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REVIEW

Morphological classification and definition of benign, preneoplastic and non-invasive neoplastic lesions of the urinary bladder

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The morphological classification used in this essay has been based on the most recent World Health Organization (WHO) classification of tumours of the urinary system (i.e. 2004 WHO classification). It includes epithelial abnormalities and metaplasias as well as dysplasias and carcinomas *in situ*. The lesions are broadly subdivided into two major groups: benign, preneoplastic and non-invasive neoplastic lesions of the urothelium; and benign, preneoplastic and non-invasive neoplastic bladder lesions other than urothelial. Each of these lesions is defined with strict morphological criteria to provide more accurate information to urologists and oncologists in managing patients. There is still debate in the literature as to whether the 2004 WHO system should be the only one to be used and whether the 1973 WHO system should be abandoned.

Keywords: bladder metaplasia, bladder neoplasms, carcinoma *in situ,* flat urothelial hyperplasia, reactive urothelial atypia, urothelial dysplasia, urothelial papillary carcinoma

Abbreviations: CEA, carcinoembryonic antigen; CIS, carcinoma *in situ;* CK, cytokeratin; ISUP, International Society of Urologic Pathology; PUNLMP, papillary urothelial neoplasm of low malignant potential; WHO, World Health Organization

Introduction

Bladder cancer is morphologically heterogeneous; >90% of bladder cancer cases are urothelial (transitional cell) carcinoma, whereas primary squamous cell carcinoma, adenocarcinoma and other tumours are less common. Several classifications for the non-invasive neoplasms have been proposed in recent years.

For over two decades the 1973 World Health Organization (WHO) classification of urothelial neoplasms[1] has dominated. In the early 1990s several factors emerged that resulted in the need to re-evaluate this approach:

1. The controversy of calling grade 1 papillary tumours 'carcinoma' arose, with several groups led by William Murphy beginning to call all tumours in the low-grade end papilloma.[2]

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2. The use of intravesical therapy as standard practice in the treatment of high-risk non-invasive papillary tumours demanded that high-risk tumours be identified.

3. The 1973 WHO classification was criticized for the imprecision of the histological criteria, leading many pathologists to create five grade groups (1, 1–2, 2, 2–3 and 3). The effect was confusion among clinicians.

In 1998, a system of classifying non-invasive flat and papillary urothelial neoplasms of the urinary bladder was proposed by the International Society of Urologic Pathology (ISUP) in association with the WHO.[3] This became known as the 1998 ISUP/WHO classification system. In 2004, this classification system was adopted in *Pathology and genetics of tumours of the urinary system and male genital organs,* one of a series of WHO 'Blue Books' for the classification of tumours.[4] This is known as the 2004 WHO classification.

The aim of this paper is to review the current approach to the morphological classification and definition of the benign, preneoplastic and non-invasive neoplastic lesions of the urinary bladder. This review has been based on the 2004 WHO classification.[4] These lesions are subdivided into two major groups:

- Benign, preneoplastic and non-invasive neoplastic lesions of the urothelium; and
- Benign, preneoplastic and non-invasive neoplastic bladder lesions other than urothelial.

The precise identification of these lesions requires knowledge of the histology of the normal urothelium and the range of variations. This serves as reference when lesions are evaluated for their type and degree of alteration.

Normal urothelium

Urothelium is a multilayered epithelium composed of basal, intermediate and very large surface cells called 'umbrella cells' (Figure 1A). The latter may show some degree of nuclear pleomorphism, which should not be misconstrued to be dysplastic. The thickness of the urothelium varies with the state of distension of the bladder (two to four cell layers when dilated and five to seven layers when contracted).[5]

The urothelium of the renal pelvis, urethra and the bladder neck is usually composed of slightly larger cells, which have diminished cytoplasmic clearing and hence may be misinterpreted as dysplasia.

If the sections are thick, the urothelium may appear hyperchromatic, and this artefact, compounded by tangential sectioning, may result in changes felt to represent dysplasia. Vagaries of staining and fixation may also impart hyperchromasia to normal nuclei.[6]

Benign, preneoplastic and non-invasive neoplastic lesions of the urothelium

This group of urothelial lesions is subdivided into three major subgroups, depending on the relationship with the surface of the surrounding urothelial mucosa:[7]

- Flat
- Papillary (exophytic)
- Endophytic.

Each of these three subgroups is further subdivided into:

- Lesions without cytological atypia
- Lesions with cytological atypia.

FLAT LESIONS

The current classification of flat lesions of the urothelium was originally proposed by Amin *et al.*,[8] was subsequently incorporated into the 1998 ISUP/WHO and 2004 WHO classifications, and was extensively commented on by Lopez-Beltran *et al.*[9]

Flat lesions without cytological atypia

Flat hyperplasia. Urothelial hyperplasia is characterized by markedly thickened mucosa with an increase in the number of cell layers, usually ≥10. However, it is not necessary to count the number of cell layers for the diagnosis. The cells in urothelial hyperplasia do not show any significant cytological abnormalities, although slight nuclear enlargement may be focally present.[9,10] Morphological evidence of maturation from base to surface is generally evident (Figure 1B).

When seen as an isolated phenomenon, there is no evidence to suggest that primary urothelial hyperplasia has premalignant potential. However, molecular analysis has shown that this lesion may be clonally related to the papillary tumours in bladder cancer patients. Flat urothelial hyperplasia has been considered by some authors to be the source of papillary neoplasia, usually associated with low-grade tumours.[9,10]

Flat lesions with cytological atypia

Reactive (inflammatory) atypia. In reactive atypia the epithelium may or may not be thickened. Nuclei are uniformly enlarged, vesicular, and may have prominent, usually centrally located nucleoli. Mitoses may be frequent in the lower epithelial layers (Table 1). Inflammation is almost always present (Figure 1C). There is usually a history of instrumentation, infection or treatment with intravesicle agents. Some patterns of reactive atypia are associated with specific aetiologies.[9,11]

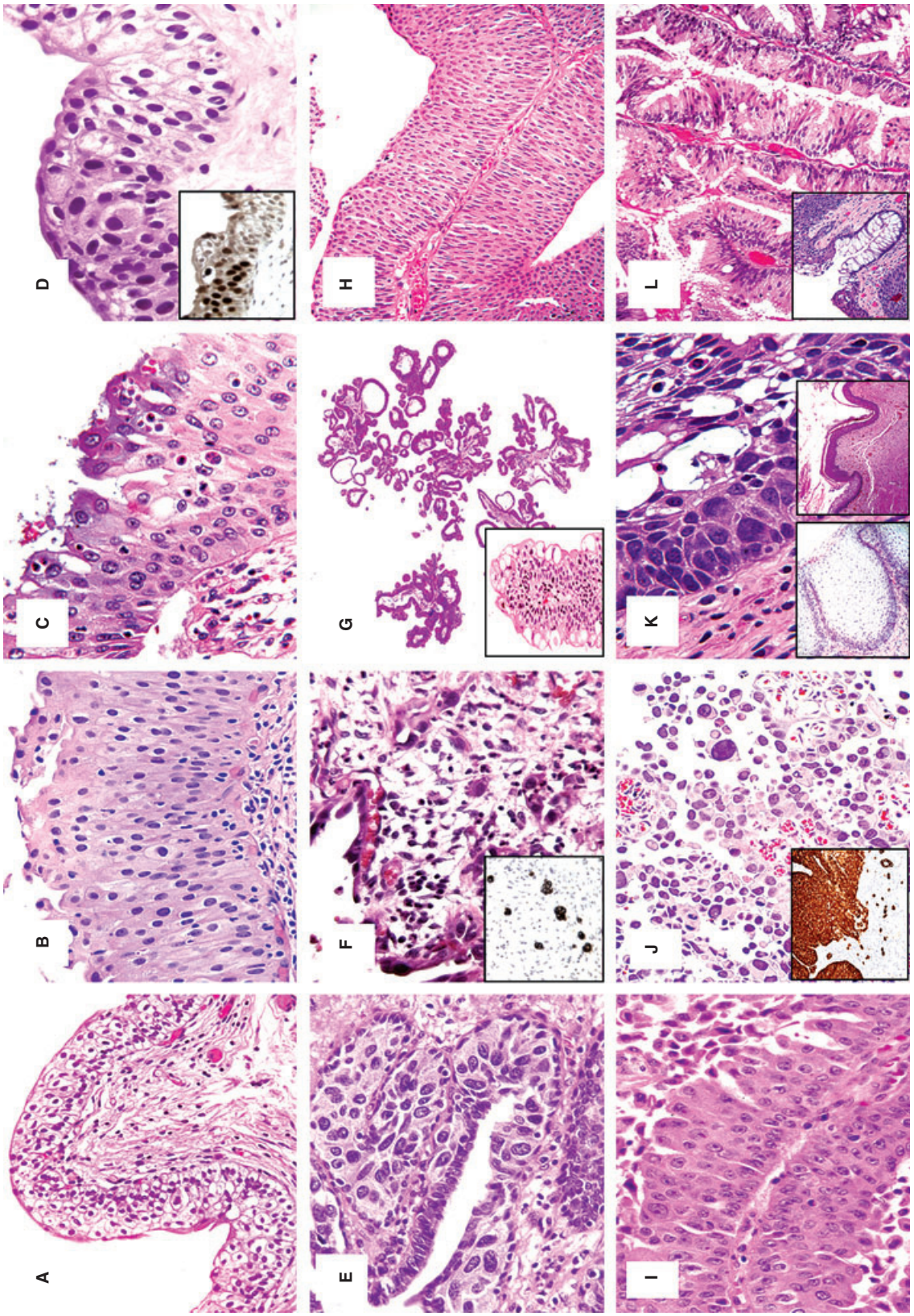

Figure 1. **A**, Normal urothelium. **B**, Flat urothelial hyperplasia. **C**, Reactive atypia. **D**, Urothelial dysplasia (left part of the image) adjacent to normal urothelium (right) (insert: p53 expression in dysplasia). **E**, Urothelial carcinoma *in situ* (CIS), pagetoid type. **F**, Urothelial CIS with microinvasion (the invading cells are highlighted by immunohistochemistry with antibody against AE1–AE3 cytokeratins). **G**, Urothelial papilloma (insert: magnification of the lesion). **H**, Papillary urothelial neoplasm with low malignant potential. **I**, Urothelial papillary carcinoma of low grade. **J**, Urothelial papillary carcinoma of high grade (insert: microinvasion detected with antibody against AE1–AE3 cytokeratins). **K**, Squamous cell CIS (insert 1: squamous cell metaplasia, vaginal type; insert 2: squamous cell metaplasia, keratinizing type). **L**, Villous adenoma (insert: intestinal metaplasia).

Table 1. Comparison of reactive atypia, hyperplasia, dysplasia and carcinoma *in situ*

Features	Reactive atypia	Hyperplasia	Dysplasia	CIS*
Cell layers	Variable	≥10	Variable	Variable
Polarization	Slightly abnormal	Normal	Disordered	Disordered
Cytoplasm	Often vacuolated	Homogeneous	Variable, homogeneous to granular	Variable
N/C ratio	Normal to slightly increased	Normal to slightly increased	Slightly increased	Increased
Nuclear size	Enlarged	Normal	Enlarged	Enlarged with variation in size
Nuclear borders	Regular/smooth	Regular/smoth	Notches/creases	Pleomorphic
Chromatin	Fine/dusty	Fine	Slight hyperchromasia	Coarse
Nucleoli	Large, single	Small/absent	Small	Large, often multiple
Mitotic figures	Variable	Absent	Rare, basal	Frequent, all levels
Umbrella cells	Uniformly present	Present	Present	May be present
Denudation	Variable	No	No	Variable

*Full thickness involvement is not required for the diagnosis of urothelial carcinoma *in situ* (CIS).

Atypia of unknown significance. This category was created to include those instances where a lesion cannot be confidently placed in the reactive versus dysplastic groups. The degree of cytological atypia is judged to be outside of the accepted range for reactive processes, although this possibility cannot be excluded. Histologically, there is usually an inflammatory background. Re-evaluation after inflammation subsides may resolve the problem, particularly in the follow-up of patients with known urothelial neoplasia who have been treated with intravesicle therapy. There is no evidence supporting a premalignant nature of atypia of unknown significance. Progression to urothelial carcinoma has not been documented. The utility of creating this diagnostic category has been questioned and its use is discouraged.[8,9,12] Reproducibility studies have demonstrated lack of diagnostic consistency.

Urothelial dysplasia. Histologically, there is some architectural distortion.[13] The nuclei are irregularly enlarged with some hyperchromasia and pleomorphism. Overall, the features are those of a neoplastic atypia but fall short of the criteria for carcinoma *in situ* (CIS) outlined below (Table 1 and Figure 1D). This category suffers from a significant problem in diagnostic reproducibility. It is most often diagnosed in the context of known urothelial neoplasia.[14] There is some evidence, largely genetic, that dysplasia shares some abnormalities with CIS and therefore is likely to represent a precursor lesion. One study that applied the 1998 ISUP/WHO criteria indicated a 19% risk of developing cancer with a mean follow-up of 4.9 years[15] (Table 2).

Urothelial carcinoma in situ. CIS is characterized by architectural disorder and nuclear pleomorphism[9,10] (Figure 1E). The cytologically atypical cells need not involve the full thickness of the epithelium and, at the minimum, single malignant cells growing in a pagetoid fashion are sufficient for the diagnosis of CIS. Individual cells tend to show marked cytologic atypia, but an increased nuclear:cytoplasmic ratio is not a prerequisite (not present in the large cell type of CIS).[16] In some cases only a few isolated cells are present clinging to the basement membrane (Table 3). The category of CIS includes lesions that had been graded in the severe dysplasia category in previous systems. Table 1 summarizes the morphological comparison of reactive atypia, hyperplasia, dysplasia and CIS. A list of problems and pitfalls in the diagnosis of flat lesions with atypia is shown in Table 4.

A panel of immunohistochemical antibodies consisting of cytokeratin (CK) 20, p53 and CD44 (standard isoform) may have utility in the distinction of CIS from reactive atypia[17,18] (Table 5). A pattern similar to that of CIS can be seen in urothelial dysplasia[17–24] (Figure 1D, insert).

Table 2. Prognosis of flat urothelial lesions (based on the published literature)

	Reactive atypia	Flat hyperplasia	Dysplasia	Carcinoma *in situ*
Recurrence	No	Unknown	Unknown* 73% versus 43% in cases without dysplasia†	Unknown* Unknown†
Progression	No	Unknown	13–19%‡,* 30–36%§,†	28%§,* 42–83%§,†

*Primary.
†Secondary.
‡Progression to carcinoma *in situ*.
§Progression to muscle-invasive carcinoma.

Table 3. Morphological patterns of carcinoma *in situ* (CIS)

Small cell CIS
Large cell CIS
Denuding CIS ('denuding cystitis')
Undermining (lepedic) growth
Pagetoid CIS

Table 4. Problems and pitfalls in the diagnosis of flat lesions with atypia

Inflammatory atypia
Therapy-associated atypia
Extensive denudation
Truncated papillae of treated papillary carcinoma
CIS involving von Brunn's nest (overdiagnosis of invasion)
CIS with microinvasion (underdiagnosis of invasion)
Polyomavirus infection

CIS, carcinoma *in situ*.

CIS is accepted as a direct precursor of invasive carcinoma. The development of invasion is seen in the follow-up in 20–30% of cases. Prognosis is reported in Table 2.

CIS with microinvasion. CIS with microinvasion of the urinary bladder is defined by invasion into the lamina propria to a depth of 5 mm from the basement membrane,[25,26] and, according to Lopez-Beltran *et al.*,[9] should not exceed 20 cells in the subepithelial connective tissue. It appears as direct extension cords (tentacular), single cells, or single cells and clusters of cells (Figure 1F). The neoplastic cells may be interspersed among and masked by chronic inflammation. In this case immunohistochemistry with antibodies against carcinoembryonic antigen (CEA) or CKs (such as AE1–AE3) should be applied to identify the invading cells (Figure 1F, insert).[9] Desmoplasia or retraction artefacts that may mimic vascular invasion are useful in recognizing invasion. The urologist is most often unsuspecting of invasive disease on the basis of cystoscopic evaluation.

CIS with microinvasion is a clinically relevant lesion. Of totally embedded cystectomy specimens that contained extensive CIS, i.e. involving ≥25% of the bladder, 34% were found to contain microinvasion; 5.8% had lymph node metastases and died of disease.[25,27]

Table 5. Diagnosis of flat lesions. Adjunctive role of immunohistochemistry

	Normal urothelium	Reactive atypia	Carcinoma *in situ*
Cytokeratin 20	Umbrella cells	Umbrella cells	Full thickness
CD44	Basal and parabasal cells	All cell layers	Residual normal basal cells of the normal urothelium
p53	Negative	Negative	Full thickness

PAPILLARY OR EXOPHYTIC LESIONS

Histological grading according to the 1973 WHO classification

Histological grading is one of the most important prognostic factors in bladder cancer. The first widely accepted grading system for papillary urothelial neoplasms was the 1973 WHO classification system, which divided urothelial papillary tumours into four categories: papilloma, grade 1 carcinoma, grade 2 carcinoma and grade 3 carcinoma.[1] Histological grading is based on the degree of anaplasia, with grade 1 tumours having the least degree of anaplasia compatible with a diagnosis of malignancy, grade 3 tumours have the most severe degree of anaplasia, and grade 2 tumours have an intermediate degree of anaplasia. Anaplasia is defined by the authors of the 1973 WHO classification as increased cellularity, nuclear crowding, disturbed cellular polarity, failure of differentiation from the base to the surface, nuclear polymorphism, irregular cell size, variations in nuclear shape and chromatin pattern, displaced or abnormal mitotic figures, and giant cells.[1]

The 1973 WHO histological grading of bladder cancer is one of most successful grading systems among all organ sites and has been validated since its introduction three decades ago. It has been accepted by pathologists, urologists, oncologists and cancer registrars in Europe and elsewhere. An enormous amount of data has been accumulated using this system in studies of the morphological properties, clinical behaviour, treatment and follow-up of urothelial tumours. Because of its relative simplicity and its well-documented powerful predictive value, it has been well accepted by urologists and used globally for several decades in making clinical decisions for management of patients with urothelial cancer.

In an effort to improve understanding and to standardize use of the 1973 WHO classification, an expanded and refined contemporary description of the scheme was presented in 2001. This proposal is known as the Ancona refinement of the 1973 WHO grading system.[28,29] This effort was inspired by discussions during the international consensus meeting on bladder cancer held in Ancona, Italy, 2001. The diagnostic criteria for each of these categories were refined and optimized for reproducibility.[28,29]

Histological grading according to the 2004 WHO classification

According to its proponents, the key points of the 2004 WHO classification of non-invasive urothelial tumours are:[4]

1. The description of the categories has been expanded to improve their recognition; one group (papillary urothelial neoplasm of low malignant potential, PUNLMP) with particularly good prognosis does not carry the label of 'cancer'.
2. It avoids use of ambiguous grading such as grade 1/2 or 2/3.
3. The group of non-invasive high-grade carcinoma is large enough to contain virtually all those tumours that have biological properties (and a high level of genetic instability) similar to those seen in invasive urothelial carcinoma.

Exophytic lesions without cytological atypia

Pseudopapillary hyperplasia (papillary urothelial hyperplasia). In the 1998 ISUP/WHO classification, papillary hyperplasia was included as a category with the group of papillary lesions. In the 2004 WHO classification, this is no longer included as a specific designation, but it is recognized that hyperplasias may be flat or pseudopapillary.[4] Hyperplasia with a pseudopapillary architecture refers to a slight tenting or undulation of the urothelium lacking a well-defined central fibrovascular core, although small vessels may be present at the base of the papillae. There is no significant cytological or architectural atypia. Pseudopapillary hyperplasia has most often been described in the setting of known papillary neoplasia. When identified *de novo*, the significance regarding subsequent development of neoplasia is unknown.

Urothelial papilloma. There has been long-standing controversy regarding the nature of papillary lesions with minimal cytological atypia. The application of this term by some experts to up to 1/3 of all papillary lesions was a major stimulant to the re-evaluation of these lesions that began in 1997. The current classification retains the very restrictive traditional criteria. Histologically, papilloma is characterized by a few fine papillary fronds without fusion or complexity. Individual fronds are covered by an essentially normal urothelium without architectural or cytological atypia. The number of cell layers is not a criterion for diagnosis (Table 6 and Figure 1G, including insert).

Papillomas meeting these restricted criteria occur at a younger age than other urothelial bladder tumours and often present with only one or a few papillary processes. They have a low recurrence rate[30–32] (Table 7).

Papillary urothelial neoplasms of low malignant potential. The creation of this category represented a compromise between the 'papilloma' supporters and those insisting on the use of 'carcinoma' for all papillary lesions. The 1998 consensus statement

Table 6. Comparison of papilloma, papillary neoplasm of low malignant potential, low-grade papillary carcinoma and high-grade papillary carcinoma

Features	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.

Table 7. Prognosis of urothelial papillary lesions*

	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

*From Lopez-Beltran and Montironi.[40]

acknowledged that the lower grade papillary neoplasms were not intrinsically malignant, but were associated with significant risk for the development of new papillary tumours (i.e. recurrence).[3] These lesions at the lower end of the spectrum were acknowledged to be clinically significant, with close clinical follow-up necessary but further intravesicle therapy not indicated.

Morphologically, PUNLMP largely, though not completely, corresponds to grade 1 papillary carcinoma in the old WHO system (see below). The tumour consists of delicate papillae with little or no fusion. The covering urothelium shows minimal architectural irregularity (Figure 1H). Nuclei lack significant nuclear hyperchromasia or pleomorphism. The chromatin is fine and nucleoli are inconspicuous. Mitoses are infrequent and basally located.

These tumours have a significantly lower rate of recurrence than either low- or high-grade papillary carcinomas and a very low rate of grade and stage progression.[33–39] In a review of published studies, Lopez-Beltran[40] has found the mean tumour recurrence rate to be 36% and stage progression rate to be 3.7%.

Exophytic lesions with cytological atypia

Papillary urothelial carcinoma, low grade. This category contains the intermediate group of lesions. In the 1973 WHO system this would include the lower half of grade 2 papillary carcinoma. Histologically, the papillae are largely delicate and separate, but some fusion may be seen. At low magnification there is a generally ordered appearance of cells within the epithelium. The nuclei tend to be uniformly enlarged, but retain the elongated to oval shape of normal urothelial cells. The chromatin remains fine with small nucleoli (Figure 1I). Mitoses may be present, but are few and remain basally located.

These tumours have a significantly higher recurrence rate than for PUNLMP and similar to high-grade papillary carcinomas. They also have a significantly higher rate of stage progression than PUNLMP, but significantly lower than for high-grade papillary carcinoma.[33,37–39] A review of the literature has revealed a mean recurrence rate of 50% and mean stage progression rate of 10%.[40]

Papillary urothelial carcinoma, high grade. This category contains grade 3 and the upper half of grade 2 papillary carcinoma of the 1973 WHO system. Histologically, the papillae are frequently fused, forming apparent solid masses. The overall impression is one of disordered growth (Figure 1J). The epithelium is of variable thickness. Individual cells are haphazardly arranged within the epithelium and have a generally discohesive nature. Nuclei are hyperchromatic and pleomorphic. The chromatin is dense, irregularly distributed and often clumped. Nucleoli may be single or multiple and are often prominent. Mitoses are generally frequent and may be seen at any level of the epithelium.[10] It is often associated with invasive disease at the time of diagnosis (Figure 1J, insert).

These tumours not only have a risk of invasion but have a significant risk of recurrence and progression. The overall progression rate (to invasive carcinoma) ranges from 15% to 40% (Table 7).[41,42] These tumours, when non-invasive (pTa), are all likely to require additional intravesicle therapy. Heterogeneity of grade is recognized in papillary lesions[43] and the consensus was that tumours should be graded on their worst part, although this needs further study.

Table 6 summarizes the morphological comparison of papilloma, papillary neoplasm of low malignant potential, low-grade papillary carcinoma, and high-grade papillary carcinoma. Prognosis of the papillary lesions is reported in Table 7.

Several studies have looked at a variety of biological markers in papillary tumours and their relationship to the three groups; for the most part, these have demonstrated significant differences of the respective marker in the different categories.[39,44,45]

Morphological comparison between papillary and flat lesions

PUNLMP, low-grade papillary carcinoma and high-grade papillary carcinoma show morphological similarities to flat hyperplasia, dysplasia and CIS, respectively.[7]

Relation of 1973 WHO to 2004 WHO classification

A major misconception is that there is a one-to-one translation between the 1973 and 2004 WHO classifications. Only at the extremes of grades in the 1973 WHO classification does this correlation hold true.[7,10] Lesions called papilloma in the 1973 WHO classification system would also be called papilloma in the 2004 WHO system. At the other end of the grading extreme, lesions called WHO grade 3 are by definition high-grade carcinoma in the 2004 WHO system. However, for WHO grades 1 and 2, there is no direct translation to the 2004 WHO system. Some lesions classified as WHO grade 1 in the 1973 system, which upon review show no cytological atypia, some nuclear enlargement and merely thickened urothelium, are PUNLMPs in the 2004 WHO system. However, other WHO grade 1 lesions showing slight cytological atypia and mitoses are diagnosed in the 2004 WHO system as low-grade papillary urothelial carcinomas. WHO grade 2 is a very broad category. It includes lesions that are relatively bland, which in some places are diagnosed as WHO grade 1–2; these lesions in the 2004 WHO system would be called low-grade papillary urothelial carcinoma. In other cases, WHO grade 2 lesions border on higher grade lesions, which in many institutions are called WHO grade 2–3; these lesions in the 2004 WHO classification system would be called high-grade papillary urothelial carcinoma.[7,10]

Has the 2004 WHO classification system facilitated changes in clinical management of papillary urothelial neoplasms?

In the past few decades it has been and still is well understood by most practising urologists and oncologists that non-invasive papillary urothelial tumours of all 1973 WHO grades require follow-up to detect recurrence or progression, despite the fact that grade 1 tumours are characteristically associated with an excellent prognosis. The length of clinical follow-up, the frequency of surveillance cystoscopy and the adjunctive use of intravesicle instillations of bacillus Calmette–Guérin or a variety of chemotherapeutic agents are influenced by many factors, including histological grade, tumour size, tumour multiplicity, depth of tumour invasion, recurrence history and apparent grade of migration with recurrence.

Currently, both in North America and Europe, there is no uniformity in the clinical management of patients with non-invasive papillary urothelial tumours diagnosed according to the 2004 WHO grading system. Patients with PUNLMP and non-invasive low-grade carcinoma are typically treated by transurethral resection of their tumours and are subsequently monitored for recurrence or progression by regular cystoscopy. Although low-grade non-invasive carcinoma has been found to have a statistically significant higher progression rate than PUNLMP in the study by Samaratunga *et al.* (8% for PUNLMP versus 13% for low-grade non-invasive urothelial carcinoma),[46] the reported high incidence of recurrence (up to 60%)[47] and progression (up to 8%)[46,47] for PUNLMP suggest that it is prudent to follow patients with a diagnosis of PUNLMP in an identical manner to those with a diagnosis of low-grade non-invasive carcinoma. Indeed, investigators studying the recurrence and progression rate of PUNLMP have recommended long-term clinical follow-up for patients with these lesions.[35,38,46–48]

To our knowledge, there has not been a published recommended surveillance protocol for PUNLMP tumours that differs significantly from the standard surveillance for low-grade non-invasive urothelial carcinoma. Nor, to our knowledge, have there been any published recommendations for following non-invasive urothelial tumours diagnosed according to the 2004 WHO grading system, nor for the use of intravesicle therapy, that vary significantly from the traditions long established for following comparable lesions diagnosed according to the 1973 WHO grading system. In short, those who are charged with following these lesions appear to have gained minimal benefit from the new grading system in terms of surveillance or intravesicle therapy protocols.[49]

ENDOPHYTIC UROTHELIAL LESIONS

A series of urothelial lesions, ranging from hyperplasia to carcinoma, can have an exclusively endophytic pattern of growth, thus causing problems in differential diagnosis and evaluation of invasion. Similarly to the flat and exophytic lesions, the endophytic changes can be without atypia and with atypia.[7]

von Brunn's nests and cystitis cystica

Von Brunn's nests refer to small groups of basal-like cells lying in the subepithelial connective tissue and attached the basal cell layer of the urothelium. Cystitis cystica is made of cystically dilated von Brunn's nests acquiring a luminal space. Mild nuclear atypia and nucleolar prominence can be present. Cystitis cystica is a benign proliferative consequence of inflammation or other irritation. Urothelial CIS may rarely occur in the von Brunn's nests and cystitis cystica, and not be detectable in the overlying flat urothelium.[50] In these cases it is usually associated with previously diagnosed CIS or infiltrating at other sites in the bladder.

Several patterns of invasive urothelial carcinoma (nested variant, tubular, and microcystic) are deceptively bland and may mimic von Brunn's nests and cystitis cystica, particularly when the proliferation becomes florid.[51,52]

Inverted urothelial papilloma

Inverted papilloma is a distinct clinical pathological entity typically arising in the trigone region in a younger patient population than papillary neoplasms. Grossly, inverted papilloma shows an exophytic polypoid growth pattern. Histologically, it consists of anastomosing trabeculae of urothelium covered by a normal or attenuated urothelium. There is no significant nuclear pleomorphism and few mitoses can be seen. Squamous or glandular differentiation may be present. In transurethral resection material, the fragmentation of the lesion may result in apparent true papillary structures, making diagnosis difficult. Distinction from carcinoma with an inverted growth pattern can be problematic (see below). Cases of synchronous inverted papilloma and papillary carcinoma are known. Inverted papilloma is associated with a low risk of recurrence (<5%).[53,54]

Endophytic growth patterns in urothelial carcinoma

Some papillary urothelial carcinomas exhibit a prominent endophytic growth pattern, resulting in considerable difficulty in assessing invasion. Endophytic growth is evident either as interanastomosing cords and columns of urothelium, often with a striking resemblance to inverted papilloma (inverted papilloma-

like pattern), or as broad, pushing bulbous invaginations into the lamina propria (broad-front pattern). The endophytic growth pattern in urothelial carcinoma described here is similar to that originally presented by Amin and colleagues[55] and by Montironi *et al.*[7]

Distinction from inverted papilloma requires attention to architectural and cytological features. Architectural features favouring a diagnosis of urothelial carcinoma with an inverted growth pattern include thick columns with irregularity in their width and transition into more solid areas. The characteristic orderly maturation, spindling, and peripheral palisading seen in inverted papilloma are generally absent or inconspicuous in carcinoma with an inverted growth pattern. Unequivocal invasion into the lamina propria or muscularis propria rules out the diagnosis of inverted papilloma, but this feature is rarely found. Cytological atypia, including nuclear pleomorphism, irregularities of nuclear borders and chromatin distribution, prominent nucleoli, and appreciable mitotic rate, is an important feature for the diagnosis of carcinoma.

The second, and more common, histological appearance of urothelial carcinoma with an endophytic growth pattern is the pushing broad-front extension into the lamina propria, akin to cutaneous and mucosal verrucous carcinoma. The downward projection can be so pronounced that the base of the tumour lies on the muscularis propria.

Diagnosis of invasion requires the unquestionable presence within the lamina propria of irregularly shaped nests or single cells that may have evoked a desmoplastic or inflammatory response. When a stromal response is absent, irregularity of the contours of the invasive nests, architectural complexity and recognition of single-cell invasion are helpful. Occasionally, the cells in the invading nests appear morphologically different from those at the base of the tumour, and they may appear as smaller aggregates present within empty spaces. These spaces may mimic vascular invasion closely, but are believed to be retraction artefacts.[7]

Benign, preneoplastic and non-invasive neoplastic bladder lesions other than urothelial

Squamous cell lesions

Squamous papilloma. Squamous papilloma is a rare benign neoplasm. It is the squamous counterpart of urothelial papilloma and is unrelated to human papillomavirus infection. It usually occurs in elderly women and follows a benign clinical course. Histologically, it is composed of papillary cores with overlying benign squamous epithelium.[56]

Squamous metaplasia. It occurs in two variants: vaginal and keratinizing. The vaginal type is considered normal in the female trigone (Figure 1K, insert 1). There is no known association with carcinoma. The keratinizing type (Figure 1K, insert 2) is usually associated with chronic irritation, e.g. indwelling catheters, or stones. Squamous metaplasia is a well-known phenomenon in association with bilharzia infestation in North African countries, especially in Egypt. The development of invasive squamous cell carcinoma in the setting of extensive keratinizing squamous metaplasia is not uncommon (see Squamous cell carcinoma *in situ*).[57]

Squamous cell carcinoma in situ. Only a few reports on squamous cell CIS of the bladder are available.[58] Histologically, it is identical to squamous cell CIS found in other organ sites (Figure 1K). This finding is often associated with subsequent or concurrent invasive carcinoma. Wide-range human papillomavirus DNA signal has occasionally been detected. Enhanced expression of epidermal growth factor receptor in these bladder squamous lesions suggests a possible therapeutic target in cases that are difficult to manage clinically.[58]

Glandular lesions

Glandular (intestinal) metaplasia (cystitis glandularis). It is characterized by the presence of epithelial cells of colonic type with goblet cell appearance (and rarely Paneth, argentaffin or argyrophil cells) within the surface epithelium (flat pattern) or/and in association with cystitis cystica (endophytic pattern, i.e. cystitis glandularis). It has been considered a preneoplastic condition.[9] The development of adenocarcinoma has been documented in very few patients.

Mucin-secreting metaplasia with striking resemblance to intestinal mucosa, including a crypt-like architecture, is called intestinal metaplasia (Figure 1L, insert). Extensive intestinal metaplasia can be seen in bladder extrophy and is associated with increased risk for the development of adenocarcinoma.[59] The appearance of cellular atypia, such as nuclear pleomorphism and nucleolar prominence, is considered indicative of glandular dysplasia and adenocarcinoma *in situ*, i.e. an intermediate step between glandular metaplasia and invasive adenocarcinoma.[60–62]

Villous adenoma. Villous adenoma is an uncommon glandular epithelial neoplasm with exophytic growth that can be associated with urachal adenocarcinoma.[63]

Patients often present with haematuria and/or irritative symptoms. Mucusuria may be present in rare cases. There is no apparent gender predominance. The tumour usually occurs in elderly patients with a predilection for the urachus, dome, and trigone of the urinary bladder. Its cystoscopic appearance is that of an exophytic tumour. Histologically, villous adenoma of the bladder is identical to villous adenoma of the colon, with columnar mucin-filled goblet cells lining delicate fibrovascular stalks (Figure 1L). Nuclear findings include pseudostratification, crowding, occasional prominent nucleoli and nuclear hyperchromasia, as in the colon. Villous adenoma of the bladder shows immunopositivity for CK20 (100% of cases), CK7 (56%) and CEA (89%). Patients with an isolated villous adenoma have an excellent prognosis, but progression to adenocarcinoma appears to occur in 21–33% of cases. Villous adenoma of the bladder may coexist with *in situ* and invasive adenocarcinoma.[63]

Conclusions and future perspectives

There is still debate as to whether the 2004 WHO system should be the only one to be used and whether the 1973 WHO system should be abandoned.[64] Reporting both grades has been recommended.[65]

In terms of clinical management of patients with non-invasive papillary urothelial neoplasms, there have been, to our knowledge, no published recommendations for following non-invasive urothelial tumours diagnosed according to the 2004 WHO grading system, nor for the use of intravesicle therapy, that vary from the traditions long established for following comparable lesions diagnosed according to the 1973 WHO grading system. If the original focus in 1998 had been simply to retain the original 1973 WHO classification scheme, but to embellish it by expanding and clearly defining the morphological characteristics of the original three grades of carcinoma, a long and unproductive period of controversy and uncertainty about the questionable merits of the new terminology could have been avoided.[49]

Enough is now known about the molecular aspects of bladder tumours. The variance in biological behaviour of low- versus high-grade tumours correlates with known dual molecular lines of genetic development. The first and more common pathway (low grade) leads to non-invasive, papillary tumours, those whose status as a carcinoma might be legitimately challenged because they usually follow an indolent course. The second pathway leads to the development of high-grade papillary carcinoma or flat CIS and ultimately muscle-invasive carcinoma if left untreated. In their earliest, but commonly progressive phase, these lesions will be staged as CIS or Ta. Although not invasive, they share molecular alterations common in invasive disease and represent the stage before invasive disease.[66]

There is a need of a universally accepted new classification of bladder non-invasive neoplasms in which essential morphological elements from both WHO classifications as well as information on molecular marker expression are incorporated.

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