Grading Flat and Papillary Urothelial Lesions: Genitourinary Pathology Society (GUPS) Recommendations

Ming Zhou, MD, PhD
Chair and Pathologist-in-Chief
Tufts Medical Center
Department of Anatomic and Clinical Pathology
Tufts School of Medicine
Boston, MA
mzhou3@tuftsmmedicalcenter.org
Genitourinary Pathology Society (GUPS)

- Established in 2018
- International organization aiming to promote the care of patients with urologic diseases by encouraging best practice, research, and education in urologic pathology

www.gupathsociety.org
Genitourinary Pathology Society (GUPS) Bladder Project

- Critical review of the recent advances in bladder neoplasia, focusing on evidence accumulated post-2016 WHO classification
- 2 manuscripts published in *Advances in Anatomic Pathology* (May, 2021)
  - Classification and grading of flat and papillary urothelial neoplasia
  - Variants/subtypes
  - Substaging and reporting T1 cancer
  - Molecular taxonomy
  - Immune checkpoint inhibitors and PD-L1 testing
Flat Lesions of the Urinary Tract

- Flat urothelial lesions
  - Flat urothelial hyperplasia
  - Flat lesions with atypia
    - Reactive atypia
    - Atypia of unknown significance
    - Urothelial dysplasia
    - Urothelial carcinoma in situ (CIS)

- Flat squamous lesions

- Flat glandular lesions
Flat Urothelial Lesions with Atypia

3-Step Diagnostic Approach

1. Architectural features (Low magnification) → Uniformity
   - Size
   - Shape
   - Spatial arrangement
     - Spacing
     - Parallel to each other
     - Perpendicular to basement membrane

2. Cytological features (High magnification)
   - Nuclear size (compare with stromal lymphocytes)
   - Nuclear attributes
     - Membrane
     - Chromatin
     - Nucleoli
     - Mitosis

3. Rule out conditions that may cause atypia
   - Inflammation, stone
   - Intravesical treatment
   - Radiation
Architectural features (Low magnification)

1. Uniformity
   - Size
   - Shape
   - Spatial arrangement
   - Spacing
     - Parallel to each other
     - Perpendicular to basement membrane

Normal

Abnormal
Cytological features (High magnification)

"Rule of stromal lymphocyte"

Normal: 2X

Dysplasia: 3-4X

CIS: 5-6X

Nuclear size (compare with stromal lymphocytes)
Cytological features (High magnification)

Nuclear attributes
- Membrane
- Chromatin
- Nucleoli
- Mitosis

Normal

CIS
3. Rule out conditions that may cause atypia

- Inflammation
- Stone
- Intravesical treatment
- Radiation

Reactive atypia due to inflammation

Degenerative atypia due to radiation
Flat Urothelial Hyperplasia

- Significantly thickened urothelium
  - No specific criterion (typically >9 cell layers)
  - Increased cell density
- Minimal to no cytological atypia
  - If significant atypia present - Dysplasia/CIS
- Flat architecture
  - Slight undulation of the urothelium is acceptable, but no true papillary formation
  - Tangential sectioning ruled out
- 2016 WHO renamed it with papillary hyperplasia as urothelial proliferation of uncertain malignant potential (UPUMP)
- GUPS: atypical urothelial proliferation - flat
Normal

Flat hyperplasia

Flat with “tenting”

Tangential sectioning ≠ hyperplasia
Flat Urothelial Hyperplasia

Clinical Significance

- Typically a “shoulder lesion” - lateral extension of low grade urothelial neoplasia
  - No need to report

- Less common as a de novo finding
  - Not as closely associated with subsequent neoplasia compared to papillary hyperplasia

- Diagnosis: flat urothelial hyperplasia (UPUMP/atypical urothelial proliferation-flat)
  - May be associated with or a precursor to early non-invasive low-grade neoplasia
Urothelial Carcinoma in Situ

- Normal
- Small cell
- Large cell
- Clinging (denuding cystitis)
- Plasmacytoid
- Pagetoid
Urothelial Carcinoma in Situ

- Primarily a cytologic diagnosis
  - Full thickness involvement of the urothelium not required
  - Umbrella cells may be present
  - Correlation with concurrent urine cytology: diagnostically helpful
  - Be aware of certain subtypes (pagetoid, plasmacytoid) at frozen sections

- Different patterns have no impact on clinical outcomes; do not mention in the report
Flat Urothelial Proliferative Lesions: A Morphological Continuum

Degree of atypia

Benign  Dysplasia  CIS

None  Mild to moderate  Severe
Urothelial Dysplasia

Diagnostic Criteria

- WHO: appreciable cytological and architectural features that are believed to be preneoplastic but fall short of the diagnostic threshold for urothelial CIS
- Lacks objective criteria; poor reproducibility
Urothelial Dysplasia

- Architecture: slightly disordered architecture (irregular spacing)
- Nuclei: enlarged (3-4X), hyperchromasia, increased mitosis
- Inflammation: absent
Reactive Atypia

- Uniformity maintained (size, shape, spacing); polarity may be lost
- Nuclei uniformly enlarged, smooth nuclear membrane and chromatin, prominent nucleoli
- Inflammation in the mucosa or lamina propria
- History of stone, trauma, cystitis, therapy
Urothelial Atypia with Unknown Significance
(Diagnostic category, not an entity!)

- Architecture: Loss of polarity, irregular spacing
- Nuclei: enlarged (5-6X), variation in nuclear size and shape
- Inflammation: brisk
Urothelial Atypia with Unknown Significance

- Flat lesion with significant atypia AND significant inflammation
- Diagnostic category, not a biological entity
  - Reactive lesion with significant architectural and cytological atypia
  - Dysplasia or CIS associated with significant inflammation
- Implication for urologists: treat inflammation and follow up with repeat biopsy
- Do not abuse it: not for “a diagnosis that I am not sure about or have no clue for”
Working up Flat Urothelial Lesions

Low power
Uniformity (size, shape, spacing)
Polarity

High power
Nuclear size
Nuclear attributes

Background
Inflammation

Uniformity +
Nuclear enlarged
Prominent nucleoli
Significant inflammation

Uniformity -
Nuclear atypia
No significant inflammation

Uniformity -
Nuclear atypia
Significant inflammation

Reactive atypia
Dysplasia
CIS
Atypia of unknown significance
Flat Urothelial Lesions
Immunohistochemistry

<table>
<thead>
<tr>
<th></th>
<th>H&amp;E</th>
<th>CK20</th>
<th>CD44</th>
<th>p53</th>
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<tbody>
<tr>
<td>Benign</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>Reactive</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
<tr>
<td>CIS/Dysplasia</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Flat Urothelial Lesions
Immunohistochemistry

- Markers often have discordant or indeterminate staining patterns

- For flat atypical urothelial lesions
  - Concurrent or history of bladder cancer, not the staining pattern, predicts recurrence (Arias-Stella et al Arch Path Lab Med 2018)
  - IHC does not contribute to resolving “atypical flat lesions” (McIntire et al Ann Diag Pathol 2019)

- Immunohistochemistry is NOT recommended to be used in this diagnostic setting
Flat Squamous Lesions of the Urinary Tract

Normal

Non-keratinizing squamous metaplasia

Keratinizing squamous metaplasia without atypia

Keratinizing squamous metaplasia with atypia
# Flat Squamous Lesions

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Significance</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-keratinizing squamous metaplasia</td>
<td>Common in women</td>
<td>Do not report</td>
</tr>
<tr>
<td></td>
<td>Normal variant histology</td>
<td></td>
</tr>
<tr>
<td>Keratinizing squamous metaplasia without atypia</td>
<td>- Commonly adjacent to squamous cell Ca</td>
<td>Report and comment on the significance of</td>
</tr>
<tr>
<td></td>
<td>- Predisposing factor for squamous neoplasia (risk difficult to determine )</td>
<td>“extensive”</td>
</tr>
<tr>
<td></td>
<td>- Extensive (&gt;50% bladder mucosa) more likely to be associated with adverse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>outcomes (bladder Ca, contracture)</td>
<td></td>
</tr>
<tr>
<td>Squamous dysplasia</td>
<td>Definitive precursor to invasive squamous cell Ca</td>
<td>Report</td>
</tr>
</tbody>
</table>
Non-invasive Glandular Lesions

- Intestinal metaplasia without atypia
- Intestinal metaplasia with dysplasia
- Adenocarcinoma in situ
- Urothelial Ca with glandular diff
# Non-invasive Glandular Lesions

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Significance</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial CIS with glandular diff</td>
<td>Most common&lt;br&gt;Often seen with invasive HGUC/small cell Ca</td>
<td>Optional to report</td>
</tr>
<tr>
<td>Intestinal metaplasia w/o dysplasia</td>
<td>- 0.1-0.9%&lt;br&gt;- Associated with chronic irritation/inflammation&lt;br&gt;- Not an obligate precursor lesion for Ca (oncogenic mutations in some cases)</td>
<td>No need to report</td>
</tr>
<tr>
<td>Intestinal metaplasia with dysplasia</td>
<td>- Concurrent with adenoca (often) and UC (rarely)&lt;br&gt;- Risk for adenoca and UC</td>
<td>Report</td>
</tr>
</tbody>
</table>
Early Proliferative Papillary Lesions

- “Tweener” lesions, not fully developed papillary architectures
  - Tented/undulating appearance
  - No discrete and detached papillae

Flat vs papillary?
Early Proliferative Papillary Lesions

- Thickened urothelium with varying degree of atypia
  - No cytological atypia
  - Atypia analogous to dysplasia
  - Atypia analogous to CIS
Early Proliferative Papillary Lesions

- Classification based on cytological features
  - No/minimum cytologic atypia: Papillary urothelial hyperplasia
  - With cytological atypia: Papillary urothelial carcinoma

- Two scenarios where morphology is "early proliferative papillary (neither completely flat nor papillary)"
  - "Early" papillary lesions may be biopsied due to frequent cystoscopic surveillance
  - "Truncated papillae" following intravesical treatment of papillary tumors
Papillary Urothelial Hyperplasia

- Undulating mucosa with tented morphology, no discrete and detached papillae
- Increased vascularity at the base of folds
- Thickened urothelium w/o atypia
Papillary Urothelial Hyperplasia

- 2016 WHO renamed papillary hyperplasia and flat urothelial hyperplasia as urothelial proliferation of uncertain malignant potential (UPUMP)
- Not well accepted
- GUPS recommendation: Atypical Urothelial Proliferation (AUP)-tented
Papillary Urothelial Hyperplasia/AUP-tented

- Typically discovered on routine follow-up cystoscopy for papillary urothelial tumors
- Likely a precursor lesion to low grade papillary tumors
- Less commonly *de novo* diagnosis (in patients w/o concurrent or prior h/o urothelial neoplasia)
- Reasonable to suggest that patients require clinical follow up
Papillary Hyperplasia with Atypia

- Undulating mucosa, not completely flat or papillary, no discrete and detached papillae
- Early papillary lesions without fully developed papillae
- Cytological atypia analogous to dysplasia/CIS
Papillary Hyperplasia with Atypia

- Atypia analogous to low grade/dysplasia
  - “Early low grade papillary urothelial carcinoma”
  - Do not report as dysplasia with early papillary formations, as the clinical, biological and prognostic significance of urothelial dysplasia is not clearly established

- Atypia analogous to high grade/CIS
  - “CIS with early papillary formations”
  - CIS and high grade papillary UC may have distinct clinical significance

- Diagnosis of papillary UC is appropriate if there is a history of papillary UC and cystoscopically evident papillary tumor
WHO Classification of Papillary Urothelial Neoplasms (2016/2021)

- Papilloma
- Papillary neoplasm of low malignant potential (PUNLMP)
- Papillary carcinoma, low grade
- Papillary carcinoma, high grade

- First introduced in 1998 to replace 1973 WHO classification
- PUNLMP - to define a group of papillary tumors with minimal cytologic and architectural atypia, never associated with invasion at the time of first diagnosis, and rarely, if ever, progress to invasive disease
- Poor inter-observer reproducibility (similar to 1973 classification)
- Continuous effort to revisit/revise the classification
Simplified Approach for Grading Papillary Urothelial Tumors

<table>
<thead>
<tr>
<th>Normal urothelium on a simple stalk</th>
<th>→</th>
<th>Papilloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thick, normal appearing urothelium on a stalk</td>
<td>→</td>
<td>PUNLMP</td>
</tr>
<tr>
<td>Abnormal urothelium w/ uniformity on a stalk</td>
<td>→</td>
<td>Low grade</td>
</tr>
<tr>
<td>Abnormal urothelium w/o uniformity on a stalk</td>
<td>→</td>
<td>High grade</td>
</tr>
</tbody>
</table>
Papilloma

Simple papillae covered with normal urothelium

Not papilloma if:
- Thickened urothelium
- Fused or branching papillae
- Appreciable atypia
Normal appearing, but thicker mucosa
Not PUNLMP if:
- Appreciable atypia/mitosis at low power
Low Grade Papillary Carcinoma with Focal High-grade Component

- Grade heterogeneity in up to 1/3 papillary tumors
Limited % of high grade cells (<10%), does not significantly change the outcomes of low grade cancer
Papillary Carcinoma with Mixed Grades: Diagnosis

- **Mixed tumors with >10% high grade component:**
  High grade papillary urothelial carcinoma

- **Mixed tumors with ≤10% high grade component:**
  Noninvasive low-grade papillary urothelial carcinoma with a focal (<10%) high-grade component

Comment: There is limited data on the prognostic significance of a minor component of high-grade tumor in an otherwise lower grade carcinoma, and the studies suggest that they generally behave more like low-grade tumors.
Invasive Low Grade Papillary Urothelial Carcinoma with Low Grade Invasive Component
Invasive Low Grade Papillary Urothelial Carcinoma with Low Grade Invasive Component

- Rare, may be under-reported (pathologists may report any invasive UC as high grade)
- Prognostic significance uncertain
  - T1 low grade similar to T1 high grade
  - Risk stratification tools put more weight on staging rather than grade

Diagnosis:
Invasive low grade papillary urothelial carcinoma

Comment: Invasive low grade UCs are uncommon and have a similar prognosis, stage for stage, comparable to invasive high grade UCs; there are no data to suggest there should be difference in therapy based on the histological grade of the invasive component
Urothelial Lesions with Inverted Growth

Urothelial nests in lamina propria, not necessarily invasive
Urothelial Lesions with Inverted Growth

- **Reactive conditions**
  - Florid von Brunn nests, cystitis cystica et glandularis
  - Pseudocarcinomatous hyperplasia (radiation, chemotherapy)

- **Benign urothelial neoplasm**
  - Inverted papilloma

- **Urothelial neoplasms**
  - Non-invasive PUNLUMP, low and high grade urothelial carcinoma with inverted growth
  - Urothelial carcinoma with inverted growth pattern and invasion
  - Nested variant urothelial carcinoma, including large nested variant
Urothelial Lesions with Inverted Growth

Critical Differential Diagnosis

- Florid von Brunn nests vs nested variant urothelial carcinoma
- Inverted papilloma vs non-invasive urothelial carcinoma with inverted growth
Florid von Brunn Nests

- Large nests
- Regular spacing
- Lobulated
- Flat, non-infiltrative base
Florid von Brunn Nests

Cytological atypia: absent
Stroma: loose and edematous, inflammation
Muscularis propria invasion: absent
Invasive Urothelial Carcinoma, Nested Variant

Numerous urothelial nests of variable sizes, irregular spaced...
Confluent growth

Irregular spacing

Irregular, infiltrative base
Muscle invasion
# Nested Variant Urothelial Carcinoma vs Florid von Brunn Nests

<table>
<thead>
<tr>
<th></th>
<th>Urothelial carcinoma, nested variant</th>
<th>Florid von Brunn nests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urothelial nests</strong></td>
<td>Crowdaded nests of variable sizes and shapes</td>
<td>Large, regularly spaced, rounded nests</td>
</tr>
<tr>
<td><strong>Lumen formation</strong></td>
<td>Uncommon</td>
<td>Commonly associated with cystitis cystica et glandularis</td>
</tr>
<tr>
<td><strong>Architecture</strong></td>
<td>Not circumscribed</td>
<td>Circumscribed</td>
</tr>
<tr>
<td><strong>Base of the lesion</strong></td>
<td>Uneven, infiltrative</td>
<td>Smooth, flat, not infiltrative</td>
</tr>
<tr>
<td><strong>Muscle invasion</strong></td>
<td>Yes, frequent</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cytological atypia</strong></td>
<td>Present, especially at the invasive front</td>
<td>No</td>
</tr>
</tbody>
</table>
Urothelial Lesions with Inverted Growth

Critical Differential Diagnosis

- Florid von Brunn nests vs nested variant urothelial carcinoma

- Inverted papilloma vs non-invasive urothelial carcinoma with inverted growth
Ramifying cords and trabeculae extending down from the smooth surface
Trabeculae of uniform thickness
Extensively involves lamina propria but spare muscularis propria
Palisading basal cells
Central spindling and streaming
Stroma: non-reactive, no inflammation
Low Grade Urothelial Carcinoma with Inverted Growth
High Grade Urothelial Carcinoma with Inverted Growth
## Differential Diagnosis of Inverted Papilloma and Urothelial Carcinoma with Inverted Growth

<table>
<thead>
<tr>
<th></th>
<th>Inverted Papilloma</th>
<th>Urothelial Carcinoma with Inverted Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surface</strong></td>
<td>Smooth, minimal/no exophytic component</td>
<td>Often have exophytic component</td>
</tr>
<tr>
<td><strong>Shape of trabeculae</strong></td>
<td>Thin, uniform thickness</td>
<td>Uneven, solid</td>
</tr>
<tr>
<td><strong>Base</strong></td>
<td>Smooth without infiltration</td>
<td>May have obvious invasion</td>
</tr>
<tr>
<td><strong>Cytological atypia</strong></td>
<td>Minimum/no</td>
<td>May be significant</td>
</tr>
</tbody>
</table>
Urothelial Tumors with Inverted Growth

- Vast majority are non-invasive with a variable exophytic papillary component
- Wide spectrum of morphologic and cytologic features
  - PUNLMP
  - Low grade
  - High grade
- Grading criteria same as those for exophytic papillary tumors
- Inverted urothelial tumor with pure to predominant inverted growth: >80% of inverted growth morphology
Urothelial Tumors with Pure to Predominant Inverted Growth: Clinical outcomes

- Data extremely limited
  - A trend towards better prognosis in inverted tumors

<table>
<thead>
<tr>
<th>Lesion</th>
<th>PUNLMP with pure inverted growth</th>
<th>PUNLMP w/o inverted growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence/progression</td>
<td>0%</td>
<td>21%</td>
</tr>
</tbody>
</table>

- Low grade non-invasive: inverted vs exophytic
  - Lower recurrence rate, longer time to first recurrence and fewer recurrence episodes
  - All inverted tumors with recurrence recurred only once, no tumor with >80% inverted growth recurred (Arslankoz et al Balkan Med J 2017)

- Report pure or predominant inverted growth in PUNLMP and low grade tumors, and comment on its significance

Maxell et al Diagn Pathol 2015
Grading Flat and Papillary Urothelial Lesions: Summary

- IHC is not recommended for work-up of difficult flat urothelial lesions
- Extensive keratinizing squamous metaplasia is more likely to be associated with adverse outcomes (neoplasia and contracture)
- Low grade UC with <10% high grade: low grade with focal high grade
- T1 low grade UC: prognostically similar stage for stage to T1 high grade
- Report papillary UC with >80% inverted component as “papillary UC with inverted histology”; may have better prognosis
Questions?

MZhou3@tuftsm supremalcenter.org