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Platinum Opinion

European Association of Urology Guidelines Panel on Renal Cell Carcinoma Update on the New World Health Organization Classification of Kidney Tumours 2022: The Urologist's Point of View

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The Genitourinary Pathology Society (GUPS; https://www.gupathsociety.org/) and the World Health Organization (WHO) [1,2] reviewed the 2016 WHO classification of renal neoplasia [3–5] and provided an update on the entities, including diagnostic criteria, molecular correlates, and updated nomenclature. The fifth edition of the WHO classification of urogenital tumours published in 2022 [6,7] will also be implemented in the European Association of Urology (EAU) guidelines on renal cell carcinoma (RCC) for 2023. The purpose of this update, prepared by the RCC EAU guidelines panel, is to summarise changes in the new WHO classification of renal tumours from a clinician perspective.

RCCs and other renal tumours comprise a broad spectrum of histopathological entities. As a major novelty, the WHO fifth edition introduced "essential and desirable diagnostic criteria" for each entity, including morphological diagnostic criteria, combined with key immunohistochemistry and relevant molecular findings. The availability and use of massive parallel sequencing (next-generation sequencing) introduced molecular diagnostic techniques for characterising several renal entities, resulting in a diagnostic shift from morphology to more molecularly based analysis of renal tumours. Therefore, a molecular-driven renal tumour classification has been introduced in addition to the primarily morphology-based classification. Such molecularly defined epithelial renal tumours include *SMARCB1*-deficient renal medullary carcinoma, *TFE3*- and *TFEB*-altered RCC, *ALK*-rearranged RCC, fumarate hydratase–deficient RCC, succinate dehydrogenase–deficient

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RCC, and elongin C (*ELOC*)-mutated RCC. An overview of all the histological types is shown in Table 1, which is based on the online classification (https://tumourclassification.iarc.who.int/welcome/). The most significant changes in the 2022 WHO classification relate mainly to less common kidney tumours, while the most prevalent tumour types remain largely unchanged.

There are still three main RCC types: clear cell RCC (ccRCC), papillary RCC (pRCC), and chromophobe (ChRCC). No substantial changes were made for ccRCC. Multilocular cystic renal neoplasm of low malignant potential, introduced in the WHO 2016 edition, remains in the WHO 2022 classification as a separate RCC type with indolent behaviour. It is recommended that pRCC is no longer divided into type I and type II pRCC. The former pRCC type I is now referred to as "pRCC of classic pattern". Three additional morphological patterns of pRCC have been introduced: (1) a biphasic (alveolo-squamoid) pattern exhibiting mostly solid growth; (2) papillary neoplasm with reverse nuclear polarity, previously described as "oncocytic low-grade PRCC"; and (3) Warthin-like pRCC that exhibits brisk inflammation mimicking Warthin tumour of the salivary gland. For chRCC, histological grading using the WHO/International Society of Urological Pathology (ISUP) system is not recommended. Sarcomatoid RCC (RCC with sarcomatoid features) is not a specific subtype, but essen-

Table 1 – Classification of renal cell tumours

1	Renal cell tumours			
		01.I	Clear cell renal tumours	
				Clear cell RCC
				Multilocular cystic renal neoplasm of low malignant potential
		01.II	Papillary renal tumours	
				Papillary adenoma
				Papillary RCC
		01.III	Oncocytic and chromophobe renal tumours	
				Oncocytoma of the kidney
				Chromophobe RCC
				Other oncocytic tumours of the kidney
		01.IV	Collecting duct tumours	
				Collecting duct carcinoma
		01.V	Other renal tumours	
				Clear cell papillary renal cell tumour
				Mucinous tubular and spindle cell carcinoma
				Tubulocystic RCC
				Acquired cystic disease–associated RCC
				Eosinophilic solid and cystic RCC
				RCC NOS
		01.VI	Molecularly defined renal tumours	
				TFE3-rearranged RCC
				TFEB-altered RCC (*TFEB*-rearranged RCC and *TFEB* amplified RCC)
				ELOC (formerly *TCEB1*)-mutated RCC
				Fumarate hydratase–deficient RCC
				Succinate dehydrogenase–deficient RCC
				ALK-rearranged RCCs
				SMARCB1-deficient renal medullary carcinoma
2	Metanephric tumours			
				Metanephric adenoma
				Metanephric adenofibroma
				Metanephric stromal tumour
3	Mixed epithelial and stromal tumour family			
				Mixed epithelial and stromal tumour
				Adult cystic nephroma
4	Renal mesenchymal tumours			
		04.I	Adult renal mesenchymal tumours	
				Classic angiomyolipoma/PEComa of the kidney
				Epitheloid angiomyolipoma/epithelioid PEComa of the kidney
				Renal haemangioblastoma
				Juxtaglomerular cell tumour
				Renomedullary interstitial cell tumour
		04.II	Paediatric renal mesenchymal tumours	
				Ossifying renal tumour of infancy
				Congenial mesoblastic nephroma
				Rhabdoid tumour of the kidney
				Clear cell sarcoma of the kidney
5	Embryonal neoplasms of the kidney			
			Nephroblastic tumours	
				Nephrogenic rests
				Paediatric cystic nephroma
				Cystic partially differentiated nephroblastoma
				Nephroblastoma
6	Miscellaneous tumours			
			Germ cell tumours of the kidney	

NOS = not otherwise specified; PEComa = perivascular epithelioid cell tumour; RCC = renal cell carcinoma.

tially represents a pattern of dedifferentiation associated with adverse outcomes and poor cancer-specific survival, irrespective of the underlying RCC subtype; it should be graded as WHO/ISUP grade IV. The term "collecting duct carcinoma" is preferred over the previous "Bellini duct carcinoma". True collecting duct carcinoma is quite rare, and the diagnosis should be made after excluding other tumours, especially the recently described fumarate hydratase–deficient RCC and SMARCB1-deficient RCC, as well as urothelial carcinoma and metastases. A new group called "oncocytic and chromophobe tumours" encompasses oncocytoma and chRCC, as well as "other oncocytic tumours of the kidney", a heterogeneous group of oncocytic tumours that are not classifiable as either oncocytoma or chRCC. Importantly, these tumours are typically indolent, and it is important to distinguish such low-grade oncocytic tumours from the high-grade unclassified RCCs that typically behave aggressively. For multiple/bilateral tumours with intermediate features, associated with Birt-Hogg-Dubé syndrome or other hereditary syndromes, the term "hybrid oncocytic-chromophobe tumours" has been proposed. It is recommended that the term "hybrid" is strictly used for such hereditary oncocytic tumours. However, the group of "other oncocytic tumours of the kidney" has been significantly reduced in the WHO 2022 classification because of the recent recognition of two distinct benign oncocytic tumour entities, low-grade oncocytic tumour and eosinophilic vacuolated tumour. The WHO 2022 classification also cautions against a definite diagnosis of oncocytoma from a needle core biopsy because chRCC can show areas similar to oncocytoma, and because of the heterogeneity of other oncocytic tumours with intermediate features. This statement provides a new dimension to the EAU RCC guideline recommendation to "Offer active surveillance to patients with biopsy-proven oncocytomas, as an acceptable alternative to surgery or ablation" [8]. The 2022 WHO classification also introduced a change in the nomenclature of renal medullary carcinoma, because such carcinomas showed uniform loss of expression of SMARCB1 protein, and have been renamed as "SMARCB1-deficient renal medullary carcinomas". These carcinomas are very rare and aggressive and occur almost exclusively in the renal medulla of young, mostly male patients of African ancestry, who have sickle cell trait or rarely other hemoglobinopathies. Rare patients have also been reported with identical tumours, but without associated haemoglobinopathy, and such tumours have been termed "unclassified RCC with medullary phenotype"; they probably represent subtypes of SMARCB1-deficient medullary carcinomas.

In the previous 2016 WHO classification, *TFE3*-rearranged RCC and *TFEB*-rearranged RCC were grouped together as "MIT family of RCCs", while in the 2022 WHO classification these entities are described separately. Given the recent recognition of *TFEB*-amplified RCCs and their specific demographic predilection and clinical relevance (older patients and worse prognosis) in comparison to *TFEB*-rearranged RCCs, both TFEB RCC types are now grouped together as "TFEB-altered RCCs".

ELOC (formerly *TCEB1*)-mutated RCC was included in the WHO 2022 classification as a new entity. *ELOC*-mutated RCC shows recurrent hotspot mutations of the *ELOC* (*TCEB1*) gene (8q21), encoding elongin C, and this is considered an essential criterion for diagnosing this entity. However, some sporadic RCCs driven by *TSC/mTOR* mutations, referred to as RCC with fibromyomatous (or leiomyomatous) stroma, and a subset of similar tumours in tuberous sclerosis patients can show morphological features that are essentially indistinguishable from *ELOC*-mutated RCCs. To date, fewer than 20 *ELOC*-mutated RCC cases have been described, most of which were indolent; only two metastatic cases have been reported. The name "fumarate hydratase (FH)-deficient RCC" is preferred in the 2022 WHO classification over the previous term "hereditary leiomyomatosis associated renal cell carcinoma" (HLRCC) because these carcinomas show uniform absence of FH reactivity on immunohistochemistry, but patients often do not have a personal or family history of skin and uterine leiomyomas. These carcinomas are often very aggressive and require genetic counselling and regular follow-up via imaging. *SDH*-deficient RCC is associated with germline mutations of the *SDH* gene and represents a rare hereditary RCC. Most cases are indolent, but adverse factors include high-grade transformation, coagulative necrosis, and sarcomatoid transformation, all associated with a high risk of metastasis. *ALK*-rearranged RCC is characterised by *ALK* gene fusion with various genes; approximately 40 cases have been described to date. *ALK*-rearranged RCC is clinically important because of the availability of ALK inhibitor targeted therapies. The great majority of *ALK*-rearranged RCCs are indolent, but cases with an aggressive clinical course with metastatic disease have been reported. For angiomyolipoma (AML) the preferred term in the new classification is classic angiomyolipoma or PEComa (perivascular epithelioid cell tumour) of the kidney. AML subtypes include oncocytic AML and AML with epithelial cysts. Clear-cell papillary renal cell tumour is the new name for the entity previously known as clear-cell papillary renal cell carcinoma. The term "tumour" has replaced the term "carcinoma" because of the uniformly benign behaviour of this entity. Mixed epithelial and stromal tumour encompasses two benign entities: mixed epithelial and stromal tumour of the kidney (MEST) and adult cystic nephroma. MEST is typically solid, and cystic nephroma is typically cystic; on imaging they correspond to Bosniak type III and IIF/IV. Both are overwhelmingly found among women (7:1 ratio). Paediatric cystic nephroma is now included in the group of nephroblastic tumours.

Details on hereditary renal tumours [9] can be found in the chapter on Genetic tumour syndromes of the urinary and male genital tracts [6]. Syndromes associated with kidney tumours are as follows: BAP1 tumour predisposition syndrome, hyperparathyroidism-jaw tumour syndrome, FH-deficient RCC, Birt-Hogg-Dubé syndrome, hereditary pRCC, Cowden syndrome, *SDH*-deficient tumour syndromes, tuberous sclerosis, and von Hippel-Lindau syndrome (type 1 and 2; type 2 is part of hereditary phaeochromocytoma-paraganglioma syndrome).

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