Classification and grading of the non-invasive urothelial neoplasms: recent advances and controversies

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The classification and grading of the non-invasive, intraepithelial neoplasms of the urothelium are based on the morphological pattern of growth—that is, papillary or flat (and endophytic)—and on their degree of architectural and cytological abnormalities. Recent advances in the morphological, molecular, and quantitative evaluation of these lesions have contributed to the refinement of the current classification and grading schemes. However, some controversies on the precise criteria and terminology, especially when the papillary lesions are concerned, are still present.

Early clinical observations regarding the biology of the “at risk” field suggested that sites of urothelial preneoplastic changes could follow several distinct clinical courses (fig 1). It is possible that areas of dysplasia remain simply dysplastic. Alternatively, the urinary epithelium can progress either to superficial bladder neoplasm, characterised by recurrence but rare life threatening progression, or along the path towards invasion, with its well recognised risk of mortality. Evidence in support of these disparate pathways comes from the low progression rate of most superficial bladder tumours, coupled with that fact that many invasive neoplasms present as such initially.7

From the morphological point of view, two basic pathways are identified on the basis of the pattern of growth of the intraepithelial lesions (papillary and flat), the behaviour of these lesions being related to the degree of architectural and cytological alteration of the urothelium. Several classification and grading schemes (including revisions and refinements) of urothelial non-invasive or intraepithelial lesions have been reported in the literature.7 8

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The grading of papillary urothelial carcinoma is based on the worst grade present. G1 carcinoma consists of a urothelium more than seven cell layers thick containing cells that display minimal to slight nuclear enlargement, normal or slightly distorted architecture, and rare or absent mitotic figures. In contrast, G2 carcinoma displays greater nuclear pleomorphism, coarsely clumped chromatin, and some disruption of the normal architecture. Malmstrom et al subdivided G2 into G2A and G2B in 1987.7 12 Morphologically, G1 and G2A are similar to urothelial flat dysplasia (see below). Grade 3 carcinoma displays the most extreme nuclear abnormalities, similar to those seen in carcinoma in situ (CIS). Cellular anaplasia, characteristic of grade 3 carcinoma, is defined as increased cellularity, nuclear crowding, disturbance of cellular polarity, absence of differentiation from the base to the mucosal surface, nuclear pleomorphism, irregularity in the size of the cells, variation in nuclear shape and chromatin pattern, increased number of mitotic figures, and the occasional presence of neoplastic giant cells.1 The morphological criteria useful for classification and grading have been continuously refined and updated.11 14 Recent efforts to grade...
urothelial carcinoma using image analysis based on nuclear morphometry, silver staining nucleolar organiser regions, diagnostic decision support systems (Bayesian belief networks), and other markers have also been successful, but are not used routinely. This has led to a high degree of reproducibility and accuracy in the classification and grading of papillary neoplasms.

WHO/ISUP 1998 and WHO 1999 classifications

The WHO/International Society of Urological Pathology (ISUP) consensus classification of 1998 (WHO/ISUP 1998) distinguishes between papilloma, papillary urothelial neoplasm of low malignant potential (PUNLMP), and low and high grade carcinoma. The term “papillary urothelial neoplasm of low malignant potential” was introduced to replace WHO 1973 G1 carcinoma in recognition of the low probability of recurrence or progression of this neoplasm, especially after complete removal, and the preference not to label these patients with the term “cancer”. The WHO classification introduced in 1999 (WHO 1999) is almost identical to the WHO/ISUP classification, the difference being that the WHO 1999 scheme subdivides the low and high grade spectrum into three grades (grades I, II, and III).


The topic of the best contemporary classification of the papillary neoplasia was debated at the Ancona international consultation on the diagnosis of non invasive urothelial neoplasms (11–12 May 2001, Ancona, Italy). The discussion was basically around the WHO 1973 scheme versus the WHO/ISUP 1998 and WHO 1999 classifications. In particular, the following problems were considered:

- Are detailed morphological criteria available for the WHO 1973 scheme and for the WHO/ISUP 1998 and WHO 1999 classifications?
- Reproducibility: is reproducibility better with the WHO/ISUP 1998 and WHO 1999 classifications?
- G1 papillary carcinoma (1973 scheme): is this a misnomer for a lesion that does not have the morphological and clinical features of cancer? Should the term “papillary neoplasia with low malignancy potential” be used to avoid the term carcinoma?
- Translation from the WHO 1973 scheme to the WHO/ISUP 1998 and 1999 WHO classifications: is it feasible and easy?
- How much clinical and prognostic information is available in favour of the WHO 1973 scheme and how much in favour of the WHO/ISUP 1998 and WHO 1999 classifications?

A full consensus on which classification should be used by practising pathologists and followed by urologists and oncologists was not reached. Drs Bostwick and Mikuz represented the majority opinion—for example:

- The WHO 1973 classification for papillary urothelial neoplasms was still superior to all existing alternatives (including WHO/ISUP 1998 and WHO 1999), although some refinement of diagnostic criteria would be useful.
- Some pathologists may prefer to report additional, synonymous classifications in other schemes, but this is discouraged owing to variations and difficulties in translation.

Figure 1: Morphological pathways for bladder tumour classification and grading. Reproduced, with permission, from Jones et al.
The lack of rules for the distinction of G1 from G2 tumours, particular, they affirmed that:

- The fibroblast growth factor receptor 3 (FGFR3) mutation is observed progression in 8% of patients with PUNLMP and in 11% of patients with G1 papillary carcinoma (WHO 1973). The same group claim an advantage of the WHO/ISUP 1998 system over the WHO 1973 system in that the WHO/ISUP 1998 classification recognised a larger proportion of cancers with a poor prognosis.4
- Oosterhuis et al. found that the prognostic value of the WHO/ISUP 1998 classification is limited, thus questioning the clinical role of this new system in comparison with conventional grading systems.23
- The WHO 1973 standard for classification and grading of bladder tumours is a robust, clinically confirmed, widely used, time tested, and reasonably reproducible method for pathological reporting, and is recommended with minor modifications.24

INTRAEPITHELIAL FLAT LESIONS

The most recently revised classification of flat (and endophytic) lesions was published by Lopez-Beltran et al.22 This included epithelial abnormalities (reactive urothelial atypia and flat urothelial hyperplasia), presumed preneoplastic lesions and conditions (keratinising squamous and glandular metaplasia, and malignancy associated cellular changes), in addition to preneoplastic (dysplasia) and neoplastic non-invasive (CIS) lesions. Each of these lesions was defined with strict morphological criteria to provide more accurate information to urologists in managing patients. Particular attention was paid to the definition and importance of dysplasia and CIS.

In general, the morphology of dysplasia shows cohesive cells with umbrella cells usually present and characterised by mild nuclear/nucleolar changes that focally include irregular nuclear crowding, and slight hyperchromasia. Anisonucleosis is usually present, and there may be an increased number of cell layers. Nucleoli may be prominent and mitotic figures, when present, are generally basally located. Most cellular abnormalities in dysplasia are restricted to the basal and intermediate layers. Nuclear and architectural features are considered most useful in distinguishing between reactive atypia and dysplasia. Cytokeratin 20 and high molecular weight cytokeratin immunoreactivity might be objective markers of dysplasia in selected cases.34 To use the term dysplasia without a qualifier is preferable to describe the morphological spectrum of dysplastic lesions of the urothelium.

The morphological diagnosis of CIS requires the presence of severe cytological atypia (nuclear anaplasia); full thickness change is not essential, although it is usually present. Interobserver agreement with CIS is high. The cells of CIS may form a layer that is only one cell thick, of normal thickness (up to seven cells), or the thickness of hyperplasia (greater than seven cells). Prominent disorganisation of cells is characteristic, with loss of polarity and cohesiveness. Superficial (umbrella) cells may be present except in areas of full thickness abnormality. The tumour cells tend to be large and pleomorphic, with moderate to abundant cytoplasm, although they are sometimes small with a high nucleus to cytoplasmic ratio. The chromatin tends to be coarse and clumped.38-40 Morphetically, the cells display increased nuclear area, nuclear perimeter, and maximum nuclear diameter. Nucleoli are usually large and prominent in at least some of the cells, and may be multiple. Mitotic figures are also seen in the uppermost layers of the urothelium, and may be atypical.41-43 Tissue oedema, vascular ectasia, and proliferation of small capillaries are frequent in the lamina propria in cases of CIS.
MOLECULAR AND GENETIC BASIS OF CLASSIFICATION AND GRADING

Loss of heterozygosity (LOH) on chromosome 9 is an early event in the generation of superficial bladder cancer, such as G1 and at least part of the spectrum of G2. On the other hand, mutation of p53 represents an early genetic alteration in CIS (and G3). Later on, during progressive growth, p53 also contributes to the carcinogenesis of superficial bladder tumours, whereas LOH on 1p and 9q is involved in the development of CIS to T1–3 tumours. The final progression of superficial carcinomas and CIS seems to require another large series of genetic aberrations (fig 2). The exact sequence of these alterations has not yet been elucidated, even though it is correlated with the morphological classification and grading schemes.

Take home messages

- Contemporary classification and grading of human papillary urothelial neoplasms remains unsettled. One of the chief motivations for new approaches was to avoid the use of the term “cancer” for neoplasms with a low likelihood of invasion, recurrence, and death.
- According to Bostwick and Mikuz, the World Health Organisation (WHO) 1973 classification and grading of bladder tumours is recommended with minor modifications for international use to allow valid comparison of results between different clinical centres. As with all existing classification and grading methods, the WHO classification should be regularly reviewed and updated as appropriate when new and confirmed data emerge.
- Molecular pathology could have a role in the further refinement of the classification and grading systems.

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