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Review Article

Updates from the 2022 WHO Classification of Kidney Epithelial Tumors

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Abstract

During the past few years, numerous advances have been made in the characterization and categorization of renal tumors, particularly malignant tumors. During these years, new treatment approaches have also been developed, along with the emergence of new molecular data on renal tumors, paving the way for precision diagnostics and therapeutics. The World Health Organization (WHO) Classification of Tumors series for urinary and male genital tract tumors represents the major global platform for updates in the pathology of urological cancers including renal cell carcinoma. The latest WHO classification was published in 2022 and incorporates significant changes from the previous (WHO 2016) classification. The aim of this review is to describe the diagnostic updates and the major changes in the latest classification of kidney epithelial tumors and the rationale behind these changes.

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Introduction

The diagnosis and classification of kidney tumors have undergone significant evolutionary changes over the last few decades. Beginning with two types of renal malignant tumors, the list now includes more than 20 distinct tumor types and it is likely to expand further in the future. Traditionally, the mainstay of diagnosis and classification of these tumors consisted of their morphological features, as in other urologic tumors.[1,2] However, during the past few years, the field of renal tumor pathology has undergone considerable evolution based on the extensive application and improved integration of the histopathology, histochemistry, immunohistochemistry (IHC), and genetics of renal tumors. During this evolution, our understanding of the biological relevance of morphological patterns has expanded, methodologies for grading and staging have been standardized and refined, and the advances of molecular science have opened new possibilities for the prediction of outcome and therapeutic response, paving the way for personalized medicine.[3–5] The World Health Organization (WHO) in collaboration with the International Society of Urologic Pathology (ISUP) has spearheaded the task of updating the diagnostic criteria and classification strategies of kidney tumors. The WHO Classification of Tumors, published as a series of books (popularly known as the WHO Blue Books) and now available online in digital format at https://tumourclassification.iarc.who.int, represents an essential global framework for standardizing the terminology as well as the diagnostic and classification criteria of all tumors of all anatomical sites of the human body. The diagnostic criteria and standards that form the basis of classification are rigorously formulated by careful evaluation and deliberation of the available and emerging evidence by experts in the field in consultation with ISUP.[2,3]

Since the morphology shows significant overlap among the tumors, IHC provides a valuable and cost-effective ancillary tool to use when morphology alone is insufficient for discrimination in such cases. In addition, genetic information has transformed and revolutionized virtually all aspects of tumor pathology, including their diagnosis, classification, and prognosis.[6,7] The application of high throughput molecular profiling has substantially impacted tumor taxonomy and classification of human malignancies, most notably observed in kidney cancer among the urological malignancies.[8–10] As is well known, tumor classification is an evolving and dynamic process, integrating multiple new pieces of information and evidence gathered from enhanced IHC and molecular studies conducted by numerous investigators worldwide. This review focuses on the major modifications in the diagnosis and classification of renal epithelial cell tumors. Mesenchymal and mixed epithelial-stromal as well as pediatric kidney tumors will not be explored. Only the changes in diagnostic criteria or classification will be highlighted, and individual tumors will not be described in detail.

Updates in the classification of renal epithelial tumors

Based on the results of various new genetic and IHC studies on renal epithelial tumors, several important changes have been made in their classification along with the validation of multiple new and clinically important entities in

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Table 1. Summary of most significant changes in the classification of renal cell carcinomas in WHO 2022 classification

Major changes	Examples
Structural reorganization	Creation of five morphological groups and a new category of molecularly defined renal carcinomas
Abolition of subclassification	Papillary RCC (PRCC) is no longer divided into type 1 and type 2 PRCC
Changes in nomenclature	Clear cell papillary renal cell carcinoma renamed Clear cell papillary renal cell tumor; Hereditary leiomyomatosis-associated RCC has been renamed as fumarate hydratase (*FH*)-deficient RCC; *TCEB1*-mutated RCC has been renamed as *ELOC*-mutated RCC
Molecularly defined renal carcinomas	*TFE3*-rearranged renal cell carcinomas; *TFEB*-altered renal cell carcinomas; *ELOC* (formerly *TCEB1*)-mutated renal cell carcinoma; Fumarate hydratase (*FH*)-deficient renal cell carcinoma; Succinate dehydrogenase (*SDH*)-deficient renal cell carcinoma; *ALK*-rearranged renal cell carcinomas; *SMARCB1*-deficient renal medullary carcinoma
Other renal tumors category	Clear cell papillary renal cell tumor; Mucinous tubular and spindle cell carcinoma; Tubulocystic renal cell carcinoma; Acquired cystic disease-associated renal cell carcinoma; Eosinophilic solid and cystic renal cell carcinoma; Renal cell carcinoma NOS
Novel/emerging/ provisional tumors	Thyroid-like follicular carcinoma; Biphasic hyalinizing psammomatous RCC; Low-grade oncocytic tumor; Eosinophilic vauolated tumor

NOS, not otherwise specified; RCC, renal cell carcinoma; PRCC, papillary renal cell carcinoma; WHO, World Health Organization.

the new classification.[11–13] However, even in the latest WHO 2022 classification, the mainstay of the diagnosis and classification of renal tumors remains the morphology.[2] Nevertheless, with increasing availability and widespread use of high throughput molecular techniques, the role of molecular genetics is becoming increasingly important in the arenas of tumor diagnosis, prognosis, and management. Thus, in the WHO 2022 classification, while morphology remains the foundation for the taxonomy, there is, in addition, a group of molecularly defined renal tumors comprising seven distinct entities, which may increase in number in the future. One major nomenclature change includes the replacement of the term histologic "variants" with "subtypes" in all tumor types of all major organs including the kidney. Another major change in this updated classification is that the kidney tumors are re-organized hierarchically and grouped into broad morphology-based categories.[2] Several other significant changes have also been made in the classification of kidney tumors as shown in Table 1. As is obvious from this table, the major changes in the latest WHO 2022 classification of kidney epithelial tumors can be summarized under the following headings:

1. Emphasis on histopathological criteria for classification of renal tumors;
2. Reorganization of tumors into broad categories;
3. Updates/changes in the established tumors;
4. Creation of a new category of molecularly defined renal cancers;
5. Creation of a category of "other renal tumors" and some emerging/provisional tumors.

The above changes are described in detail below.

Emphasis on histopathological criteria

While major and significant advancements have been made in characterizing and classifying renal cell carcinomas (RCCs) during the past two decades using ancillary techniques of IHC and genomic profiling, the morphological and cytological features remain the cornerstone for classifying renal carcinomas.[2,6,7] This is reflected in the dominance of morphological tumor groups in the latest classification in which the majority of tumors are segregated based on morphological and cytological features of tumor cells compared to only one category of molecularly defined tumors. In addition, the diagnostic and prognostic utility of time-tested histopathological features remains of paramount importance in the current management of these tumors (Fig. 1).

Structural reorganization of renal tumors

While in the previous fourth edition of the WHO Blue Books all renal epithelial tumors were lumped together including both benign and malignant types non-hierarchically,[14] in the fifth edition of the WHO classification, these tumors have been organized hierarchically, starting with the benign followed by the malignant tumors.[2] Each tumor type in the WHO 2022 Blue Books is listed within a hierarchical taxonomic classification that follows the format of site, category, family or class, type, and subtype. This was done to structure all the blue books in a unified and systematic manner.[2] The bulk of renal epithelial tumors have been categorized according to their morphological and cytological appearances, such as clear cell renal tumors, papillary renal tumors, etc. Five categories based on morphological features have been identified with one category named "other renal tumors" (Table 2). This approach underscores the primacy and the continuing importance of morphology in the classification of renal epithelial tumors.

Updates/changes in the established renal tumors

A number of changes were introduced to the existing tumor types in the current classification to better reflect recent advances in tumor biology and clinical behavior and to reduce interobserver variability in the diagnosis.[2,7,8,10]

Among these, the most important change includes the elimination of subtyping of papillary RCC (PRCC). Type 1 PRCC is now the classic PRCC. Many tumors previously diagnosed as type 2 PRCC now constitute independent entities and have been moved to other categories. Essential and desirable morphological diagnostic criteria for classic PRCC have been proposed while some novel patterns of PRCC have also been introduced, such as biphasic (alveosquamoid) PRCC, papillary renal neoplasm with reverse nuclear polarity, and Warthin-like PRCC. Some of these subtypes are associated with distinct molecular and immunohistochemical features.[10]

The name of clear cell PRCC has been changed to clear cell papillary renal cell tumor (CCPRCT) in the new WHO 2022 classification due to consistently indolent behavior with no reports of metastasis or aggressive behavior since its first description. It is a low-stage and low-grade tumor with papillary, tubular, and cystic architecture and the tu-

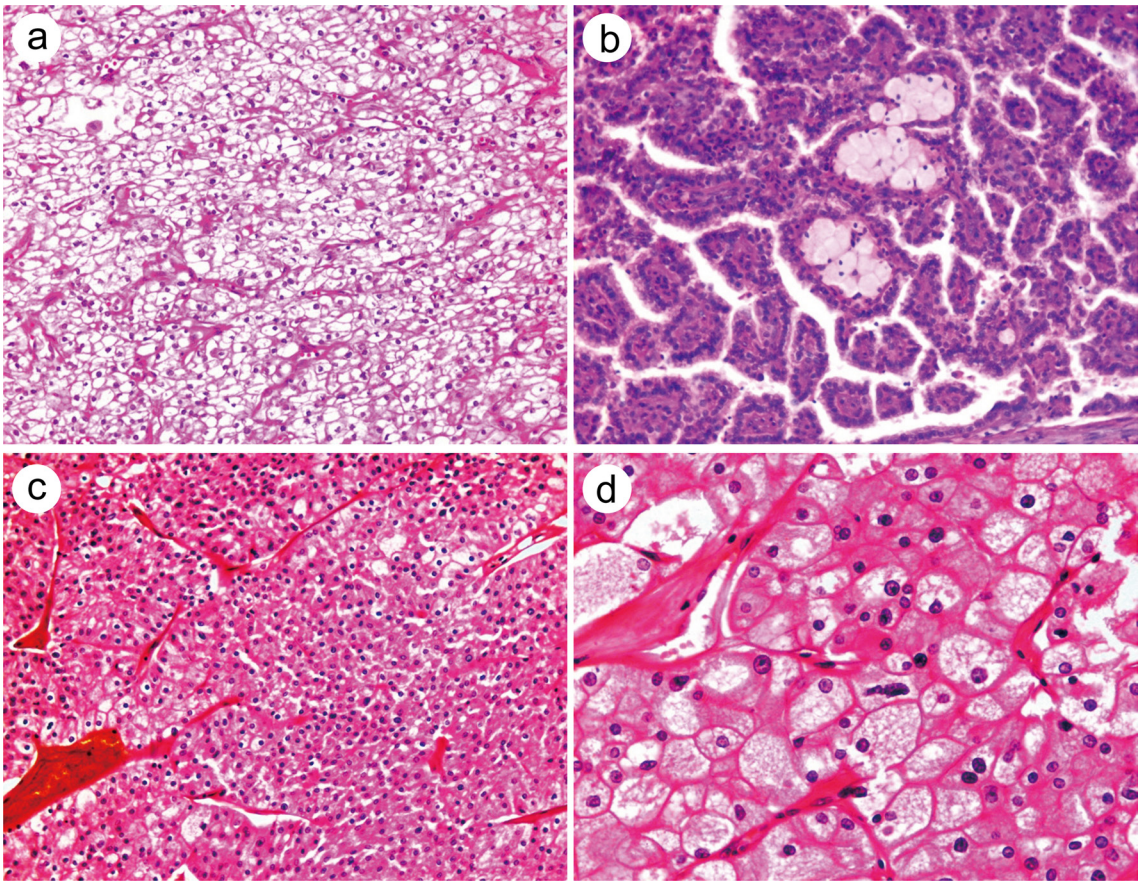

Fig. 1. The microscopic features of the main morphological types of renal cell tumors. (a) The nested arrangement of tumor cells with clear cytoplasm surrounded by fibrovascular septae in a case of clear cell renal cell carcinoma (RCC). The tumor cells have abundant cytoplasm and low-grade nuclei. Tumor cell nests are surrounded by incomplete fibrovascular septae (H&E, magnification: 200×). (b) RCC with papillary architecture in papillary RCC. Some of the papillary cores contain foamy histiocytes in their center (H&E, magnification: 200×). (c) Medium-power view of oncocytoma characterized by nests and sheets of eosinophilic cells with round centrally located nuclei with little pleomorphism (H&E, magnification: 200×). (d) Chromophobe RCC with tumor cells arranged in solid sheets separated by thin septae. Two tumor cells have raisinoid nuclei (H&E, magnification: 400×). H&E, hematoxylin and eosin.

mor cells have clear cytoplasm with linearly aligned luminally placed nuclei.

Chromophobe RCC (ChRCC) can have non-conventional morphology with trabecular, alveolar, papillary, microcystic, or cystic architecture, but all these phenotypes typically maintain CK7/CKIT co-expression, characteristic chromosomal monosomies, and favorable prognosis.[15–17] A new entity of "other oncocytic tumors" of the kidney has been added with oncocytoma/chRCC-like features to accommodate tumors that do not fall clearly into one of these tumor types. "Hybrid oncocytic/chromophobe tumor (HOCT)" has been suggested as the name for eosinophilic/oncocytic tumor with borderline or mixed morphological features of oncocytoma and ChRCC or "ambiguous architectural or cytological features" that cannot be ascribed to either oncocytoma or ChRCC.[18] These tumors can occur in a hereditary setting, such as Birt-Hogg-Dube syndrome, or sporadically (Fig. 2a).

The name "RCC-Unclassified" has been changed to "RCC-NOS" in this classification. This designation is assigned to tumors that do not fall into any one of the other categories.[2,10]

An unequivocal diagnosis of some tumor entities such as multilocular cystic renal neoplasm of low malignant potential

Table 2. The main diagnostic categories of renal cell tumors according to WHO 2022 classification

Diagnostic categories	Main basis of classification
Clear cell renal tumors	Morphology, histochemistry, and IHC
Papillary renal tumors	Morphology, histochemistry, and IHC
Oncocytic and chromophobe renal tumors	Morphology, histochemistry, and IHC
Collecting duct tumors	Morphology, histochemistry, and IHC
Other renal tumors	Morphology, histochemistry, and IHC
Molecularly defined renal carcinomas	Molecular genetic alterations

IHC, immunohistochemistry; WHO, World Health Organization.

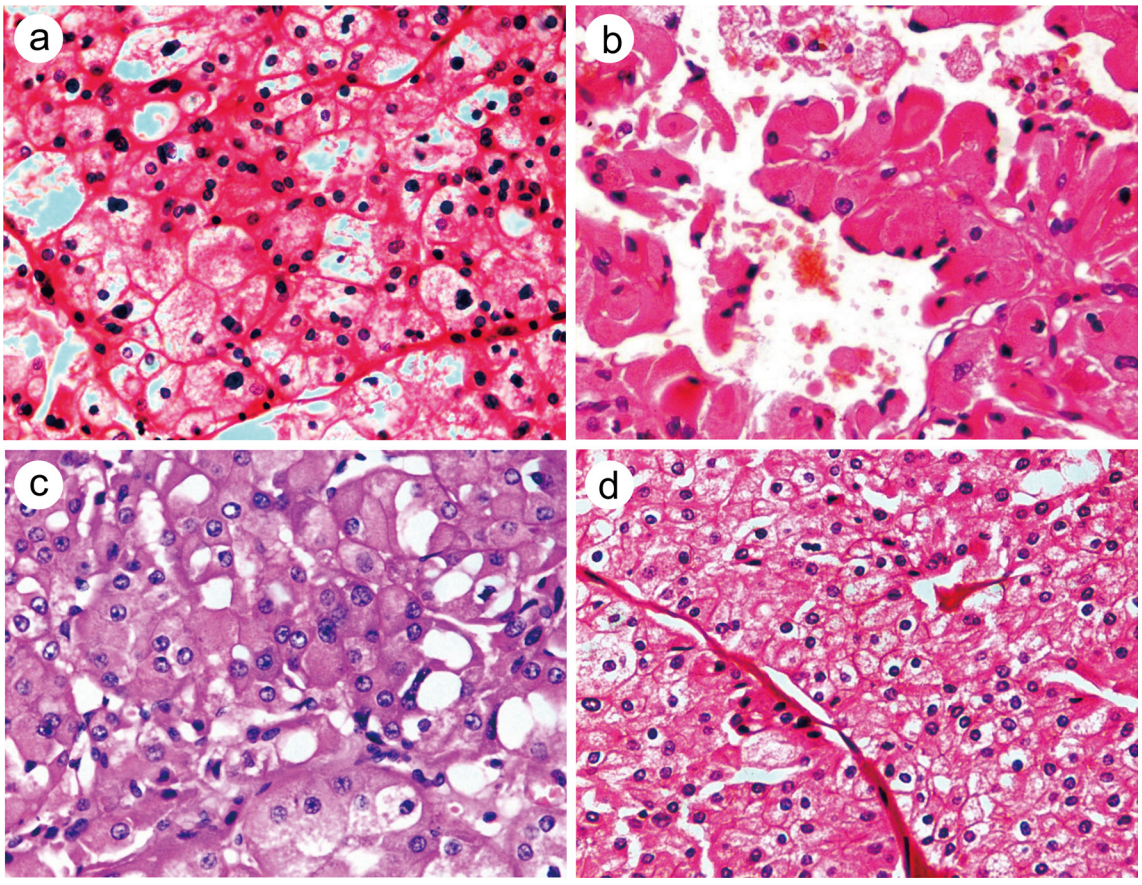

Fig. 2. The main morphological types of some emerging/novel renal cell tumors. (a) The predominantly solid arrangement of tumor cells with eosinophilic cytoplasm with scattered large nuclei in an example of a hybrid oncocytic/chromophobe tumor (HOCT) (H&E, magnification: 400×). (b) Renal tumor with papillary architecture lined by eosinophilic tumor cells with abundant cytoplasm and bland luminally-oriented nuclei in an example of eosinophilic papillary tumor with reverse nuclear polarity (H&E, magnification: 400×). (c) The tumor cells in an eosinophilic vacuolated tumor (EVT) show large intracytoplasmic vacuoles and round to oval nuclei with prominent nucleoli (H&E, magnification: 400×). (d) The tumor cells in a low-grade oncocytic tumor (LOT) show abundant eosinophilic cytoplasm and round to oval nuclei with perinuclear halos around many nuclei (H&E, magnification: 400×). H&E, hematoxylin and eosin.

(MCNLMP) should not be made on needle biopsy alone, as this method provides limited sampling and the features of MCNLMP overlap with those of cystic CCRCC and even solid CCRCC with a focal cystic/degenerative component. Additionally, CCPRCT can manifest as a nearly entirely cystic tumor and mimic MCNLMP.

Creation of a new category of molecularly defined renal tumors

In the fourth WHO classification (2016), both morphological and molecular tumor types (which were few then) were intermingled (Table 3). In the WHO 2022 classification, they have segregated these two groups of tumors and added a new category of molecularly defined tumors (Table 2). This tumor category was introduced in renal tumors for the first time in the latest classification. It comprises a heterogeneous group of tumors showing highly varied morphologies often with multiple patterns but unified by the requirement of molecular markers for diagnosis. The molecular approach to classify renal tumors was first introduced in the 2004 WHO classification defined on the basis of a specific molecular alteration (e.g. translocation-associated RCC). In the 2016 WHO classification, a few more molecularly defined entities were introduced. However, these were intermingled with the morphological types (Table 3). In the current WHO classification, a separate category has been created for molecularly defined renal tumors and the number of tumors has also increased in this category (Table 1). This category consists of a heterogeneous group of neoplasms with significant morphological overlap with other renal tumors.[19–21] Molecularly defined renal carcinomas include *TFE3*-rearranged RCCs, *TFEB*-rearranged and *TFEB*-amplified RCC, *ELOC* (formerly *TCEB1*)-mutated RCC, *ALK*-rearranged RCCs, *SMARCB1 (INI1)*-deficient RCC, and others. Their definitive diagnosis requires molecular tests such as next-generation sequencing (NGS), reverse transcriptase-polymerase chain reaction (RT-PCR), RNA sequencing (RNAseq), or fluorescent in situ hybridization (FISH).

Some tumors in this molecularly defined category have been renamed, e.g. the MiT family of translocation RCCs has been split into two distinct entities, namely, TFE3-rearranged RCC and TFEB-altered RCC. Similarly, hereditary leiomyomatosis-associated RCC has been renamed as fumarate hydratase (FH)-deficient RCC. Renal medullary carcinoma has been given a molecularly defined name as SMRCB1 (INI1)-deficient renal medullary carcinoma and moved to the molecularly defined tumors category. Other entities included are novel or new entities such as *ALK*-rearranged RCCs. Other molecularly defined entities have been retained as such with no change in their nomenclature or criteria such as succinate

Table 3. WHO 2016 classification of renal epithelial tumors

Main tumor types	Shortcomings of classification
Clear cell renal cell carcinoma (CCRCC)	Haphazardly arranged tumor types
Multilocular cystic renal neoplasm of low malignant potential (MCNLMP)	Mixture of benign and malignant tumors
Papillary renal cell carcinoma (PRCC)	Mixture of morphologic and molecular types of tumors
Hereditary leiomyomatosis and renal cell carcinoma (RCC)-associated RCC	
Chromophobe renal cell carcinoma(ChRCC)	
Collecting duct carcinoma	
Renal medullary carcinoma	
MiT family translocation RCCs	
Succinate dehydrogenase-deficient renal carcinoma	
Mucinous tubular and spindle cell carcinoma	
Tubulocystic RCC	
Acquired cystic disease-associated RCC	
Clear cell PRCC	
RCC, unclassified	
Papillary adenoma	
Oncocytoma	

WHO, World Health Organization.

hydrogenase-deficient RCC.

The increasing emphasis on molecular characterization underscores the need for suitable auxiliary technology in pathology laboratories, particularly in developing countries. The provision of high-quality IHC and molecular tests has become crucial for accurate diagnosis, classification, prognosis, and prediction of malignant tumors.

Creation of "other renal tumors" category and some novel, emerging/provisional tumors and categories

The category of "other renal tumors" was created to lump together all renal tumors that could not be placed under the aforementioned morphological or molecular categories. It is a heterogeneous group and does not represent a specific entity. In essence, it represents primarily a clinical management tumor category, rather than a specific diagnosis or entity. It also includes some novel entities such as eosinophilic solid and cystic RCC (ESC RCC) and some emerging/provisional tumors.[2,10,20]

The latter tumors are not yet included in the WHO 2022 classification but have been discussed. Other emerging tumors include thyroid-like follicular carcinoma, biphasic hyalinizing psammomatous RCC, low-grade oncocytic tumor (LOT), eosinophilic vacuolated tumor (EVT), and papillary renal neoplasm with reverse polarity. A brief description of the main tumor types in this category follows.

ESC RCC is a novel distinct entity in the "other renal tumors" category. This tumor was originally described in patients with tuberous sclerosis complex (TSC), but it can occur sporadically due to TSC1 or TSC2 mutations. It is an indolent tumor affecting women more commonly than men, with only rare reported metastases. It has a solid and cystic architecture, voluminous eosinophilic cytoplasm, and coarse basophilic cytoplasmic stippling. CK20 and cathepsin K are positive and there is a lack of CK7/CD117 expression.

Papillary renal neoplasm with reverse polarity was formerly considered a subtype of PRCC. It is an eosinophilic tumor with branching papillary architecture and reverse polarity of low-grade nuclei (Fig. 2b). It stains positive for GATA3 and negative for vimentin and shows variable results for alpha methylacyl CoA racemase (AMACR). It exhibits recurrent mutations of KRAS and lacks trisomy 7/17.

EVT is characterized by solid growth, cytoplasmic vacuolization, prominent nucleoli (Fig. 2c), entrapped tubules, large vessels at the periphery of the tumor, a CK7-/CD117+ immunoprofile, and mutations in mammalian target of rapamycin (mTOR) pathway genes.

LOT is also a low-grade tumor with solid architecture and regular, even, bland low-grade oncocytoma-like nuclei but with perinuclear halos (Fig. 2d). On immunohistochemistry, it exhibits CK7+/ CD117- and FOX1- immunoprofile while on molecular genetic analysis, it shows mutations in mTOR pathway genes.

Conclusions

In conclusion, considerable advances have been made in the diagnosis, classification, and prognostication of tumors of the genitourinary organs with important input from molecular studies and IHC markers. The new classification has better organized tumors according to morphological features as previously, the morphological and molecular types were intermingled. The WHO/ISUP grading has now been recommended for all RCCs and there is a need for both urologic pathologists and urologists to keep abreast of these advances to improve patient care.

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Conflict of interest

None to declare.

Author contributions

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