The new “Blue Book” of the 2016 World Health Organization (WHO) classification of urogenital tumors contains significant changes, which were discussed at the WHO Consensus Conference in March 2015 in Zurich, Switzerland [1]. The Vancouver consensus conference of the International Society of Urological Pathology (ISUP) provided the basis for much of the 2016 WHO renal tumor classification [2]. The revision of the 2004 WHO renal tumor classification was performed by a large group of uropathologists under consideration of new knowledge on pathology, epidemiology and genetics [3, 4]. This review will summarize the most important changes of the new WHO classification, including changes from existing renal tumor types, novel renal tumors, provisional/emerging tumor entities and the WHO/ISUP grading system for renal tumors.

Important changes from existing WHO-tumor types

1. The new 2016 WHO-classification refers to subtypes that have been named on the basis of predominant cytoplasmic features (e.g. clear cell and chromophobe RCC’s), architectural features (e.g. papillary RCC), anatomical location of tumors (e.g. collecting duct and renal medullary carcinomas), correlation with a specific renal disease background (e.g. acquired cystic disease-associated renal cell carcinomas) as well as molecular alterations pathognomonic for RCC subtypes (e.g. MIT family translocation carcinomas and Succinate Dehydrogenase-deficient renal carcinomas) or familial predisposition syndromes (e.g. hereditary leiomyomatosis and RCC (HLRCC) syndrome-associated RCC). In contrast to the 2004 WHO classification, familial forms of RCC, which also occur in a sporadic form (e.g. clear cell RCC in VHL syndrome patients or chromophobe RCC in patients with Birt-Hogg-Dubé syndrome) are now discussed with the corresponding sporadic tumor types in joint chapters.

2. Multiple publications report no recurrence or metastasis in patients with multilocular cystic renal cell carcinoma [5]. Multilocular cystic renal neoplasm of low malignant potential, therefore, is now the WHO-recommended term for this lesion. Such tumors are defined as tumors composed entirely of numerous cysts with low grade tumor cells
WHO/ISUP grade 1 or 2). The cysts are lined by a single layer of tumor cells with abundant clear cytoplasm. The septa contain at the maximum groups of clear cells but without expansile growth.

3. The entity of papillary renal cell carcinoma has traditionally been subdivided into two types: type 1 and type 2 papillary renal cell carcinomas [6, 7]. It has been accepted that a subset of tumors have mixed histology. Recent molecular studies suggest that type 2 papillary renal cell carcinomas may not constitute a single well-defined entity, but rather individual subgroups with a different molecular background [8]. Papillary renal cell carcinomas with eosinophilic (oncocytic) cytoplasm and oncocytoma-like low-grade nuclei have been called oncocytic papillary renal cell carcinomas. Since tumors with this morphology have not yet been fully characterized, they are not considered an own WHO entity. The Vancouver consensus conference has recommended to diagnose such tumors as type 2 PRCC for the time being [2].

4. Papillary adenomas have been defined until 2015 as tumors measuring ≤ 0.5 cm. The WHO 2016 classification defines papillary adenomas as unencapsulated tumors with papillary or tubular architecture, low WHO/ISUP grade and a diameter ≤ 1.5 cm. The decision to increase the size cut-off was due to available data that unencapsulated grade 1-2 tumors have no capacity to metastasize [9]. However, it is emphasized that a diagnosis of papillary adenoma based on needle biopsy should be made with extreme caution, because the presence of any capsule or grade heterogeneity may not be visualized. Current protocols, which defined papillary adenomas with ≤ 0.5 cm in size state that the presence of papillary adenoma in a donor kidney is not a contraindication for renal transplantation. The new cut-off of ≤ 1.5 cm could have a significant impact on some clinical situations (e.g. small renal papillary tumors detected in transplanted kidneys).

5. Mixed epithelial and stromal tumors (MEST) encompass a spectrum of tumors ranging from predominantly cystic tumors (adult cystic nephromas) to tumors that are more solid. Adult cystic nephroma was previously classified along with pediatric cystic nephroma as a separate entity from MEST. On the basis of similar age and sex distributions and a similar histochemical profile, adult cystic nephroma is now classified within this spectrum of MEST and the WHO renal tumor subcommittee
recommended to use the term “mixed epithelial and stromal tumor family” for both entities. In contrast to adult cystic nephroma, pediatric cystic nephroma is a distinct entity with specific DICER-1 mutations [10].

6. Most carcinoids of the kidney have a poor prognosis with frequent occurrence of metastasis after nephrectomy. The renal tumor subcommittee recommended “renal carcinoids” should be newly designated as well differentiated neuroendocrine tumors of the kidney and simultaneously placed within the group of endocrine tumors encompassing also small cell neuroendocrine carcinomas, large cell neuroendocrine carcinomas as well as paragangliomas (extrarenal pheochromocytoma). The term carcinoid of the kidney obsolete.

**New tumor entities**

Over the last decade several new tumor entities have emerged. Therefore, the WHO working group was entrusted with the responsibility to decide, if enough molecular, clinical follow-up data and pathological data justify the recognition as a new distinct tumor entity within the classification system. The newly recognized epithelial renal tumors in the 2016 WHO classification are HLRCC-associated RCC, SDHB-deficient RCC, tubulocystic RCC, acquired cystic RCC and clear cell papillary RCC. Pediatric cystic nephroma represents a new entity in the group of nephroblastic and cystic tumours occurring mainly in children (see above).

*Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated RCC* are rare tumors occurring in the setting of non-renal leiomyomatosis and demonstrate germline Fumarate hydratase (*FH*) mutations [11]. The tumors have papillary architecture with abundant eosinophilic cytoplasm, large nuclei and very prominent nucleoli with perinucleolar clearing. The prognosis of these tumors is poor [12].

*Succinate dehydrogenase (SDH)-deficient RCC* is composed of vacuolated eosinophilic or clear cells [13, 14]. Immunohistochemistry is a useful tool for their diagnosis, because there is a loss of SDHB expression, a marker of dysfunction of mitochondrial complex II. It presents mainly in young adults and most patients have germline mutations in a *SDH* gene [14]. Most tumors are solid, with a brown, sometimes red cut surface. The most distinctive feature is the presence of cytoplasmic vacuoles. There are sometimes flocculent inclusions. The majority of SDH-deficient RCC have a good prognosis. In cases with sarcomatoid differentiation and necrosis, the prognosis is less favourable.
Tubulocystic RCC is a dominantly cystic renal epithelial neoplasm. Macroscopically, they are composed of multiple small to medium sized cysts and have a spongy cut surface. The nuclei are enlarged with WHO/ISUP grade 3 nucleoli. The cytoplasm has abundant eosinophilic and oncocytoma-like aspects. Only 4 of 70 reported cases showed metastasis to bone, liver and lymph nodes [15-18].

Acquired cystic disease associated RCC occurs in the kidneys of end-stage renal disease and acquired cystic kidney disease [19]. Histologically, they show a broad spectrum with a cribriform/microcystic/sieve-like architecture. They have an eosinophilic and/or clear cytoplasm and prominent nucleoli. Calcium oxalate crystal deposition is common. CK7 is typically not expressed. Most tumors have an indolent behavior.

Clear cell papillary RCC is a renal epithelial neoplasm composed of low grade clear epithelial cells arranged in tubules and papillae with a predominantly linear nuclear alignment away from the basement membrane [19]. They account for up to 5% of all resected renal tumors and arise sporadically, in end-stage renal disease and von Hippel-Lindau syndrome [20, 21]. Some of these tumors were previously referred as renal angioadenomatous tumors. The tumor cells have a characteristic diffuse CK7 positivity and a carbonic anhydrase IX positivity in a cup-like distribution. CD10 is negative or only focally positive. According to current knowledge, these tumors have an indolent behaviour.

Emerging / provisional renal tumor entities

The 2013 ISUP Vancouver classification identified a category of emerging or provisional new entities. Some of these emerging entities have been accepted by the WHO, others are still kept as emerging. The WHO classification noted that although these entities appear to be distinct, these are rare tumors, which are not yet fully characterized by morphology, immunohistochemistry and molecular studies. Therefore, further reports are needed to refine their diagnostic criteria and established clinical outcomes. SDH-deficient RCC was regarded as emerging entity in the Vancouver classification but is now considered to be an established entity. RCC in neuroblastoma survivors was included in the 2004 WHO-classification [22], but it is now recognized that some of these tumors represent MiT-family translocation RCCs [23]. Others are difficult to classify based on the published pathological details. Therefore, it was decided to remove this entity from the 2016 WHO classification, despite they appear to be a distinct variant, which for the purpose of the current classification is considered an emerging entity. Very few thyroid-like follicular RCCs have been described [24, 25]. Most of these tumors have indolent behavior. Less than 10 RCCs associated with ALK-gene rearrangements have been reported in the literature [26-28]. Some of them are medullary
based tumors. Recently, reports of RCC associated with prominent angioleiomyomatous stroma have been published. One term was renal angiomyoadenomatous tumor. If they represent variants of clear cell RCC or clear cell papillary RCC has to be shown [29]. Some tumors occurred sporadically and some are associated with tuberous sclerosis [30]. A recent report identified TCEB1-gene mutations in tumors with this morphology [31].

**Grading of renal tumors**

Many grading systems have been proposed for renal cell neoplasia. The Fuhrman system was the most frequently used grading system in RCC but should not be applied for chromophobe RCC [32]. Further, the Fuhrman system has not been validated for most of the new subtypes of renal carcinoma. For these reasons, the 4-tiered WHO/International Society of Urological Pathology grading system is recommended by the WHO [33]. For grade 1 to 3 tumors, the system defines tumor grade on the basis of nucleolar prominence. Grade 4 is defined by the presence of pronounced nuclear pleomorphism, tumor giant cells, and/or rhabdoid and/or sarcomatoid differentiation. This grading system has been validated for clear cell RCC and papillary RCC. It has not yet been validated for other tumor types due to the small numbers of reported cases.

**Selection of important future issues**

1. The VHL tumor suppressor protein pVHL functions as a tumor suppressor via HIF-dependent regulation in most clear cell RCC. However, the chromosome 3p locus contains up to seven potential ccRCC tumor suppressor genes: VHL, PBRM1, BAP1, SETD2, RASSF1A, TU3A, and DLEC1. The elucidation of the effects of different combinations of mutations on the initiation and progression of ccRCC will be an important future area of research [4].

2. The identification of novel therapeutic agents that are effective against RCC cells that harbor specific genetic alterations is an important ongoing research topic [34]. This includes also emerging immunotherapies targeting immune checkpoints and tumor associated antigens in patients with RCC [35]. In contrast to other solid tumors (e.g. melanoma or lung cancer), there are at present no predictive molecular biomarkers suitable for routine use [36]. The use of such biomarker has to consider the considerable genetic intratumoral heterogeneity with the parallel evolution of multiple tumor clones [37, 38].
3. There has been a remarkable expansion of knowledge on the genetics of renal cancer in the last years. This has led to a greater understanding of the molecular pathogenesis of renal cancer [39]. Such knowledge will be incorporated in a future WHO classification and clarify the position of some emerging renal tumor entities (e.g. TCEB1 mutated RCC; angiomyoadenomatous RCC) or subgroups of papillary RCC [8, 29, 31].

4. The novel WHO/ISUP grading system has been validated for clear cell RCC and papillary RCC, but not for other tumor types [33]. Several grading schemes have been proposed for chromophobe RCC to predict its behavioral outcome [40-43]. It is important to have an internationally accepted chromophobe RCC grading system in the near future.

References:


