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Latest Novelties on the World Health Organization Morphological Classifications of Genitourinary Cancers

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Abstract

The World Health Organization (WHO) releases a periodic press classification describing updates of standard worldwide nomenclature of tumors in different organs and a brief synopsis on their primarily pathological diagnostic criteria and clinical significance. The prior edition of the WHO book on the classification of Tumors of the Urinary System and Male Genital Organs was published in 2004. In the current review, we provide the updates that were included in the 2016 edition of the WHO Classification of Tumors of the Urinary System and Male Genital Organs and are most pertinent to clinical practice. Due to a large time gap between the 2004 and 2016 editions, there are many changes that are substantially influential for both clinical and pathological practices of urological oncology. This review covers the updates in the urothelial tract, kidney, testicular, and prostate tumors as well as authors' practices in the areas that remained unresolved.

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1. Introduction

The World Health Organization (WHO) releases a periodic press classification describing updates of the standard worldwide nomenclature of tumors in different organs and a brief synopsis on their primarily pathological diagnostic criteria and clinical significance. In 1956, the WHO passed a resolution to explore the possibility that the WHO might organize centers whose main purpose was to develop histological definitions of cancer types and to facilitate a wide adoption of uniform nomenclature. The prior edition of the WHO book on the classification of Tumors of the Urinary System and Male Genital Organs was published in 2004. The 2016 edition of the WHO Classification of Tumors of the Urinary System and Male Genital Organs has many evidence-based updates that included changes in the nomenclature, new entities, and better understanding of the previously described tumors [1]. This classification reflects the experience of the experts from around the globe that convened for a Consensus and Editorial Meeting at the University Hospital Zürich, Zürich, March 11–13, 2015. Although molecular information on urological cancers is rapidly expanding, there are only a few specific examples of incorporating molecular tests into a routine clinical practice in 2016 WHO edition. We cover the updates in the urothelial tract, kidney, testicular, and prostate tumors, and comment on our practices regarding the topics that

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remained unresolved. As there was a 12-yr gap between the 2004 and 2016 WHO editions, there is an overwhelming amount of new information and it is beyond the scope of this manuscript to cover all the updates but rather we focus on those that the authors believe are most clinically relevant and more likely to be encountered in day-to-day practice.

2. What is new for urothelial tract tumors in WHO 2016?

The chapter on tumors of the urinary tract covers urothelial neoplasia spanning the renal pelvicaliceal system down to the urethra. The new classification separates the usual invasive urothelial carcinoma, urothelial carcinoma with divergent differentiation (squamous, glandular, or trophoblastic), and variant histologies of urothelial carcinoma (Table 1).

The classification of noninvasive urothelial carcinoma remained dichotomized with flat neoplastic lesions classified as urothelial dysplasia (low-grade) or in situ urothelial carcinoma (CIS; high-grade), and papillary lesions classified as noninvasive low- or high-grade papillary urothelial carcinoma. Although it is advised to grade the tumor according to the highest grade, in our own study of predominantly low-grade noninvasive papillary urothelial carcinomas with <5% of a high-grade component, there was a trend for more aggressive behavior compared with pure low-grade cancers but significantly better behavior than cancers with a more extensive high-grade component [2]. While in the WHO 2004 classification, invasion of prostatic stroma was considered stage pT4, the 2016 edition clarifies that only cancers originating in the bladder and directly invading into the prostate should be classified as pT4. In cases of cystectomy specimens with concurrent urothelial carcinoma involving the prostatic urethra, separate staging of the bladder and prostatic urothelial carcinoma is recommended. When CIS involves the prostatic urethra with extension down into prostatic acini and subsequent stromal invasion, the urothelial carcinoma is currently staged as prostatic urethral pT2. In cases with extensive CIS involving prostatic urethra and extending into prostatic ducts and acini without stromal invasion, the latter findings do not alter the stage of invasive cancer.

Table 1 – World Health Organization classification of tumors: tumors of the urothelial tract (differences in epithelial tumors between the third and fourth editions)

Third edition	Fourth edition[a]
Infiltrating urothelial carcinoma	Infiltrating urothelial carcinoma
with squamous differentiation	with divergent differentiation
with glandular differentiation	
with trophoblastic differentiation	
Nested	Nested, including large nested
Microcystic	Microcystic
Micropapillary	Micropapillary
Lymphoepithelioma-like	Lymphoepithelioma-like
Lymphoma-like	Plasmacytoid/signet ring cell/diffuse
Plasmacytoid	Sarcomatoid
Sarcomatoid	Giant cell
Giant cell	Poorly differentiated
Undifferentiated	Lipid rich
	Clear cell

[a] Entities highlighted in red indicate change in nomenclature or new entities.

Another important consensus reached was that based on the available data, it is recommended to provide an assessment of the depth and/or extent of subepithelial (lamina propria) invasion in pT1 cases. However, it was also acknowledged, that in T1 disease several substaging methods have been proposed to improve outcome prediction, but none have been routinely adopted. Generally, two large systems have been investigated, assessing the size of invasion in mm or assessing the depth of invasion in respect to muscularis mucosa as a landmark. In a study by Brimo et al [3], the authors demonstrated by multivariate analysis that there was a significant association of subsequent progression with muscularis mucosa invasion ($p = 0.007$), depth of invasion ($p = 0.0001$), and diameter of invasive focus ($p = 0.014$), where the presence of both a depth of invasion of 3 mm and diameter of 6 mm predicted 94% of recurrences. Lee et al [4] studied 119 patients with superficial lamina propria invasion (pT1a), 57 with invasion into the muscularis mucosa (pT1b), and seven with the invasion beyond the muscularis mucosa but not into the muscularis propria/detrusor muscle (pT1c). Although there was no statistically significant difference in recurrence rates between pT1a (32.8%) and pT1b/c (40.6%), the progression rate was significantly different (5.8% vs 21.9%, $p = 0.003$) and cancer-specific mortality also differed significantly (4.2% vs 14.0%, $p = 0.036$) in multivariate analysis. In a study by van Rhijn et al [5], in 136 patients with pT1 bladder cancer treated with Bacillus Calmette-Guérin and a median follow-up of 6.4 yr, in addition to pT1a-c substaging, the authors dichotomized the cases into T1-microinvasive ($\leq$ 0.5 mm single focus) and T1-extensive-invasive (> 0.5 mm or multifocal). Substaging into microinvasive and extensive-invasive was significantly associated with progression ($p = 0.001$) and disease-specific survival ($p = 0.032$), compared with T1a-c substaging which lacked statistically significant predictive power. Given the lack of consensus on how to quantify the extent of lamina propria invasion in pT1 disease on transurethral resection specimen, no one technique is recommended. At the very least, one should semiquantitatively report lamina propria invasion as *focal* or *extensive* to give urologists some indication as to the likelihood of understaging. We routinely comment, if possible, if the carcinoma invades above or into and below the level of muscularis mucosa. Although the presence of concomitant carcinoma in situ with invasive cancer may be regarded as a less important factor, it has correlated with outcome in studies by Lee et al [4] and van Rhijn et al [5], but was not predictive in the study by Brimo et al [3]. In our practices, we comment on the presence of in situ urothelial carcinoma in papillary tumors when either a separate bladder biopsy is submitted or there is an extensive amount of flat urothelial mucosa adjacent to a papillary tumor in resection specimen. One has to be cautious not to

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