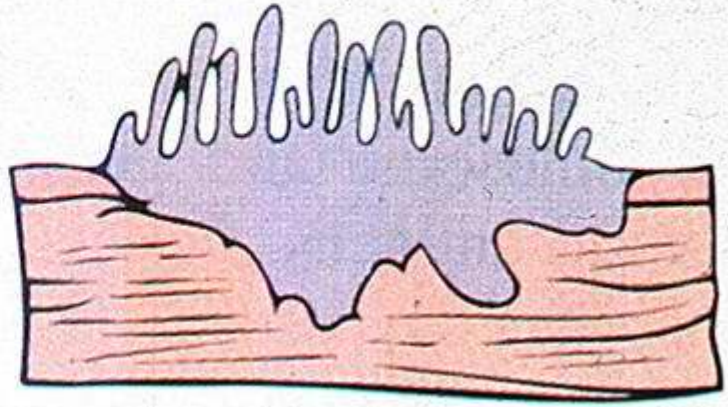
UROTHELIAL NEOPLASMS OF THE BLADDER



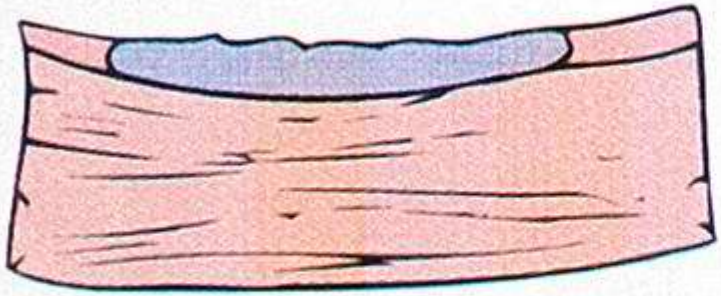
Pathways may be distinct or interrelated



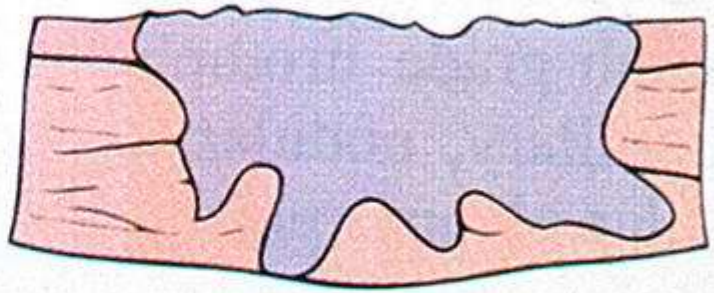
Papilloma–
papillary carcinoma



Invasive
papillary carcinoma



Flat noninvasive
carcinoma



Flat invasive
carcinoma

UROTHELIAL NEOPLASMS

CLINICIANS PERSPECTIVE

"Superficial Cancer"

- Non-invasive papillary cancer
- Urothelial CIS
- Invasive tumor NOT into muscularis propria

"Invasive Cancer"

- Tumors that Invade into the muscularis propria

WHO/ISUP 2004 CLASSIFICATION

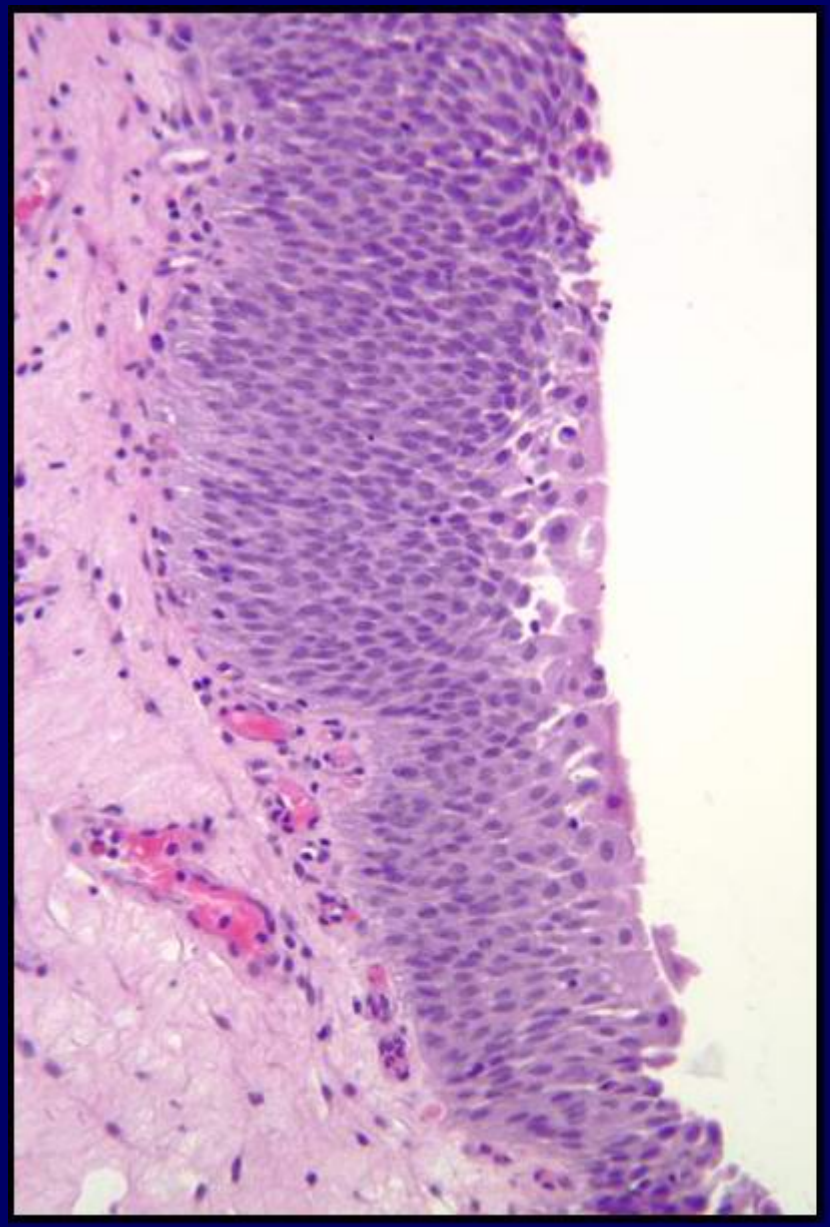
- NORMAL
- HYPERPLASIA
- FLAT LESIONS WITH ATYPIA
  - Reactive (inflammatory) atypia
  - Atypia of unknown significance
  - Dysplasia (low grade intraurothelial neoplasia)
  - Carcinoma in situ (high grade intraurothelial neoplasia)
- PAPILLARY NEOPLASMS
  - Papilloma
  - Inverted papilloma
  - Papillary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

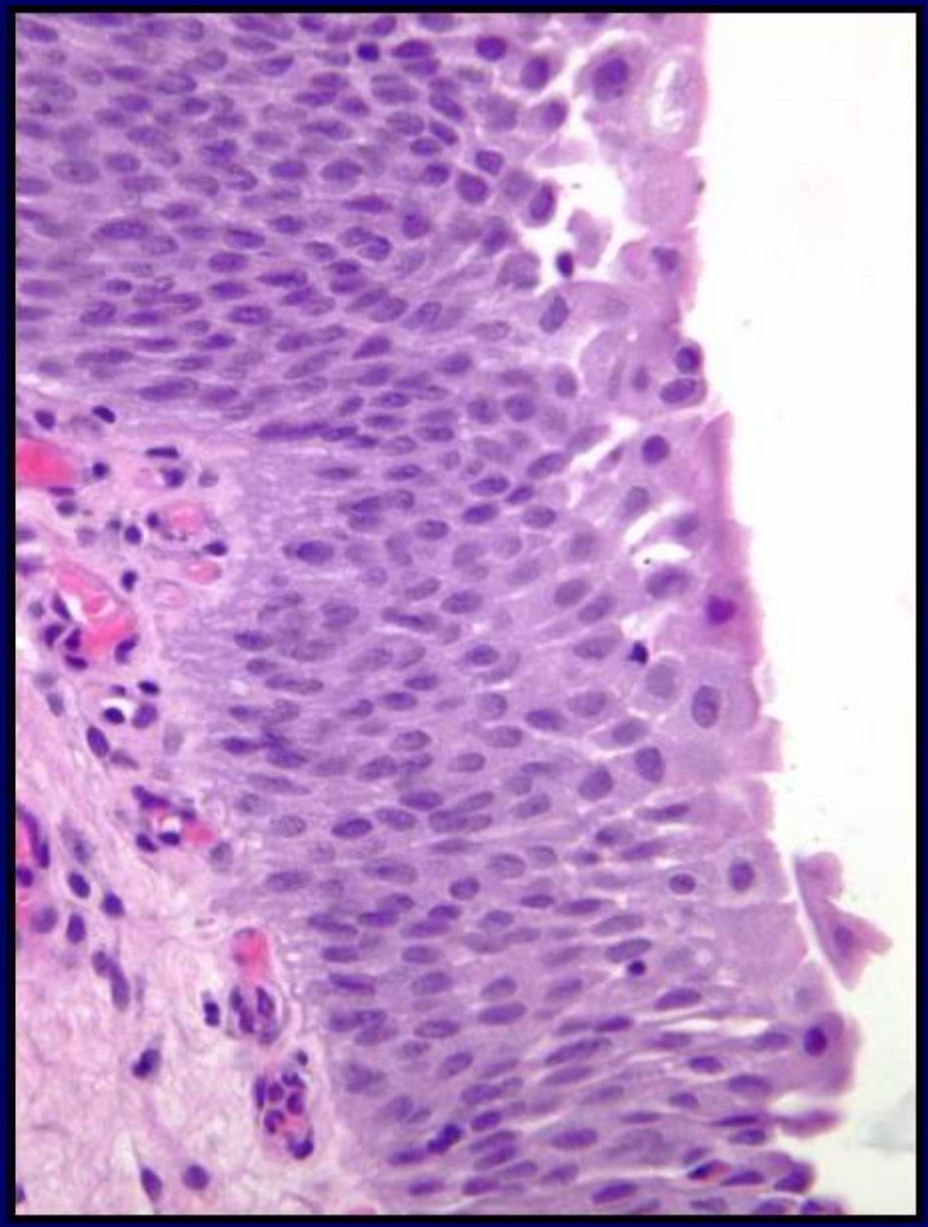
Flat Urothelium

WHO 2004 CLASSIFICATION
UROTHELIAL HYPERPLASIA

- Historically defined as > 7 cell layers
- "Markedly thickened mucosa without atypia"
- Counting cell layers not recommended
- Association with neoplasia uncertain
- Flat or pseudopapillary architecture

HYPERPLASIA



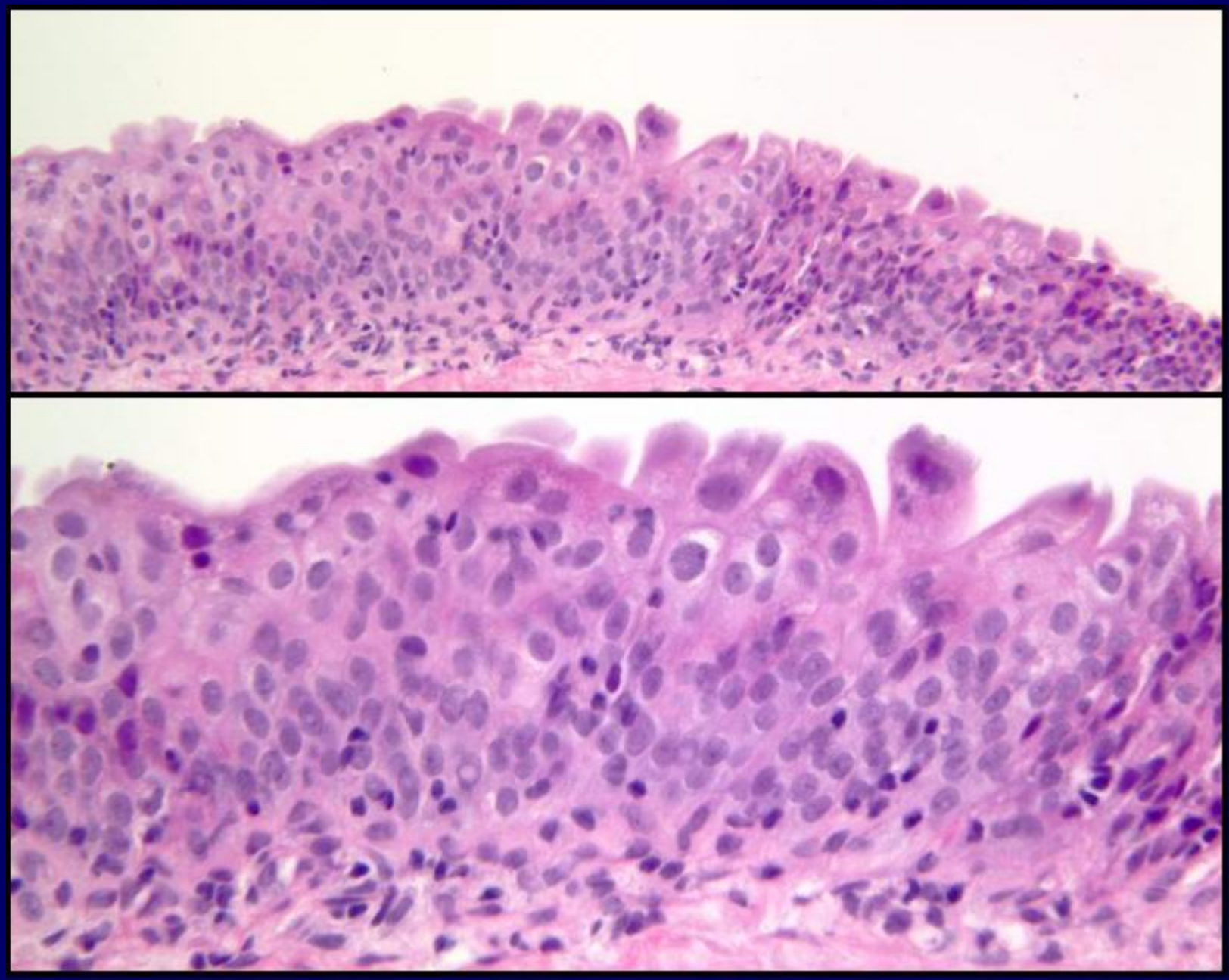


WHO 2004 CLASSIFICATION

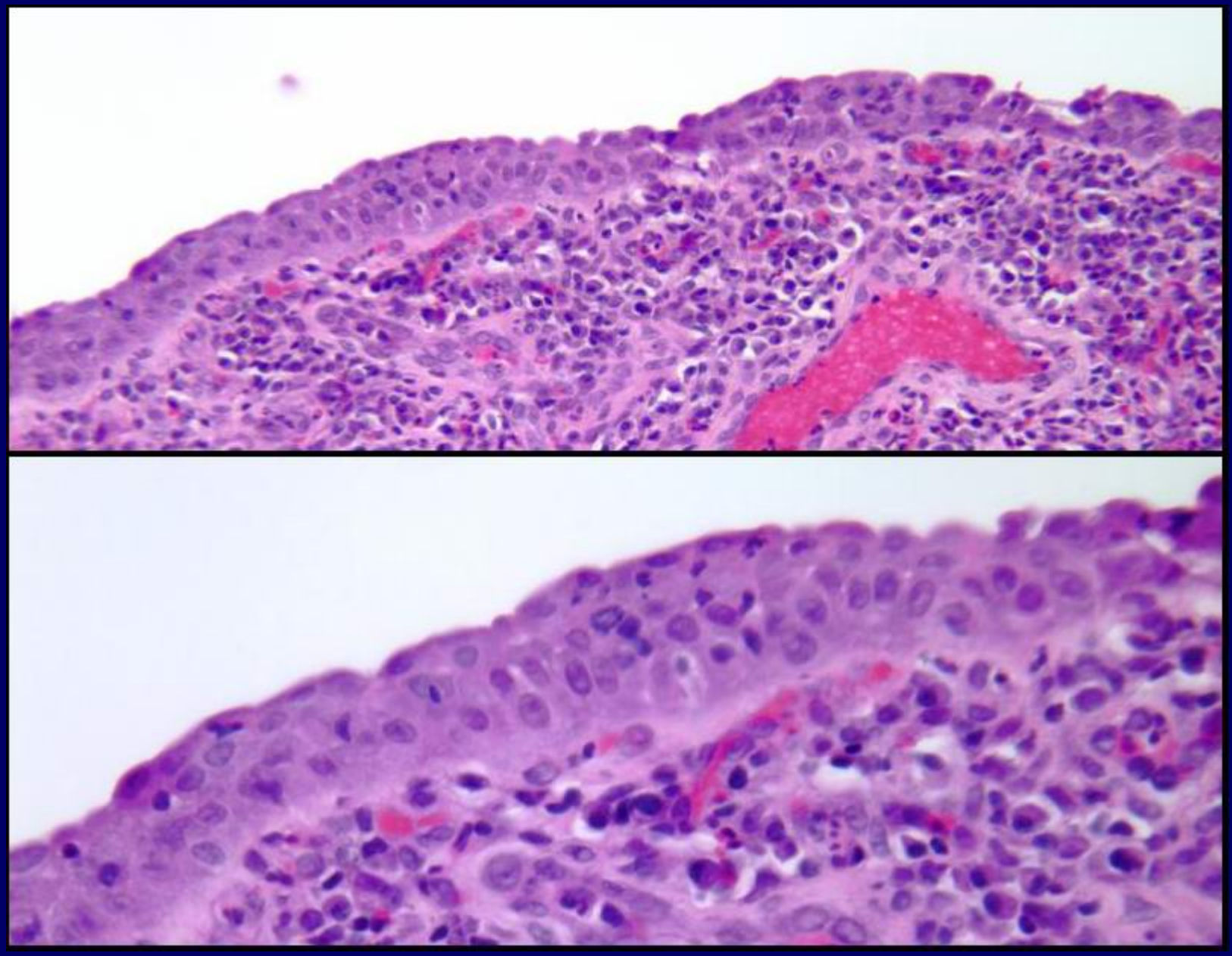
REACTIVE ATYPIA

- 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

REACTIVE ATYPIA



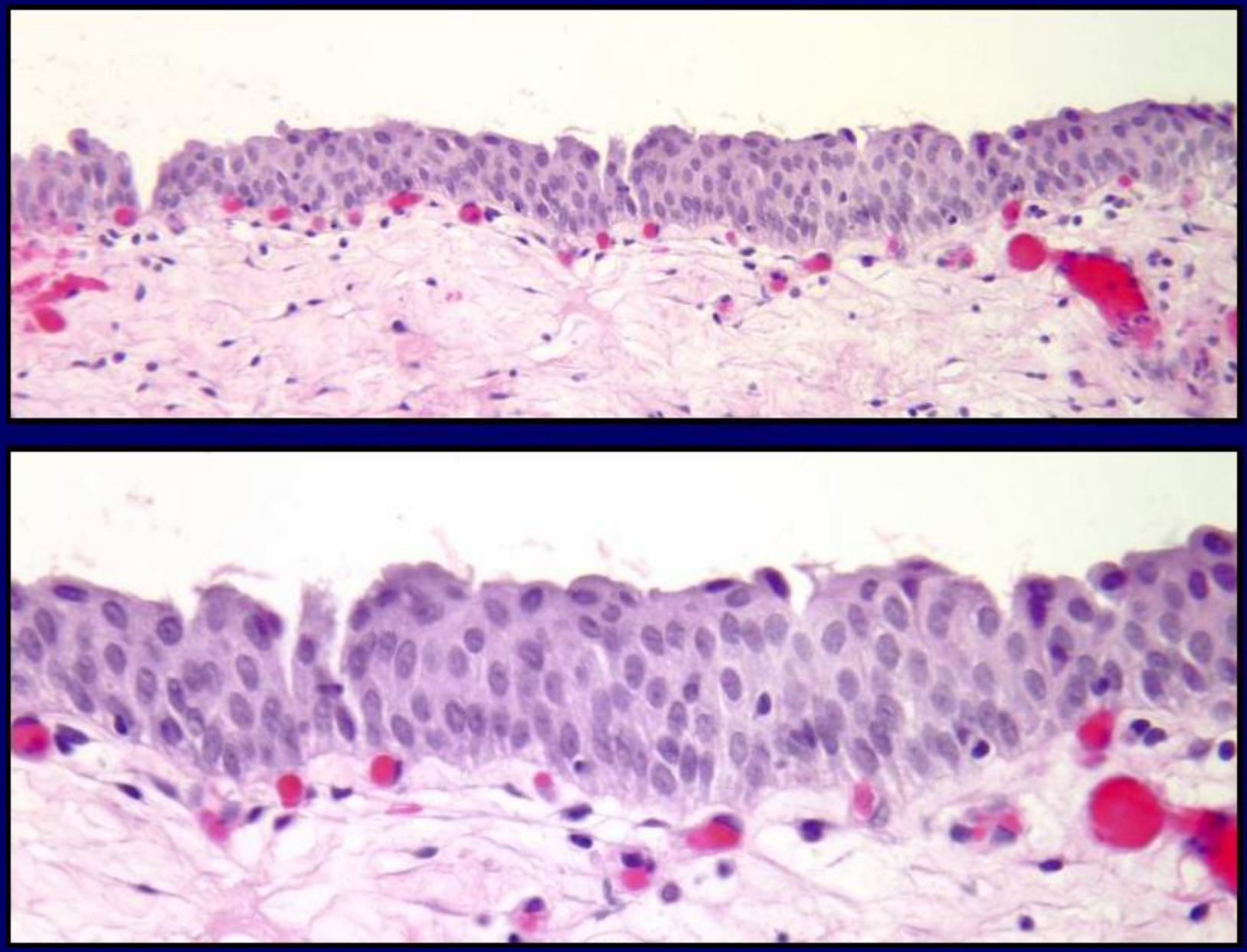
REACTIVE ATYPIA



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

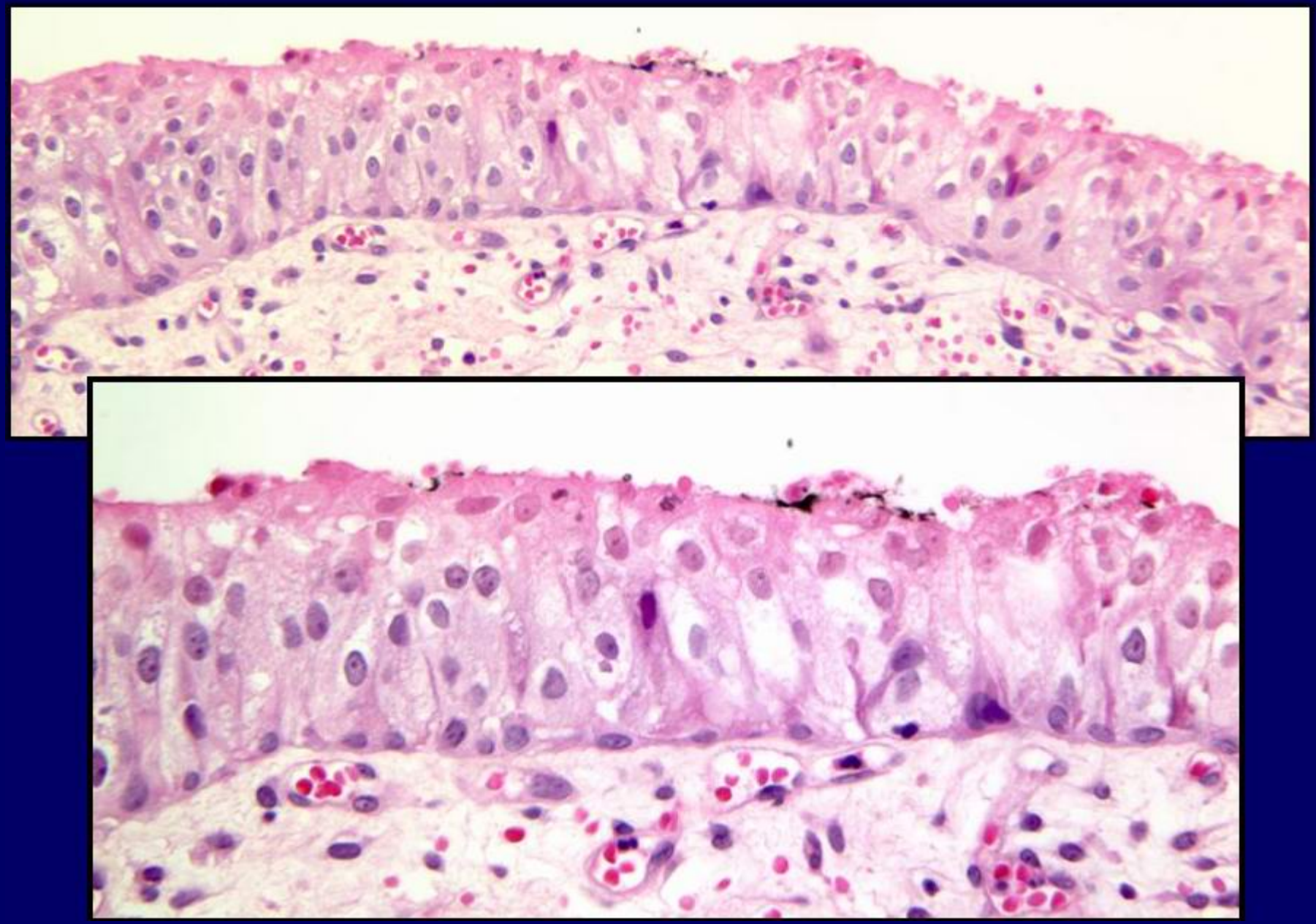


WHO 2004 CLASSIFICATION

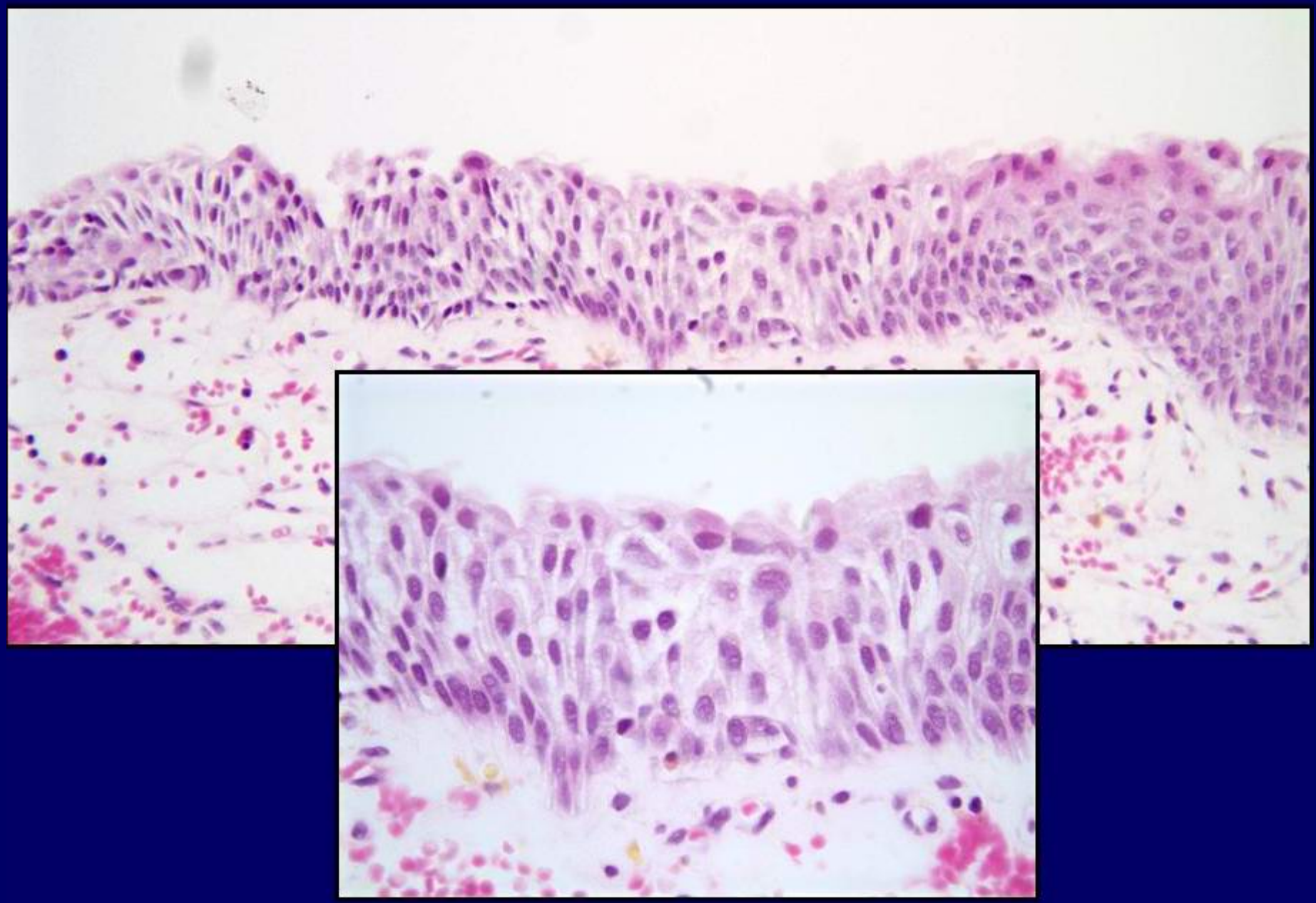
DYSPLASIA (LOW GRADE INTRAUROTHELIAL NEOPLASIA)

- 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



DYSPLASIA

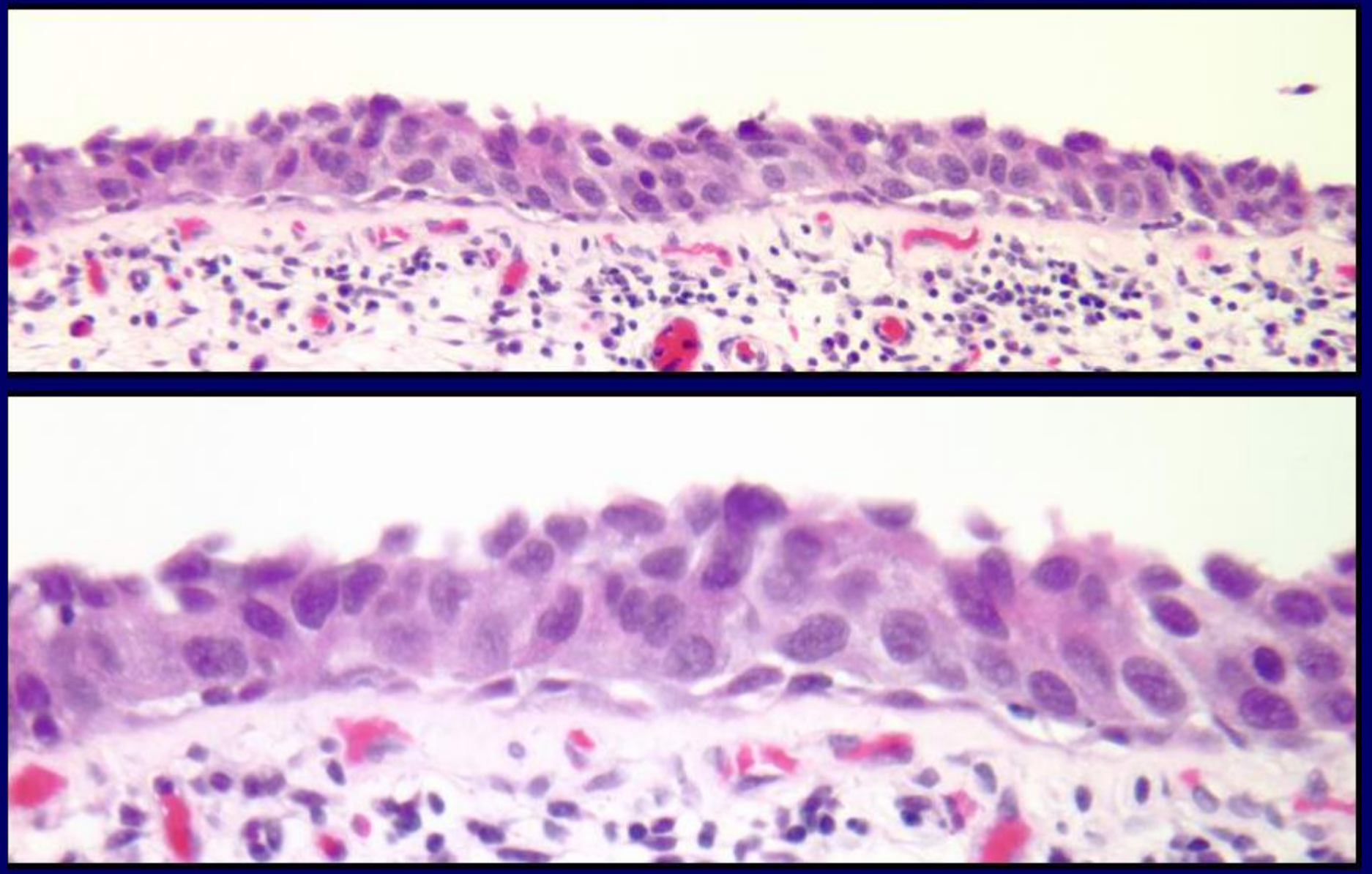


WHO 2004 CLASSIFICATION

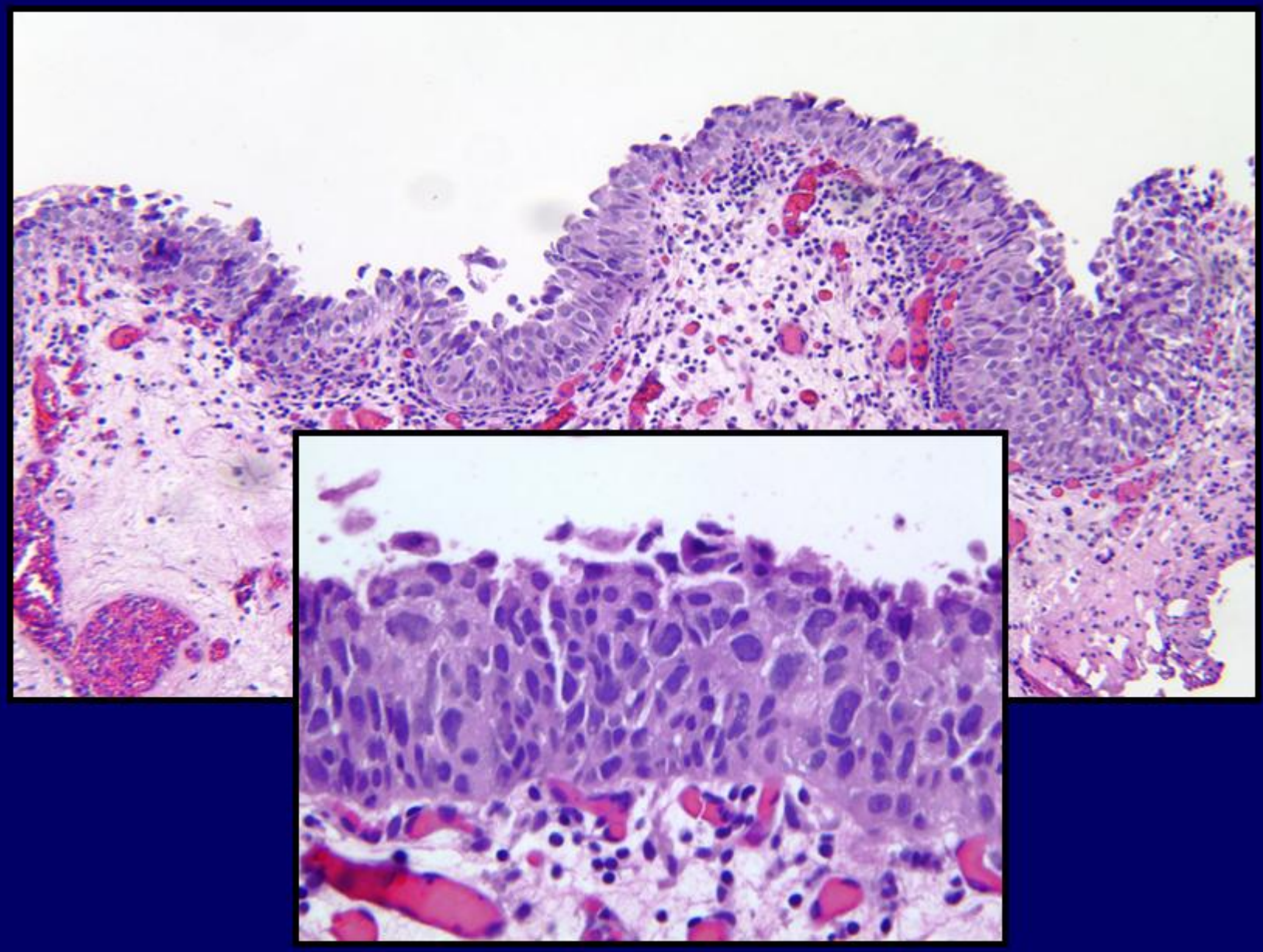
CARCINOMA IN SITU (HIGH GRADE INTRAUROTHELIAL NEOPLASIA)

- 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”

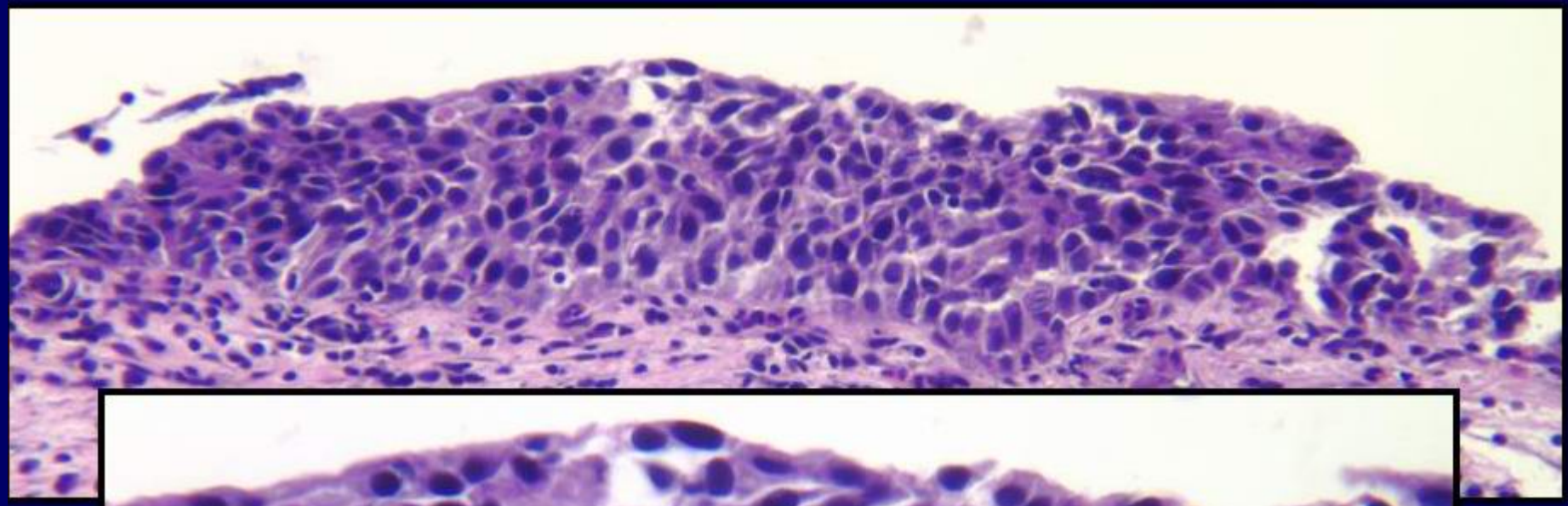
CIS - LARGE CELL

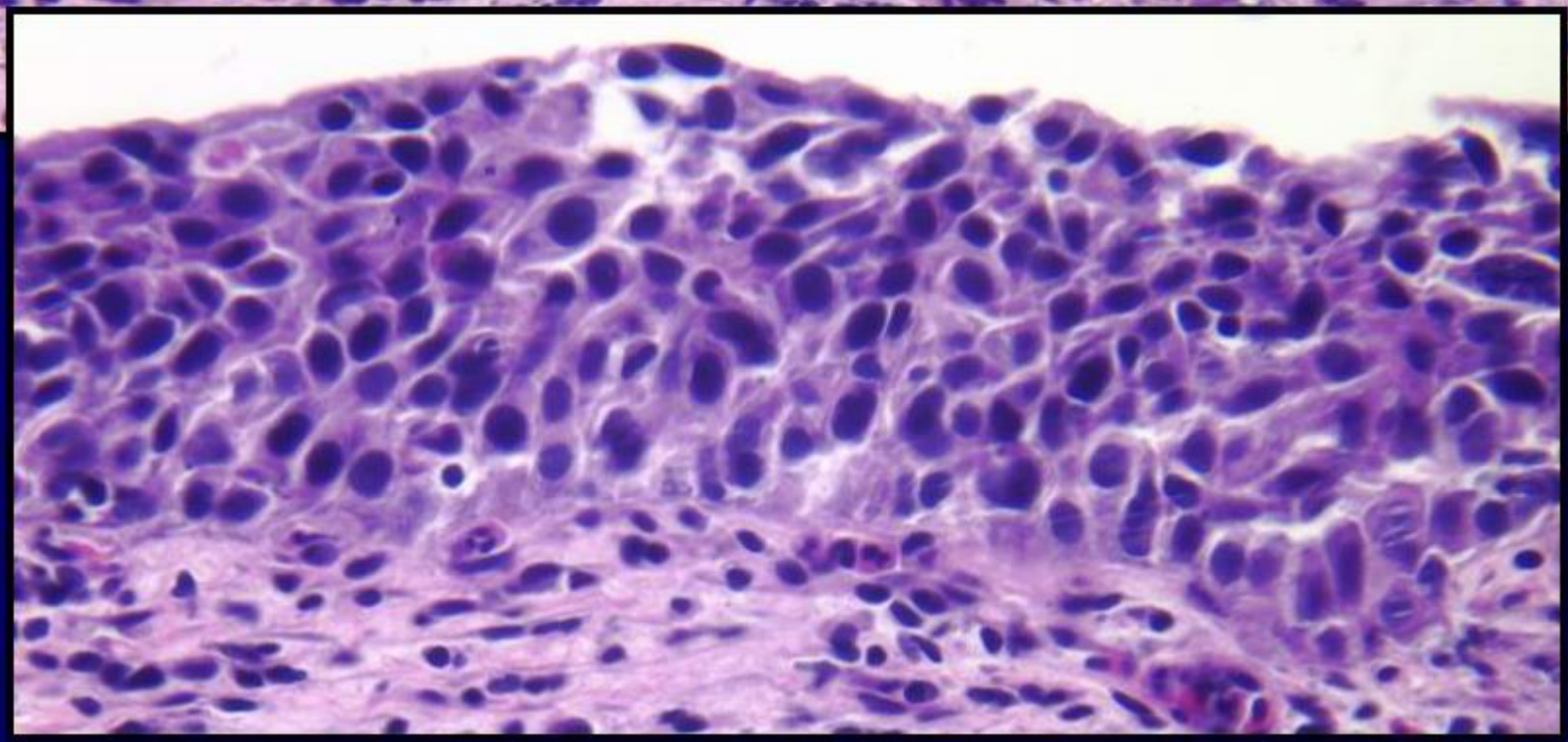


CIS - LARGE CELL

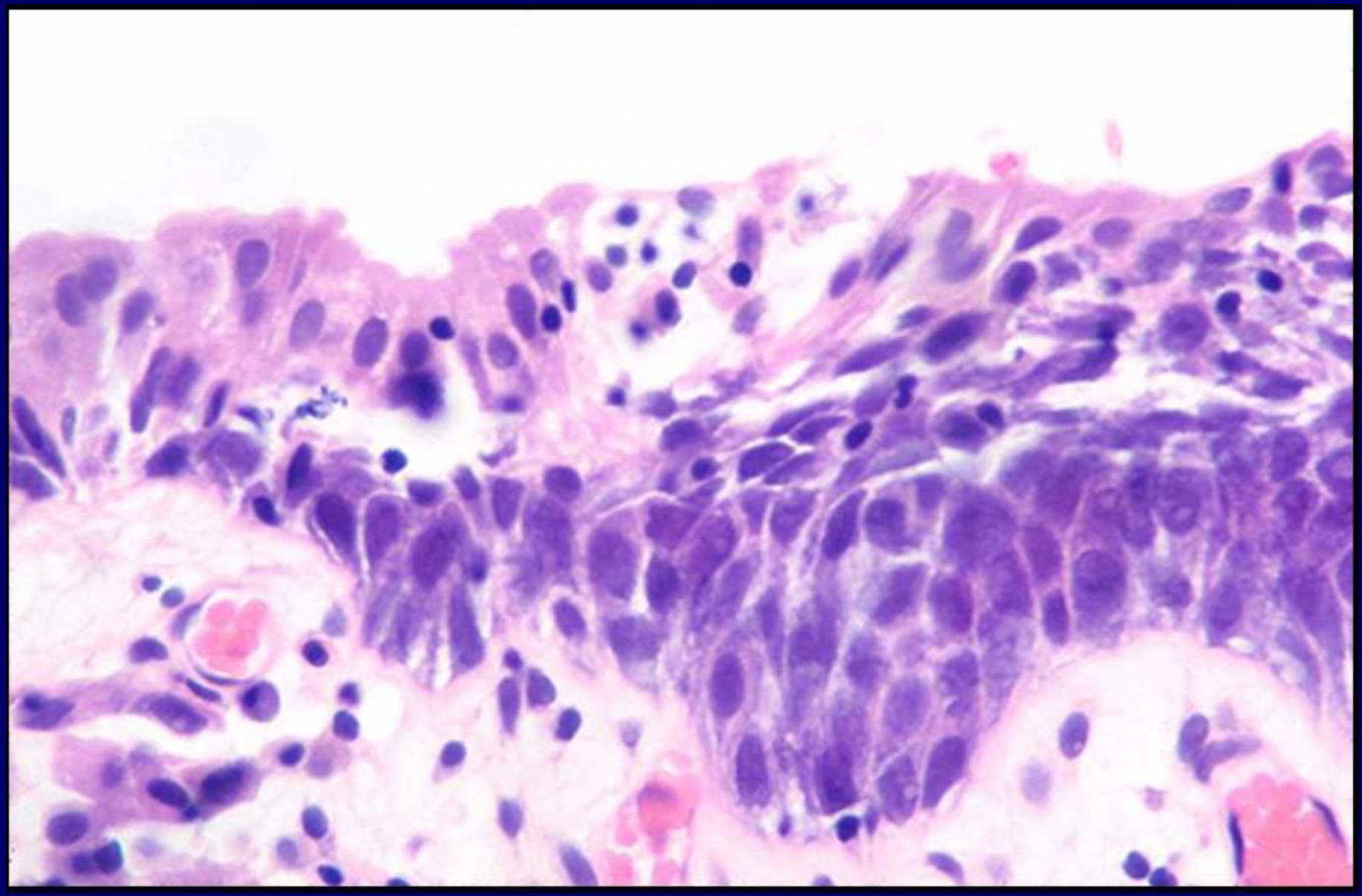


CIS - SMALL CELL

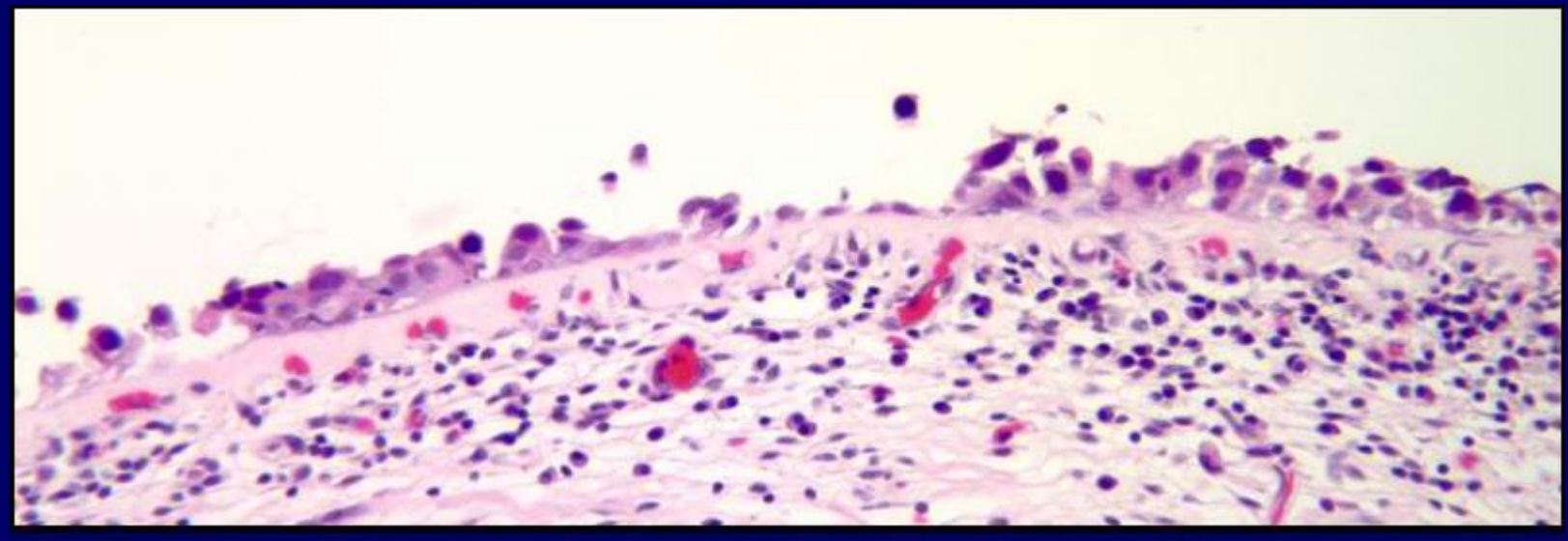


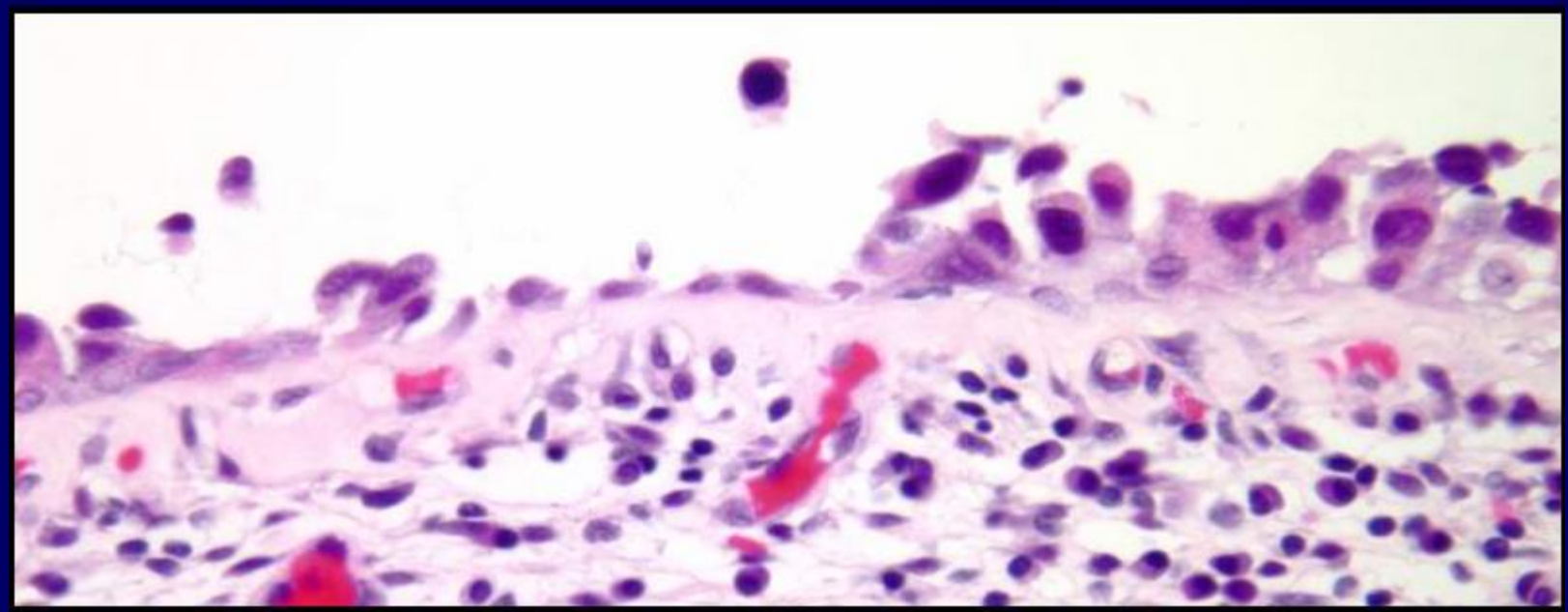


CIS - UNDERMINING

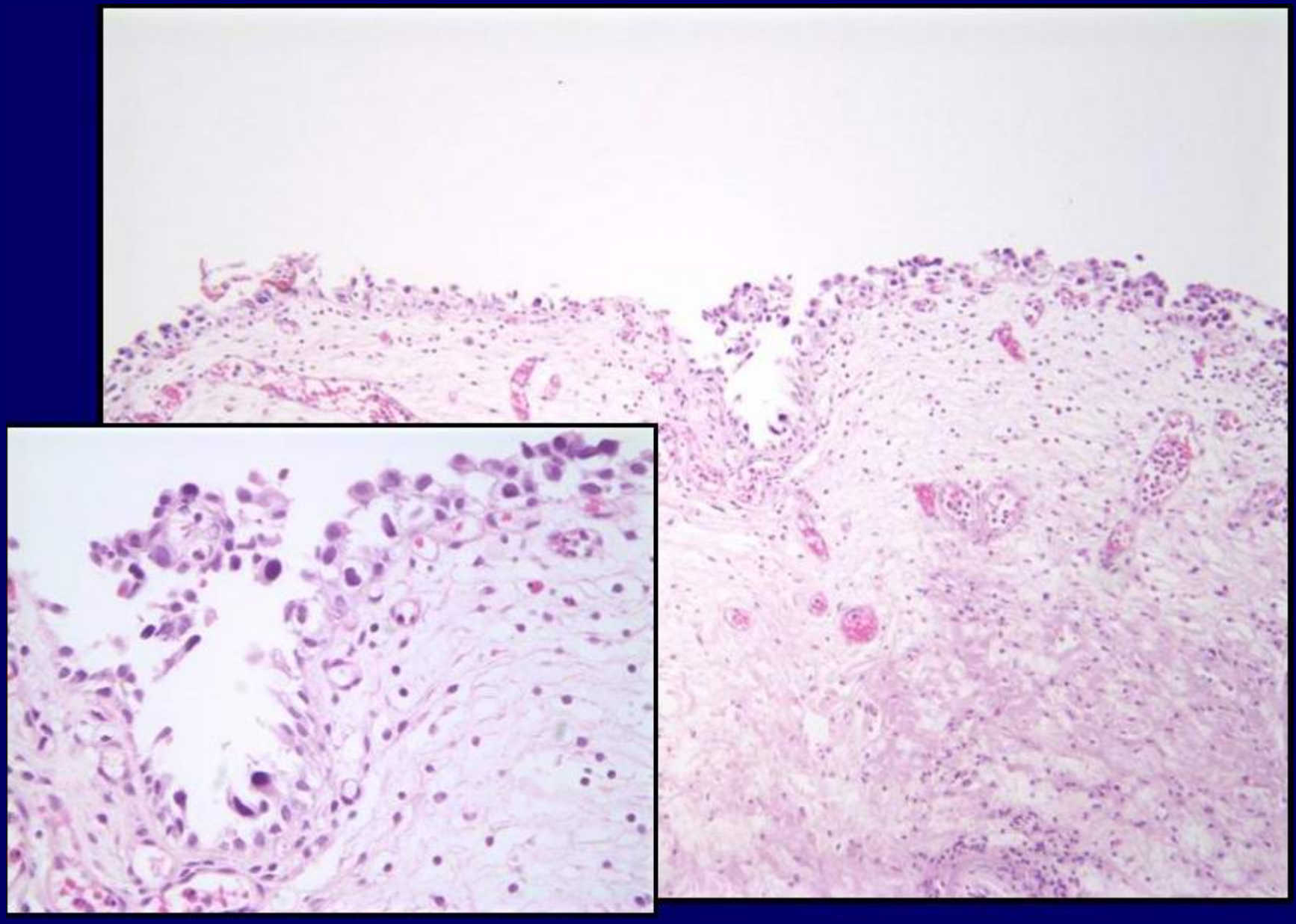


CIS - DENUDING

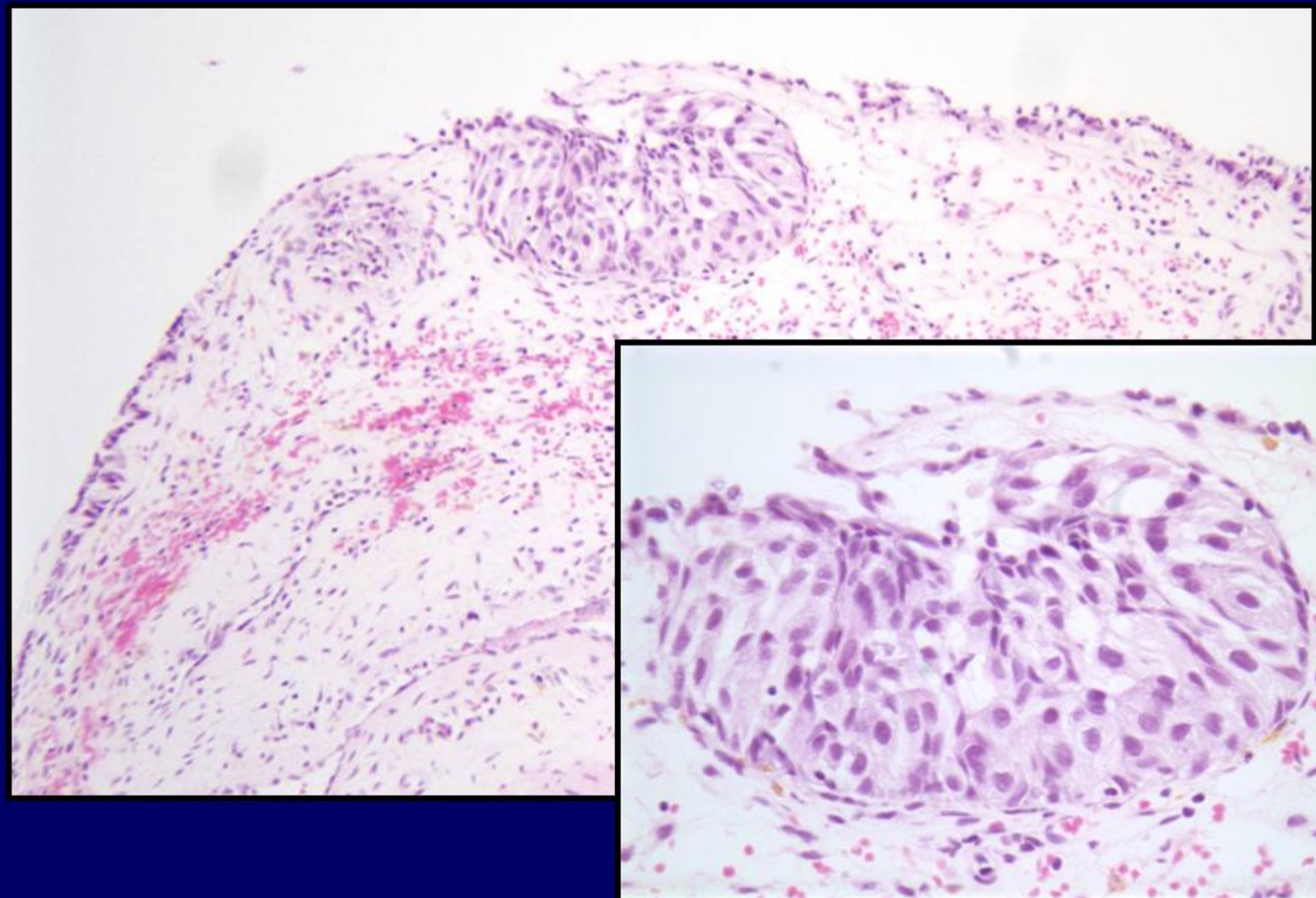




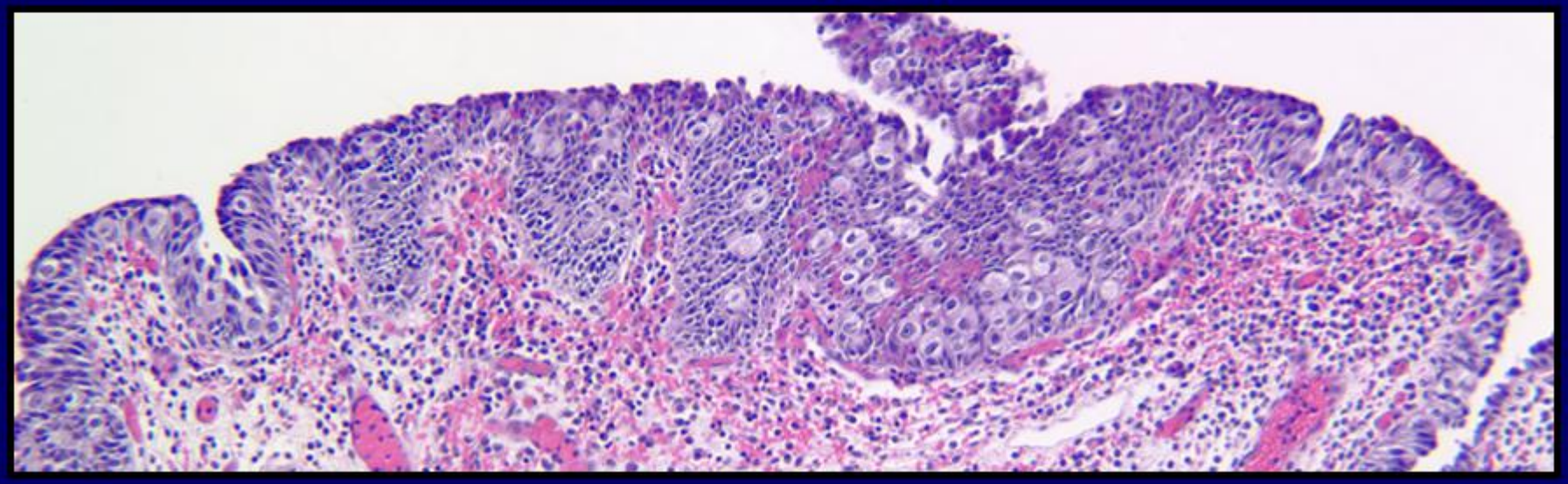
CIS - DENUDING

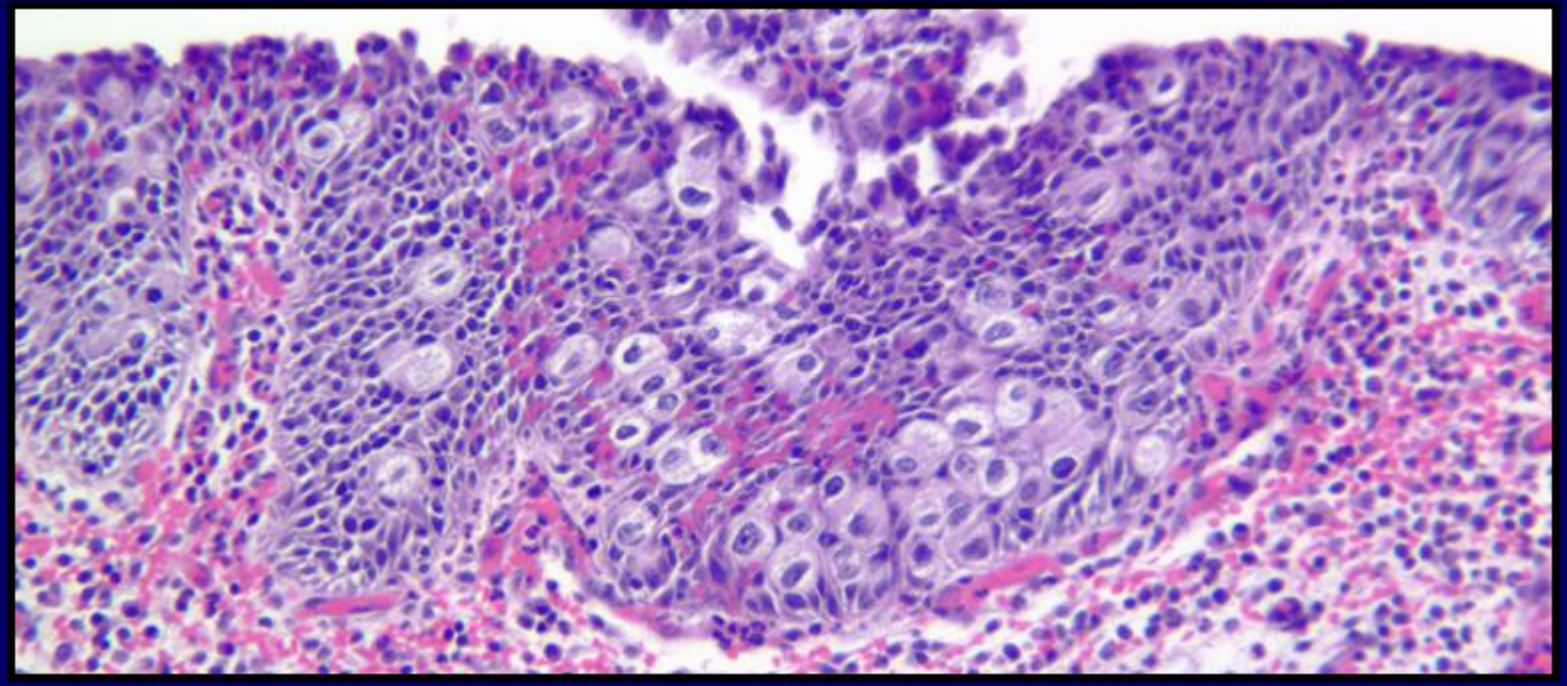


CIS - DENUDING



CIS - PAGETOID





Papillary Urothelium

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

WHO/ISUP CLASSIFICATION INVERTED PAPILLOMA

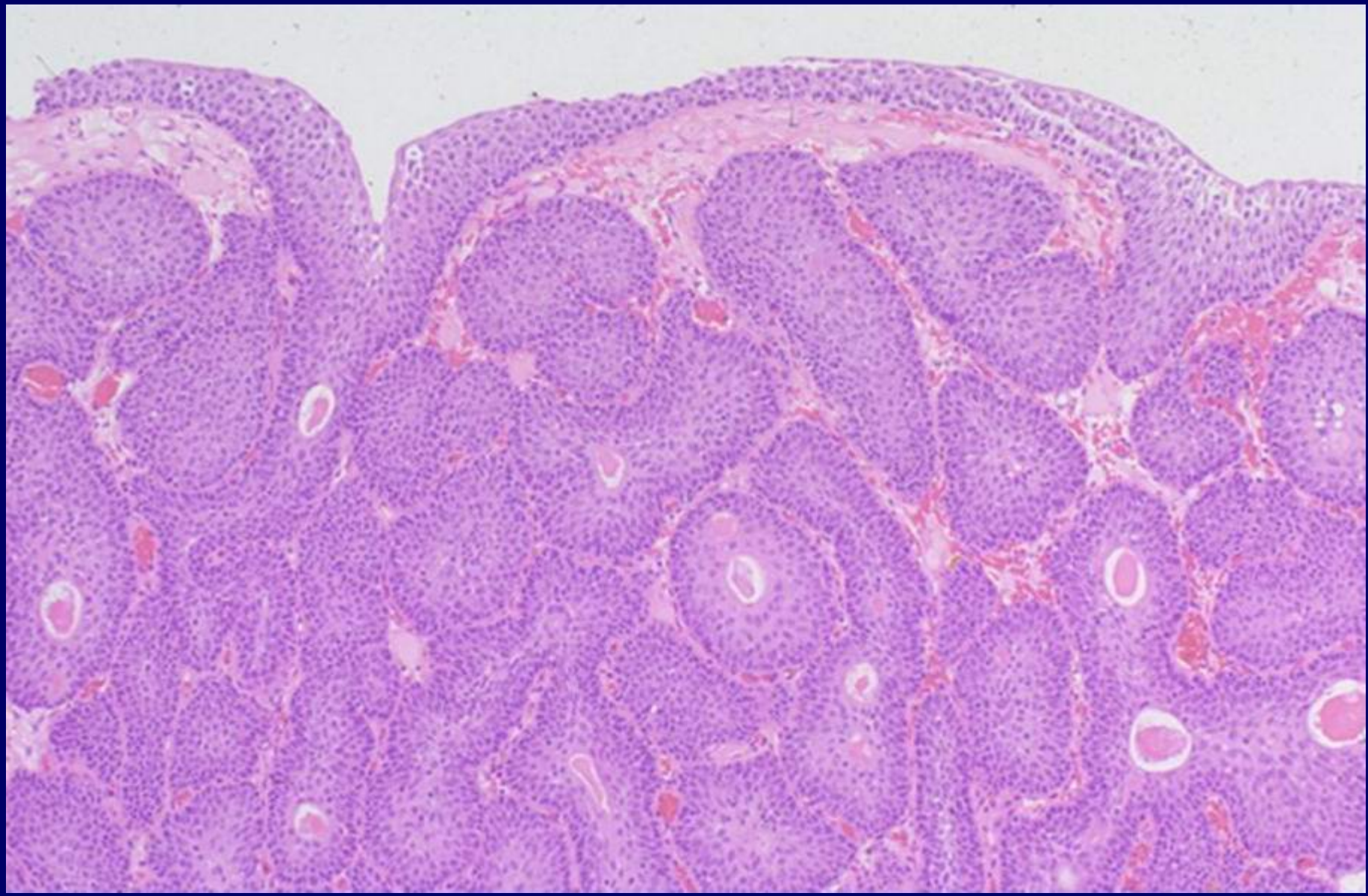
- BACKGROUND
  - Well defined clinical entity
  - Not a true “papillary lesion”
  - Low risk of recurrence
  - Reported cases associated with carcinoma
- CONSENSUS
  - No changes needed for this category
  - Lesions with an associated exophytic component should be classified as papillary neoplasm with inverted growth pattern

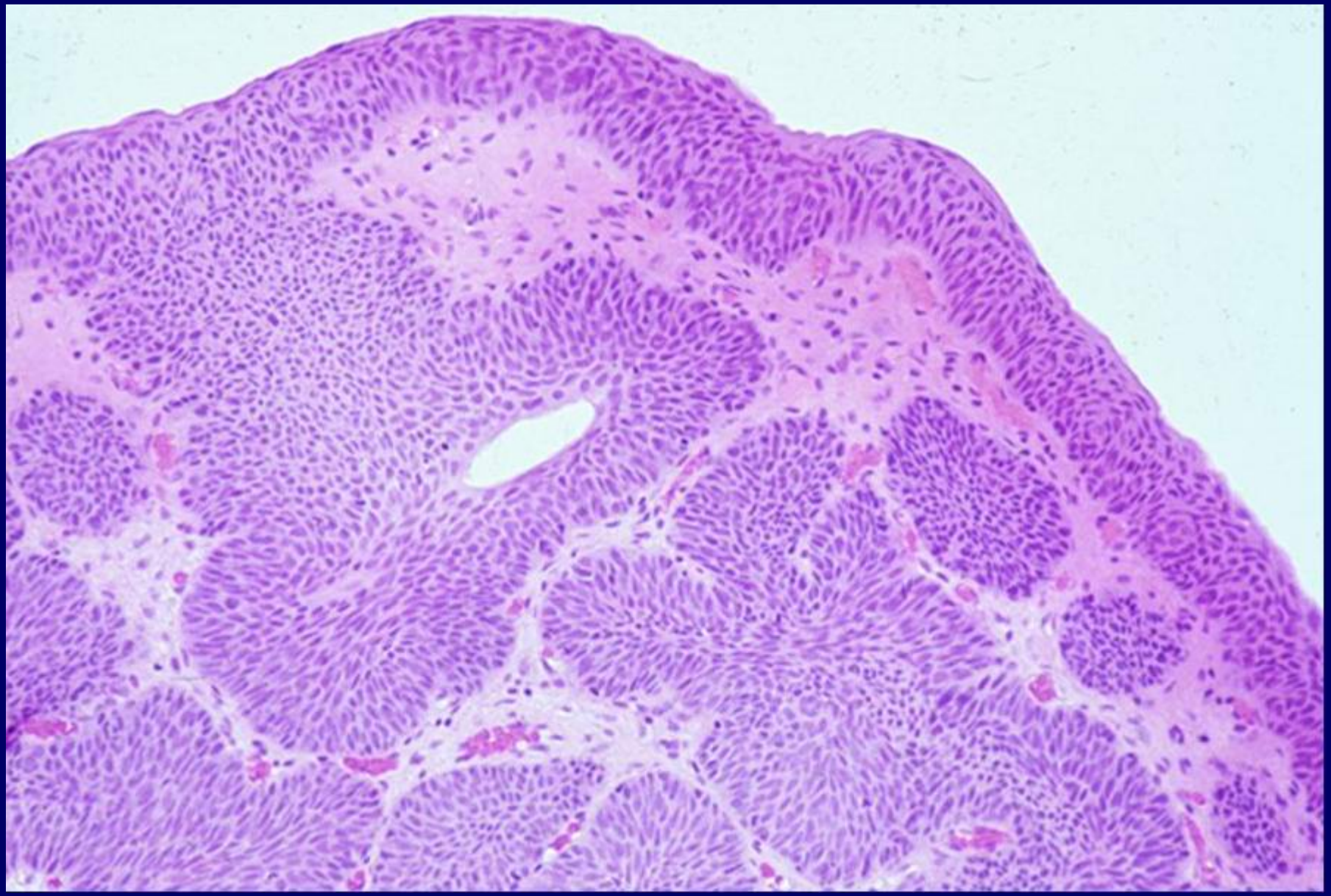
Am J Surg Pathol 22: 1435, 1988

WHO/ISUP CLASSIFICATION INVERTED PAPILLOMA

- HISTOLOGY
  - Often polyploid architecture
  - Covered by normal or attenuated urothelium with anastamosing cords arising from surface at multiple sites
  - No significant nuclear pleomorphism
  - Minimal mitotic activity
  - Squamous or glandular differentiation
  - May be fragmented with pieces mimicking true papillae

Am J Surg Pathol 22: 1435, 1988





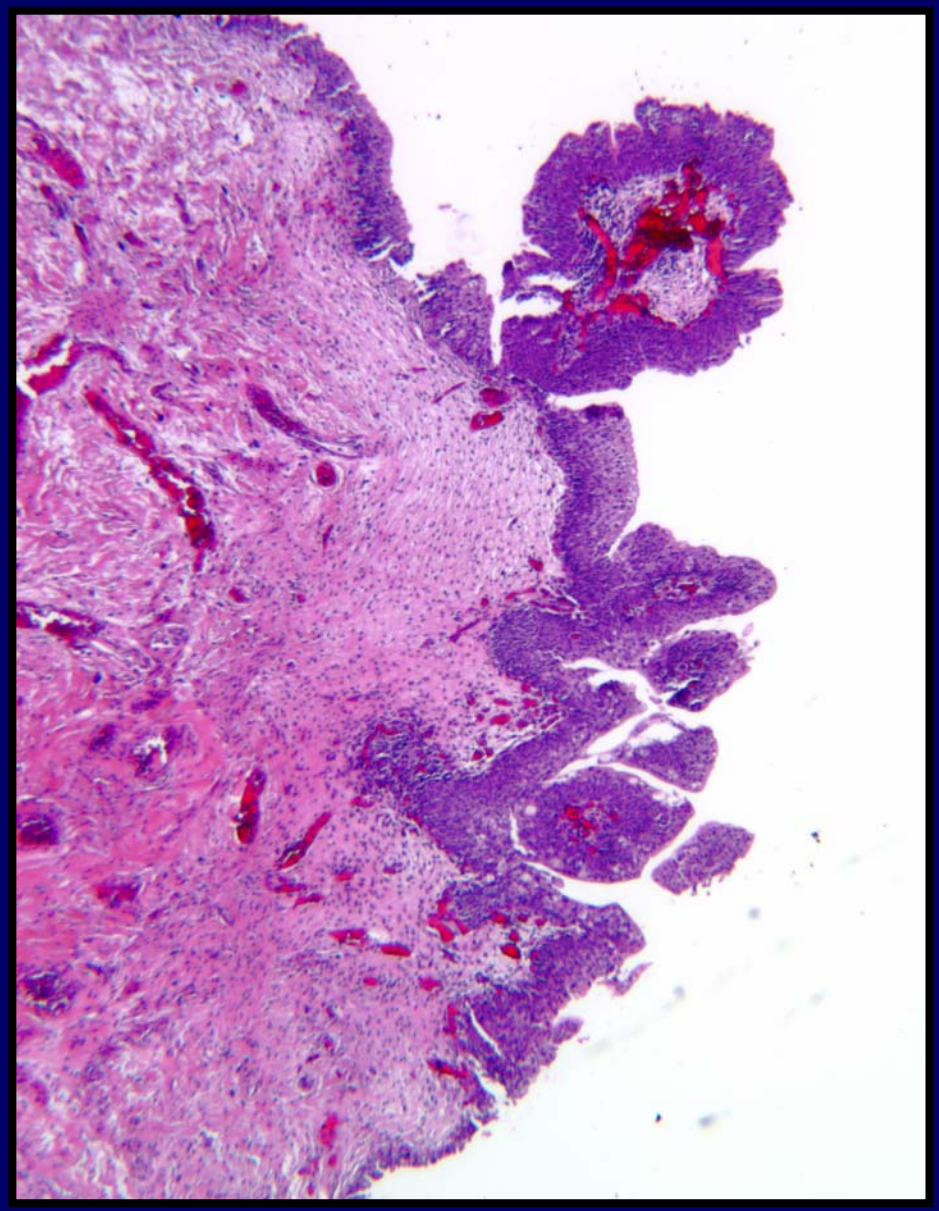
WHO/ISUP CLASSIFICATION UROTHELIAL PAPILLOMA

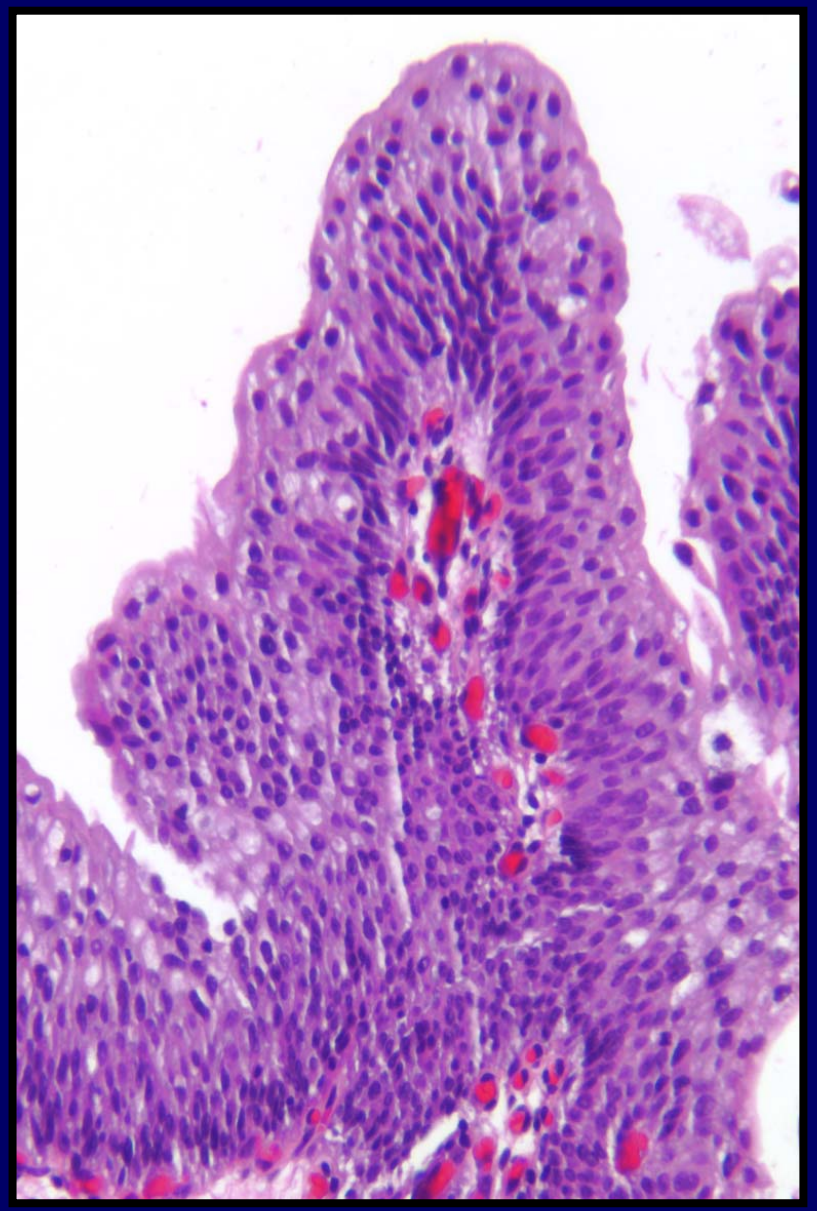
- BACKGROUND
  - Long standing controversy over distinction of papilloma/low grade papillary carcinoma
  - Occasionally see small papillary lesions in children or young adults
- CONSENSUS
  - Following consensus on LMP terminology, role for restrictive papilloma category agreed upon

WHO/ISUP CLASSIFICATION UROTHELIAL PAPILLOMA

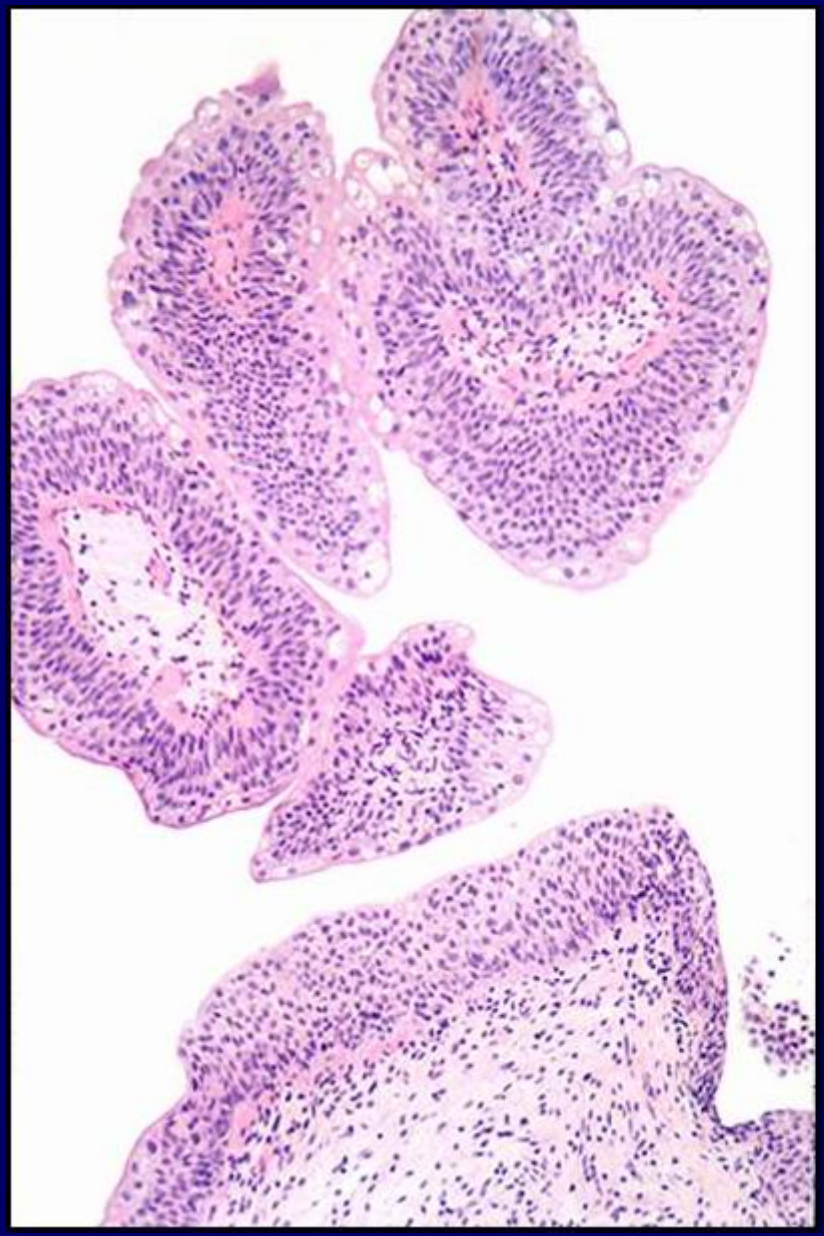
- HISTOLOGY
  - Restrictive criteria of WHO continue
  - Few fine papillary fronds
  - Covered by essentially normal appearing urothelium with no atypia
  - Cell layer counting not necessary

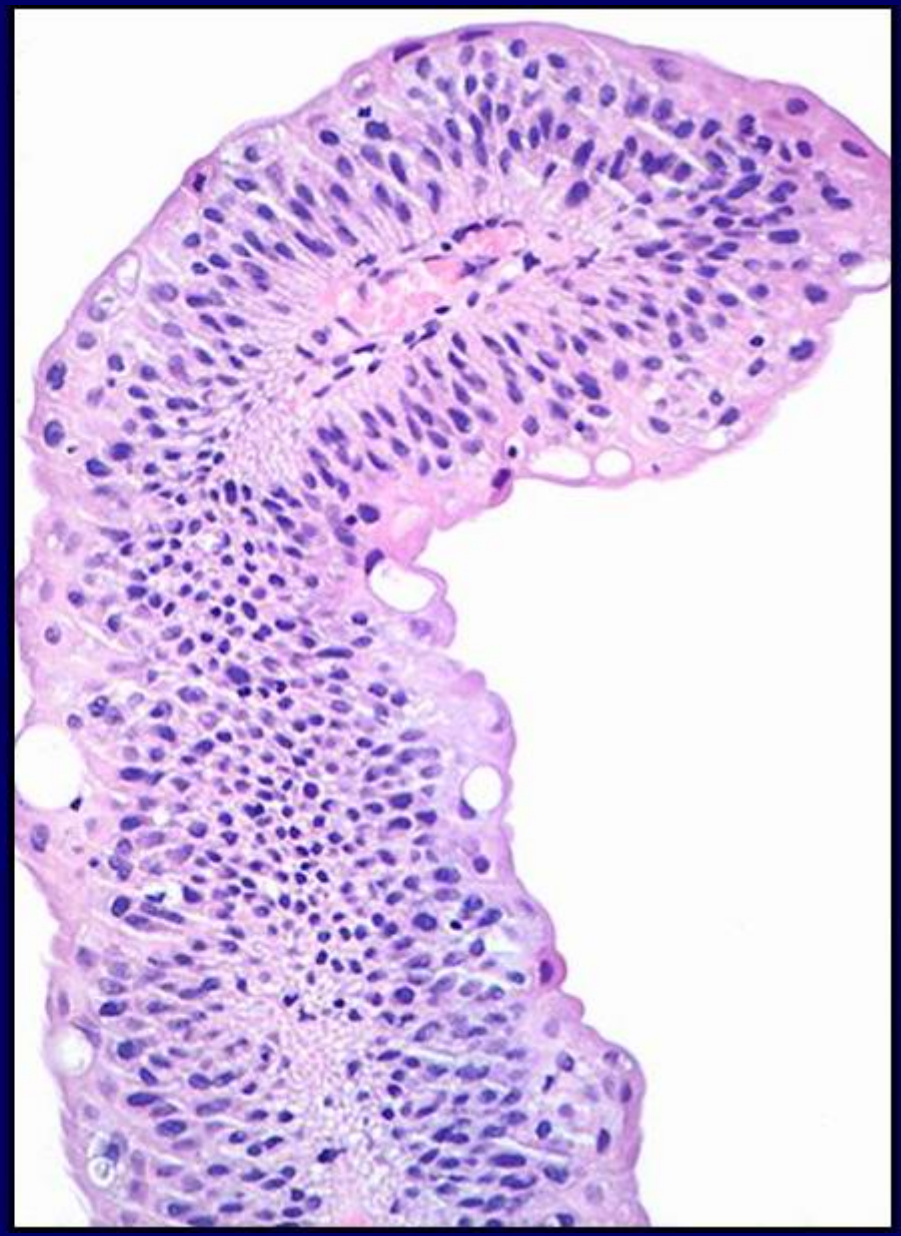
PAPILLOMA

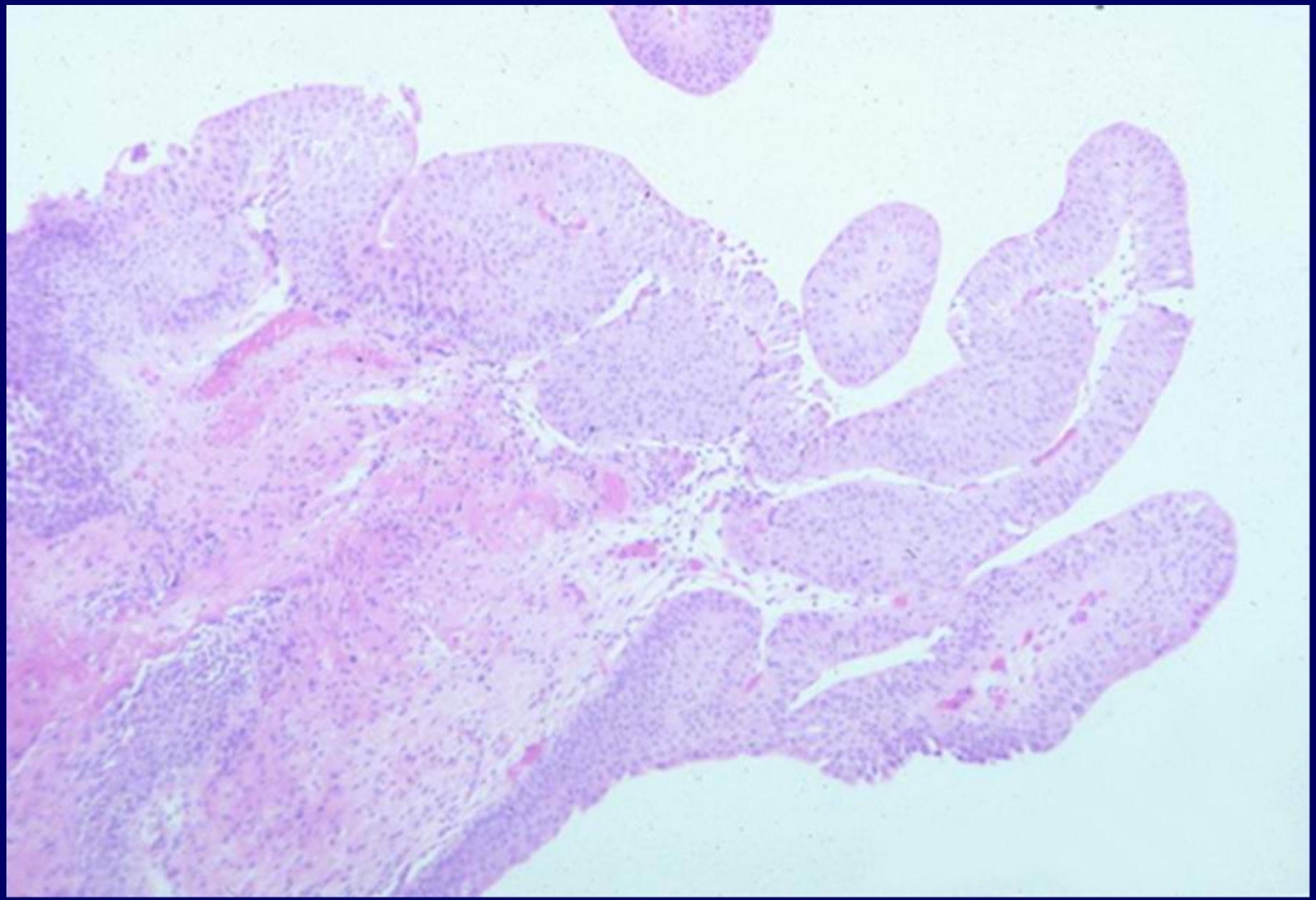


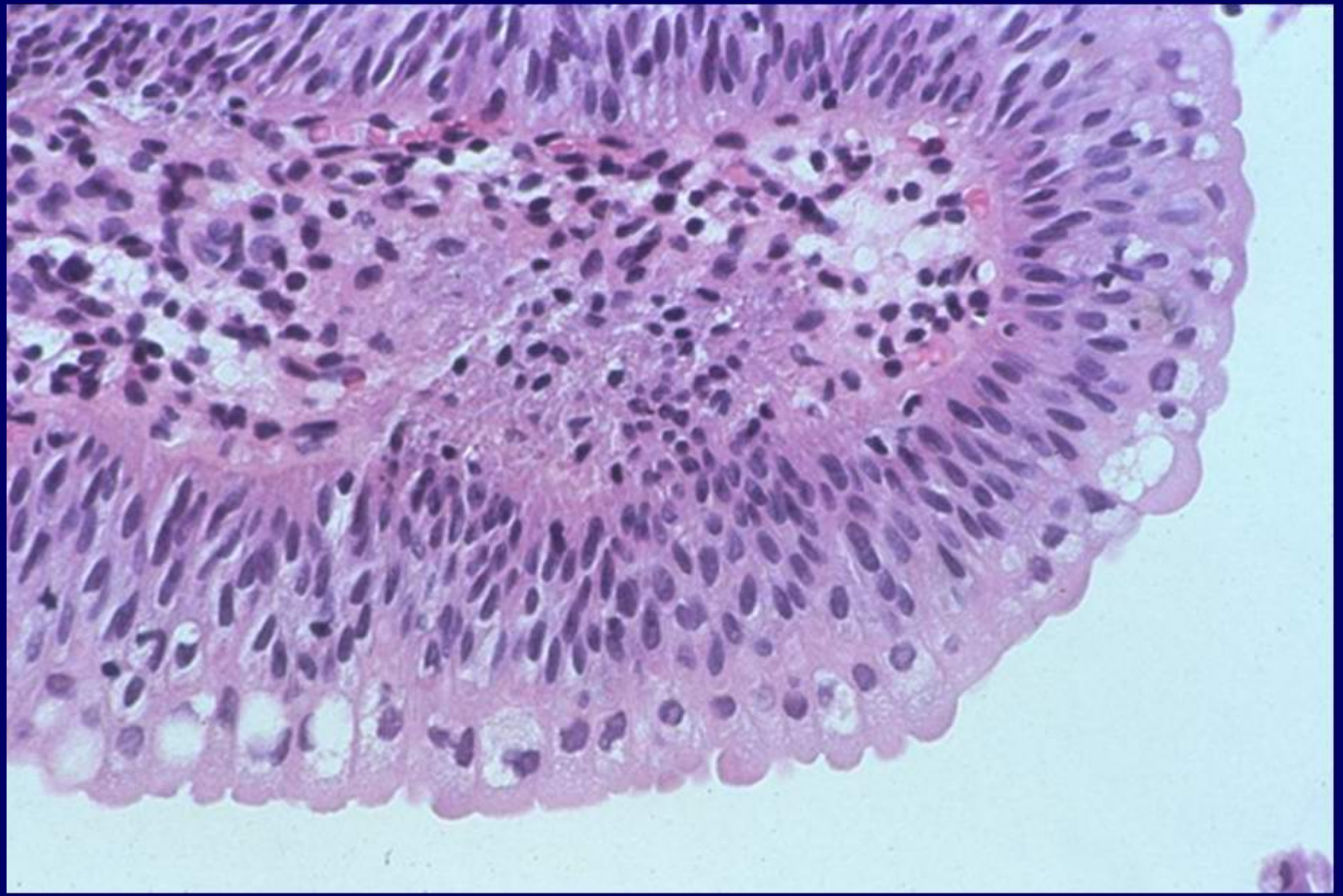


PAPILLOMA







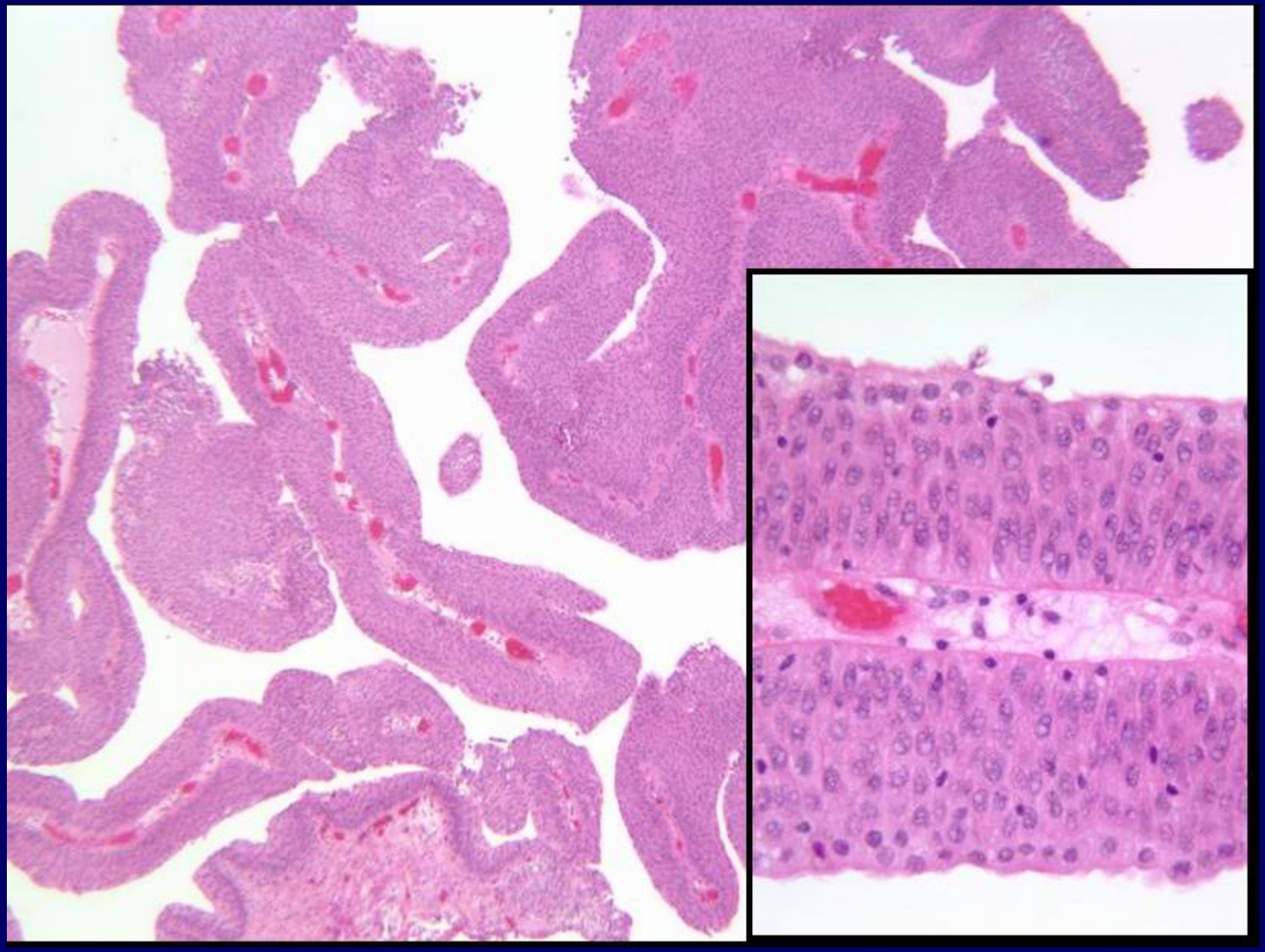


WHO 2004 CLASSIFICATION

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



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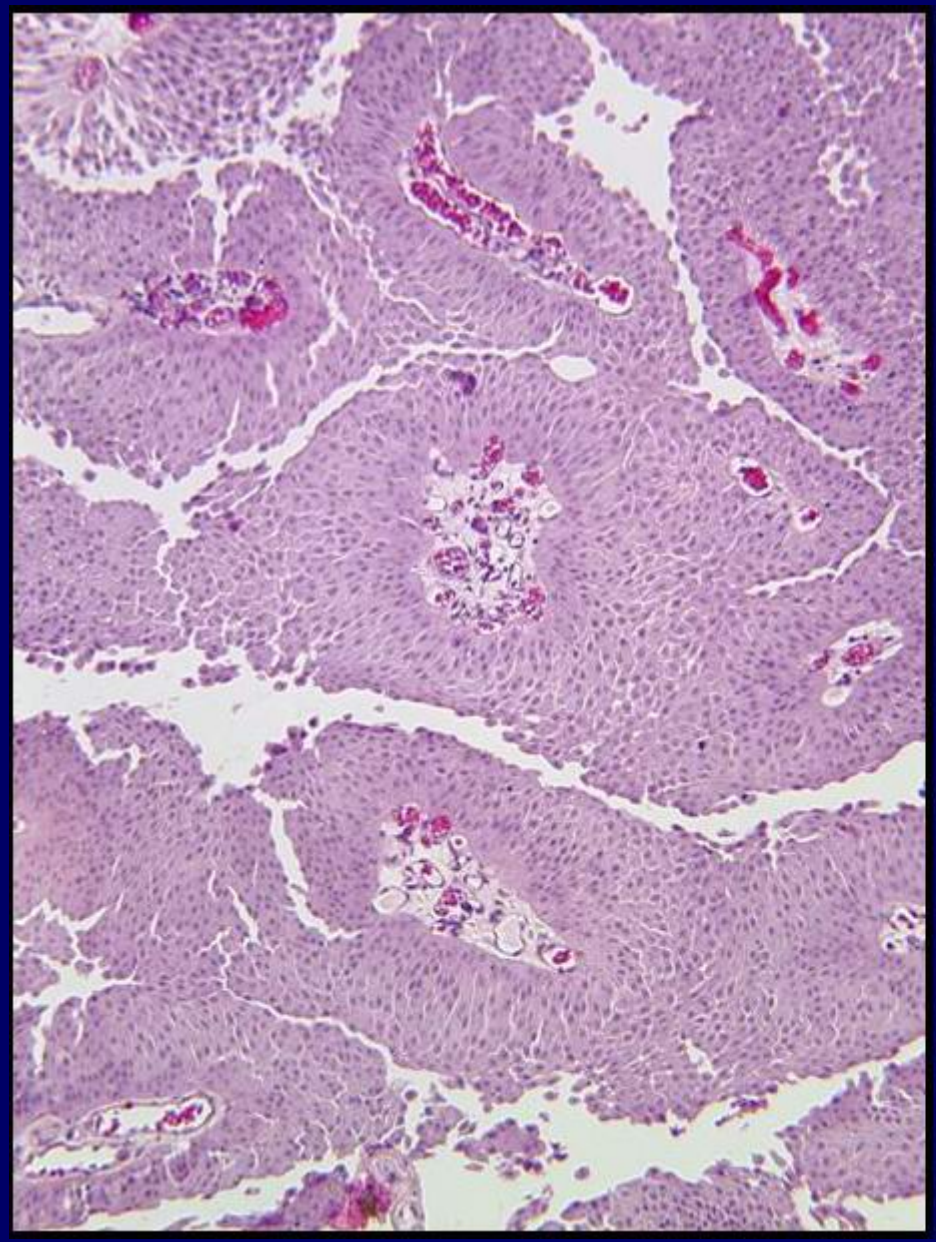

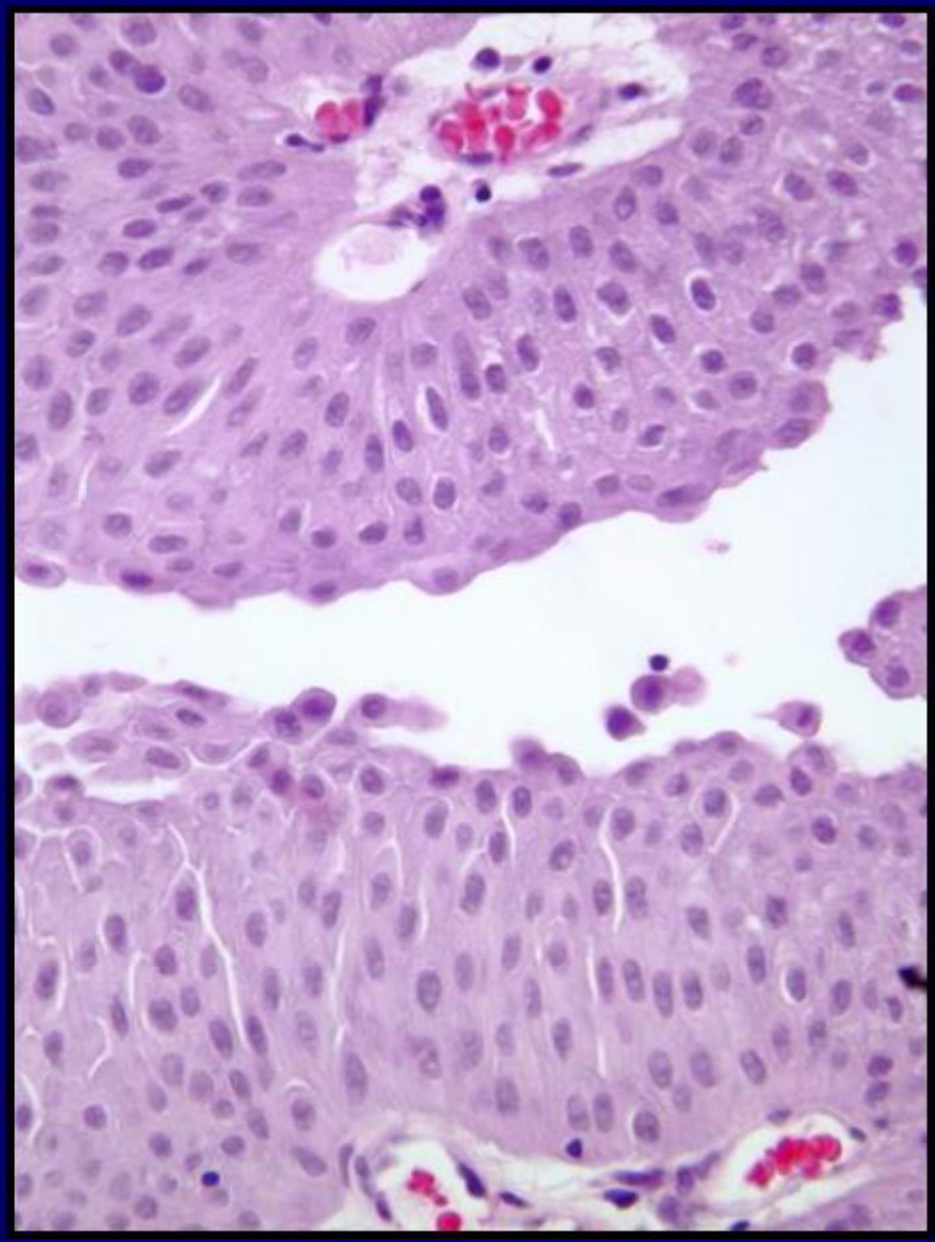

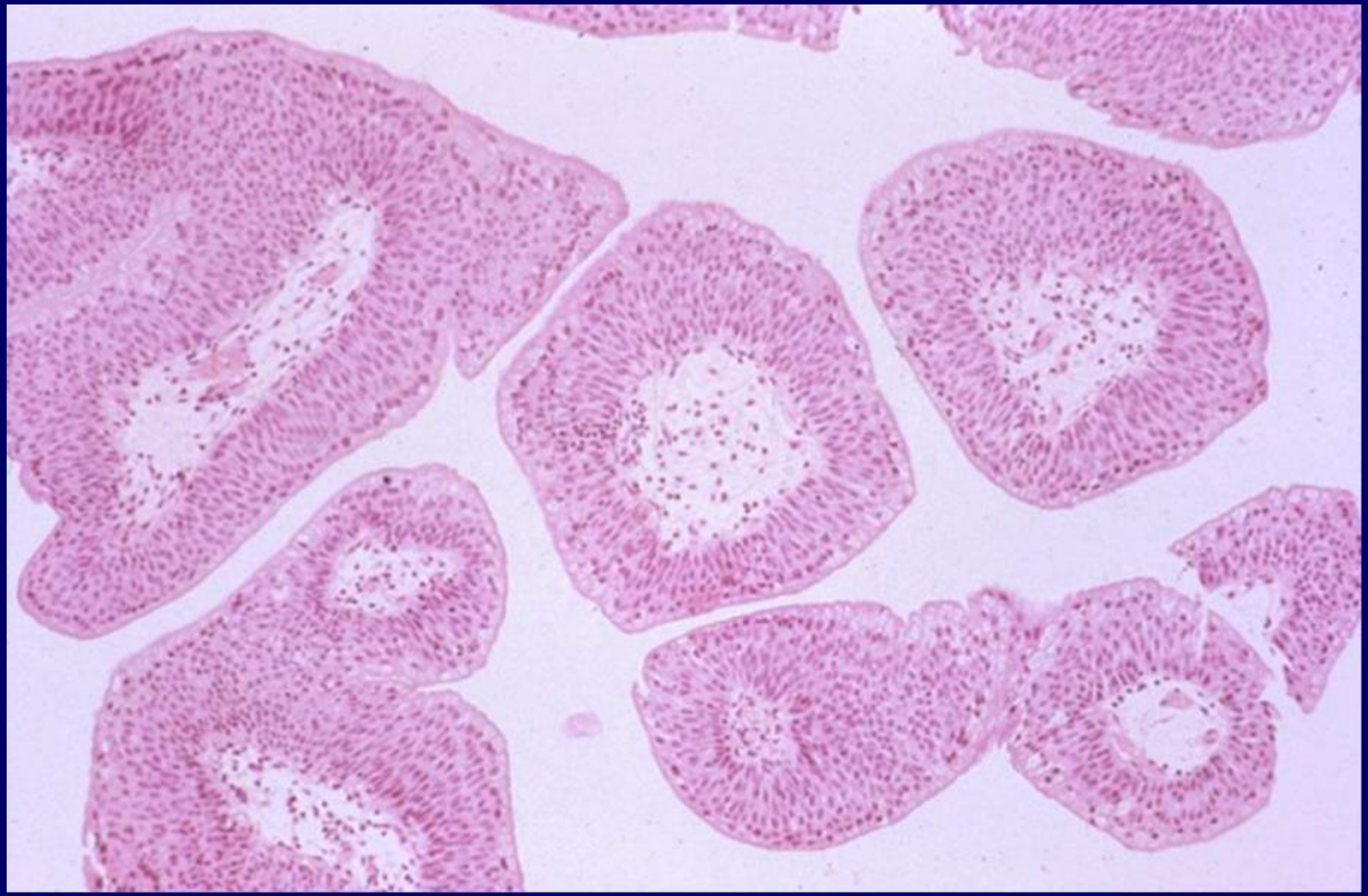

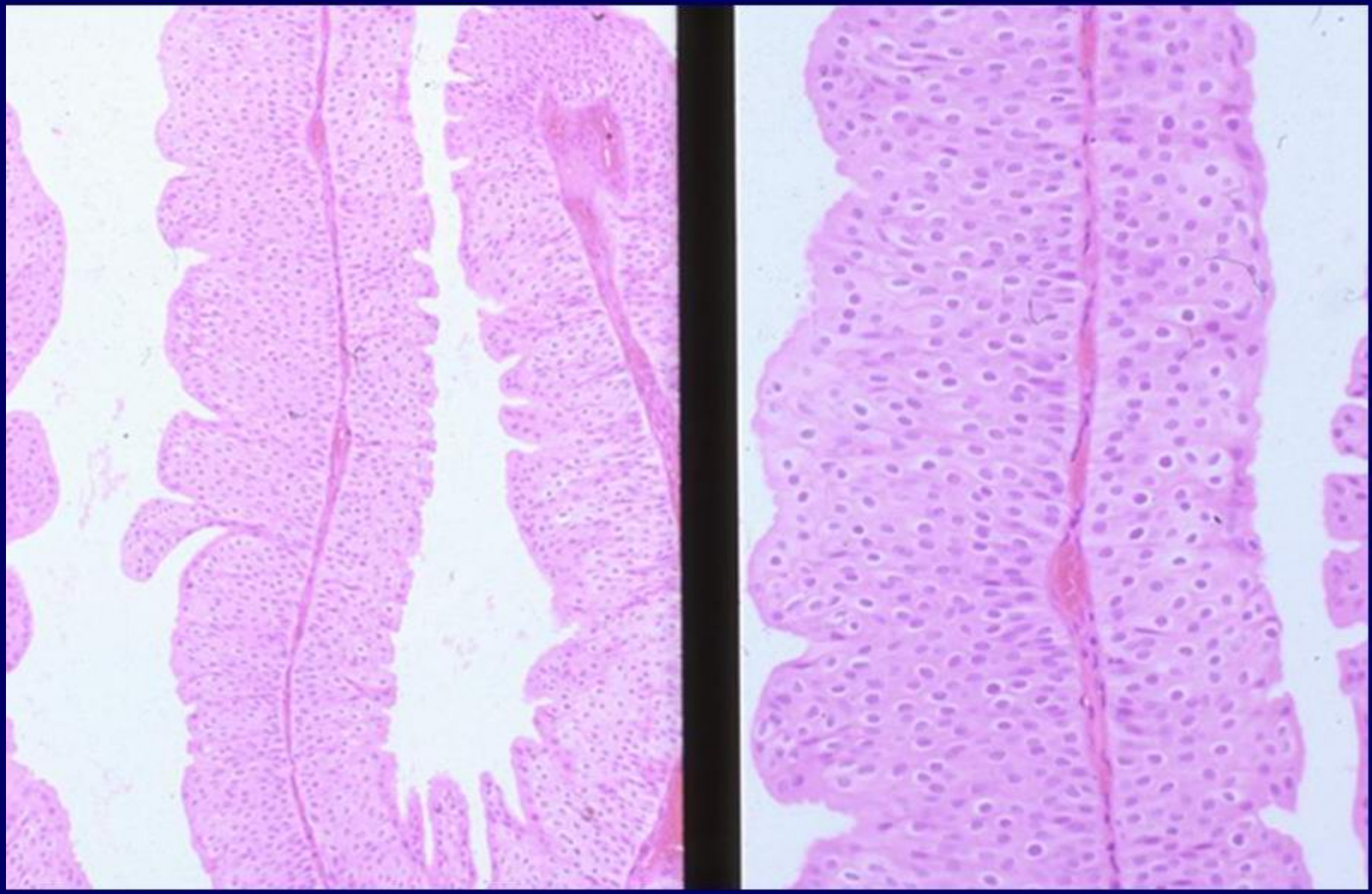

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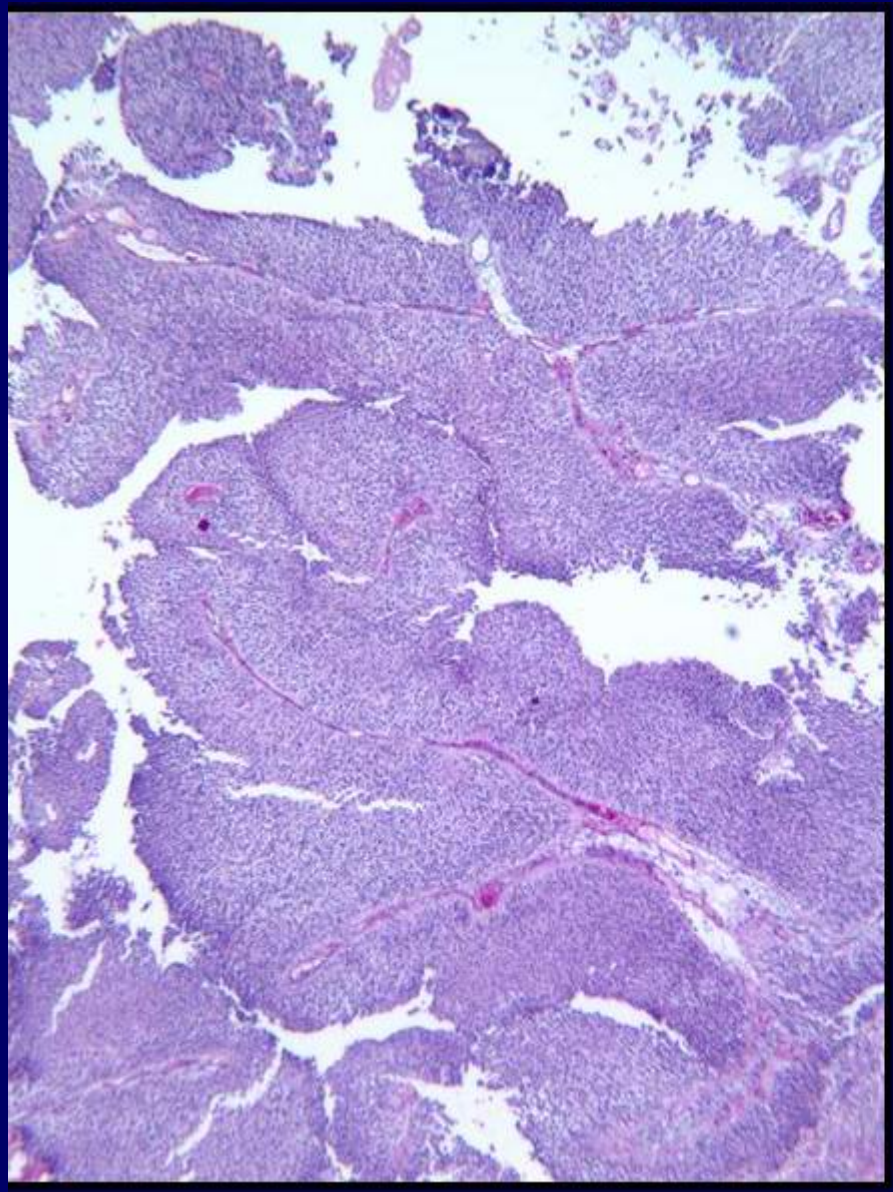
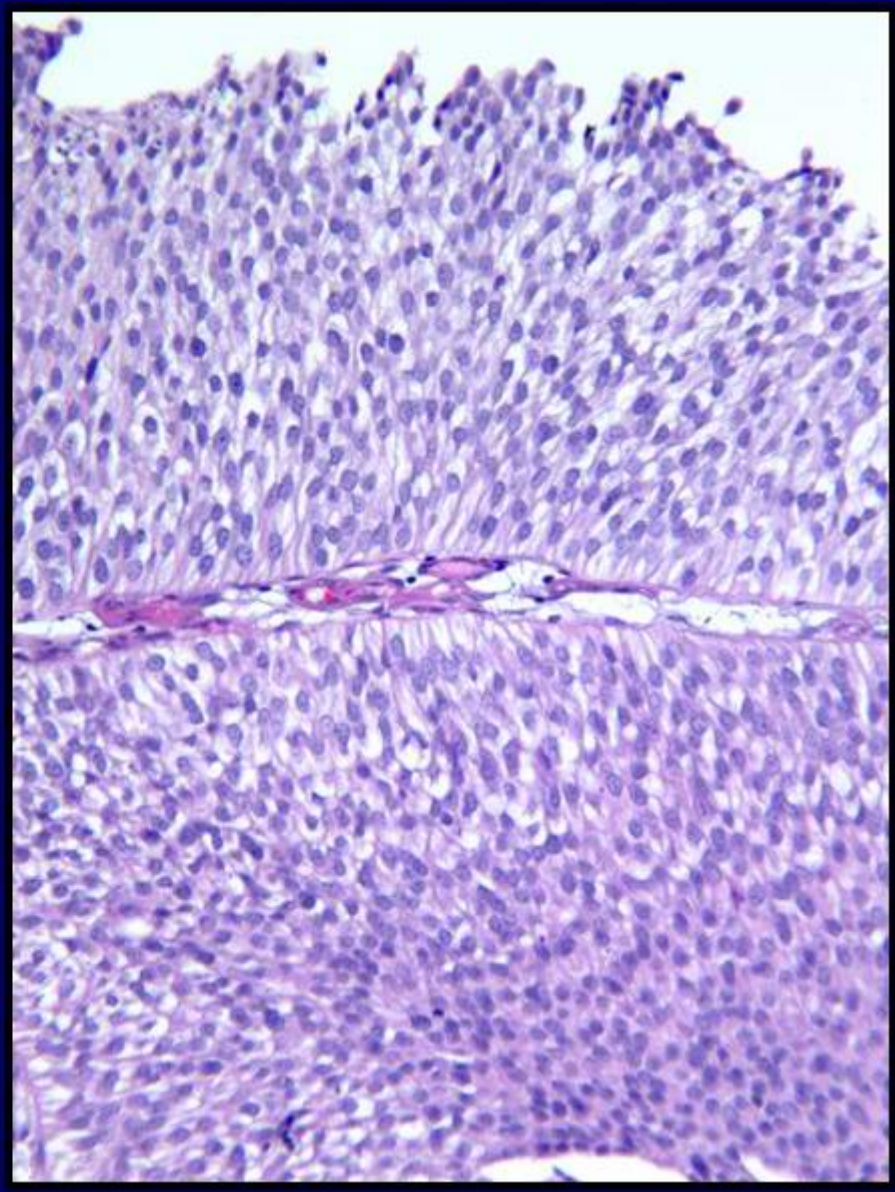


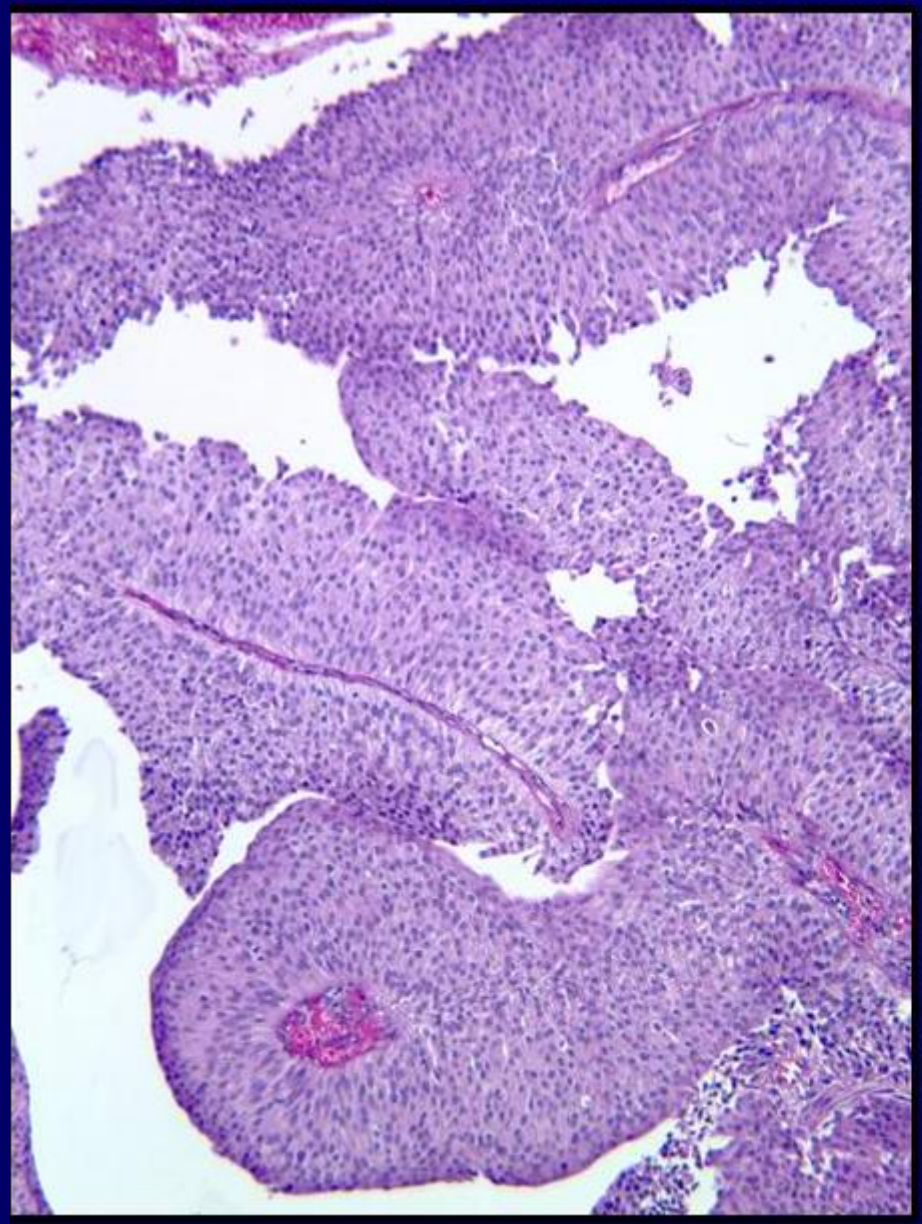


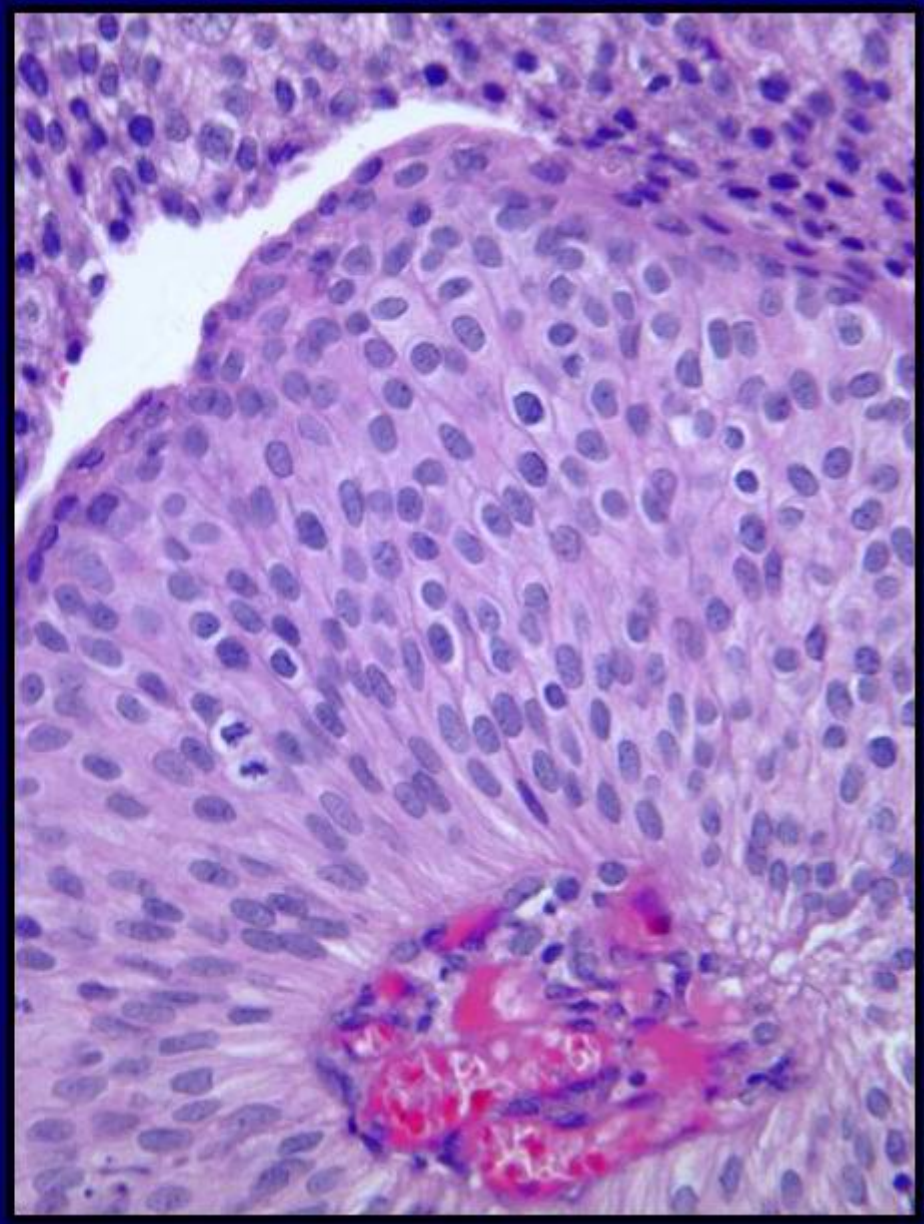
WHO 2004 CLASSIFICATION

PAPILLARY CARCINOMA, LOW GRADE

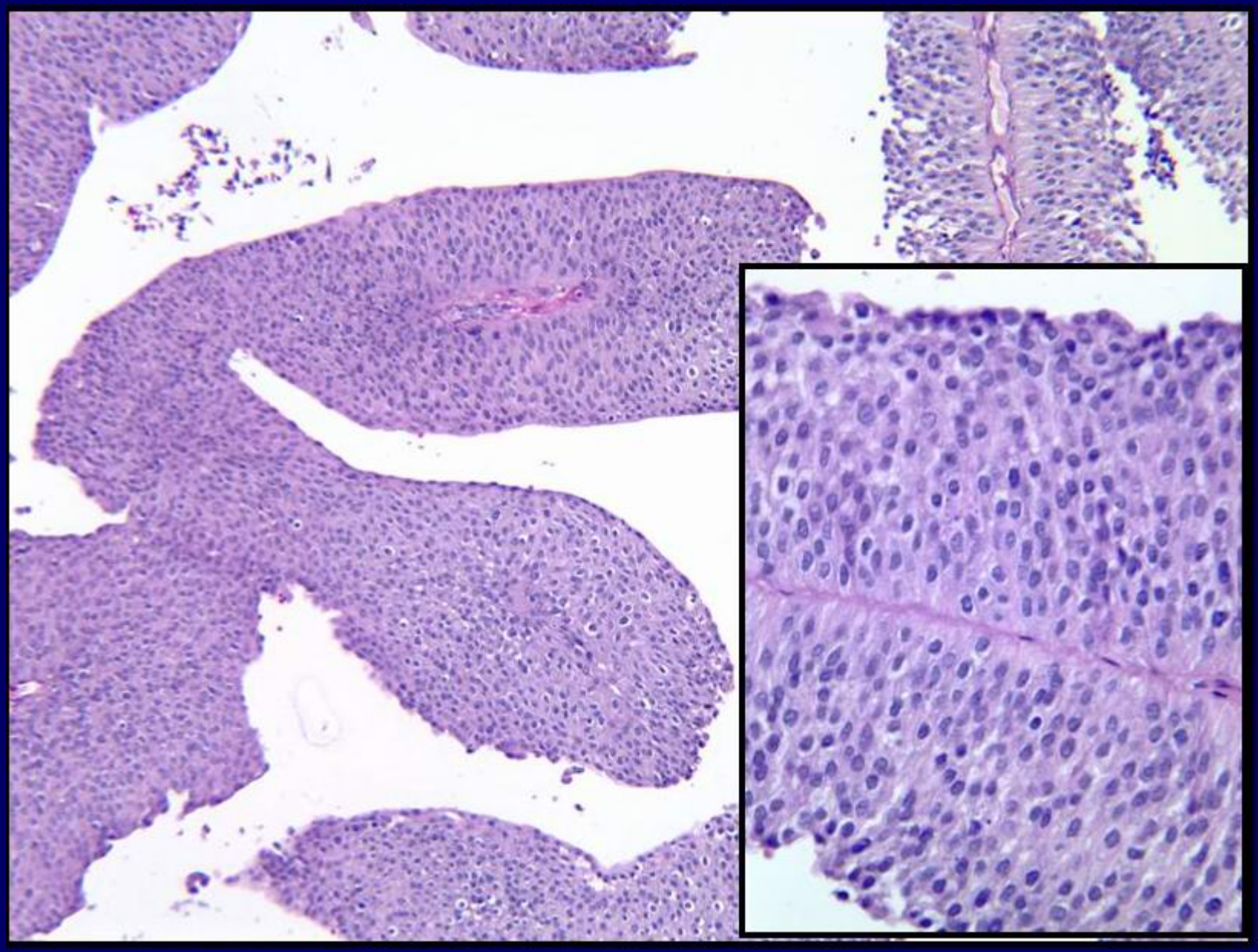
- Largely made up lower half of WHO II (1973)
- Significant risk of recurrence but low risk of invasion
- Delicate, occasionally fused papillae
- Characterized by an overall orderly appearance but shows definite though mild cytologic abnormalities

LOW GRADE





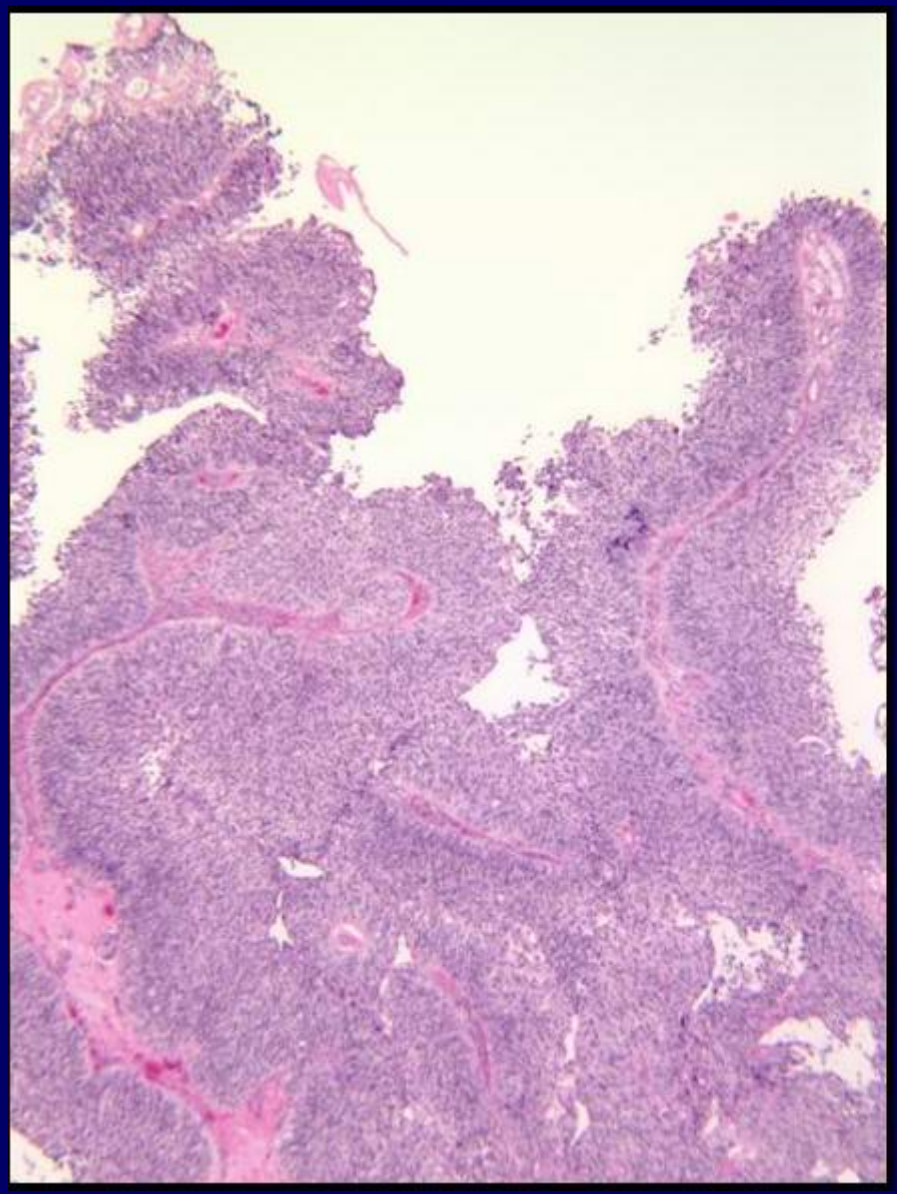
LOW GRADE

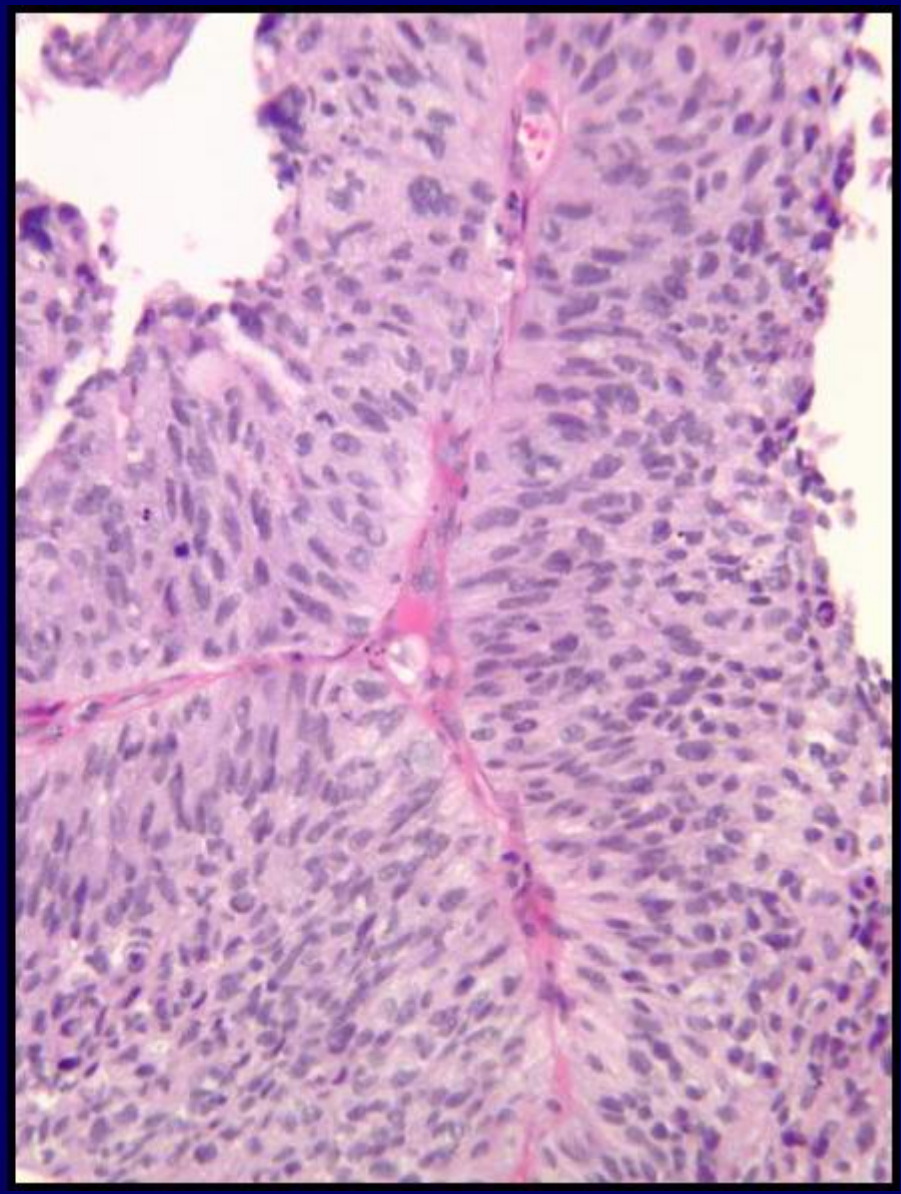


WHO 2004 CLASSIFICATION
PAPILLARY CARCINOMA, HIGH GRADE

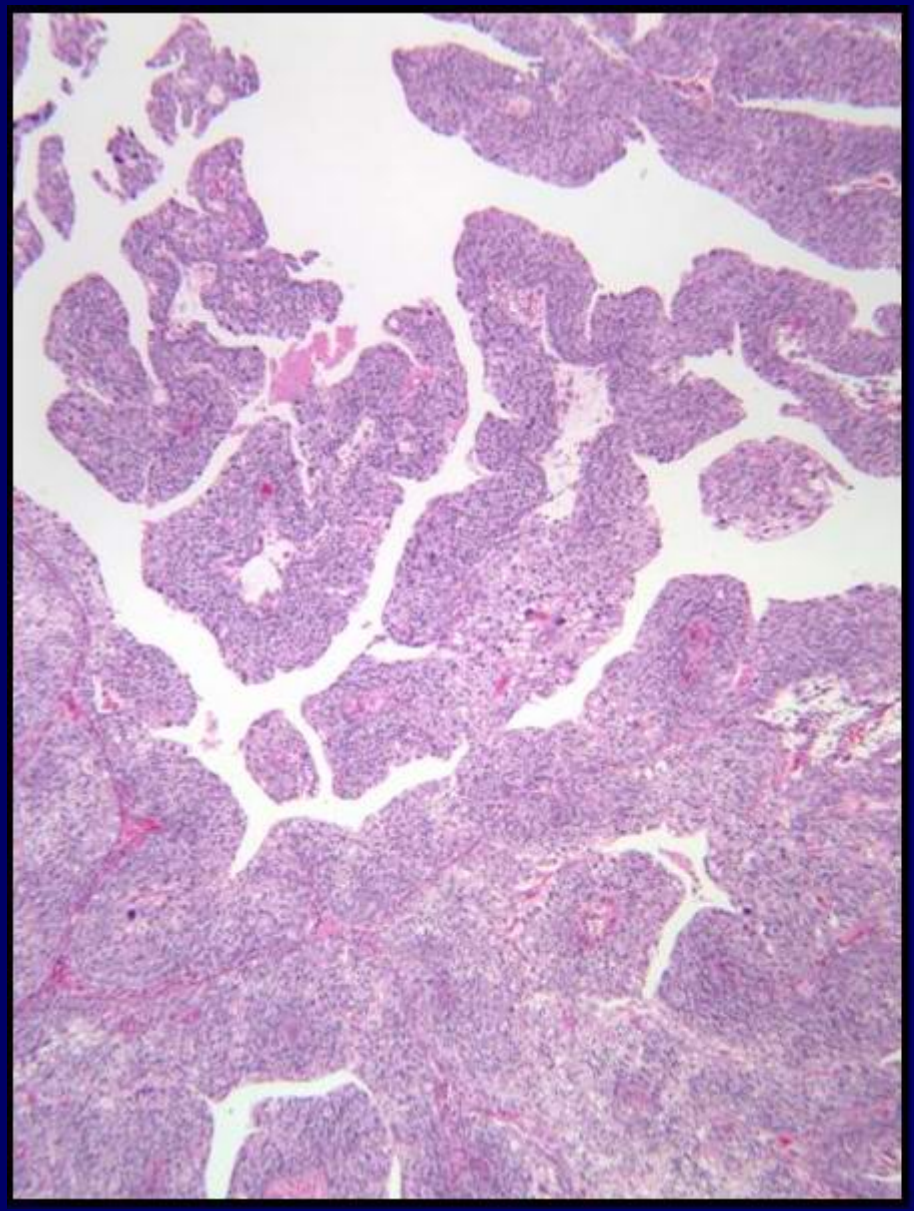
- Significant risk of progression
- Generally requires intravesical therapy
- Overall impression is one of disorder
- Irregular, often fused papillae
- Significant cytologic atypia is characteristic

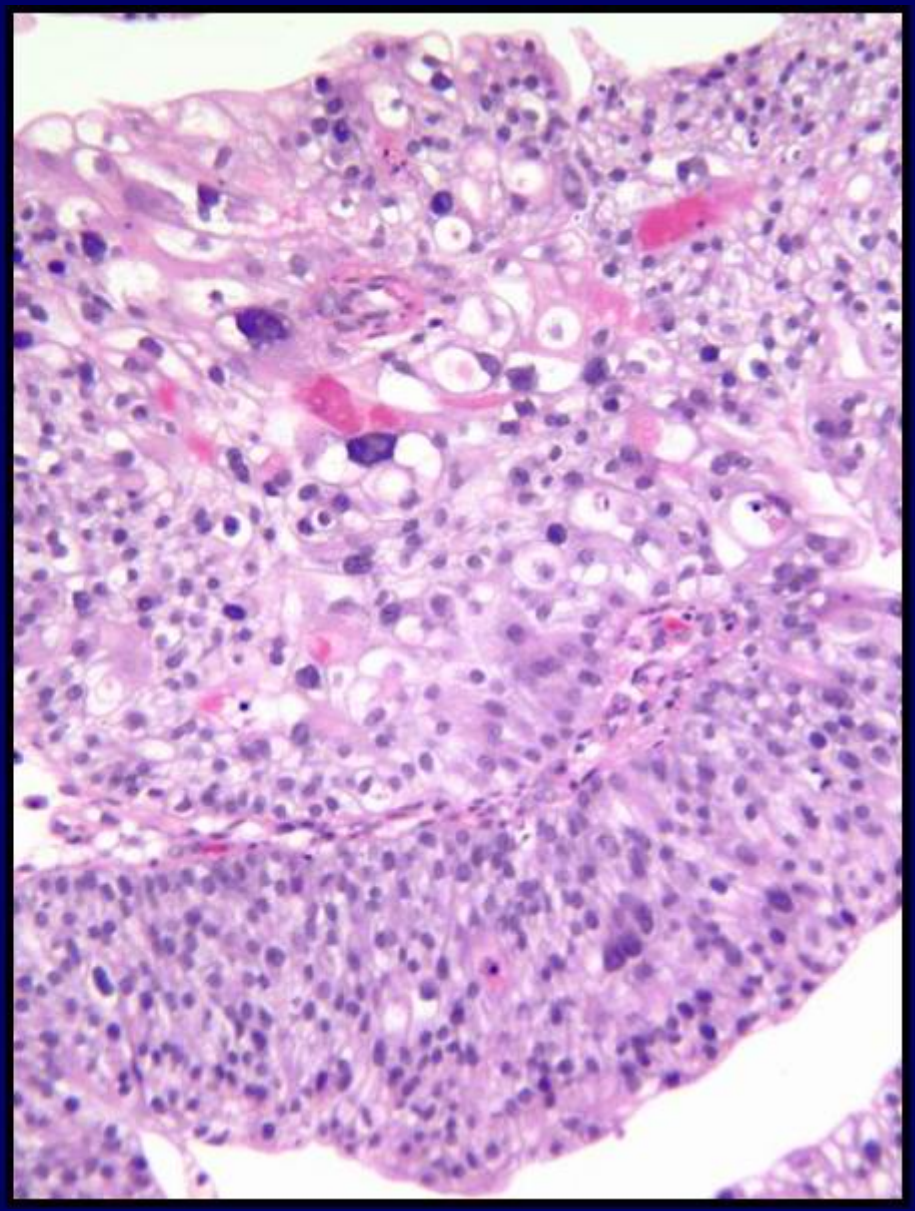
HIGH GRADE





HIGH GRADE





WHO/ISUP CLASSIFICATION PAPILLARY UROTHELIAL NEOPLASM OF LOW MALIGNANT POTENTIAL

- BACKGROUND
  - Major controversy regarding terminology
  - General acceptance that “Grade 1” papillary TCC is not intrinsically malignant
  - However also acknowledged that these are associated with significant risk for recurrence
  - Follow up but not addition tx is necessary

- CONSENSUS
  - Clinically important lesion
  - “LMP” compromise to recognize neoplastic nature but not labeled as malignant (“carcinoma”)

WHO/ISUP CLASSIFICATION PAPILLARY UROTHELIAL NEOPLASM OF LOW MALIGNANT POTENTIAL

- HISTOLOGY
  - Exophytic papillary growth
  - Delicate papillae
  - Covering urothelium with little to no architectural abnormalities
  - Normal nuclear size and shape
  - Fine chromatin with absent nucleoli
  - No or only rare mitoses

WHO/ISUP CLASSIFICATION
LOW GRADE PAPILLARY CARCINOMA

- BACKGROUND
  - Intermediate group of lesions well recognized from numerous clinical studies
  - These tumors have a low but definite risk of invasion
  - Recurrence common and progression occurs

- CONSENSUS
  - Tumors in the lower 1/2 of traditional WHO grade II have a low but definite risk of invasion and progression
  - Require close follow-up but may not need additional intravesicle therapy

WHO/ISUP CLASSIFICATION
LOW GRADE PAPILLARY CARCINOMA

- HISTOLOGY
  - Delicate, occasionally fused papillae
  - Characterized by an overall orderly appearance
  - Nuclei uniformly enlarged
  - Retain elongated, round to oval shape
  - Chromatin fine with absent to inconspicuous nucleoli
  - Few mitoses, basally located

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

PATTERN BASED GRADING OUTCOME

Grade	Recur	Progress	Dead	Cases
1	35%	0%	0%	26%
2A	68%	3%	3%	44%
2B	74%	19%	12%	26%
3	46%	38%	15%	4%

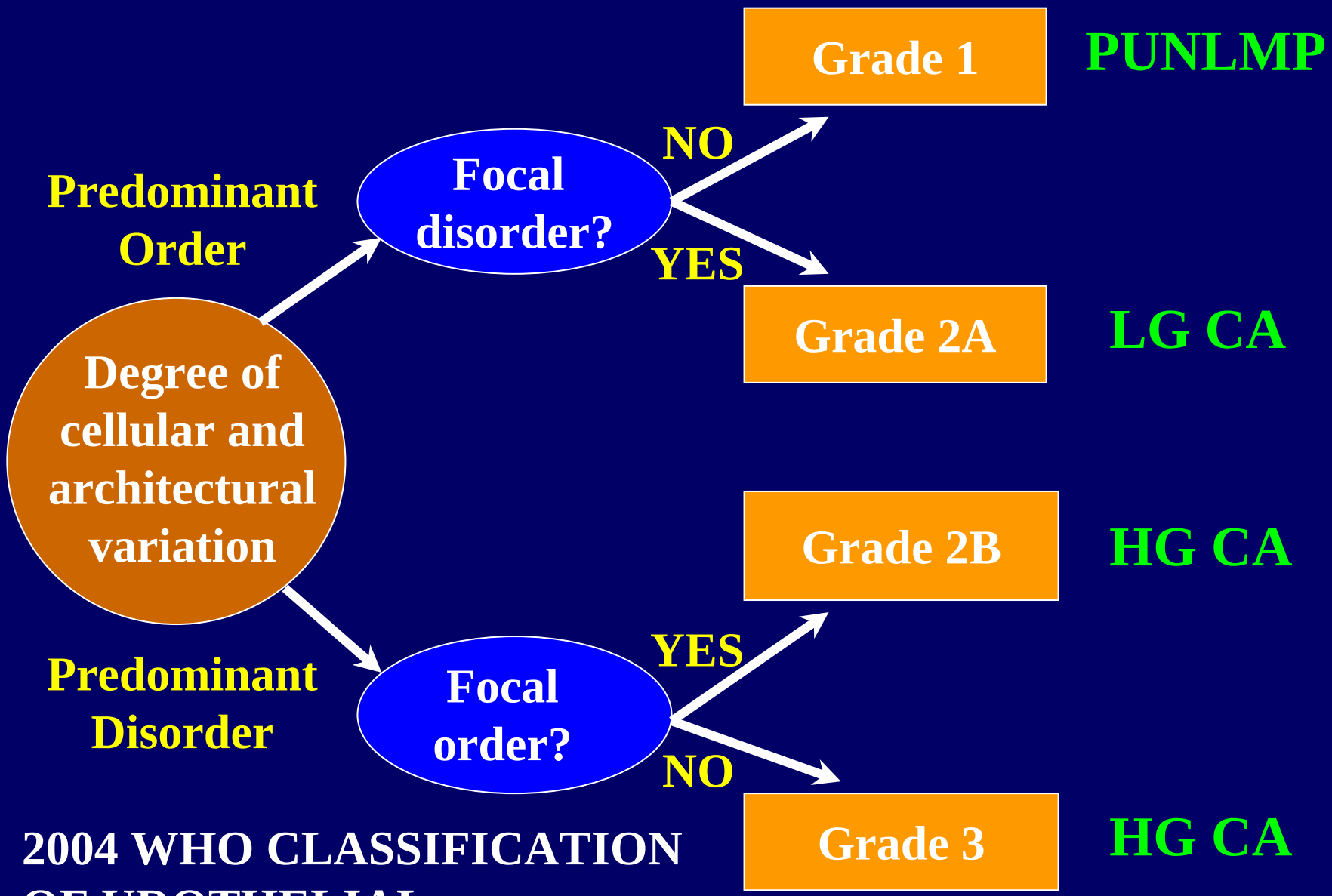
Rationale

THE TERM “CARCINOMA” IS REMOVED FROM THE LOWEST GRADE PAPILLARY TUMORS

ALL TUMORS ARE BETTER DEFINED AND ILLUSTRATED THAN IN 1973 WHO

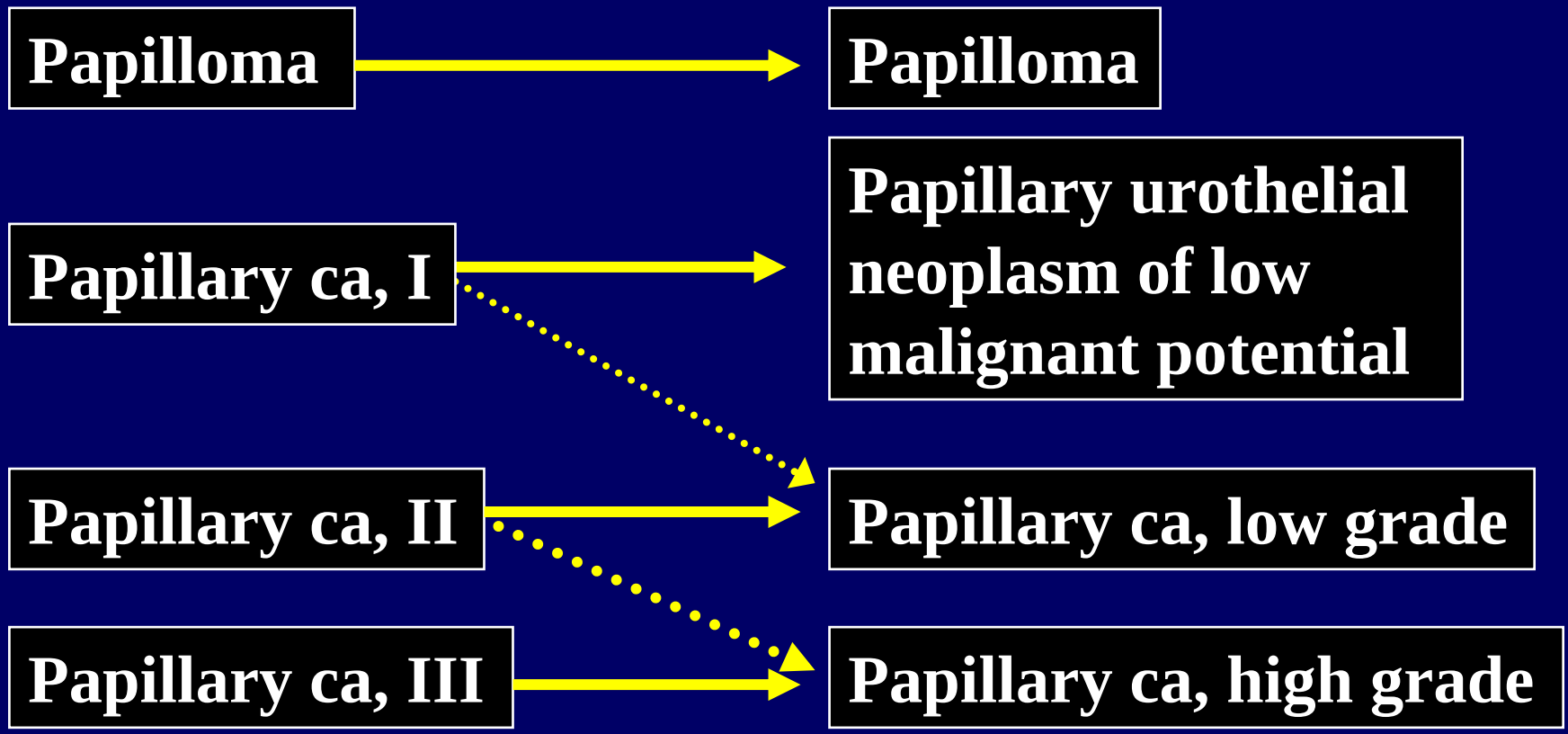
MOST TRUE CARCINOMAS ARE HIGH-GRADE

URINARY CYTOPATHOLOGY IS RECOGNIZED

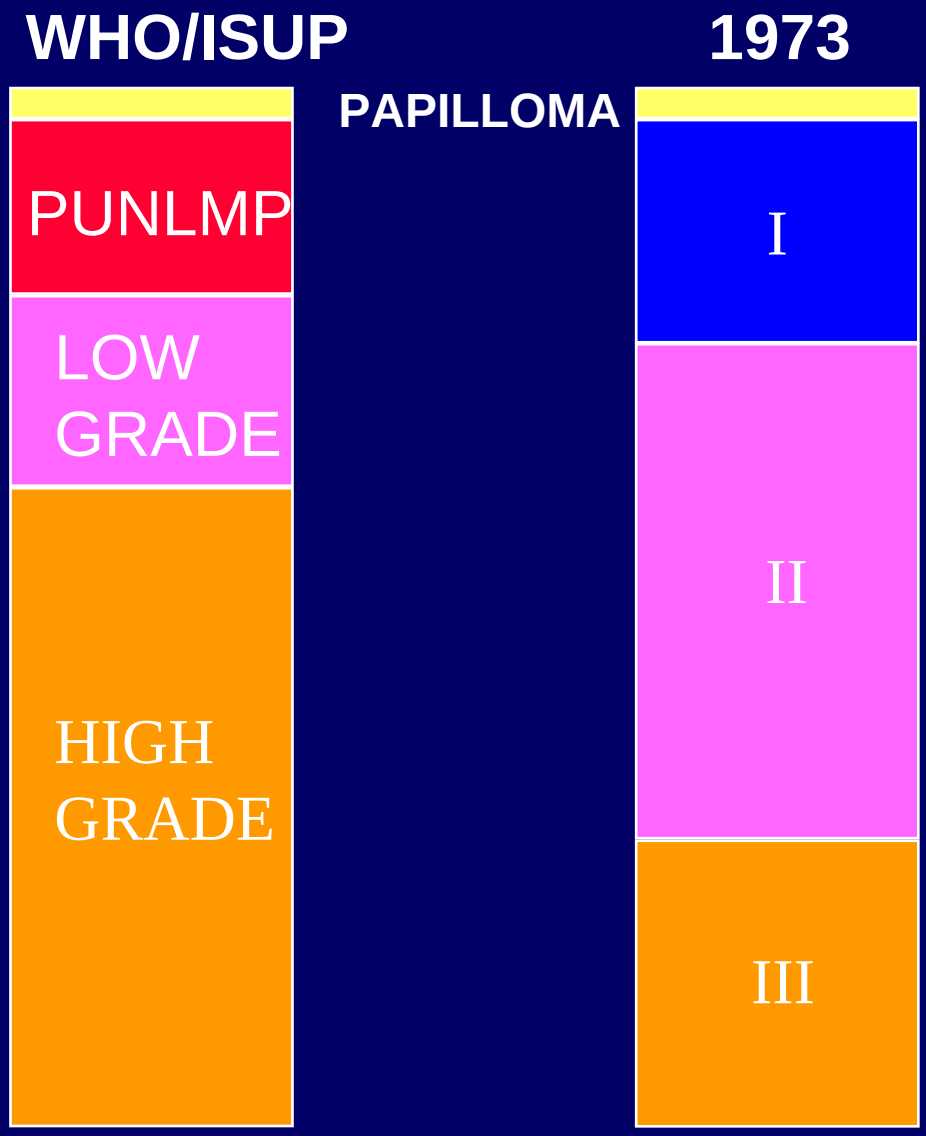


2004 WHO CLASSIFICATION OF UROTHELIAL NEOPLASMS

WHO 1973 *vs* WHO 2004



CORRELATIONS OF WHO CLASSIFICATIONS



CLASSIFICATION OF UROTHELIAL NEOPLASMS

(1998 WHO/ISUP, 2004 WHO, 2004 AFIP FASCICLE)

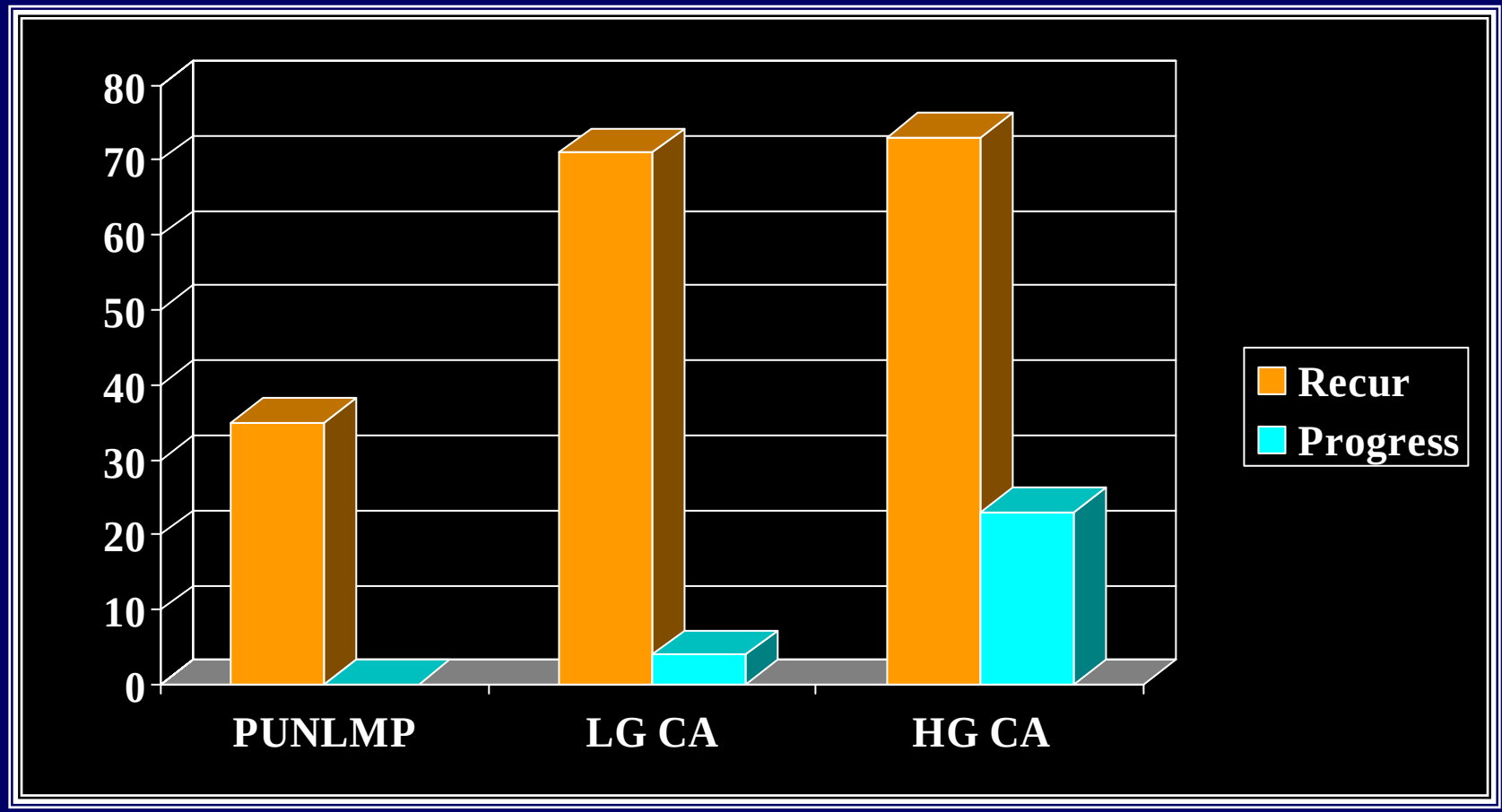
- ATYPIA
  - REACTIVE
  - OF UNKOWN SIGNIFICANCE
- DYSPLASIA
- CIS

- PAPILLOMA
- PUNLMP
- CARCINOMA
- LOW GRADE
- HIGH GRADE

PATIENT PROGRESSION by GRADE (380 CASES)

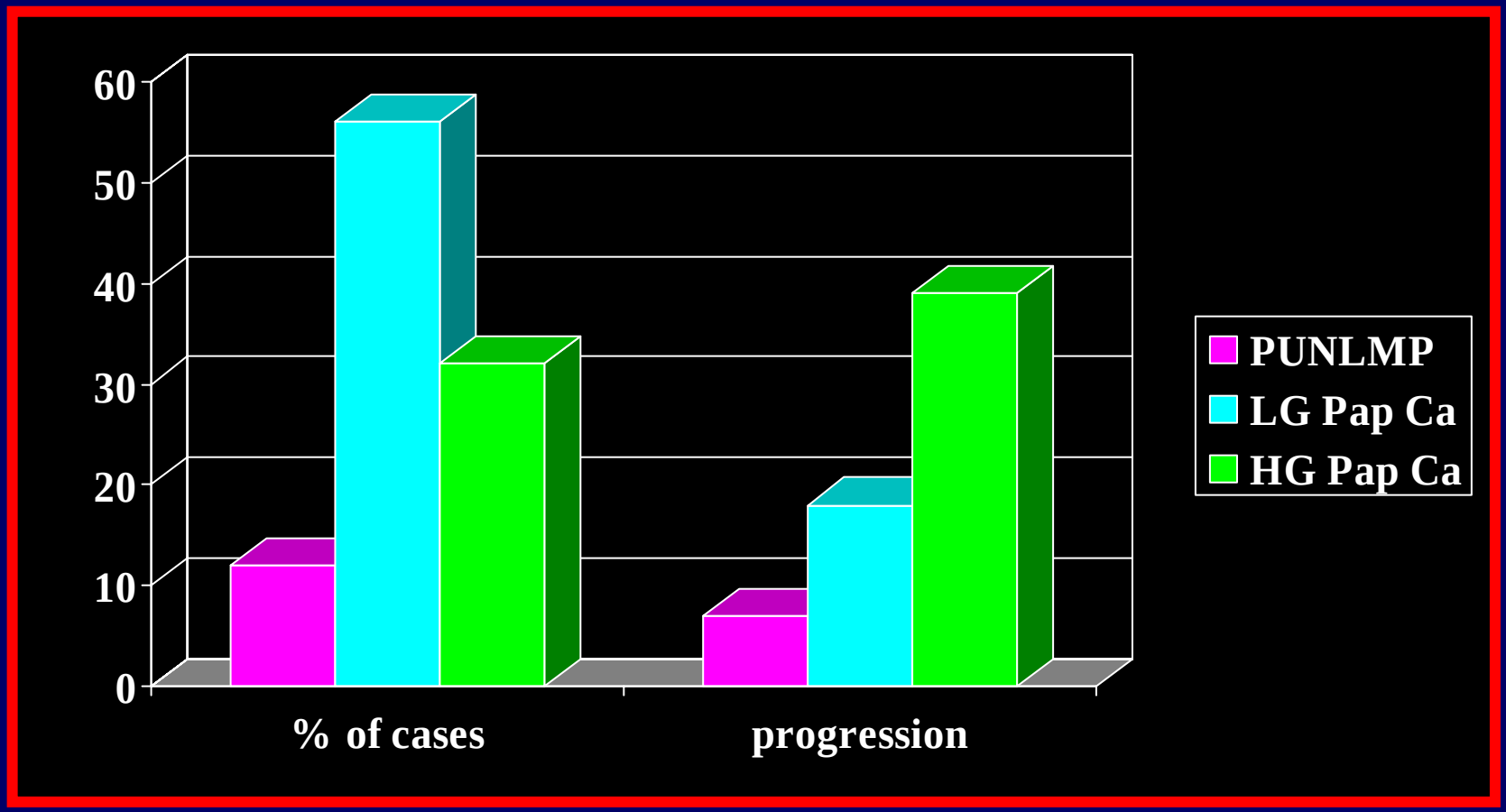
- **PUNLMP** **7.7%**
- **LOW-GRADE** **12.0%**
- **HIGH-GRADE** **61.9%**

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

THE NEXT STEP IN THE CLASSIFICATION OF UROTHELIAL NEOPLASMS

UROTHELIAL NEOPLASM, LOW-GRADE

UROTHELIAL CARCINOMA, HIGH-GRADE

LOW-GRADE UROTHELIAL NEOPLASMS (PAPILLOMA, PUNLMP, LOW-GRADE CA)

CELLS LACK MALIGNANT FEATURES

CYTOLOGIC DETECTION 30-60%

INVASION <10%
RECURRENCE <50%
PROGRESSION 7-15%
PATIENT SURVIVAL >90%

HIGH-GRADE UROTHELIAL NEOPLASMS (HIGH-GRADE CARCINOMA)

CELLS HAVE MALIGNANT FEATURES 85%

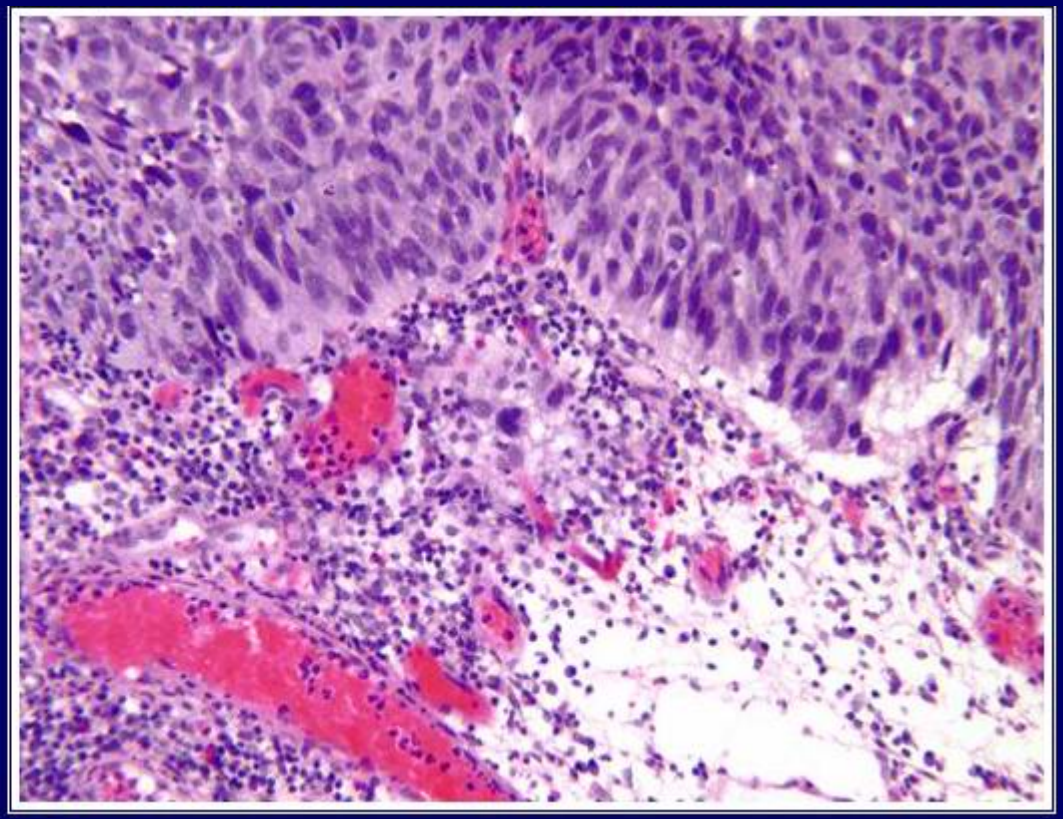
CYTOLOGIC DETECTION 70-95%

INVASION >50%
RECURRENCE 30 - >50%
PROGRESSION 30 - 60%
PATIENT SURVIVAL <50%
EVEN IF TUMOR-FREE AT F/U

Invasive Urothelial Neoplasia

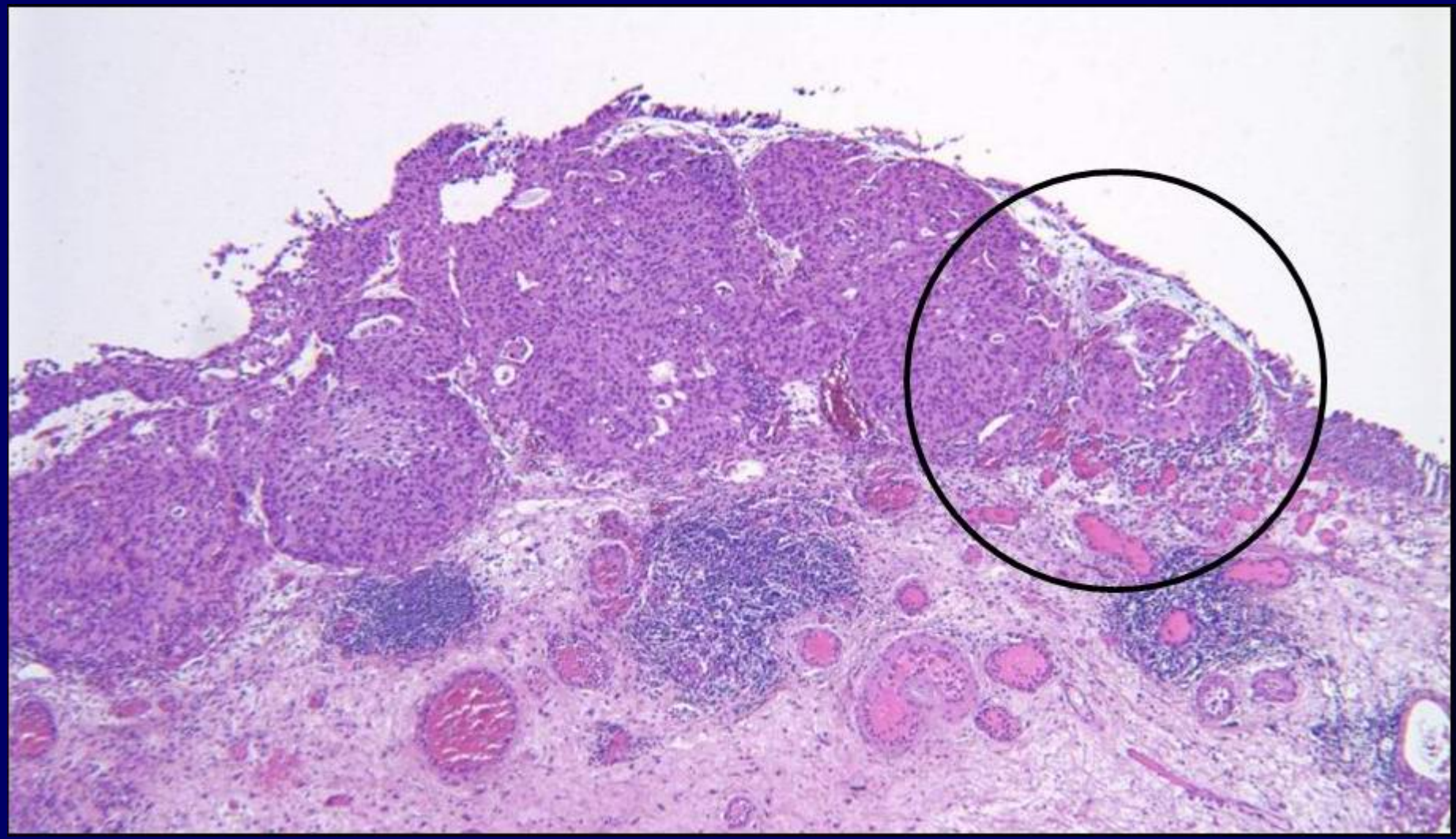
UROTHELIAL CARCINOMA "MICROINVASION"

- 68 cystectomies for CIS
- microinvasion (<5mm) identified in 23 (34%)
- bladder cancer deaths in:
  - 1/46 (2%) without microinvasion
  - 3/22 (14%) with microinvasion

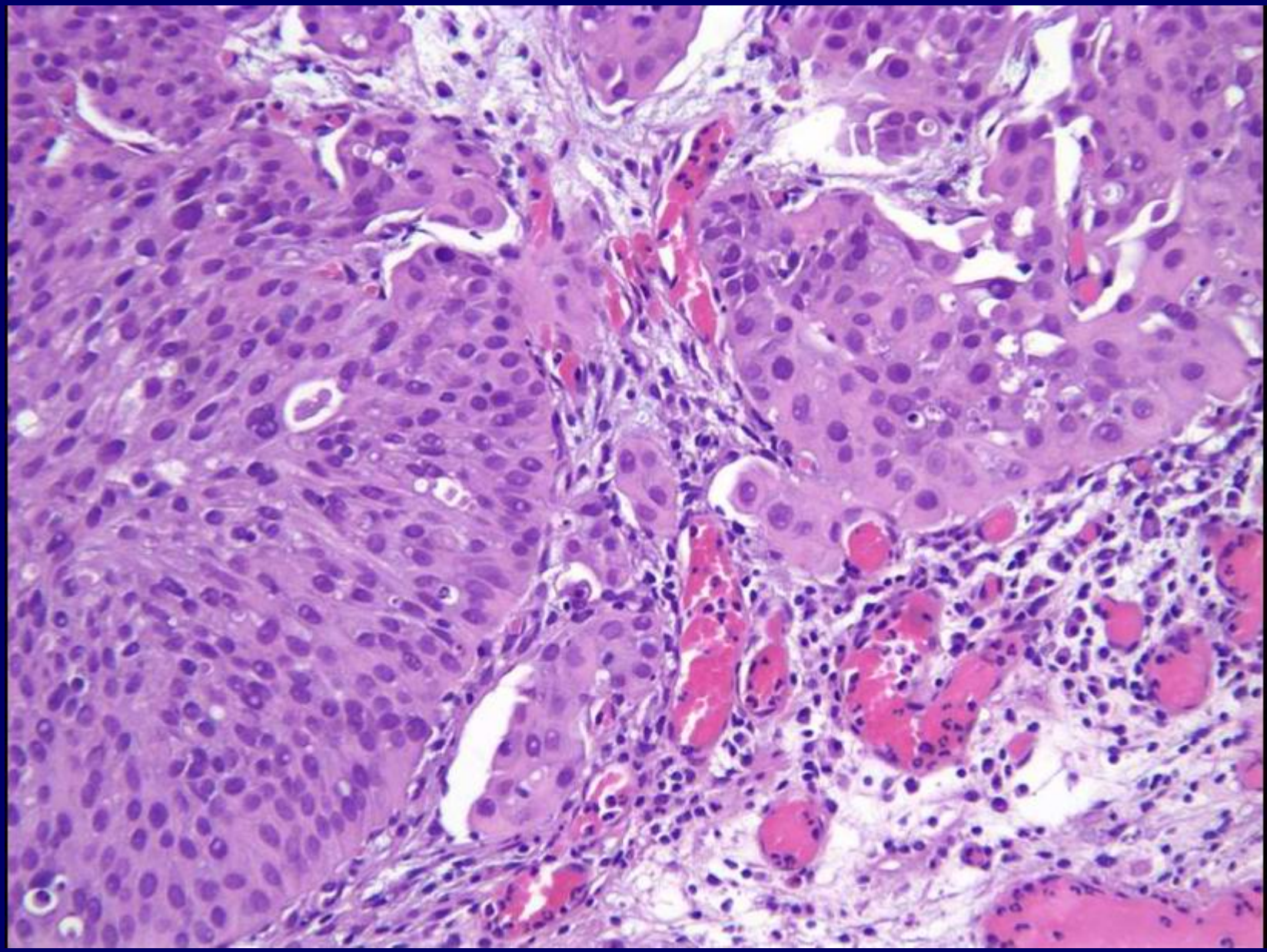


Farrow and Utz, Clin Oncol 1:609, 1982

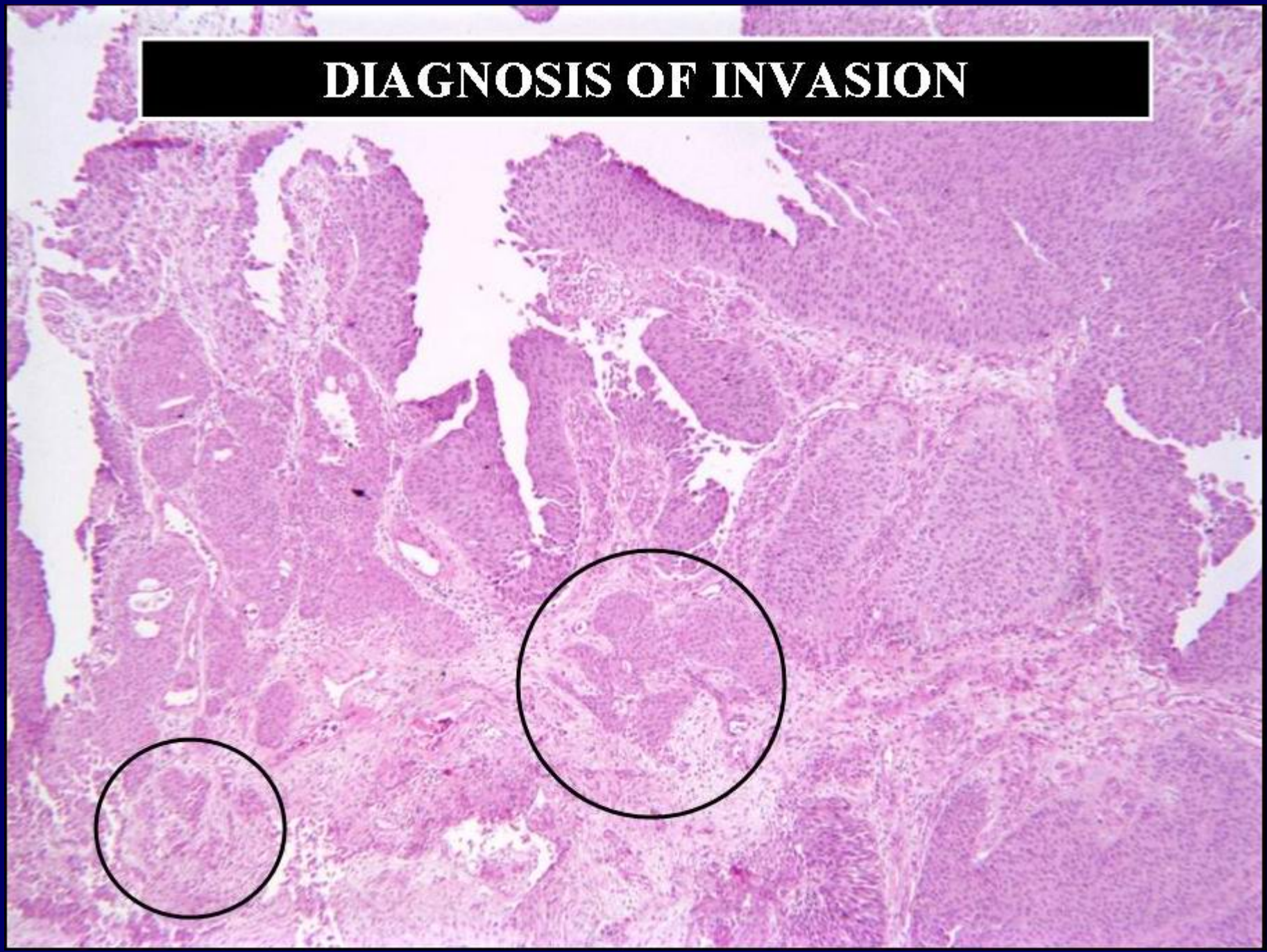
LAMINA PROPRIA INVASION



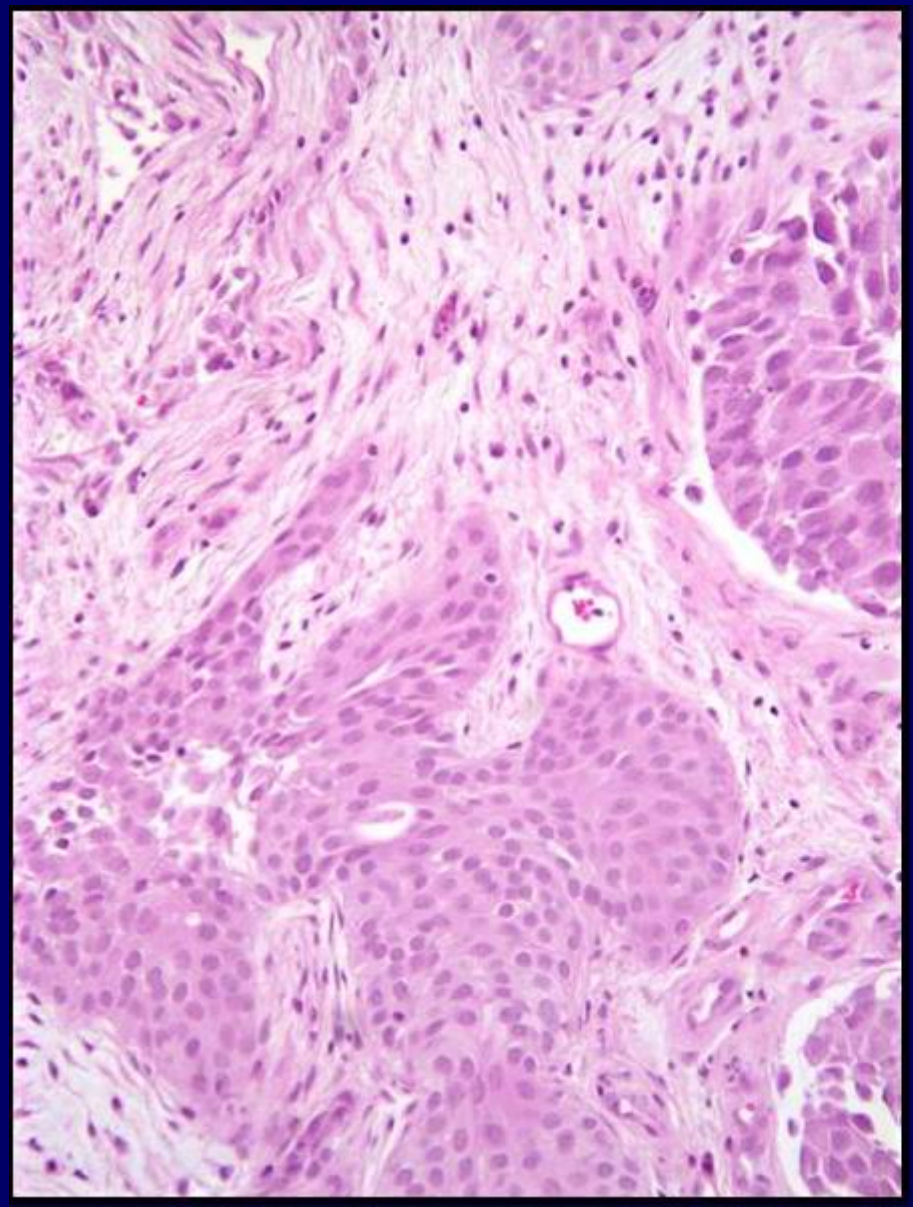
LAMINA PROPRIA INVASION

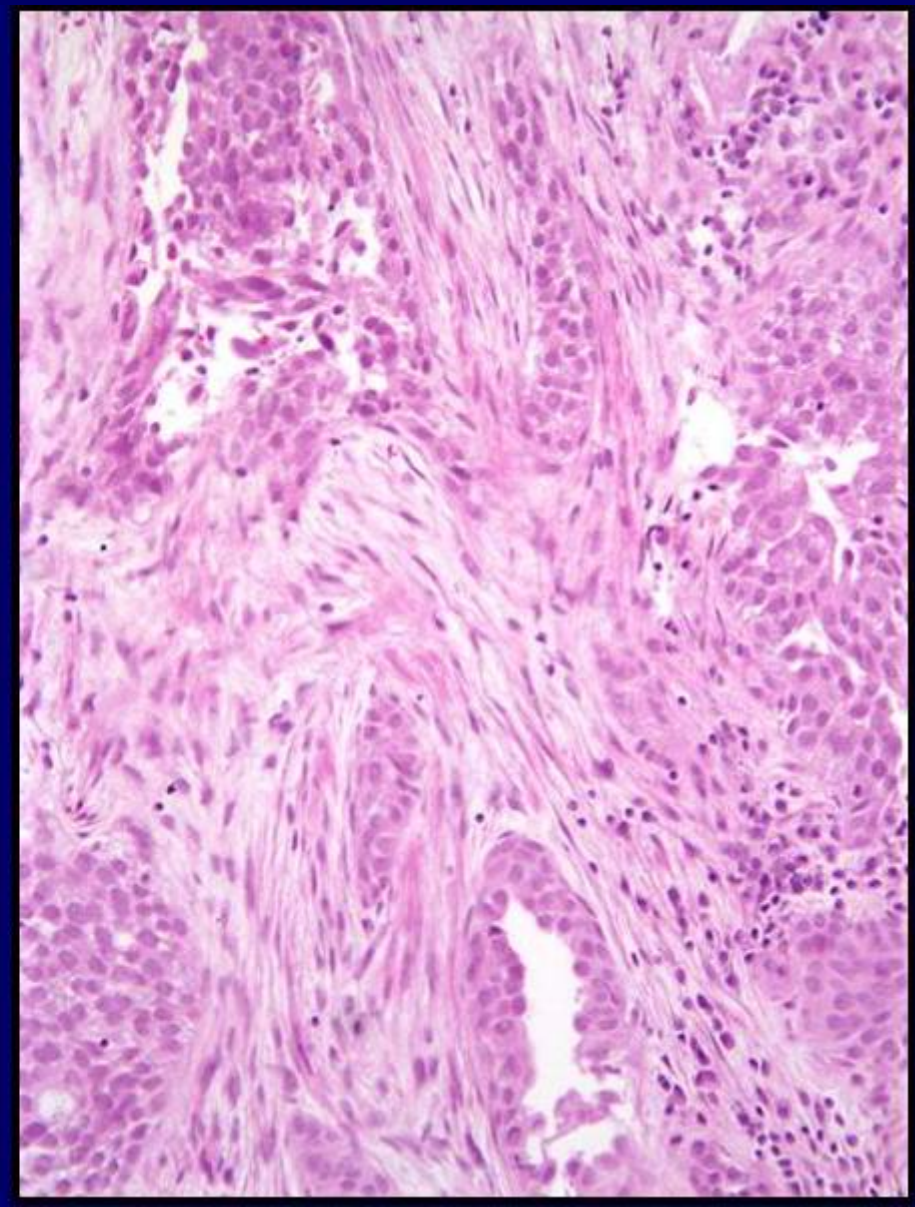


DIAGNOSIS OF INVASION

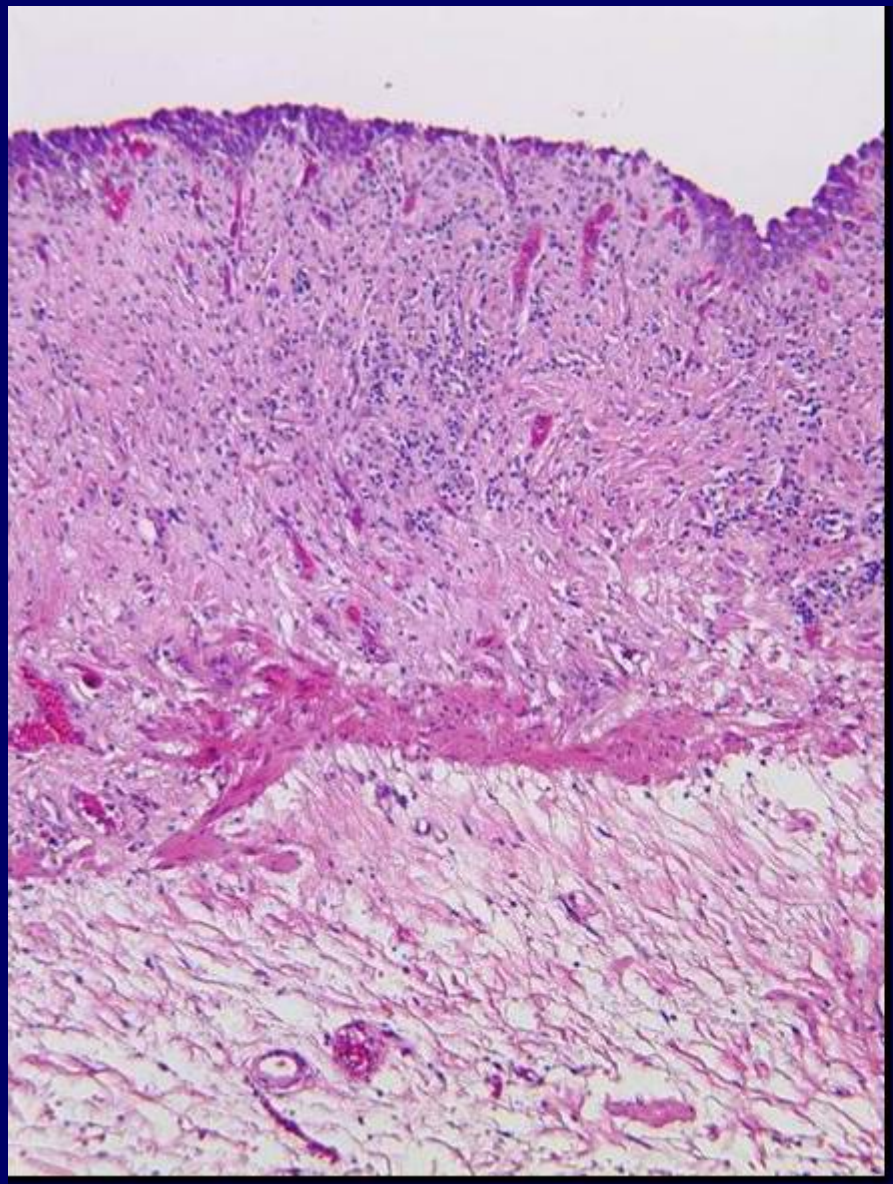


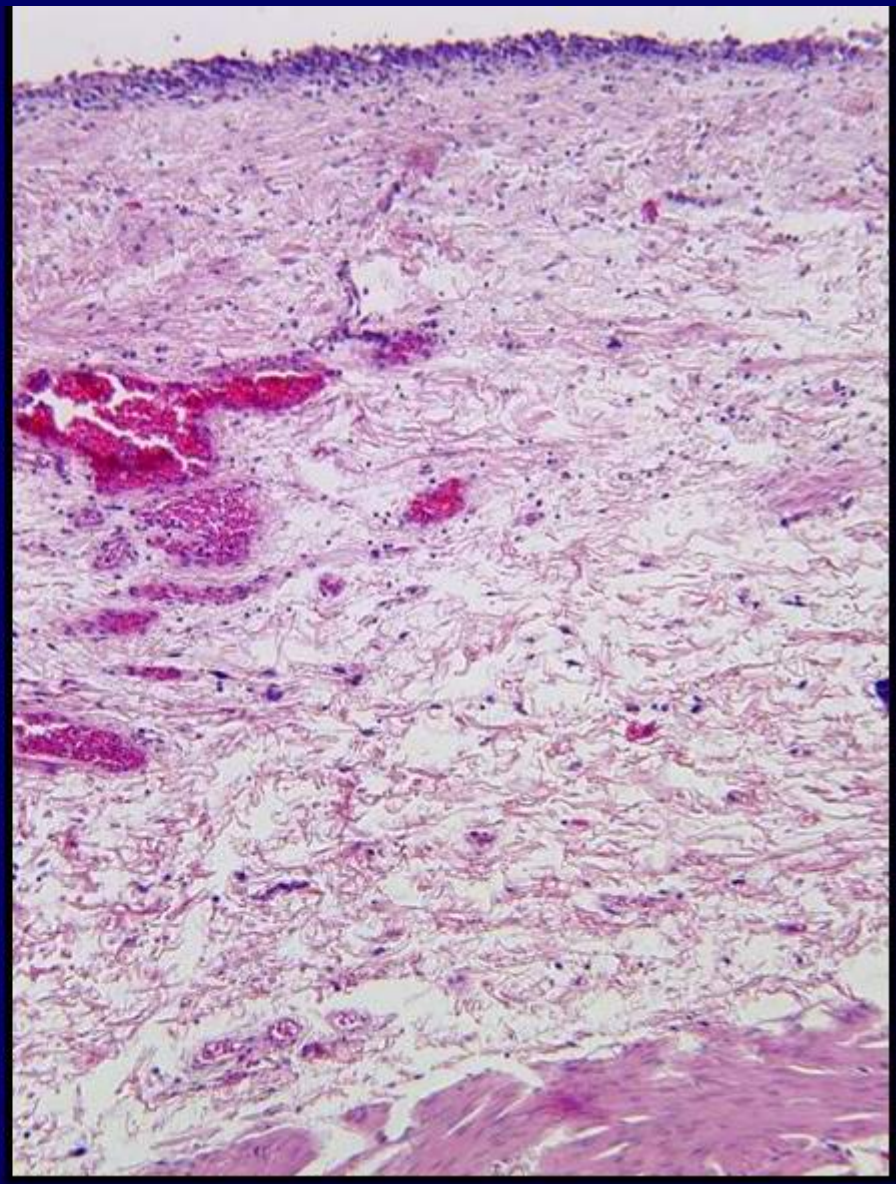
DIAGNOSIS OF INVASION





MUSCULARIS MUCOSAE





MUSCULARIS MUCOSAE DEVELOPMENT IN THE NORMAL URINARY BLADDER

Pattern	Ro (1987)	Keep (1989)
Continuous	3%	13%
Interrupted	20%	45%
Scattered	71%	43%
Absent	6%	0%

pTa BLADDER CA
LONG TERM OUTCOME

- 146 patients with 15 or more years FU
- all treated with TURBT and BCG

LOW GRADE (23)

- 15 year progression-free survival - 95%
- 15 year disease-specific survival - 100%

HIGH GRADE (125)

- 15 year progression-free survival - 61%
- 15 year disease-specific survival - 74%

Herr HW, J Urol 163:60, 2000

Issue of Substaging of T1 Cancer

pT1a
invasion up to m. mucosae

pT 1b
invasion beyond m. mucosae

- 3 studies have explored significance.
- T1b tumors higher rate of progression.
- 5-yr survival of T1 b tumors comparable to pT2 tumors.

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

STAGING OF BLADDER CANCER (2002 TNM)

- **pTa** Non-invasive, papillary
- **pTIS** Non-invasive, flat
- **pT1** Invasion of submucosa
- **pT2** Invasion of muscularis propria
- **pT3** Invasion of perivesical tissue
- **pT4** Invasion of adjacent structures