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

<table>
<thead>
<tr>
<th></th>
<th>CK20</th>
<th>P53</th>
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<tbody>
<tr>
<td>Normal/Reactive</td>
<td>Umbrella cell</td>
<td>None</td>
</tr>
<tr>
<td>CIS</td>
<td>All layers</td>
<td>Frequent</td>
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</tbody>
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**Normal/Reactive: CK20**

![Normal/Reactive: CK20 Image]

**CIS: CK20**

![CIS: CK20 Image]
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.”
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
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
  – Paradoxic 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
IHC Markers in Staging UCa

Smoothelin

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

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