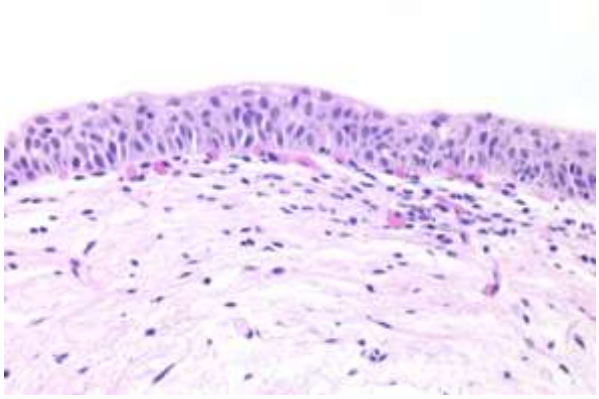
THE CLASSIFICATION, GRADING, AND STAGING OF UROTHELIAL NEOPLASMS

Normal Urothelium

- **Overuse of the diagnosis "mild dysplasia"**
  - **Mild staining and fixation alterations**
  - **Normal vs. mild dysplasia**
  - **Urologists desensitized to the diagnosis of dysplasia**
- **Do not use the term "mild dysplasia" – diagnose as "normal"**

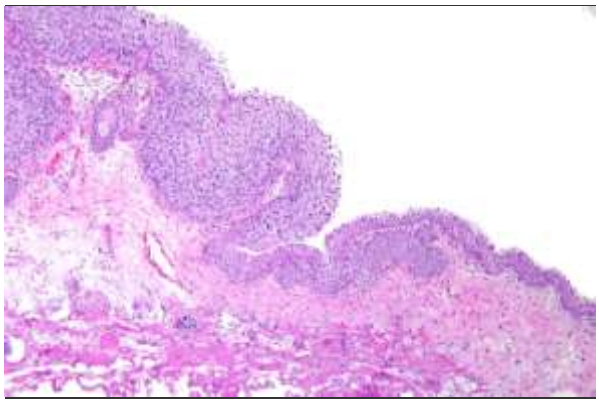


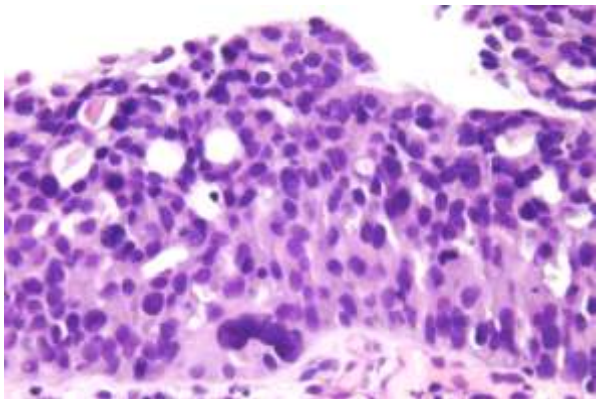
Carcinoma in Situ

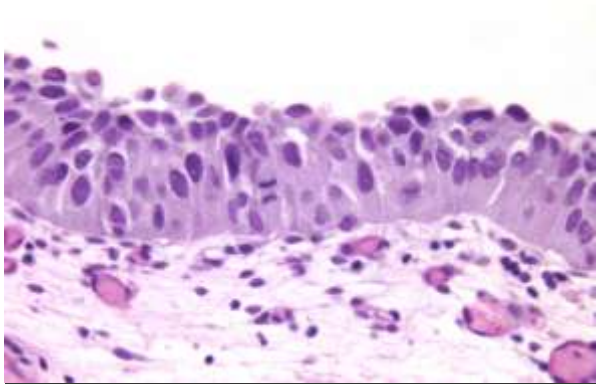
- Do not grade CIS – by definition high grade
- Do not use "severe dysplasia" – equals CIS
- Flat lesions: 1) Normal 2) Dysplasia 3) CIS

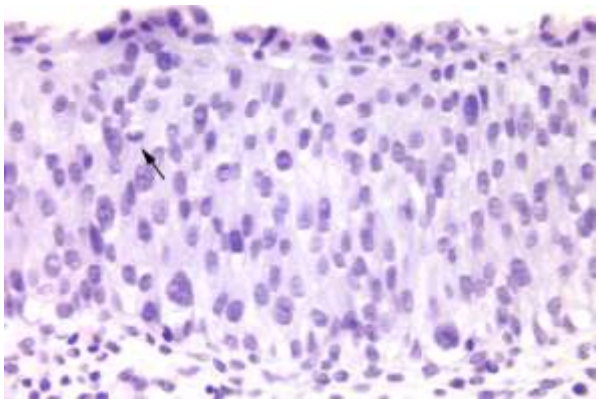
Histology: CIS

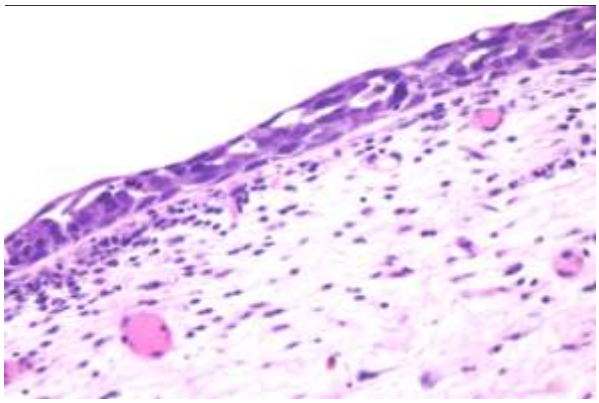
- Presence of cytologically malignant cells regardless of quantity
  - Not need to be full thickness
  - Pagetoid
  - Spectrum of atypia
- CIS cells 5x size of stromal lymphocytes, compared to normal cells which are 2x size of lymphocytes
- Enlarged & hyperchromatic
- Dyscohesive – "denuding cystitis"
- May see umbrella cell layer

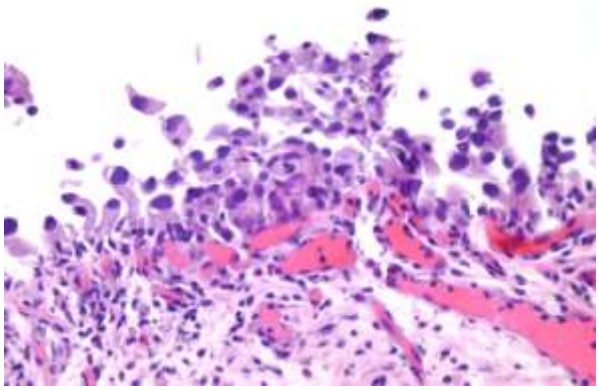


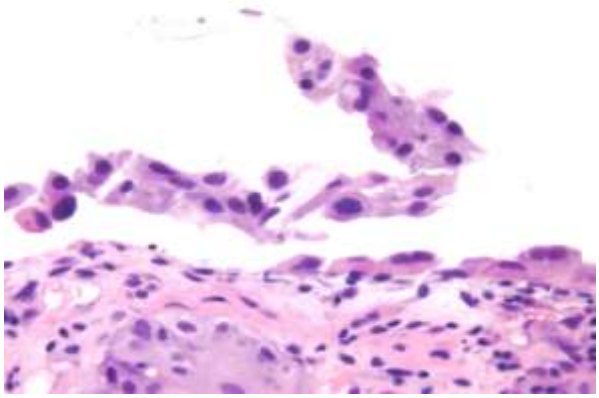


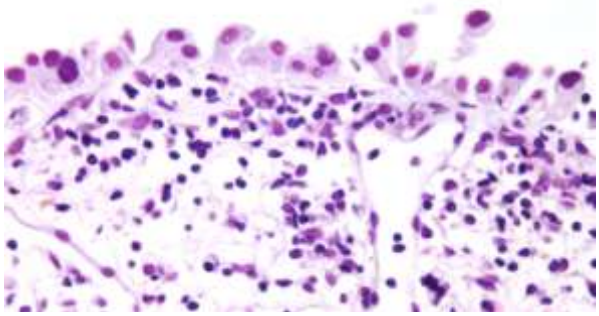


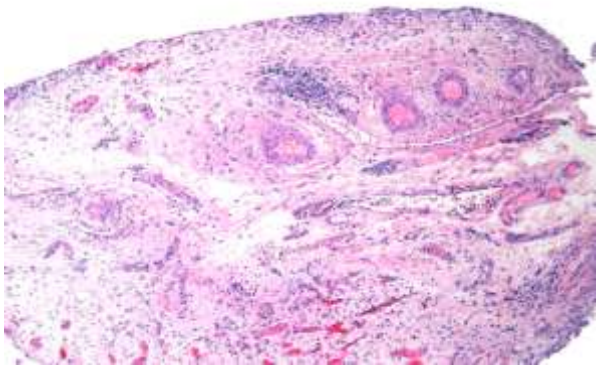


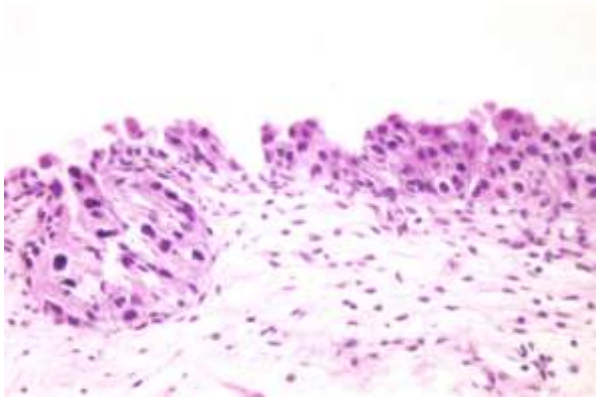


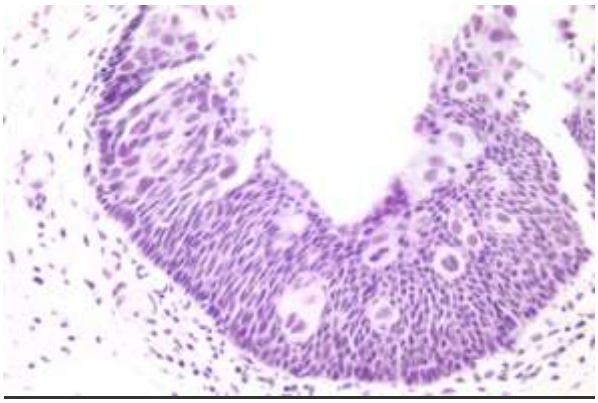






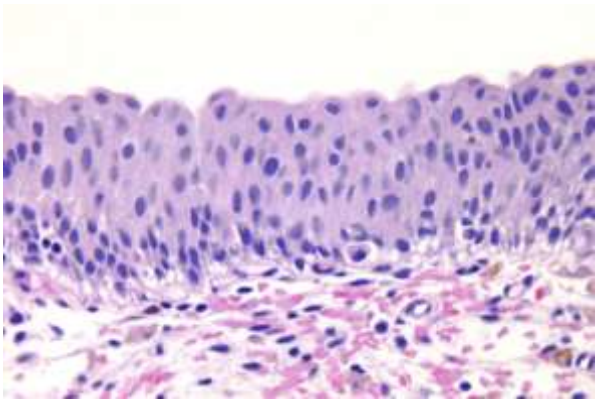






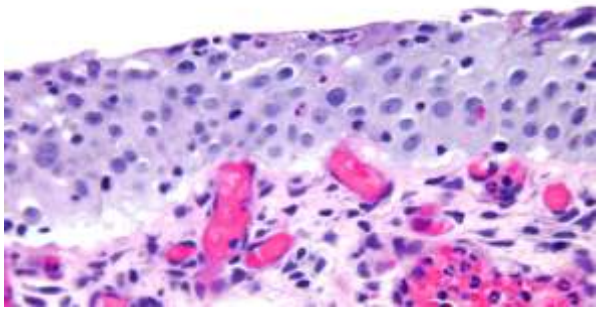
Dysplasia

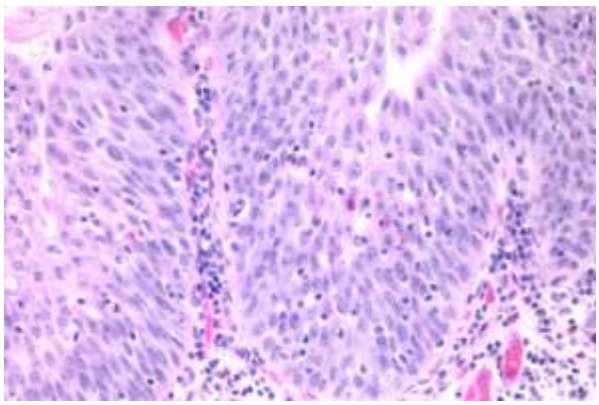
- Preneoplastic atypia short of CIS yet more than mild dysplasia.
- Without qualifier, equals “moderate dysplasia”
- Relatively uncommon diagnosis – most cases either normal or significant atypia (CIS)



Reactive Urothelial Atypia

- Acute or chronically inflamed urothelium
- Vesicular uniformly enlarged nuclei with central prominent nucleoli.
- Mitotic figures may be common.
- History of instrumentation, infection, stones, therapy

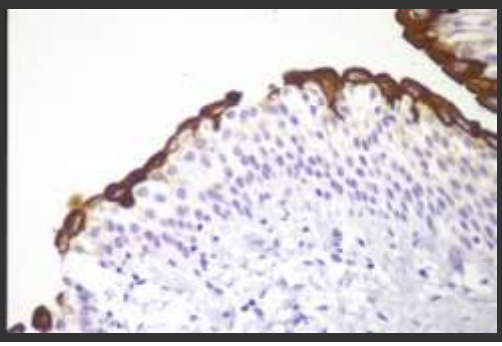




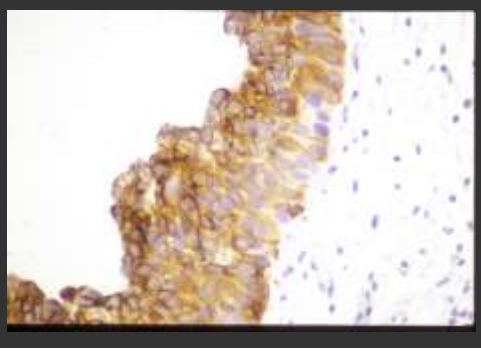
Reactive vs. CIS: Immunohistochemistry

	CK20	P53
Normal/Reactive	Umbrella cell	None
CIS	All layers	Frequent

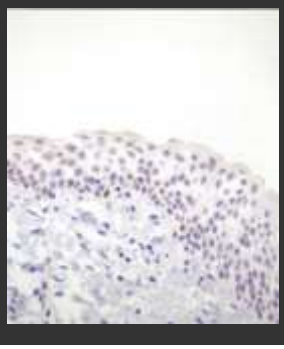
Normal/Reactive: CK20



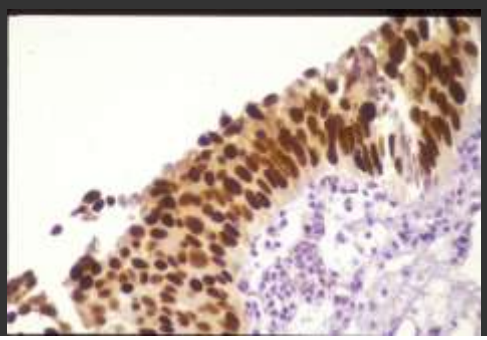
CIS: CK20



Normal/Reactive P53

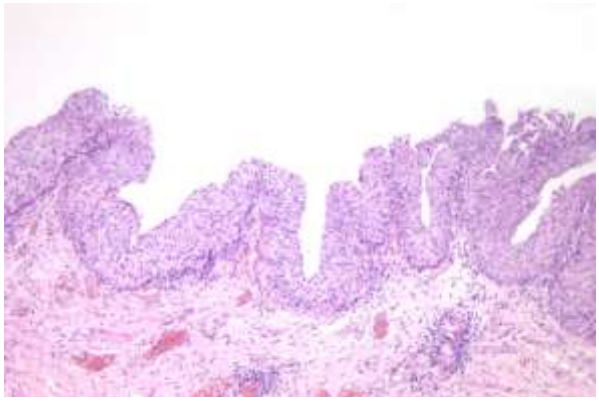


CIS:P53

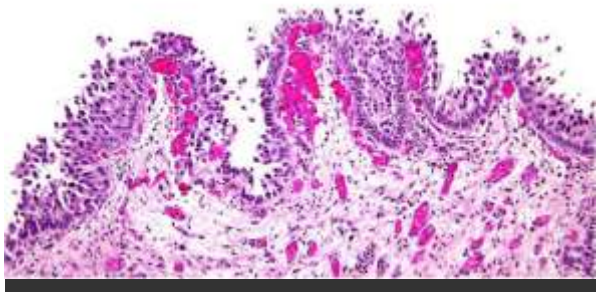


Papillary Urothelial Hyperplasia

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



CIS with early papillary features

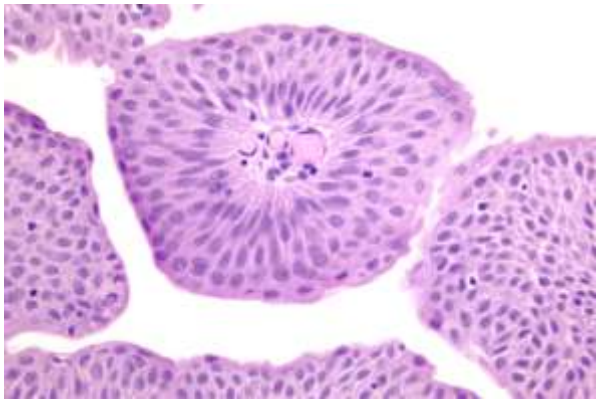


Relation to Urothelial Neoplasms

- **Papillary hyperplasia w/o atypia frequently associated with prior or concurrent low grade papillary neoplasms (papilloma, PUNLMP, low grade papillary urothelial cancer).**
- **Lesions with architecture of papillary hyperplasia with CIS urothelium associated with CIS or high grade papillary urothelial cancer (CIS with early papillary formation).**

Urothelial Papilloma

- Discrete papillary growth with a central fibrovascular core lined by urothelium of normal thickness and cytology.
- No need to count cell layers
- Rare lesion, typically yet not exclusively seen in younger patients



Urothelial Papilloma

- 34 de novo papillomas
- 24 males; 10 females
- Follow-up available in 26 cases
- 3 (9%) recurrences 4, 15, 18 months
- 3 (9%) progression to LGUC 11, 15, 104 months

Controversy in Grading Urothelial Cancers

- Numerous grading systems
- Preponderance of cases falling into the intermediate category

WHO 1973

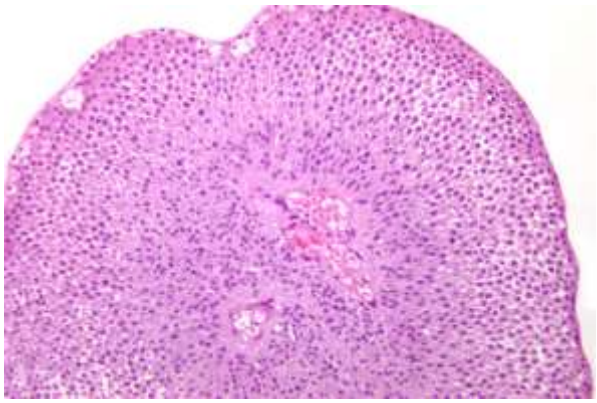
"Grade 1 tumors have the least degree of anaplasia compatible with the diagnosis of malignancy. Grade 3 applies to tumors with the most severe degrees of cellular anaplasia and grade 2 lies in between."

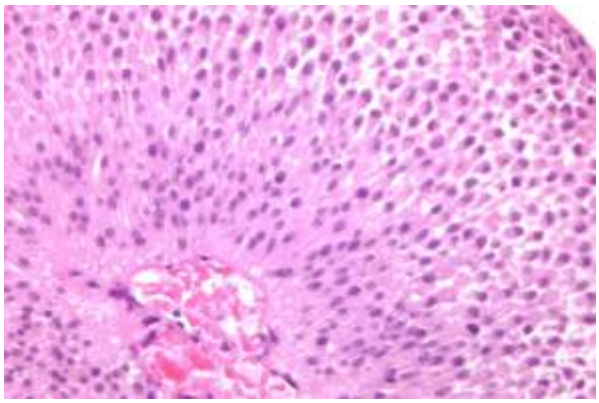
HISTOLOGIC FEATURES OF PAPILLARY UROTHELIAL LESIONS

	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.

Papillary Urothelial Neoplasm of Low Malignant Potential (PUNLMP)

- Orderly arrangement
- Thicker than papilloma
- No atypia, at most nuclear enlargement
- At most rare mitoses at base
- Not associated with invasion



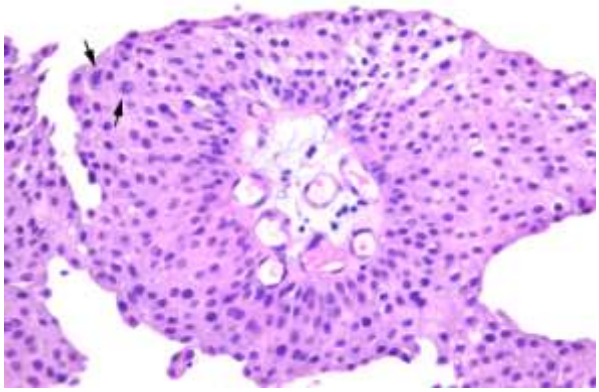


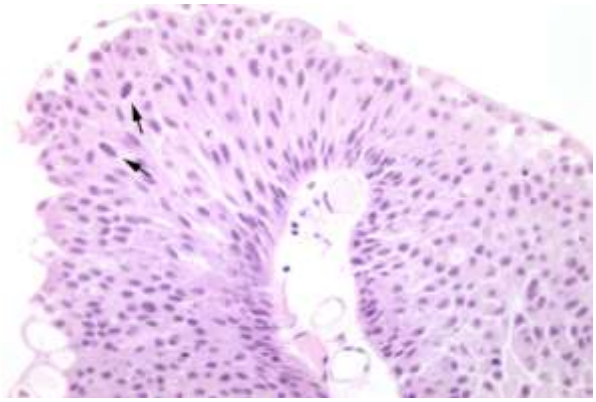
Terminology – Papillary Carcinoma

- Non-invasive papillary urothelial carcinoma
- Invasive papillary urothelial carcinoma
- Low grade papillary carcinoma
- High grade papillary carcinoma

Low Grade Papillary Carcinoma

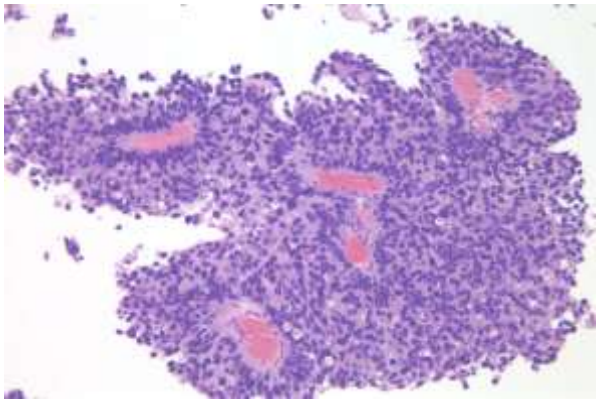
- Overall orderly arrangement with minimal variation in polarity
- Minimal atypia consisting of scattered enlarged hyperchromatic nuclei
- Scattered mitotic figures at all levels
- Grade by the worst component unless very minor (<5%)

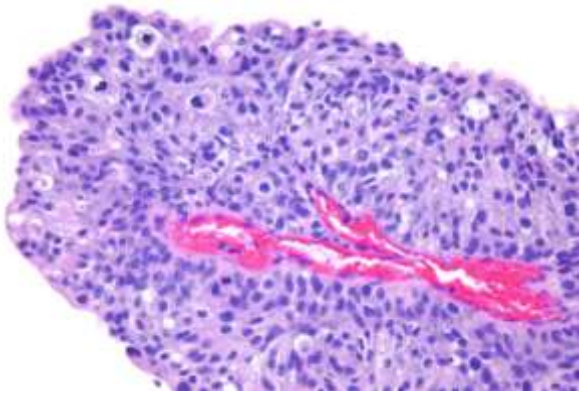




High Grade Papillary Carcinoma

- Overall disorderly arrangement with irregularly clustered cells, fused papillae
- Marked atypia analogous to CIS
- Numerous mitotic figures including atypical ones at all levels
- Dyscohesive single cells

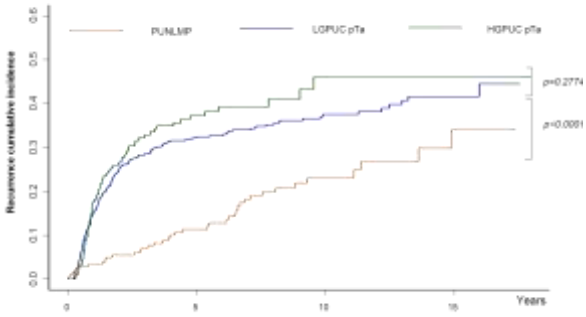




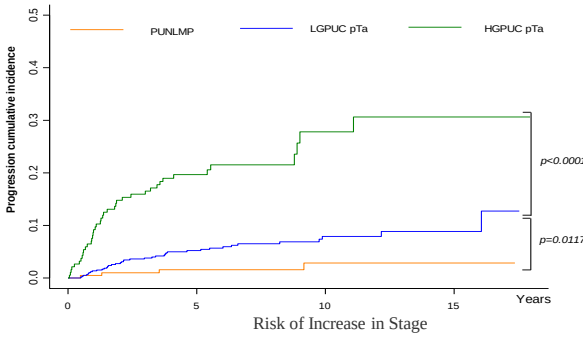
WHO 1973	WHO/ISUP
Papilloma	Papilloma
TCC I	LMP
TCC II	LG
TCC III	HG

Prognostic Significance of the 2004 WHO/ISUP Classification: A Study of 1515 Cases

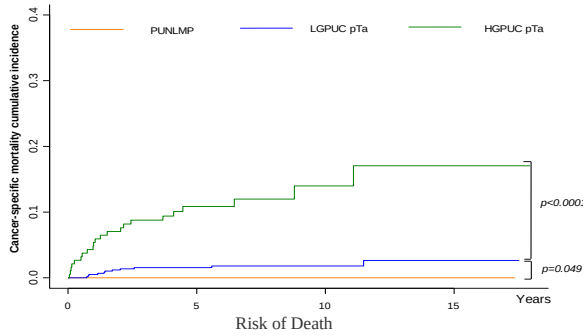
C.C. Pan et al. AJCP 2010



Risk of Recurrence



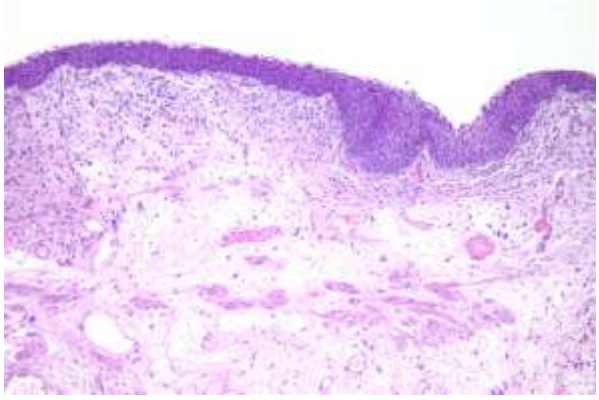
Risk of Increase in Stage

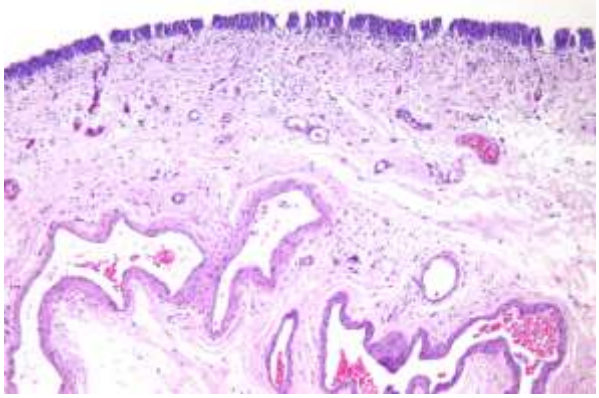


Risk of Death

Terminology - Muscle

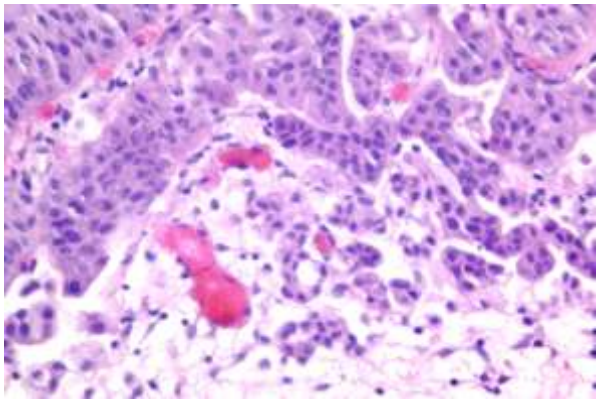
- Muscularis propria (detrusor muscle) invasion
- Muscularis mucosae invasion (usually do not mention)
- Do not use “superficial muscle” or “deep muscle”
- Do not use “superficial bladder cancer”

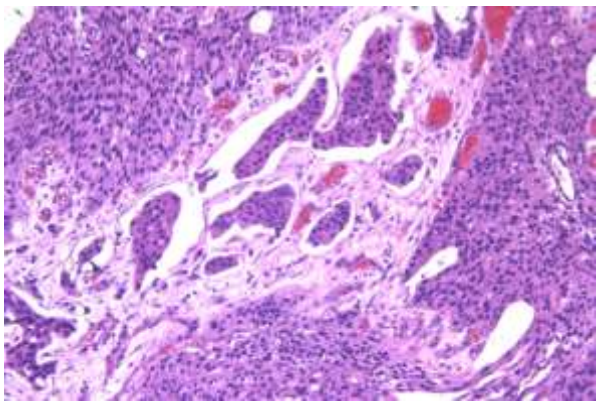


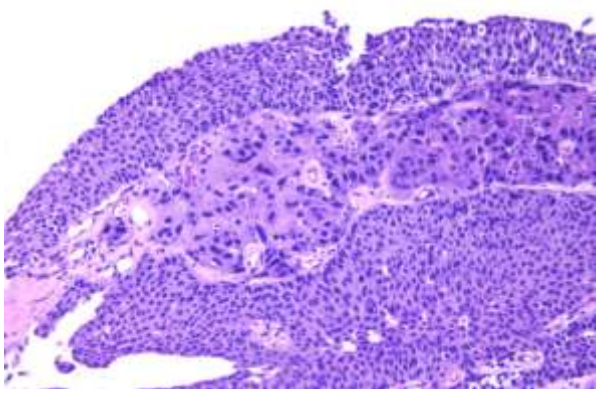


Lamina Propria Invasion

- Inverted growth of noninvasive tumor vs. true invasion
  - Small nests
  - Retraction artifact
  - Paradoxical differentiation
- Substaging – focal vs. extensive or relative to muscularis mucosae
- Vascular invasion uncommon

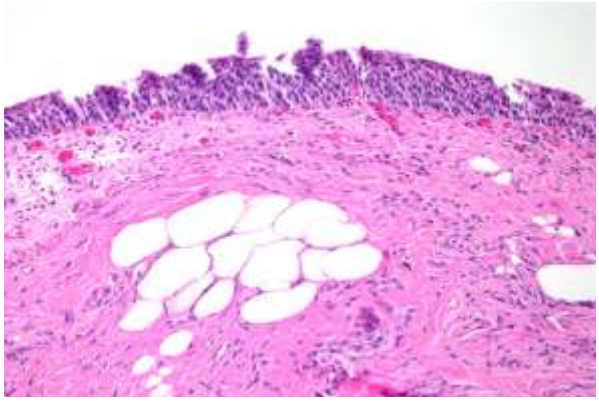


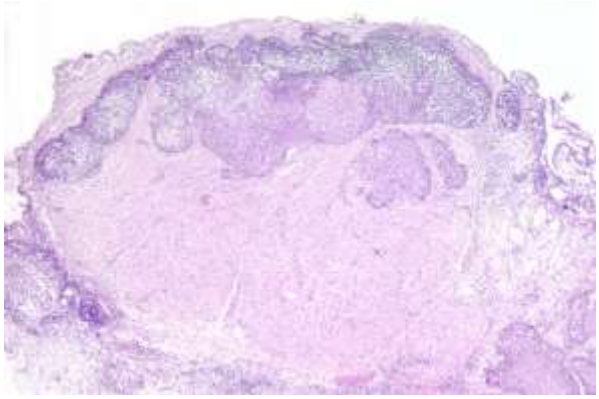


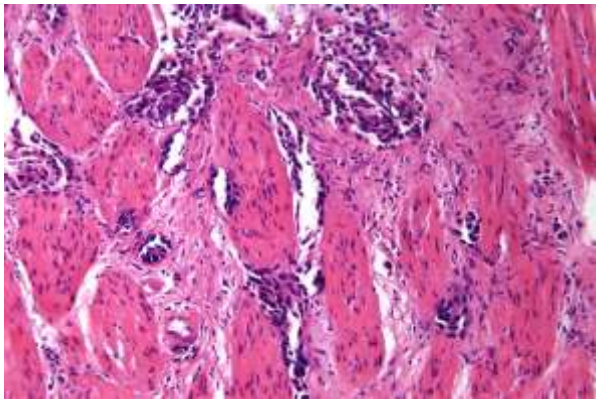


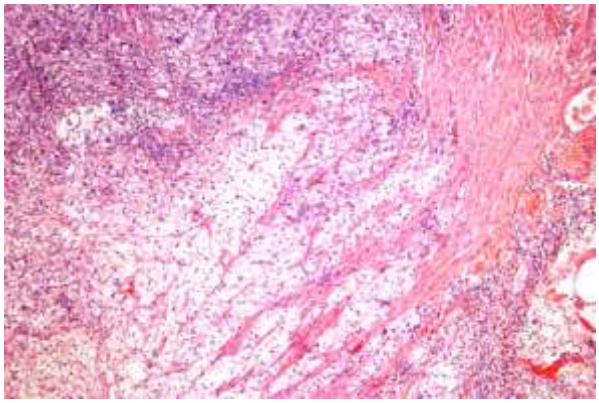
Muscularis Propria (MP) Invasion

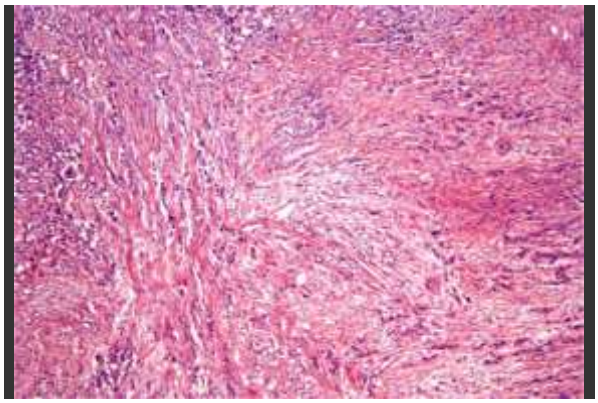
- Infiltration of thick muscle bundles
- If uncertain MP vs. MM specify to urologists
- Do not attempt to substage MP invasion
- Fat seen at all levels, such that does not indicate extension out of the bladder

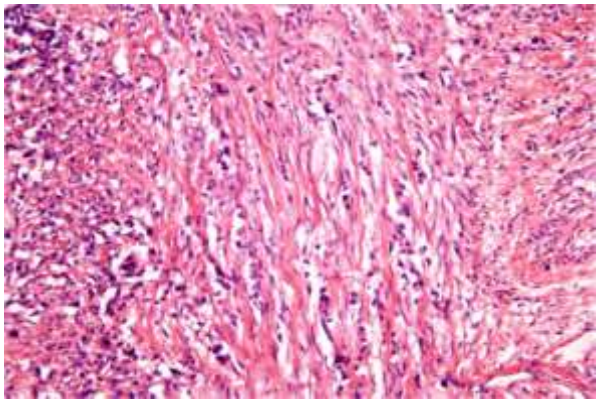


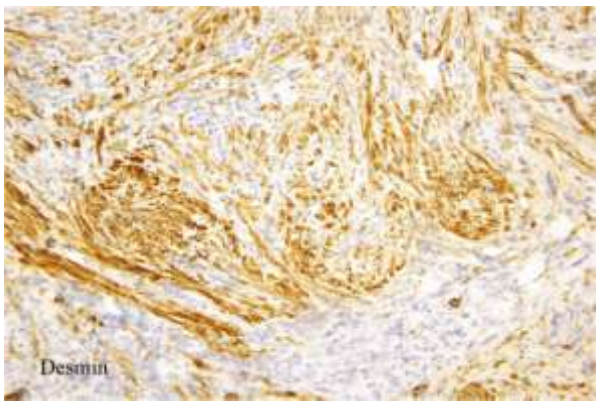








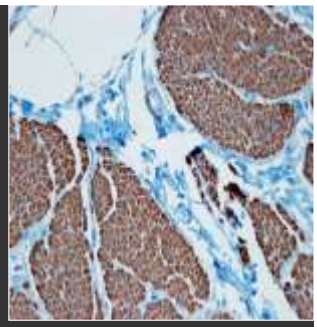



Desmin

IHC Markers in Staging UCa

Smoothelin

- Contractile protein
- Fully differentiated muscle cells
- Hyperplastic muscularis mucosae (-) to weak
- Diffuse positivity in muscularis propria



- Caution: Susceptible to variation in antibody titer
- Must be interpreted in the context of morphology