Diagnosis and Classification of Flat, Papillary, and Invasive Urothelial Carcinoma: The WHO/ISUP Consensus

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The World Health Organization/International Society of Urologic Pathology (WHO/ISUP) consensus classification arises from a consensus of the WHO and the ISUP in an attempt to develop a universally acceptable classification system for bladder neoplasia that could be used effectively by pathologists, urologists, and oncologists (Tables 1 and 2).1-4

Overall Terminology

- Favor use of the term urothelial rather than transitional as to the specific nature of urothelium and the nonspecific nature of the term “transitional.” Because there was a slight majority opinion in favor of the term “urothelial,” it was adopted as the preferred term, but “transitional” can be used synonymously.

Normal Urothelium

- Flat lesions with benign cytology and minimal disorder should not be designated as mild dysplasia but rather as normal urothelium.

Flat Urothelial Hyperplasia

- Markedly thickened mucosa without cytological atypia.
- Rather than relying on a specific number of cell layers, marked thickening of the epithelium is needed to diagnose flat hyperplasia.
- This lesion may be seen in the flat mucosa adjacent to low-grade papillary urothelial lesions.
- When seen by itself there is no evidence suggesting that it has any premalignant potential.

Papillary Urothelial Hyperplasia

- Usually asymptomatic and generally found on routine follow-up cystoscopy for papillary urothelial neoplasms.
- Characterized by slight “tenting,” undulating, or an elevated configuration of the urothelium of varying thickness, lacking nuclear atypia. The lesion often has one or a few small, dilated capillaries at its base but it lacks a well-developed fibrovascular core.
- Frequently associated with either a prior or concurrent history of papillary urothelial neoplasms, suggesting a link. A de novo diagnosis of papillary urothelial hyperplasia does not necessarily place the patient at risk to develop papillary tumors, but follow-up is recommended. However, in a patient with a history of a papillary urothelial tumor, this lesion may be associated with an increased risk of recurrence of papillary neoplasia.

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Dysplasia

- Appreciable cytologic and architectural changes felt to be preneoplastic, yet falling short of the diagnostic threshold for urothelial carcinoma in situ (CIS).
- Evidence along several lines of investigation that dysplasia is a precursor lesion of invasive carcinoma in at least some cases.
- Management of dysplasia varies widely amongst urologists from no therapy to the use of intravesical chemotherapy. In part, treatment relates to whether dysplasia is diagnosed de novo or in someone with a history of CIS. In the latter situation, some urologists might be more inclined to treat dysplasia as it may be considered an early manifestation of recurrent CIS.

Carcinoma In Situ (Figure 1)

- CIS is a flat lesion of the urothelium that is a documented precursor of invasive cancer.
- Characterized by the presence of cells with large, irregular, hyperchromatic nuclei that may be either present in the entire thickness of the epithelium or only a part of it. Mitotic activity is frequently observed often in the mid to upper urothelium.
- CIS encompasses lesions that in the past were designated as severe dysplasia or marked atypia. By definition, all CIS are high-grade lesions.
- CIS should not be subclassified by grade despite the spectrum of pleomorphism seen within this entity.
- When evaluating the degree of cytologic atypia, it is always important to compare the cells in question with the surrounding normal urothelium.
- If one looks at the nuclear size of the 25% largest CIS cells (upper quartile), they are 5 times the size of lymphocytes, which can always be found in the stroma. In contrast, normal urothelium is only 2 times the size of lymphocytes.
- CIS tends to be diffusely positive for CK20 and expresses p53.
- CIS is often underdiagnosed, and in the past has often been called moderate dysplasia, because it is not widely recognized that
  1. The cytologic abnormality need not involve the full thickness of the urothelium. Patterns of CIS include those with scattered CIS cells, pagetoid spread of CIS, and cases where the fragile epithelium may be disrupted either spontaneously or by the biopsy so that only a few residual cancer cells remain on the surface (clinging CIS).
  2. CIS cells do not necessarily have high nuclear to cytoplasmic ratios.
  3. An umbrella cell layer may still be present in CIS.
  4. There is a spectrum of cytologic atypia within CIS.

Reactive Urothelial Atypia (Figure 2)

- Inflamed urothelium with either acute or chronic inflammation.
- Uniformly enlarged nuclei with vesicular chromatint and central nucleoli
- Mitoses may be present
- CK20 stains only umbrella layer with negative p53.

Papilloma (Figure 3)

- “Urothelial papilloma” without qualifiers refers to the exophytic variant of papilloma, defined as a discrete papillary growth with a central fibrovascular core lined by urothelium of normal thickness and cytology.
- There is no need for counting the number of cell layers.
- A rare benign condition typically occurring as a small, isolated growth commonly, but not exclusively, in younger patients.

Papillary Urothelial Neoplasm of Low Malignant Potential (Figure 4)

- An orderly arrangement of cells within papillae with minimal architectural abnormalities and minimal nuclear atypia irrespective of the number of cell layers.
- Urothelium in papillary urothelial neoplasms of low malignant potential is much thicker than in papillomas and/or the nuclei are significantly enlarged and somewhat hyperchromatic. The urothelial papilloma, in contrast, shows no architectural or cytologic atypia. Mitotic figures are infrequent in papillary urothelial neoplasms of low malignant potential, and usually confined to the basal layer.
- Not associated with invasion or metastases. Nevertheless, it is a clinically important lesion because these patients are at an increased risk of developing recurrent or new papillary lesions. These new lesions occasionally are of higher grade and may progress.
Table 1. The WHO/ISUP Consensus Classification

<table>
<thead>
<tr>
<th>Normal</th>
<th>Hyperplasia</th>
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<tbody>
<tr>
<td>Normal</td>
<td>Flat hyperplasia</td>
</tr>
<tr>
<td>Papillary hyperplasia</td>
<td>Flat lesions with atypia</td>
</tr>
<tr>
<td>Reactive (inflammatory) atypia</td>
<td>Dysplasia (low-grade intraurothelial neoplasia)</td>
</tr>
<tr>
<td>Carcinoma in situ (high-grade intraurothelial neoplasia)</td>
<td>Papillary neoplasms</td>
</tr>
<tr>
<td>Papilloma</td>
<td>Papillary neoplasm of low malignant potential</td>
</tr>
<tr>
<td>Papillary carcinoma, low grade</td>
<td>Papillary carcinoma, high grade</td>
</tr>
<tr>
<td>Invasive neoplasms</td>
<td>Lamina propria invasion</td>
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<tr>
<td>Muscularis propria (detrusor muscle) invasion</td>
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</tbody>
</table>


*a May include cases formerly diagnosed as “mild dysplasia.”

*b Includes cases with “severe dysplasia.”

*c Option exists to add comment as to the presence of marked anaplasia.

Papillary Urothelial Carcinoma: Low Grade (Figure 5)

- An overall orderly appearance but with easily recognizable variation of architectural and or cytologic features even at scanning magnification. Variation of polarity and nuclear size, shape, and chromatin texture comprise the minimal but definitive cytologic atypia. Mitotic figures are infrequent and usually seen in the lower half, but may be seen at any level of the urothelium.
- When analyzing for the presence of order versus disorder, it is preferable to assess only those fibrovascular cores that have been cut perpendicularly to the long axis of the papillary frond. Tangential sections near the base of the urothelium may be misleading and result in sheets of immature urothelium with frequent mitotic activity. It is not uncommon to see fusion of adjacent papillae; fused papillary cores can also be overgraded.
- There may be a spectrum of cytologic and architectural abnormalities within a single lesion, such that the entire lesion should be examined, with the highest grade of abnormality noted.
- Low-grade papillary carcinomas may invade the lamina propria, and have a low (<5%) risk of further progression, although they frequently recur.

Papillary Urothelial Carcinoma: High Grade (Figure 6)

- Characterized by a predominantly or totally disorderly appearance at low magnification. The disorder results from both architectural and cytologic abnormalities. Architecturally, cells appear irregularly clustered and the epithelium is disorganized. Cytologically, there is a spectrum of pleomorphism ranging from moderate to marked. The nuclear chromatin tends to be clumped and nucleoli may be prominent. Mitotic figures, including atypical forms, are frequently seen at all levels of the urothelium.
- In tumors with variable histology, the tumor should be graded according to the highest grade. Studies are needed to determine how significant a minor component must be in order to have an impact on prognosis. Current practice is to ignore minuscule areas of higher grade tumor when assigning an overall grade.
- High-grade papillary urothelial carcinomas have a much higher risk of progression than low-grade lesions, with figures varying from 15% to 40%. These tumors also have a high risk of association with invasive disease at the time of presentation. Paralleling the high grade cytologic atypia within these lesions, the surrounding flat urothelial mucosa may also demonstrate CIS.

Lamina Propria Invasion

- Lamina propria invasion is characterized by the presence of urothelial nests, clusters, or single cells within the lamina propria sometimes with prominent retraction artifact. The cancer cells may show eosinophilic cytoplasm at the advancing edge of the infiltrating nests. Another feature of invasive tumor that is not always conspicuous is an associated desmoplastic or inflammatory stromal response. In low-grade papillary carcinomas, large rounded nests of urothelium with peripheral palisading within the lamina propria, yet surrounded by normal appearing stroma, represent an inverted growth pattern of noninvasive carcinoma.
- Prominent retraction artifact around tumor infiltrating the lamina propria is frequently overdiagnosed as vascular invasion. Vascular invasion in cases with lamina propria invasion is uncommon. It should be reserved for unequivocal cases or those confirmed by immunohistochemistry.
Figure 1. Carcinoma in situ

Figure 2. Reactive urothelial atypia

Figure 3. Urothelial papilloma

Figure 4. Papillary urothelial neoplasm of low malignant potential

Figure 5. Noninvasive low-grade papillary urothelial carcinoma with scattered cells having hyperchromatic enlarged nuclei (arrows)

Figure 6. Noninvasive high-grade papillary urothelial carcinoma with loss of polarity, diffuse atypia, and numerous mitotic figures.
In approximately half of transurethral resections (TURs), one can discern the mid-level of the lamina propria characterized by the presence of muscularis mucosae as well as thick-walled vessels. The option remains for individuals to substage tumor invading the lamina propria based on the relationship of tumor to the muscularis mucosae (above, at, or below), as this scheme has been shown to be of prognostic significance. However, it was the Committee’s recommendation that this not be universally adopted or advocated to pathologists, as it is often very difficult to identify the depth of invasion in the lamina propria because of the lack of orientation in transurethral resection chips or because of the absence of muscularis mucosae. Nevertheless, pathologists are encouraged to provide some assessment as to the extent of lamina propria invasion (ie, focal vs extensive) to help guide urologists in patient management.

In cases with lamina propria invasion where the muscularis mucosa is involved, this fact may (but need not be) mentioned in the report. If it is mentioned in the report, the wording should be unambiguous so that the urologist does not confuse muscularis mucosae with muscularis propria (detrusor muscle) invasion. Do not use the term superficial muscle invasion as urologists interpret this to mean superficial portion of muscularis propria. It was recommended that pathologists always mention whether the muscularis propria is present in the biopsy even in the presence of CIS, papillary urothelial neoplasms of low malignant potential, and noninvasive papillary urothelial carcinoma, with the purpose of giving feedback to the urologist as to the depth of their biopsy.

Invasive tumor should be graded as low-grade or high-grade analogous to the scheme used for grading noninvasive lesions.

### Muscularis Propria (Detrusor Muscle) Invasion

- Muscularis propria invasion is diagnosed when tumor is seen infiltrating thick smooth muscle bundles. The distinction on TUR of muscularis mucosae from muscularis propria invasion may occasionally be difficult. These include cases with extensive infiltrating tumor where scattered wisps of muscle could either represent muscularis mucosa or disrupted and distorted muscularis propria.
- Situations where there is uncertainty as to the presence of muscularis propria invasion should be

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**Table 2. Histologic Features of Urothelial Papillary Lesions**

<table>
<thead>
<tr>
<th></th>
<th>Center Papilloma</th>
<th>Papillary Neoplasm of Low Malignant Potential</th>
<th>Low-Grade Papillary Carcinoma</th>
<th>High-Grade Papillary Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Architecture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillae</td>
<td>Delicate</td>
<td>Delicate; occasionally fused</td>
<td>Fused, branching, and delicate</td>
<td>Fused, branching, and delicate</td>
</tr>
<tr>
<td>Organization of cells</td>
<td>Identical to normal</td>
<td>Polarity identical to normal; any thickness; cohesive</td>
<td>Predominantly ordered, yet minimal crowding and minimal loss of polarity; any thickness; cohesive</td>
<td>Predominantly disordered with frequent loss of polarity; any thickness; often dyscohesive</td>
</tr>
<tr>
<td><strong>Cytology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear size</td>
<td>Identical to normal</td>
<td>May be uniformly enlarged</td>
<td>Enlarged with variation in size</td>
<td>Enlarged with variation in size</td>
</tr>
<tr>
<td>Nuclear shape</td>
<td>Identical to normal</td>
<td>Elongated, round-oval, uniform</td>
<td>Round-oval; slight variation in shape and contour</td>
<td>Moderate-marked pleomorphism</td>
</tr>
<tr>
<td>Nuclear chromatin</td>
<td>Fine</td>
<td>Fine</td>
<td>Mild variation within and between cells</td>
<td>Moderate-marked variation both within and between cells with hyperchromasia</td>
</tr>
<tr>
<td>Nucleoli</td>
<td>Absent</td>
<td>Absent to inconspicuous</td>
<td>Usually inconspicuous*</td>
<td>Multiple prominent nucleoli may be present</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Absent</td>
<td>Rare, basal</td>
<td>Occasional, at any level</td>
<td>Usually frequent, at any level</td>
</tr>
<tr>
<td>Umbrella cells</td>
<td>Uniformly present</td>
<td>Present</td>
<td>Usually present</td>
<td>May be absent</td>
</tr>
</tbody>
</table>

*If present, small and regular and not accompanied by other features of high-grade carcinoma.
conveyed to the urologist so that a restaging TUR can be performed. The presence of numerous vessels at the mid-level of the lamina propria where the muscularis mucosae is variably present, can help classify muscle bundles as muscularis mucosae rather than muscularis propria.

- In a TUR specimen, there should be no attempt to substage the depth of muscularis propria invasion. In a transurethral resection specimen, even the presence of tumor in fat is not necessarily diagnostic of extravesicle spread, as adipose tissue may be seen in the lamina propria. The depth of muscularis propria invasion can only be assessed on the definitive resection specimen.

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References