



The WHO Classification 2016 of Tumours in the Urinary System and Male Genital Organs and Impact on the Bladder Cancer

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Abstract

12 years after the previous WHO, a new WHO classification was published in January 2016 (1). Major steps forwards have been made and were included into this new classification based on fundamental research during these last decenie. Histological concepts of the Urothelial Carcinoma (UC) underwent an evolution, the substaging of pT1 tumours is now recommended and breaking news on a molecular level have been made, permitting a novel regard on bladder cancer.

Introduction

In the current diagnosis of UC, histology is still the gold standard. The new WHO classification of « Tumours of the Urinary System and Male Genital Organs » 2016 divides UC into 2 groups: the “Non-invasive UC” and the “Infiltrating UC”. Distinction of low grade and high grade lesions still exist and the previously employed G1-3 should not be used any further. This grading system (low grade-high grade) is admitted worldwide in the pathology community, the advantage is a very good description of the histological features in each group.

The classification also underlines the interest of recognizing variant histology as a predictor of more aggressive tumour behaviour. Some variants are known to be highly aggressive such as the plasmacytoid, micropapillary, sarcomatoid and poorly differentiated UC [1]. Nevertheless some entities are still under recognized and under diagnosed. Reporting these entities is of major interest in regard of the treatment, as with a regard to the molecular classification, some of these subtypes will not respond to cisplatin-based chemotherapies [2,3], which is very important for the patients’ treatment.

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Histological Subtypes

From a histological and morphological point of view, some important changes in the classification of the subtypes have been made.

New histological entities have been added, such as the large nested UC, which displays globally the same problematic as the classical nested carcinoma [4]. Histologically they show important exophytic growth and very few atypia. This group has to be distinguished from the inverted patterns and often displays detrusor muscle invasion. It is important to report detrusor muscle invasion and to recognize this growth pattern for correct treatment.

The lymphoma-like variant which was listed in the WHO 2004 classification has been added into the group of plasmacytoid/signet ring cell/ diffuse UC. This entity is associated in more than 50% with classical high grade UC. The signet ring cell variant was listed in the glandular neoplasm group in 2004, since the concept has changed and this entity is no longer considered as a glandular neoplasm. Most of the time no extracellular mucin is observed and a striking resemblance with plasmacytoid UC exists. All of these carcinomas have diffuse growth patterns, often positive surgical margins, high stage and poor outcome [1,2,5].

Another variant, the clear cell UC, has also been introduced into the UC group. These UC are also called glycogen rich and show cellular clarity, resembling to clear cell carcinomas of the kidney. The growth pattern is mostly invasive; association with carcinoma in situ, papillary components or more classical aspects of UC is common. This entity seems to have aggressive behaviour [6]. Another newly introduced entity is the lipid-rich variant, characterised by large cells with lipoblast-like cells. The component normally accounts for 10-15% of the surface, other more classical aspects of UC are

mostly seen. Their behaviour seems to be also aggressive [7].

The undifferentiated UC group of 2004 has been renamed into “poorly differentiated”. Furthermore several entities, listed separately in the former classification, but not indicated as well separate entities have been summarised in the “Tumours of the Müllerian type” group. Another new section is the urachal carcinoma. This entity is well known, but has never been summarized in a distinct chapter up to now. A separate staging system according to Sheldon should be employed [8]. New chapters have been added in the group of miscellaneous tumours with the “Epithelial tumours of the upper urinary tract”, “Tumours arising in a bladder diverticulum” and “Urothelial tumours of the urethra”.

Substaging of T1 Tumours

The clinical behavior of pT1 tumours is highly variable, and there was an urgent need for a more detailed risk stratification which may include histological subtyping and substaging, although there exist other prognostic factors than the depth of invasion of pT1 are the grade of the lesion, such as multifocality, tumour size and concomitant CIS. For the first time the WHO 2016 also gives a comment on the substaging of T1 tumours considering substaging as clinically relevant, but still no agreement exists about which method should be employed. This decision is a very important step forward. pT1 tumours include a wide range of invasive tumour volumes, since they may consist of just a few scattered individual infiltrating cells to confluent tumour areas that destroy the underlying architecture. The ICCR (International Collaboration on Cancer Reporting) an international working group recently published recommendations on minimal items in a report of a bladder tumour. They suggests in their recommendations to use either depth of invasion in millimetres or total maximum dimension of invasive tumour in millimetres or pT1a/b (invasion above or beyond the muscularis mucosae [9]).

Genetic Alterations

One of the major problems of UC is the extremely heterogenous genetic profile. The most important criterion for optimal cancer treatment is a correct classification of the tumour. During the last three years, several very important progress have been made with a better definition of Urothelial Carcinoma (UC), especially from a molecular point of view. We start having a global understanding of UC, although many details are still not completely understood. Recent studies have made very important steps forward in the understanding of UC. Especially the group around Sjödhahl could show distinct UC groups [10,11]. They could, according to gene expression profiles distinguish 5 groups of UC: Urobasal A, Urobasal B, genomically unstable, infiltrated and squamous cell carcinoma like bladder cancers. Interestingly these tumours showed different

cytokeratin signatures and keratinization-associated antigens. They also display different mutations and FGFR3 gene expression signatures. Furthermore distinct molecular subtypes show different cell adhesion gene signatures.

It seems to be clear that in the very near future UC will not only be treated according to histological grading and staging, but molecular and genetic profiles will play a major role. This will help to select only chemo sensitive patients, but also to avoid heavy treatments to patients who will not benefit from chemotherapy. Nevertheless, histology will keep an important place as it permits quick and low cost diagnosis. Ideally both classifications should probably be employed in the future.

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