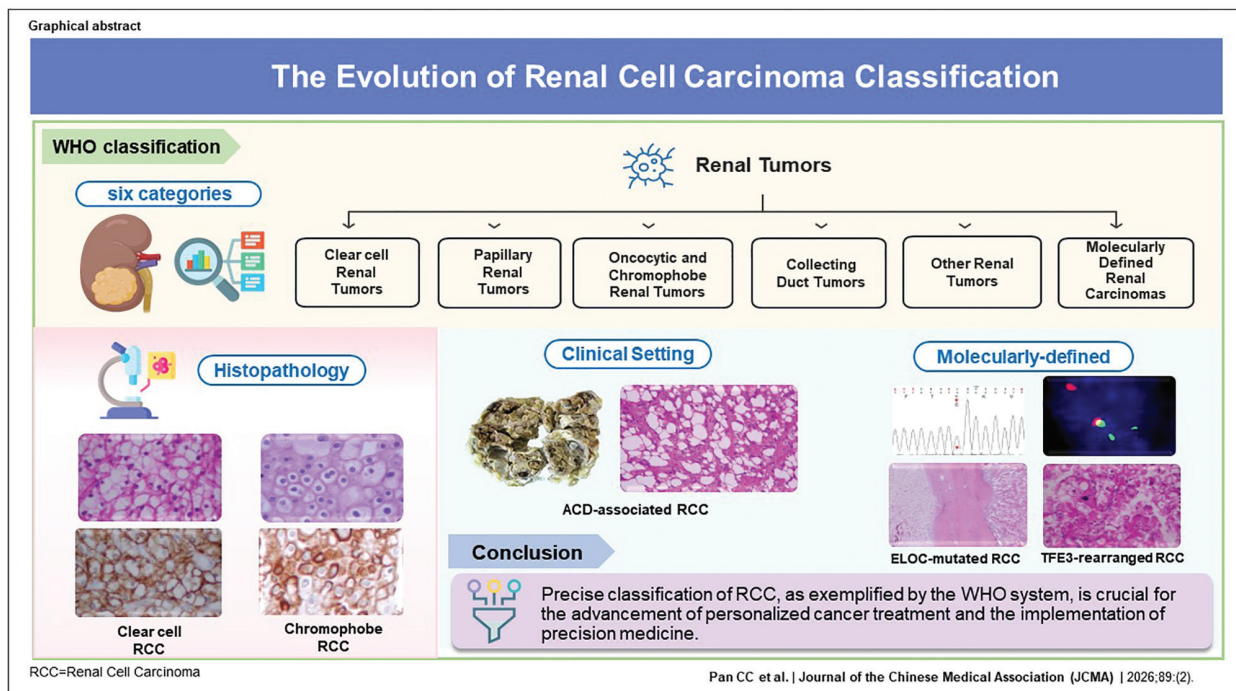


The evolution of renal cell carcinoma classification

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Abstract

Precise classification of diseases is essential for precision medicine to develop efficient, personalized treatments for cancer. Progress in renal cell carcinoma (RCC) classification is a paradigm that demonstrates how precise classification is achieved. RCC classification has evolved from purely morphological criteria to the sophisticated application of various laboratory modalities. With advancing techniques and multi-institutional collaboration, the latest World Health Organization (WHO) classification takes into account decades of studies on the nature of RCC, and is subsequently divided into six categories: clear cell renal tumors, papillary renal tumors, oncocytic and chromophobe renal tumors, collecting duct tumors, other renal tumors, and molecularly defined renal carcinomas. This review provides a historical perspective on how the current WHO classification was attained, followed by a compendium of different RCC types and their salient characteristics, including histopathological features, clinicopathological correlations, and molecular distinctiveness. This information should be shared among pathologists and clinicians to better translate pathological findings into effective clinical practice in terms of diagnosis, prognostication, and therapeutic planning.

Keywords: Classification; Renal cell carcinoma; WHO

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Lay Summary: Precision management requires a precise diagnosis. This is particularly true for the diagnosis and treatment of cancer. Renal cell carcinoma (RCC) is not a single disease but a variety of tumors with different characteristics. Traditionally, the pathological diagnosis of RCC is based on the morphological features observed under a microscope. However, with decades of advances in techniques and collaborative studies, many laboratory methods, such as immunohistochemistry and molecular studies, have been introduced. The latest World Health Organization (WHO) classification categorizes RCC into several groups based on histological characteristics, clinicopathological correlations, and molecular mechanisms. This review describes the evolution of RCC classification and provides a concise overview of the various types of RCC included in the latest WHO classification.

1. INTRODUCTION

Categorization is a human function. Pathology is no exception. Precise classification facilitates a better understanding of diseases that may have clinical implications and warrant appropriate treatment modalities. Progress in renal cell carcinoma (RCC) classification has led to this goal. RCC is by no means a single disease but a constellation of neoplasms arising from different parts of the renal tubules with varying molecular oncogenesis and divergent phenotypes. This classification has evolved from purely morphological observation to clinicopathological correlation, incorporating ancillary ultrastructural, immunohistochemical, and sophisticated molecular techniques.

This review provides a historical perspective on RCC classification and a compendium of RCCs, with their salient properties outlined over the past decades. Table 1 summarizes the nomenclature for each classification.

2. HISTORIC BACKGROUND

Miriell et al reported the first case of RCC in 1810. König put forth the first classification in 1826, solely based on gross

morphology, categorizing tumors as fungoid, medullary, scirrhous, and steatomatous.¹ He had already observed the fat-containing appearance of clear cell RCC and denoted these tumors as steatomatous. He might also have observed a desmoplastic reaction in high-grade tumors, described as scirrhous. Notably, the fungoid and medullary types may have represented urothelial carcinomas.

Paul Albert Grawitz, the assistant of the eminent Rudolf Virchow, designated RCC as hypernephroma because he assumed a derivation from intrarenal adrenal rests due to the resemblance of clear cells to adrenocortical zona fasciculata under a microscope.¹ Although this postulation was incorrect, the terms hypernephroma and Grawitz tumor remained in the medical literature for a time to commemorate his contribution.

2.1. WHO 1981 classification

In 1981, the World Health Organization (WHO) published the first edition of *Histologic Typing of Kidney Tumors*, the so-called WHO blue book.² There were only two types of malignant epithelial tumors of the renal parenchyma: RCC and other types. However, the major features of RCC, including acinar, tubular, cystic, and papillary features, are described in the text. The term clear cell is used to describe the abundant intracytoplasmic lipids and glycogen, which are recognized as the most common features. Granular cell and spindle cell variants have also been reported. Remarkably, the photographs in the book already depict most RCC subtypes, even without a clear definition.

2.2. Mainz classification

The Mainz classification³ proposed by Thoenes et al can be regarded as the first comprehensive RCC classification. RCC was subtyped as clear, chromophobe, chromophilic, pleomorphic, or oncocytic based on histological, histochemical, and electron microscopic characteristics. Chromophilic RCC, now called papillary RCC, was further divided into basophilic and

Table 1
Nomenclature of RCC in each classification

Mainz	Heidelberg	WHO 1998	WHO 2004	WHO 2016	WHO 2022
Clear	Common/conventional	Clear cell Cyst-associated	Clear cell Multilocular clear cell RCC	Clear cell Multilocular cystic renal neoplasm of low malignant potential	Clear cell Multilocular cystic renal neoplasm of low malignant potential
Chromophobe	Chromophobe	Chromophobe	Chromophobe	Chromophobe	Chromophobe
Chromophilic	Papillary	Papillary	Papillary	Papillary	Papillary
Basophilic			Type 1		
Eosinophilic			Type 2		
Spindle-shaped	X	Spindle cell	X	X	X
Oncocytic	X	Granular cell	X	X	X
	Collecting duct	Collecting duct	Collecting duct Renal medullary Xp11 translocation	Collecting duct Renal medullary MiT family translocation	Collecting duct SMARCB1-deficient medullary TFE3-rearranged TFEB-altered
			Neuroblastoma-associated	X	X
			Mucinous tubular and spindle cell	Mucinous tubular and spindle cell	Mucinous tubular and spindle cell
				SDH-deficient	SDH-deficient
				Tubulocystic	Tubulocystic
				ACD-associated	ACD-associated
				Clear cell papillary RCC	Clear cell papillary renal cell tumor
				HLRCC syndrome-associated	HLRCC syndrome-associated
					FH-deficient
					Eosinophilic solid and cystic
					ALK-rearranged
					NOS
	Unclassified	X	Unclassified	Unclassified	

HLRCC = hereditary leiomyomatosis and renal cell carcinoma; NOS = not otherwise specified; RCC = renal cell carcinoma; WHO = World Health Organization.

eosinophilic variants, corresponding to type 1 and type 2 papillary RCC. The authors also proposed a three-tiered grading system. They correctly noted that eosinophilic (type 2) chromophilic/papillary RCCs were at least grade 2, an observation that still holds true today. Chromophobe RCC was defined for the first time, and 3 years later, the same group of authors published a series and suggested subclassifying them into classic and eosinophilic variants.⁴ It was not until 1995, almost a decade after the proposal of the Mainz classification, that chromophobe RCC gained wide acceptance as a distinct entity.⁵

2.3. Heidelberg classification

A collaborative workshop involving 16 renowned uropathologists published the Heidelberg classification of RCC in 1997.⁶ Several concepts were proposed to reflect the accumulated findings regarding the genetics of RCCs. Because the so-called granular RCC overlaps with clear cell RCC, and granular features may also exist in other types, granular RCC was deleted from the classification because of the lack of distinction as a specific type. In addition, clear cell RCC does not always exhibit clear cytoplasm, and the term clear cell RCC was changed to common or conventional RCC. However, this renaming was not welcomed and was later abandoned. Second, the term chromophilic RCC was not favored by most participants. Therefore, papillary RCC was considered to be of this type. Finally, the term sarcomatoid or spindle cell RCC is not recommended, given that sarcomatoid changes can be observed in every type of RCC as a high-grade transformation. A tumor should be classified according to the best-differentiated element; sarcomatoid change should be reported as a secondary feature due to its significant prognostic implications. If a tumor is entirely composed of a sarcomatoid component, it should be designated as RCC, unclassified. Chromophobe RCC and collecting duct carcinoma have previously been accepted as distinct entities.

2.4. WHO 1998 classification

The WHO published the second edition of *Histological Typing of Kidney Tumors* in 1998.⁷ It was an interim product. Six years later, the WHO revised the format of the blue books on a large scale. The 1998 WHO classification returned the name to clear-cell RCC instead of common or conventional RCC, as proposed by the Heidelberg classification. The terms papillary, chromophobe, and collecting duct renal RCCs have been preserved. This edition maintains granular cell and spindle cell carcinomas on the list.

2.5. WHO 2004 classification

The WHO 2004 third edition⁸ was a breakthrough. This edition transformed the pocketbook of previous editions, in which only concise outlines were provided, into a comprehensive volume incorporating all available neoplasms with detailed descriptions of each entity, of which a full chapter is given with sections on definition, epidemiology, clinical and pathologic features, as well as genetics, prognosis, and management. RCC classification generally follows the Heidelberg classification scheme, with clear cell, papillary, chromophobe, and collecting duct RCCs as the major types. Multilocular cystic RCC, renal medullary carcinoma, or mucinous tubular and spindle cell carcinoma were included in the diagnostic list. This edition began to include molecularly defined variants, such as RCC associated with Xp11.2 translocation.

2.6. ISUP classification

In 2013, the International Society of Urological Pathology (ISUP) was entrusted with the responsibility of reviewing available literature and making recommendations regarding additions,

changes, and refinements to the classification of RCC.⁹ A series of internationally collaborative consensus meetings was organized to address issues related to diagnosis, prognosis, and molecular findings. In addition to those described in the previous WHO classification, five additional entities were added to the diagnostic list, and three emerging entities were suggested. The ISUP consensus not only provides solid guidelines for pathology practice but also lays the foundation for further research.

At the consensus conference, a novel grading system (ISUP nucleolar grading) was formally proposed.¹⁰ The previously widely used Fuhrman grading requires simultaneous assessment of nuclear size, nuclear shape, and nucleolar prominence. However, in practice, most pathologists only evaluate nucleolar size while disregarding the other features. At the conference, a consensus was reached that the assessment of nucleolar size was practical and sufficient for prognostication.

2.7. WHO 2016 and 2022 classification

The diagnostic list continued to grow in the 2016 fourth edition,¹¹ which generally adopted the ISUP classification. Finally, the list was expanded to 19 types in the fifth edition (2022).¹² These tumors were separated into six categories: clear cell renal tumors, papillary renal tumors, oncocytic and chromophobe renal tumors, collecting duct tumors, other renal tumors, and molecularly defined renal carcinomas.

3. HISTOLOGICALLY-DEFINED RCC

3.1. Clear cell RCC

Clear cell RCC is the most common type of RCC. Clear cell RCC is a well-known prototype of a molecularly driven neoplasm¹³; however, molecular confirmation is not necessary for the pathologic diagnosis, as most cases can be diagnosed based on histology. More than 90% of clear cell RCCs have inactivation alterations involving *VHL*, accompanied by 3p loss, which is compatible with the double-hit theory of tumor suppressor genes. High-grade tumors harbor mutations in the adjacent areas of *VHL*, including *SETD2*, *BAP1*, and *PBRM1*, as well as wider chromosomal imbalances.¹⁴ These accumulated mutations are consistent with spindle or sarcomatoid transformation.

3.2. Papillary RCC

Papillary RCC is the second most common type of RCC after clear cell RCC. It is well recognized that papillary RCCs exist in two forms.³ Type 1 is chiefly composed of uniform cells with low-grade nuclei and scant cytoplasm, imparting a basophilic appearance. Type 2 tumors tend to have high-grade nuclei and abundant granular cytoplasm with pseudostratification, creating an eosinophilic appearance. Generally, patients with type 1 tumors have a better prognosis than those with type 2 tumors.

TCGA data revealed greater homogeneity of type 1 tumors regarding involvement of the *MET* pathway.¹⁵ Type 2 tumors are diverse in molecular mechanisms. Many tumors formerly classified as type 2 papillary RCC were reclassified under different diagnoses. Currently, type 2 papillary RCC is considered a diagnosis of exclusion. The WHO 2022 classification no longer recommends such subdivision.¹² Grading is sufficient to convey prognostic information.

3.3. Chromophobe RCC

Classic chromophobe RCC is not difficult to diagnose based on its distinctive cytomorphology—such as thick cell borders, perinuclear halos, and resinoid nuclei⁴—as well as typical overexpression of CD117, CK7, and MOC31.^{16,17} Differential diagnosis may be challenging in cases with overlapping features of eosinophilic variants with renal oncocytoma. Chromophobe

RCC and renal oncocytoma are thought to exist on a spectrum, although the former is malignant and the latter is benign.

A recent debate surrounding the hybrid tumor has arisen, especially for those that are related to Birt-Hogg-Dubé syndrome.¹⁸ The term low-grade oncocytic tumor¹⁹ was coined to describe tumors with borderline morphology not entirely consistent with the typical immunoprofile; among them, high-grade oncocytic tumor²⁰ or eosinophilic vacuolated tumor²¹ have been suggested to describe cases with greater atypia. The 2022 WHO blue book does not endorse these esoteric terms, but instead classifies them under the broader category of other oncocytic tumors.²²

3.4. Others

Other types of RCC are defined primarily by histologic characteristics, including mucinous tubular and spindle cell carcinoma,²³ which is composed predominantly of bland-looking spindle cells and long tubules in a myxoid stroma. Mucinous tubular and spindle cell carcinoma is an indolent tumor that can be distinguished from spindle cell or sarcomatoid RCC.

Tubulocystic carcinoma²⁴ is characterized by Swiss cheese-like histology and grade 3 nucleoli. Notably, tubulocystic patterns must be exclusive. If solid or poorly differentiated foci are present, other possibilities—such as fumarate hydratase (FH)-deficient RCC—should be considered.²⁵

Eosinophilic solid and cystic RCC²⁶ is characterized by a solid and cystic architecture, coarse granular cytoplasm, and focal-to-diffuse immunoreactivity for CK20. Tumors usually harbor mutations in the TSC genes.²⁷

4. RCC DEVELOPING IN SPECIFIC CLINICAL SETTINGS

Acquired cystic disease–associated RCC develops exclusively in patients with acquired cystic renal disease.²⁸ It does not occur in patients with noncystic end-stage kidney disease. The tumor typically shows grade 3 eosinophilic cells with a cribriform pattern. Intratumoral oxalate crystals are common.²⁹

Clear cell papillary renal cell tumor (formerly called clear cell papillary RCC) has been described as the second most common renal neoplasm in patients with end-stage kidney disease.²⁸ Nevertheless, later experience shows that clear cell papillary renal cell tumors frequently arise in sporadic settings.³⁰ Whether the tumor is synonymous with renal angiomyoadenomatous tumor, which possesses a higher proportion of leiomyomatous stroma, remains unclear. Currently, they are considered different manifestations of the same neoplasm.³¹ Cumulative evidence demonstrates indolent behavior;³² consequently, the tumor is no longer regarded as a carcinoma.

The 2004 WHO classification described a so-called RCC associated with neuroblastoma, which was believed to occur in long-term survivors of childhood neuroblastoma.³³ This entity was removed in the WHO 2016 classification due to the heterogeneity of these tumors, which no longer warrant classification as a single entity.

5. MOLECULARLY-DEFINED RCC

5.1. ELOC-mutated RCC

An integrated molecular study identified *ELOC* mutations (formerly *TCEB1*) in *VHL*–wild-type cases of clear cell RCC.³⁴ The *ELOC*-mutated RCCs often contain thick leiomyomatous stroma within the tumor and express CK7 focally.³⁵ They may sometimes be confused with clear cell papillary renal cell tumor, and also with a subset of RCCs with similar histology but associated with mutations in genes of the

mTOR pathway.³⁶ GPNMB immunostaining is considered helpful in the differential diagnosis between *ELOC*-mutated RCC (GPNMB-negative) and *TSC1/2/MTOR*-mutated cases (GPNMB-positive).³⁷ However, mTOR pathway alterations are not lineage-specific and may occasionally be detected in almost every type of high-grade RCC as part of clonal evolution.

5.2. RCC associated with alteration of genes in MiT family

The discovery of renal tumors associated with the rearrangement of the MiT gene family is a significant advance in the field of uropathology.^{38,39} Such tumors were first recognized in pediatric patients. They are now also well-documented in adults.⁴⁰ The fusion genes have been subsequently identified, mostly involving *TFE3* with a variety of partners. Another subset involves *TFEB*, either translocated with *MALAT1*⁴¹ or amplified.⁴² Some of these tumors may express melanocytic markers and melanin pigments. The morphology is determined by different fusion partners and becomes so variable that none of the histological patterns are pathognomonic.⁴³ Definitive diagnosis often requires confirmation of the hallmark gene alteration through immunohistochemistry for the expression of TFE3 or TFEB, fluorescence in situ hybridization, or sequencing. Notably, *TFE3*-rearrangement is also present in a subset of perivascular epithelioid cell tumors (PEComas),⁴⁴ a mesenchymal neoplasm with unknown histogenesis. A hypothesis regarding bidirectional epithelial and melanocytic differentiation has been proposed.⁴⁵

5.3. RCC associated with gene mutations in Krebs cycle

The recognition of *FH*-deficient RCC is a paradigm of disease characterization.⁴⁶ It was first seen as an element of hereditary leiomyomatosis and RCC syndrome, and was initially interpreted as papillary RCC. TCGA analysis segregated a CpG island methylator phenotype with consistent FH biallelic inactivation and uniformly poor prognosis.¹⁵ Histologically, FH-deficient RCC comprises eosinophilic cells in mixed papillary, cribriform, and solid patterns. Prominent inclusion-like large nucleoli are also commonly observed. The diagnosis can be readily validated by the loss of FH expression and immunohistochemical overexpression of 2SC.⁴⁷

Succinate dehydrogenase (SDH)-deficient RCC involves another member of the Krebs cycle.⁴⁸ This type shows distinctive morphological features, including pink, bland-looking eosinophilic cells with vacuolated or flocculent cytoplasm. *SDHB* was the most commonly mutated gene, followed by *SDHA* and *SDHC*. Since all types of SDH mutations result in SDHB underexpression, immunostaining for SDHB can be used as a reasonable screening tool.

In addition to FH and SDH, mutations involving *IDH2*, a member of the Krebs cycle, have been reported.⁴⁹ The *IDH2*-mutated RCC exhibits a biphasic pattern of small tubular cells and sheets of pink polygonal cells.

5.4. Others

Finally, the 2022 WHO blue book lists two additional rare molecularly defined RCCs: *ALK*-rearranged RCC⁵⁰ and *SMARCB1* (*INI1*)-deficient renal medullary carcinoma.⁵¹ The diagnoses of these tumors may be confirmed by surrogate immunohistochemistry for ALK or SMARCB1 proteins. Both have sickle cell trait-associated and sporadic forms. The fusion type in *ALK*-rearranged RCCs linked with sickle cell trait was *VCL::ALK* in all reported cases, whereas fusion partners other than *VCL* were observed in non-hemoglobinopathic cases. Secondary SMARCB1 loss has been reported in other types of RCC, especially dedifferentiated or sarcomatoid RCC.⁵² Such cases should be diagnosed according to the underlying morphological or genetic subtype.

For tumors not associated with hemoglobinopathies but showing complete loss of SMARCB1, a term such as unclassified RCC with medullary phenotype may be appropriate.

6. THERAPEUTIC CONSIDERATION

Curative surgical intervention is the mainstay of treatment for localized RCC. Patients with advanced disease may be eligible for adjuvant therapy. Therefore, different treatment regimens must be designed to address the heterogeneous oncogenesis of RCC. A series of trials combining tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) has been conducted, targeting clear cell RCC. Most trials stratified risk using traditional clinicopathological parameters—such as stage, grade, or presence of sarcomatoid differentiation—without incorporating molecular signature.⁵³

However, data on non-clear cell RCC are limited. Biomarker-driven trials have shown encouraging efficacy of crizotinib in *MET*-mutated papillary RCC.⁵⁴ FH-deficient RCC is another biomarker-driven entity requiring specific attention. A recent study demonstrated a favorable response to ICI-TKI combination therapy in advanced FH-deficient RCCs.⁵⁵

Although a detailed discussion of clinical trials is beyond the scope of this review, it is important to emphasize the need for a precise diagnosis to guide optimal therapeutic design and selection. Integrating molecular classifiers may improve the prognostic accuracy and refine patient stratification for adjuvant therapy. These findings pave the way for further research in this area. Due to the relatively low incidence of non-clear cell RCC, collaborative multi-institutional efforts are necessary.

7. CONCLUSION

RCC classification is not only an intriguing academic practice but is also of utmost clinical importance. With advances in techniques and multi-institutional collaboration, more distinct subtypes are expected to emerge. A precise pathological diagnosis requires full knowledge of the genotype, phenotype, and clinicopathological correlation of the disease. Clinicians must also be aware of the progress made in translating pathological findings into clinical applications for improved prognostication and therapeutic decision-making, especially in this era of precision medicine.

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