

WHO/ISUP Classification of Papillary Urothelial Tumors: have We Finally Settled for it?

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WHO/ISUP CLASSIFICATION OF PAPIL-LARY UROTHELIAL TUMORS: HAVE WE FINALLY SETTLED FOR IT?

ABSTRACT

Histological grading of noninvasive papillary urothelial tumors is the most important prognostic factor short of tumor invasion. Various schemes and classifications have been proposed since last few decades, all based on morphological criteria alone. Among these, 1973 WHO classification proved very successful in clinical practice and dominated for almost three decades. In late 1990s efforts were initiated to reevaluate and reassess the grading schema and these efforts resulted in the promulgation of WHO and International Society of Urologic Pathologists (ISUP) classification of noninvasive urothelial neoplasms in 1998. This classification was further refined and published in the latest WHO blue book on Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs as 2004 WHO classification. The later classification has however not completely replaced the 1973 WHO classification and many centers are using both the classifications in the pathology report. It is time to incorporate immunohistochemical, molecular genetic and omics data to further refine this prognostic classification.

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Key words: Grading; Histological classification; Prognosis; Tumors; Urothelial neoplasms

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Short of invasion, histopathological grading remains the most important prognostic factor for the papillary urothelial neoplasms^[1-5]. However, this is also the feature that has evoked much controversy and confusion with regard to its appropriate classification. In fact, the history of histological grading systems of the urothelial neoplasms rivals the lymphoma classification during the last few decades. The lymphoma classification has finally been rationalized and standardized by the Revised European-American Lymphoma (REAL) classification and WHO classifications, but this dream has yet to be fulfilled for the grading schema for the urothelial neoplasms^[6-10].

The first most widely accepted and used grading schema for noninvasive urothelial neoplasms was the 1973 WHO classification, which dominated the clinical practice for nearly three decades^[11]. Its strong points were its simplicity and the powerful predictive value. It was well received by all the concerned health care physicians involved in the diagnosis and care of bladder tumor patients, particularly the urologists and oncologists^[1-5]. Indeed, this classification is regarded by many as the most successful clinical classification in use among all the classifications. The main demerits of the classification were that the histological criteria were not described in sufficient detail so that interobserver reproducibility was poor and areas of ambiguity remained at the border zones of grade 1 and 2, and 2 and 3^[2,4,5,8,10]. Its potential weaknesses emanating from widespread use coupled with emerging evidence from newer studies highlighted the need to reevaluate this classification^[1-10]. As a result, a number of urologic pathologists, urologists, oncologists and basic scientists met in 1998 under the auspices of WHO and International Society of Urologic Pathologists (ISUP) and formulated a newer classification for flat and papillary noninvasive categories of urothelial neoplasms. This classification is popularly known as 1998 WHO/ISUP classification^[12]. A partially modified version of this classification was adopted by

WHO as 1999 WHO classification, which also retained the grading categories of 1973 WHO classification. But this classification met with very little success right from the beginning. The 1998 WHO/ISUP classification was however adopted with fine amendments in the latest Blue Book of WHO as 2004 WHO classification^[13]. The later classifications were meant to replace the 1973 WHO classification as the universal consensus classifications. However, this dream has not yet been realized completely. Its advantages for urologic pathologists are fairly straight forward. There are only two grades of carcinoma, low grade and high grade. This dichotomy is equally advantageous for the management of these tumors by oncologists. The label of carcinoma is not used for a category of very low grade urothelial neoplasms with particularly excellent long-term prognosis (Figure 1). The morphological criteria of diagnostic categories were described in detail to improve interobserver reproducibility^[12]. However, the 1973 and 2004 WHO classifications are not directly interchangeable^[13-20]. Despite the above improvements from the urologic pathologists' point of view, there is still no uniformity among the urologists and oncologists in the use of therapeutic strategies of patients with bladder tumors graded according to 2004 WHO classification. Many centers, like ours, use both the classifications simultaneously^[11-6]. This exercise is meant to educate the treating physicians about the changes brought about by 2004 WHO classification in context of the original 1973 WHO classification and may be continued till such time that the

urologists and oncologists completely adopt the new classification.

But, the most important question that arises here is that, has 2004 WHO classification attained the status of gold standard schema amongst the existing grading systems for histological grading of the noninvasive urothelial neoplasms? The most pragmatic answer is "No". The reasons lie in the inherent subjectivity and interobserver variability of all histopathological assessments. All the existing classifications of grading urothelial neoplasms including 2004 WHO classification were developed based on expert opinion and without clinical evidence base and prior validation^[2]. Although not related to urologic pathology, the Oxford classification of IgA nephropathy has recently been developed based on true international consensus process and with prior testing of reproducibility and clinical evidence base^[21]. This classification can serve as a role model for adopting a similar approach for developing a truly consensus based and reproducible classification in other areas of pathology^[22]. Moreover, the major focus of all existing classifications has been on morphological criteria only. Perhaps, it is high time that we focus our research to the discovery and use of immunohistochemical (IHC), molecular genetic and omics markers to further refine and fine tune the classification. These markers will also facilitate an objective evaluation of the biological potential of urothelial neoplasms. A few studies have found that a small battery of IHC markers can successfully meet this need. Further, large scale and multicenter studies using novel markers are

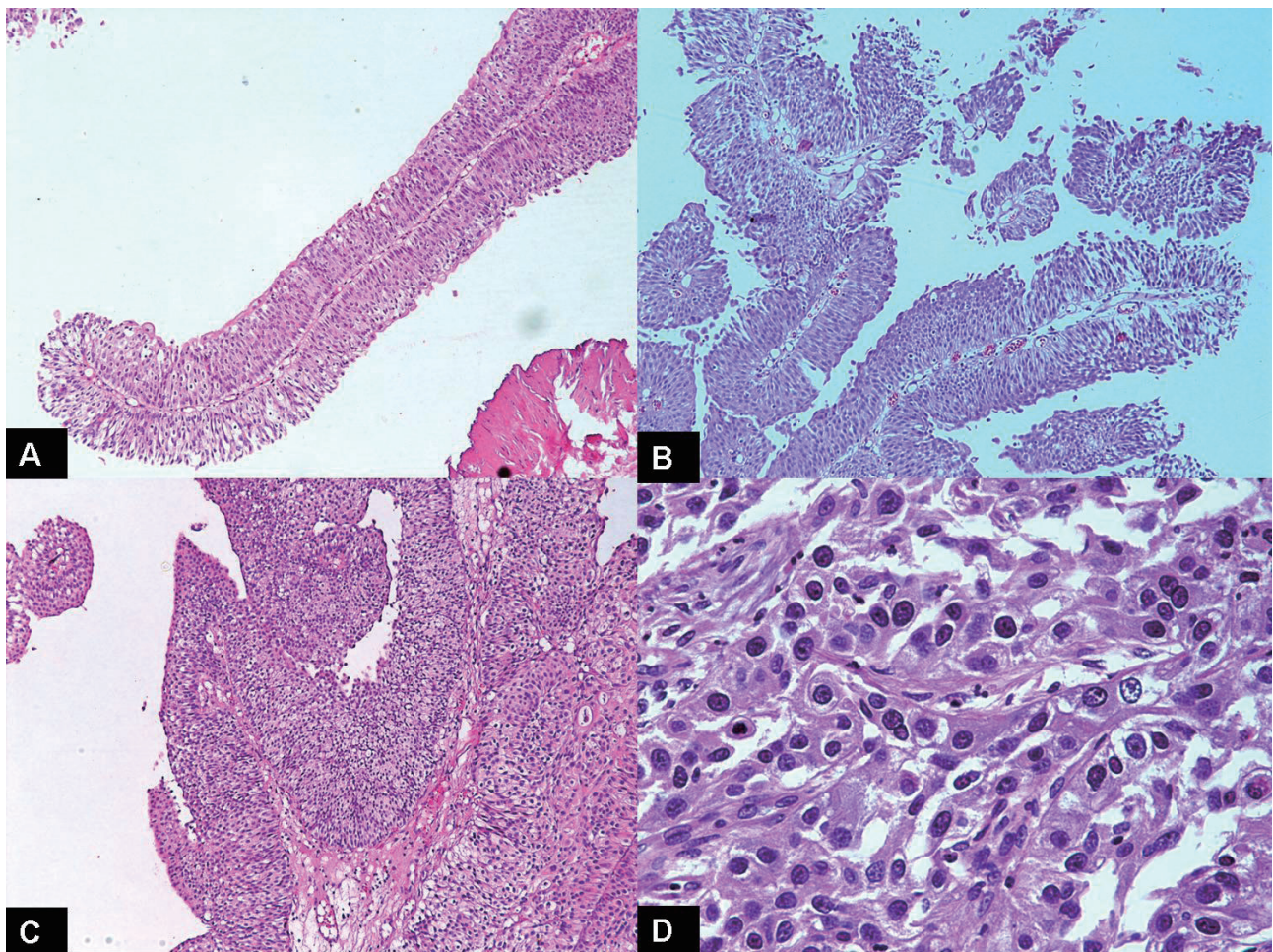


Figure 1 Main diagnostic categories of 2004 WHO classification. A: Thin delicate papillary process lined by normal urothelium in an example of papilloma. (HE, ×100); B: In this case of papillary urothelial neoplasm of low malignant potential (PUNLMP), the branching papillae are lined by moderately hyperplastic urothelium with minimal atypia (HE, ×200); C: Low grade urothelial carcinoma with marked hyperplasia and moderate atypia. (HE, ×200); D: High grade urothelial carcinoma with marked cellular and nuclear atypia, loss of polarity and prominent nucleoli. (HE, ×400).

needed to validate these findings^[23]. For now, it is helpful to use both the 1973 and 2004 WHO classifications simultaneously in order to facilitate the appropriate management of these neoplasms.

In summary, although 2004 WHO classification of noninvasive urothelial neoplasms represents a significant improvement over the previous classifications, it has not yet achieved the coveted gold standard status among the existing classifications. Its use has not been uniform throughout the world and many centers still use both 1973 and 2004 classifications.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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