

AP110 URINARY BLADDER BIOPSY INTERPRETATION

Part 1

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- TOPICS:**
- I. WHO (2004)/ISUP CLASSIFICATION OF BLADDER TUMORS**
 - II. PATTERNS OF INVASION AND PROBLEMS IN ASSESSMENT OF INVASION BY UROTHELIAL CARCINOMA**
 - III. HISTOLOGIC VARIANTS OF BLADDER CANCER: DIAGNOSTIC AND PROGNOSTIC IMPLICATIONS**

WHO (2004)/ISUP CLASSIFICATION OF BLADDER TUMORS

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The WHO/ISUP classification of bladder tumors proposed by the International Society of Urologic Pathologists and the World Health Organization is outlined below in Table 1 and is followed by comments on the classification system. The WHO 2004 system which is currently in press is essentially similar to the WHO/ISUP (1998) system, and we prefer to designate it as the WHO (2004)/ISUP classification system.

TABLE 1: WHO (2004)/ISUP CONSENSUS CLASSIFICATION

NORMAL

Normal*

HYPERPLASIA

Flat 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

Lamina Propria Invasion

Muscularis Propria (Detrusor Muscle) Invasion

*May include cases formerly diagnosed as “mild dysplasia”

** Includes cases with “severe dysplasia”

FLAT LESIONS

Urothelium, the dominant type of epithelium lining the urinary bladder, ureters, and renal pelvis has unique characteristics that separate it from all other epithelia. It is a multilayered epithelium, which typically contains longitudinal nuclear grooves in some of the cells, that matures to form very large surface cells known as “umbrella cells.” Umbrella cells may have nuclear atypia, which should not be misconstrued to be dysplastic. The surface of the umbrella cells is formed by a unique trilaminar rigid membrane, named the “asymmetric unit membrane” that is composed of a unique family of proteins named uroplakins. Because of the unique nature of this mucosa, the term “urothelial” should be used rather than “transitional.” The following paragraphs outline a basic overview of flat lesions. More details with diagnostic approach can be found in the attached syllabus following the references.

NORMAL UROTHELIAL

Many pathologists overuse the diagnosis of “mild dysplasia” for flat lesions with normal cytology, and a minimally disordered architectural pattern; vagaries of staining and fixation may also impart hyperchromasia to benign nuclei. Flat lesions with benign cytology and minimal disorder should not be designated as mild dysplasia but rather as normal.

HYPERPLASIA

Flat urothelial hyperplasia historically has been defined as urothelium greater than seven cells layers thick. In practice, counting the number of urothelial cell layers is not reproducible, as urothelial cells do not line up in neat rows.

Flat Urothelial Hyperplasia: Flat urothelial hyperplasia consists of a markedly thickened mucosa without cytological atypia. Rather than requiring a specific number of cell layers, marked thickening 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 data suggesting that it has premalignant potential.

Papillary Urothelial Hyperplasia: This lesion is usually asymptomatic and generally found on routine follow-up cystoscopy for papillary urothelial neoplasms. They are characterized by slight “tenting,” undulating, or papillary growth lined by urothelium of varying thickness, lacking atypia. The lesion often has one or a few small, dilated capillaries at its base but it lacks a well-developed fibrovascular core. 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. 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.

Flat lesions with atypia: Whereas some individual use the term “dysplasia” to denote a pre-neoplastic condition and the term “atypia” to refer to reactive lesions, others often use the latter term to imply preneoplastic lesions as well. In some geographic regions, the term “dysplasia” is used to describe developmental abnormalities rather than preneoplastic lesions. For those who do not want to use the term “dysplasia” for early neoplastic changes, the term “low-grade intraurothelial neoplasia” is an appropriate synonym.

Reactive Atypia: Consists of nuclear abnormalities occurring in acutely or chronically inflamed urothelium. In reactive atypia, nuclei are uniformly enlarged and vesicular, with central prominent nucleoli. Mitotic figures may be frequent. A history of instrumentation, stones, or therapy is often present. In the absence of appreciable nuclear hyperchromasia, pleomorphism, and irregularity in the chromatin pattern, the lesion should not be considered neoplastic.

Atypia of Unknown Significance: In some cases it is difficult to differentiate between reactive and neoplastic atypia. There may be a greater degree of pleomorphism and/or hyperchromasia out of proportion to the extent of the inflammation, such that dysplasia can not be ruled out with certainty. These cases should be designated as “atypia of unknown significance” so that the patients may be followed more closely and re-evaluated once the inflammation subsides.

Dysplasia (Low-grade Intraurothelial Neoplasia): Dysplastic urothelium has appreciable cytologic and architectural changes and is felt to be preneoplastic, yet falling short of the diagnostic threshold for transitional cell carcinoma in situ (CIS). Because of problems with interobserver reproducibility, the lack of an uniform definition, and confusing reports in the literature which often combine moderate and severe dysplasia (the latter currently regarded as CIS), the natural history of bladder dysplasia in humans is poorly understood. Dysplastic lesions are typically seen in bladders with urothelial neoplasia and are uncommon in patients without it. Morphologically and

genetically dysplasia shares certain features with CIS. In patients with bladder tumors, the presence of dysplasia in the adjacent mucosa also places them at higher risk for recurrence and progression.

Carcinoma In Situ (High-grade Intraurothelial Neoplasia): Carcinoma in situ (CIS) is a flat lesion of the urothelium that is a documented precursor of invasive cancer in some cases. The lesion is 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 which in the past were designated as severe dysplasia or marked atypia.

CIS is often underdiagnosed, and in the past has often been called moderate dysplasia, because it is not widely recognized that there need not be full thickness cytologic atypia. 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). CIS cells do not necessarily have high nuclear to cytoplasmic ratios; An umbrella cell layer may still be present in CIS. There is a spectrum of cytologic atypia within CIS. By definition, all CIS are high-grade lesions. CIS should not be subclassified by grade. When evaluating the degree of cytologic atypia, it is always important to compare the cells in question with the surrounding normal urothelium.

PAPILLARY UROTHELIAL NEOPLASMS

A continued source of controversy has been the distinction between papilloma and low-grade papillary carcinoma. Some experts in the field have required very restrictive criteria for the diagnosis of urothelial papilloma. These individuals have designated all other papillary neoplasms as papillary urothelial carcinomas. Others have adopted a broader definition of “urothelial papilloma” so as not to label patients with low-grade papillary lesions as having carcinoma.

The other area of controversy is in the grading of papillary urothelial carcinomas. Numerous grading systems exist with poor interobserver reproducibility and a preponderance of cases falling into the intermediate grade category. One system, which is a modified version of the scheme proposed by Malmström et al found to be fairly reproducible and is described below.

Urothelial Papilloma: “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. This is a rare, benign condition typically occurring as a small, isolated growth, commonly but not exclusively seen in younger patients.

Inverted Urothelial Papilloma: Although not strictly speaking a papillary lesion is classified here because it shares certain features with exophytic urothelial papilloma. The histology of inverted papillomas has been well described. Rarely, cases are hybrid in which significant portions of the lesion resemble exophytic urothelial papillomas and inverted urothelial papillomas. These lesions should be classified as papillomas with both exophytic and inverted features.

When completely excised, inverted papillomas have a very low risk of recurrence. In a minority of cases, they may be an association with urothelial carcinoma occurring either concurrently or subsequently. Rarely, cases of urothelial carcinoma arising in inverted urothelial papillomas have also been identified.

Papillary Urothelial Neoplasm of Low Malignant Potential: A papillary urothelial lesion with an orderly arrangement of cells within papillae with minimal architectural abnormalities and minimal nuclear atypia irrespective of cell thickness. The major distinction from papilloma is that in papillary urothelial neoplasm of low malignant potential the urothelium is much thicker and/or nuclei are significantly enlarged. The urothelial papilloma, in contrast, has no architectural or cytologic atypia. Mitotic figures are infrequent in papillary urothelial neoplasms of low malignant potential, and usually limited to the basal layer. This lesion is not associated with invasion or metastases, except in rare cases. 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.

Papillary Urothelial Carcinoma, Low-Grade: Low-grade papillary urothelial carcinomas are characterized by an overall orderly appearance but with easily recognizable variation of architectural and or cytologic features seen 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. Tangential sections near the base of the urothelium may be misleading and result in sheets of immature urothelium with frequent mitotic activity. A spectrum of cytologic and architectural abnormalities may exist within a single lesion, stressing the importance of examining the entire lesion and noting the highest grade of abnormality.

Papillary-Urothelial Carcinoma, High-Grade: Predominantly or totally disorderly appearance at low magnification with 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 spectrum of cytologic atypia within high-grade papillary urothelial carcinomas. In tumors with variable histology, the tumor should be graded according to the highest 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. Paralleling the high-grade cytologic

atypia within these lesions, the surrounding flat urothelial mucosa may also demonstrate CIS.

INVASIVE UROTHELIAL NEOPLASMS

Lamina Propria Invasion: Lamina propria invasion is characterized by the presence of urothelial nests, clusters, or single cells within the lamina propria 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 surrounded by normal appearing stroma, represent an inverted growth pattern of non-invasive 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. In some transurethral resections, one can discern the mid level of the lamina propria characterized by the 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.

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

Muscularis Propria (Detrusor Muscle) Invasion: The distinction on transurethral resection of muscularis mucosae from muscularis propria invasion may occasionally be difficult. Extensive infiltrating tumor with scattered wisps of muscle could either represent muscularis mucosa or disrupted and distorted muscularis propria. In these cases, experts utilize special studies, such as a Masson stain or immunohistochemistry with antibodies to actin, to help identify all smooth muscle tissue; the highlighting of numerous muscle fibers distributed throughout an extensive tumor may lead to a diagnosis of muscularis propria invasion. Situations where there is uncertainty as to the presence muscularis propria invasion should be conveyed to the urologist.

TABLE 2: HISTOLOGIC FEATURES OF UROTHELIAL PAPILLARY LESIONS

	Papilloma	Papillary neoplasm of low malignant potential	Low-grade papillary carcinoma	High-grade papillary carcinoma
Architecture				
Papillae	Delicate	Delicate. Occasional 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 discohesive
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	Occasionally at any level	Usually frequent, at any level
Umbrella cells	Uniformly present	Present	Usually present	May be absent

* If present, small and regular and not accompanied by other features of high-grade carcinoma

CLINICAL RELEVANCE OF WHO/ISUP CLASSIFICATION

Emerging clinical follow-up data suggest that the WHO/ISUP diagnostic category of papillary urothelial neoplasm of low malignant potential (PUNLMP) identifies a clinically and biologically distinct lesion within the spectrum of papillary urothelial neoplasia. Table 3 compares the recurrence rates, grade progression, stage progression and survival rates between tumors in the different categories of non-invasive papillary urothelial neoplasms of the bladder by WHO/ISUP classification system.

TABLE 3

	Papilloma	Papillary neoplasm of low malignant potential	Low-grade papillary carcinoma	High-grade papillary carcinoma
Recurrence	0-8%	27-47%	48-71%	55-58%
Grade progression	2%	11%	7%	Not applicable
Stage progression	0%	0-4%	2-12%	27-61%
Survival	100%	93-100%*	82-96%	74-90%

- 4% of PUNLMPs in one series developed invasive disease (mean interval 13.3 years) and 3% died of bladder cancer, suggesting that long-term follow-up is clearly needed for patients with these tumors
- Recurrence rate for inverted papilloma is 1-3%.

“ACCOMPLISHMENTS” OF WHO/ISUP CLASSIFICATION

The potential “accomplishments” of the WHO(2004)/ISUP system are: 1) acceptance across a broad spectrum of urological pathologists allowing for uniform terminology and common definitions; 2) detailed criteria of various preneoplastic conditions and various grades of tumor, hopefully leading to greater interobserver reproducibility; 3) the terminology used in the WHO(2004)/ISUP system is more or less consistent with what is used in urine cytology, facilitating cyto-histologic correlation and making it easier for urologists to manage patients; 4) creation of a category of tumor that identifies a tumor (PUNLMP) with a negligible risk of progression, whereby patients avoid the label of having cancer with its psychosocial and financial (i.e., insurance) implications; these patients are also not diagnosed as having a benign lesion (i.e., papilloma), whereby they might not be followed as closely; 5) identification of a distinct group of patients (high-grade papillary urothelial carcinoma and CIS) who would be ideal candidates for intravesical therapy; 6) identification of a larger group of patients at high risk for progression for urologists to follow more closely; 7) removes ambiguity in diagnostic categories (e.g., TCC grade I-II, TCC grade II-III); and 8) early studies show that this classification stratifies bladder tumors into prognostically significant categories.

References:

1. Epstein JI, Amin MB, Reuter VE, Mostofi FK: The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. *Am J Surg Pathol* 22(12):1435-1448, 1998.
- 1b. Sauter G, Algaba F, Amin MB, Busch C et al: Non-invasive urothelial tumours. In: Epstein JI, Eble JN, Sesterhenn I, Sauter G (eds): *World Health Organization Classification of Tumours Pathology and Genetics: Tumours of the Urinary System and Male Genital Organs*. IARC Press, Lyon, 2004; pp 110.
- 1c. Amin MB. Urothelial dysplasia. *In: World Health Organization Classification of Tumours. Pathology and Genetic Tumors of the Urinary System and Male Genital Organs*. Editors: Eble JN, Sauter G, Epstein J, Sesterhenn I; IARC Press, Lyon, 2004; pages 111-112.
- 1d. Epstein JI, Reuter VE, Amin MB. *Urinary Bladder Biopsy Interpretation*. Lippincott Williams & Wilkins, Philadelphia, PA, 2004.
2. Amin MB, Young RH: Intraepithelial lesions of the urinary bladder with a discussion of the histogenesis of urothelial neoplasia. *Semin Diag Pathol* 14:84-97, 1997.
3. Eble JN, Young RH: Benign and low-grade papillary lesions of the urinary bladder: a review of the papilloma-papillary carcinoma controversy and a report of 5 typical papillomas. *Semin Diagn Pathol* 6:351-371, 1989.
4. Amin MB, Murphy WM, Reuter VE, et al: Controversies in the pathology of transitional cell carcinoma of the urinary bladder. In: Rosen PP, Fechner RE (eds): *Reviews in Pathology*, Chicago IL, ASCP Press, 1996, pp.1-38.
5. Holmang S, Hedelin H, Anderstrom C, Holmberg E, Busch C, Johansson S: Recurrence and progression in low-grade papillary urothelial tumors. *J Urol* 162:702-707, 1999.
6. Cheng L, Neumann RM, Bostwick DG: Papillary urothelial neoplasms of low malignant potential. Clinical and biologic implications. *Cancer* 86:2102-2108, 1999.
7. Desai S, Lim SD, Jimenez RE, Chun T, Keane TE, McKenney JK, Zavala-Pompa A, Cohen C, Young RH, Amin MB: Relationship of cytokeratin 20 and CD44 protein expression with WHO/ISUP grade in pTa and pT1 papillary urothelial neoplasia. *Mod Pathol* 13:1315-1323, 2000.

8. Cheng L, Darson M, Cheville JC, Neumann RM, Zincke H, Nehru A, Bostwick DG: Urothelial papilloma of the bladder. Clinical and biologic implications. *Cancer* 86:2098-2101, 1999.
9. Holmang S, Andius P, Hedelin H, Wester K, Busch C, Johansson SL: Stage progression in Ta papillary urothelial tumors: relationship to grade, immunohistochemical expression of tumor markers, mitotic frequency and DNA ploidy. *J Urol* 165:1124-1128, 2001.
10. Oosterhuis JW, Schapers RF, Janssen-Heijnen ML, Paulwels RP, Newling DW, ten Kate F. Histological grading of papillary urothelial carcinoma of the bladder: prognostic value of the 1998 WHO/ISUP classification system and comparison with conventional grading systems. *J Clin Pathol* 55:900-905, 2002.
11. Samaratunga H, Makarov DV, Epstein JL: Comparison of WHO/ISUP and WHO classification of noninvasive papillary urothelial neoplasms for risk of progression. *Urology* 60:315-319, 2002.
12. McKenney JK, Amin MB, Young RH: Urothelial (transitional cell) papilloma of the urinary bladder: a clinicopathologic study of 26 cases. *Mod Pathol* 17:623-629, 2003.
13. Caro DJ, Tessler A: Inverted papilloma of the bladder: a distinct urological lesion. *Cancer* 42:708-713, 1978.
14. Holmang S, Johansson SL: Stage Ta-T1 bladder cancer: the relationship between findings at first followup cystoscopy and subsequent recurrence and progression. *J Urol* 167:1634-1637, 2002.
15. Pich A, Chiusa L, Formiconi A, Galliano D, Bortolin P, Navone R: Biologic differences between noninvasive papillary urothelial neoplasms of low malignant potential and low-grade (grade 1) papillary carcinomas of the bladder. *Am J Surg Pathol* 25:1528-1533, 2001.
16. Herr HW: Tumor progression and survival of patients with high-grade, noninvasive papillary (TaG3) bladder tumors: 15-year outcome. *J Urol* 163:79-80, 2000.
17. Saika T, Tsushima T, Nasu Y, Arata R, Kaku H, Kusaka N, Kumon H: Clinical study of G3 superficial bladder cancer without concomitant CIS treated with conservative therapy. *Jpn J Clin Oncol* 32:461-465, 2002.