Non–Clear Cell Renal Cell Carcinoma: Unpacking a Messy Term

Angelina Bania, MD[1,2]; Giannicola Genovese, MD, PhD[1-4]; and Pavlos Msaouel, MD, PhD[1,2,4,5]

[1]Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

[2]David H. Koch Center for Applied Research of Genitourinary Cancers, The University of Texas MD Anderson Cancer Center, Houston, Texas

[3]Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas

[4]The University of Texas MD Anderson Cancer Center, UTHealth Houston Graduate School of Biomedical Sciences, Houston, Texas

[5]Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas

Corresponding author:
Pavlos Msaouel, MD, PhD
Department of Genitourinary Medical Oncology
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
1155 Pressler St, Unit 1374
Houston, TX 77030
Tel: (713) 563-4585
Fax: (713) 745-0422
Email: pmsaouel@mdanderson.org

Abstract: Non–clear cell renal cell carcinoma (nccRCC) is a heterogeneous category comprising approximately 25% of epithelial renal tumors. Unlike their far more common clear cell counterpart, many nccRCC subtypes are rare, poorly understood, and often aggressive in nature. Treatment options are very limited and generally have been unsuccessfully extrapolated from ccRCC trials. Numerous subtypes also seem to emerge in the context of inherited conditions or syndromes affecting younger individuals. In recent years, the World Health Organization classification of renal tumors has been frequently updated with the recognition of novel entities beyond ccRCC. The recommendations currently demonstrate a shift from morphology-based to molecularly based classification. Thus, aberrations in genes such as *TFE3*, *TFEB*, *FH*, *SDH*, *SMARCB1*, *ELOC*, and *ALK* define separate entities that cannot be distinguished on the basis of microscopic appearance alone. This review aims to deconstruct the general and nondescriptive term of nccRCC to provide a comprehensive presentation of specific subtypes, highlighting their epidemiologic associations and distinctive biological and clinicopathologic features. Delineating these complexities reveals areas that warrant improvement, which will translate into optimal diagnosis, treatment, and overall patient care.

Keywords
Chromophobe renal cell carcinoma, molecularly defined renal cell carcinoma, non–clear cell renal cell carcinoma, papillary renal cell carcinoma, renal medullary carcinoma, 2022 World Health Organization Classification of Tumours of the Urinary System and Male Genital Organs

Introduction

Approximately 75% of epithelioid renal carcinomas (RCCs) are categorized as clear cell RCC (ccRCC).[1-4] The remaining 25% are

Table. Non–Clear Cell Renal Cell Carcinoma Subtypes Associated With Hereditary Conditions

Familial Syndrome or Disease	Inheritance	Genes	RCC subtypes	RCC Risk or Incidence	Other Associated Conditions
Tuberous sclerosis	AD	*TSC1*, *TSC2*	Chromophobe, eosinophilic solid and cystic RCC, hybrid chromophobe-oncocytoma, SDH-deficient RCC	2%-4%	Angiomyolipoma, subependymal giant cell astrocytoma, facial angiofibromas, renal cysts, eosinophilic vacuolated tumor, low-grade oncocytic tumor, others
PTEN hamartoma tumor syndrome	AD	*PTEN*	Clear cell RCC, papillary RCC, chromophobe RCC	34%	Breast cancer, endometrial cancer, thyroid cancer, colon cancer, gastrointestinal hamartomas, lipomas, Lhermitte-Duclos disease, macrocephaly (≥97th percentile), mucocutaneous lesions, others
Birt-Hogg-Dubé syndrome	AD	Folliculin	Chromophobe, hybrid chromophobe-oncocytoma, clear cell RCC, papillary (rare)	15%-25%	Skin fibrofolliculomas, oncocytoma, lung cysts, spontaneous pneumothorax
Hereditary leiomyomatosis and RCC syndrome	AD	*FH*	Papillary type 2, FH-deficient RCC	21%	Cutaneous leiomyomas, uterine leiomyomas
Hereditary papillary renal cancer	AD	*MET*	Classic papillary RCC		Renal papillary adenomas
Pheochromocytoma-paraganglioma syndrome type 4	AD	*SDH-B*	SDH-deficient RCC	14%	Pheochromocytoma, paraganglioma, gastrointestinal stromal tumors, pulmonary chondroma, pituitary tumors
Sickle cell hemoglobinopathies/ trait	AR	*HBB*	Renal medullary carcinoma	Trait: 1/20,000	Sickle cell disease

AD, autosomal dominant; AR, autosomal recessive; *FH*, fumarate hydratase; *HBB*, hemoglobin subunit beta; *PTEN*, phosphatase and tensin homolog; RCC, renal cell carcinoma; *SDH*, succinate dehydrogenase; *TSC*, tuberous sclerosis.

a histologically and molecularly heterogeneous group of tumor entities, commonly referred to as non–clear cell RCC (nccRCC), variant histology RCC, or divergent histology RCC.[1,2] Named mainly in contradistinction to ccRCC because they generally lack prominent clear cell histology and *VHL* mutations, nccRCC is an umbrella term with minimal clinical relevance, given that it comprises numerous relatively rare cancer subtypes with distinct natural history, pathology, familial syndrome associations (Table), and treatment options. The presence of mixed phenotypes and the partial overlap in certain features among subtypes pose diagnostic challenges with serious implications for choice of treatment.[5,6] This situation is further complicated by the scarcity of molecularly focused dedicated trials for each of these rare entities to inform evidence-based care recommendations.

Given the high variability of nccRCCs, further subclassification is warranted. Indeed, new entities have continually been recognized over the last decades, thus raising the number of included RCC subtypes in the World Health Organization (WHO) classification of renal tumors from 12 in 2004 to 16 in 2016 and finally 21 in 2022.[7] The most recent edition, the 5th, reveals a shift from morphologic to molecular classification and now employs driver genetic events to describe RCC entities regardless of their microscopic appearance (Figure).[7,8]

This review aims to provide a comprehensive presentation of nccRCC subtypes and highlight their distinct clinicopathologic and basic molecular features. A brief overview of the current recommendations and trends in nccRCC management per subtype is included to inform research and aid clinicians in the differential diagnosis and treatment decisions for nccRCC subtypes. More detailed discussions of the therapeutic management considerations for nccRCC have been published elsewhere.[1,2,9]

Morphology-Based Classification of nccRCC

nccRCC can be subclassified based on morphology alone into papillary RCC (pRCC), chromophobe RCC, collecting duct carcinoma (CDC), and other renal tumors.

Papillary RCC

pRCC, generally thought to originate from the proximal tubule epithelium,[10] is the most common nccRCC histologic subtype, accounting for approximately 10% of all RCCs.[4] pRCC demonstrates a strong male and Black race predominance.[11] For many years, pRCC was further histologically divided into type 1 and type 2. The 2022 WHO classification abolished the terms *type 1* and *type 2 pRCC.* Instead, it employs the term *classic papillary RCC* for the former type 1 pRCC and endorses further subcategorizations of the heterogeneous group of type 2 tumors according to their molecular features, such as *NF2*, fumarate hydratase (*FH*),[12,13] and *ALK* alterations.[7,8,14]

The classic pRCC variant was historically considered less aggressive and is commonly associated with *MET* alterations that may be therapeutically targeted. These alterations occur via either an increased chromosome 7 copy number or *MET* gene transcriptional upregulation, thus leading to pathway activation and the promotion of invasion and angiogenesis.[15] In some cases, *MET* alterations are inherited in an autosomal dominant manner, and their carriers are at increased risk for the development of multiple, bilateral hereditary papillary renal carcinomas at a young age.[16,17] An increased risk of the development of any pRCC variant has been associated with germline *PTEN* mutations in the context of PTEN hamartoma tumor syndrome/Cowden syndrome. Germline *PTEN* mutations are also associated with ccRCC and chromophobe RCC (Table).[18,19]

pRCC is generally diagnosed in earlier stages and is on average less aggressive than ccRCC.[20,21] However, it tends to be more resistant than ccRCC to immune checkpoint blockade and the targeted therapies developed primarily for ccRCC.[1,2] The phase 2 PAPMET trial established cabozantinib (Cabometyx, Exelixis), a tyrosine kinase inhibitor (TKI) targeting multiple pathways, including vascular endothelial growth factor (VEGF) and MET, as a preferred targeted agent for metastatic pRCC.[22] Cabozantinib can be used in combination with immunotherapy in aggressive disease when a rapid response is required.[1,2] Lenvatinib (Lenvima, Eisai) plus everolimus is another treatment option than can yield responses in pRCC.[23] For what was formerly called type 2 pRCC, further classification based on mutational profile can reveal additional therapeutic targets. For example, molecular evaluation of tumors with papillary architectures can subclassify them as FH-deficient RCC or *ALK*-rearranged RCC, which can be treated with bevacizumab plus erlotinib[24] or ALK inhibitors,[14] respectively. These are further discussed in the section on molecularly defined RCC.

Chromophobe RCC

Chromophobe RCC, the third most common RCC subtype, accounts for 5% of RCC cases.[4] It originates from the intercalated cells of the distal tubule.[25,26] The 2 major putative mechanisms driving the pathogenesis of chromophobe RCC are mitochondrial dysfunction leading to oxidative stress and hyperactivation of the mechanistic target of rapamycin complex 1 (mTORC1) via PTEN pathway mutations.[26] The 2 main chromophobe RCC variants that have been described are classic and eosinophilic. Classic chromophobe RCC is characterized by a pale cytoplasm and irregular, hyperchromatic nuclei surrounded by a prominent cell membrane; the eosinophilic variant, as its name implies, is characterized by cells with purely or predominantly eosinophilic cytoplasm. On immunohistochemistry, positive staining for CD117 and CK7 in addition to PAX8 can aid in differentiating eosinophilic chromophobe RCC from more indolent tumors, such as oncocytomas.[27] Furthermore, chromophobe RCCs characteristically often show whole chromophobe copy number losses at chromosomes 1, 2, 6, 10, 13, 17, 21, and the sex chromosome while harboring a somatic mutation rate 3 times lower than that of ccRCC.[28] Chromophobe RCC is usually sporadic but can occur in the context of familial syndromes, often as multiple tumors.[29,30] Birt-Hogg-Dubé syndrome, an autosomal dominant genodermatosis characterized by germline mutations in the folliculin (*FLCN*) gene, is known to cause RCCs, mostly of chromophobe or hybrid oncocytic-chromophobe histology, among other subtypes.[29,31] PTEN hamartoma tumor syndrome (*PTEN* mutation) and tuberous sclerosis (*TSC1* and *TSC2* genes) also increase chromophobe RCC risk (Table).[19,30]

Chromophobe RCC typically follows an indolent course and carries a better prognosis than ccRCC.[20] The prognosis appears to depend on tumor size and stage and the presence of histopathologic features such as sarcomatoid differentiation, vascular invasion, and microscopic necrosis.[32,33] Whereas sarcomatoid dedifferentiation can occur in most RCC subtypes,[34] chromophobe RCC can also dedifferentiate into anaplastic, glandular, and neuroendocrine components often associated with more aggressive disease.[35,36] Sarcomatoid dedifferentiation is associated with *TP53* and *PTEN* mutations followed by whole-genome duplication/imbalanced chromosomal duplication events, resulting in a flat copy number profile in comparison with the chromosomal losses found in conventional chromophobe RCC.[28,36,37]

The currently available systemic therapies (immune checkpoint inhibitors and targeted agents) used for the

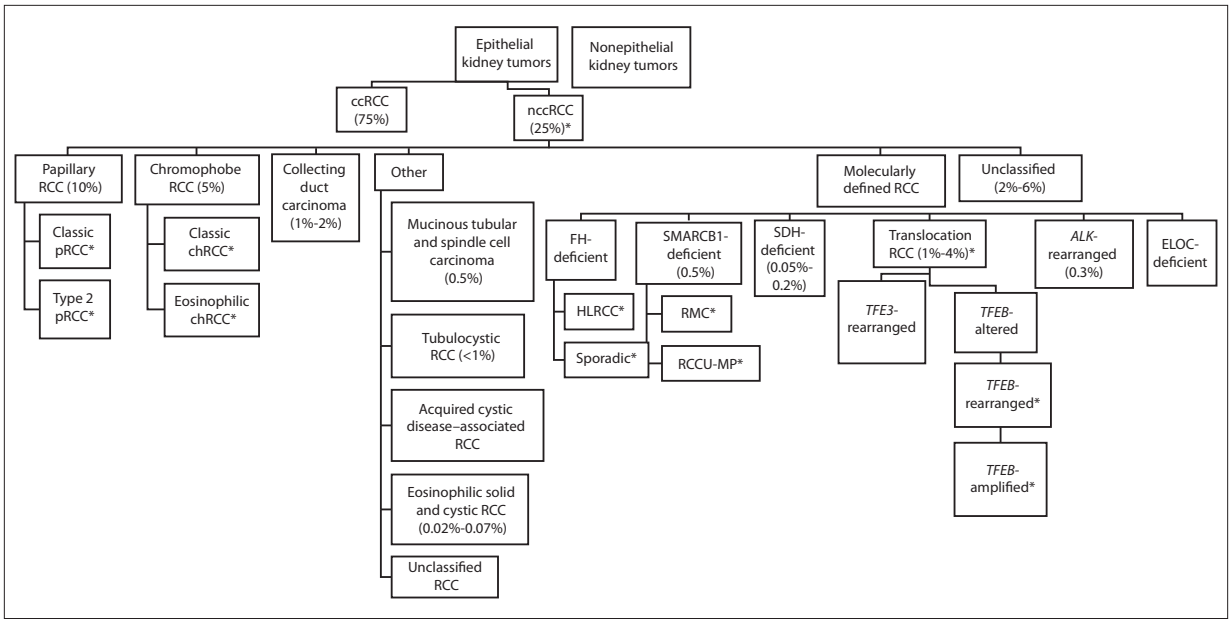

Figure. Renal cell carcinoma subtypes discussed in the text.

ALK, anaplastic lymphoma kinase; ccRCC, clear cell RCC; chRCC, chromophobe RCC; *ELOC*, elongin C; FH, fumarate hydratase; HLRCC, hereditary leiomyomatosis and RCC syndrome; nccRCC, non–clear cell RCC; pRCC, papillary RCC; RCC, renal cell carcinoma; RMC, renal medullary carcinoma. RCCU-MP, RCC unclassified with medullary phenotype; SDH, succinate dehydrogenase.

*Not a distinct entity in the 2022 World Health Organization classification.

treatment of ccRCC are far less effective against chromophobe RCC.[1,2] Metastasis-directed locoregional therapies such as surgery, radiation therapy, and interventional radiology approaches are often prioritized when possible because conventional chromophobe RCC remains relatively indolent, even when metastatic.[1,2,38] Although sarcomatoid dedifferentiation is found in only approximately 20% of patients with metastatic chromophobe RCC, it is associated with a highly aggressive polymetastatic course of disease, is refractory to currently available systemic therapies, and has a limited response to metastasis-directed locoregional therapies.[1,2] Therefore, effective tailored treatment strategies for this RCC subtype are urgently needed.[26,38]

Collecting Duct Carcinoma

CDC is a rare RCC subtype that arises from the collecting ducts and affects predominantly male patients.[1,2,39] No distinct histologic patterns have been identified, but established diagnostic criteria require at least some involvement of the medullary region, a predominance of tubule formation, a desmoplastic stromal reaction, high-grade cytologic features, an infiltrative growth pattern, and the absence of other typical RCC subtypes or urothelial carcinoma.[40,41] Nevertheless, CDC remains a diagnosis of exclusion and often morphologically overlaps with other malignancies, such as SMARCB1-deficient renal medullary carcinoma (RMC), FH-deficient RCC, and upper tract urothelial carcinoma.[1,2,39-41]

CDC is often aggressive and is one of the few RCC subtypes that is sensitive to cytotoxic chemotherapy.[1,2] Platinum-based chemotherapy, such as gemcitabine plus cisplatin or carboplatin plus paclitaxel, is the first-line option.[1,2,42] The addition of bevacizumab may improve outcomes, but concerns over toxicity exist.[43] Among TKIs, cabozantinib is the best evaluated and produces a short progression-free survival of only 4 months.[44] Evidence regarding the efficacy of immune checkpoint therapy against CDC is limited to a few case reports.[45-47]

Other Renal Tumors

Mucinous tubular and spindle cell carcinoma (MTSRCC) is a rare kidney tumor (~0.5% of RCCs) that affects predominantly female patients and is histologically characterized by tubular and spindle cell components on mucinous stroma.[48] *VSTM2A* overexpression, as determined by RNA in situ hybridization, is a sensitive and specific biomarker for MTSRCC.[49] MTSRCC is usually diagnosed at the localized stage, when it carries an excellent prognosis with nephrectomy alone. Advanced or metastatic cases have also been reported; these can respond to anti-VEGF TKIs and immune checkpoint therapy.[50-52] *CDKN2A/B* deletion and

additional complex genomic abnormalities may contribute to the aggressive behavior of the rare metastatic cases of MTSRCC.[53] Hippo pathway deregulation resulting in increased levels of nuclear YAP1 protein is a recurrent hallmark of MTSRCC that may be therapeutically targeted.[54]

Tubulocystic RCC is a rare entity that comprises fewer than 1% of RCCs and demonstrates a strong male predominance.[55] It has a distinctive histologic sponge-like appearance owing to the presence of multiple cysts filled with serous fluid, as well as a proliferation of tubules and a fibrous stroma.[7,8,55,56] The most consistent molecular features include the loss of chromosomes 9 and Y, as well as gain of chromosome 17. Other chromosomal aberrations and mutations in chromatin-modifying genes can be present.[7,8,55,56] Tubulocystic renal cell carcinoma is generally indolent, but occasional metastatic cases have been observed. Metastatic cases may morphologically resemble CDC, may harbor foci of sarcomatoid dedifferentiation, and can respond to anti-VEGF TKIs.[56] Given the rarity of aggressive tubulocystic renal cell carcinoma, FH-deficient RCC should always be included in the differential diagnosis of metastatic RCCs with tubulocystic features.[57]

Acquired cystic disease–associated renal cell carcinoma (ACD-RCC) is the neoplasm most strongly associated with end-stage renal disease, although end-stage renal disease (and the ensuing chronic inflammation) is a major risk factor for common RCC histologies, including ccRCC.[58] ACD-RCC affects predominantly male patients with a long history of dialysis and is often multiple or bilateral.[58] Histologically, ACD-RCC is described as cribriform or sieve-like with abundant granular eosinophilic cytoplasm. Hemorrhage, necrosis, and sarcomatoid histology were identified in higher-grade tumors.[59,60] Chromosomes 3 and 16 aberrations and *KMT2C* and *TSC2* mutations are the most common genetic features.[58] ACD-RCC can occasionally be aggressive; 11% of patients experienced local or distant recurrence after surgery in a large case series of 40 patients.[60]

Eosinophilic solid and cystic RCC (ESC RCC) is a novel entity in the 2022 classification that affects predominantly middle-aged women and accounts for fewer than 0.1% of RCC diagnoses.[61] ESC RCC can reach large sizes and features solid and cystic areas of varying sizes. Cells are characterized by their eosinophilic cytoplasm and granular stippling.[7,8,61] Its distinctive CK20 expression on immunohistochemistry can aid in the diagnosis.[61] Most ESC tumors harbor somatic *TSC1* and *TSC2* gene mutations, whereas germline mutations—associated with tuberous sclerosis—are found in approximately 10% of patients.[61-63] The prognosis of ESC RCC is generally very favorable following treatment with radical or partial nephrectomy,[61] although metastatic cases have occasionally been reported in the literature.[62,64] The role of *TSC1* and *TSC2* mutations in ESC RCC provides a rationale for mTOR therapeutic inhibition. For example, a durable complete response to the mTOR inhibitor everolimus was noted following progression on 3 prior TKIs in a 13-year-old female patient with multifocal metastatic ESC RCC harboring a somatic *TSC2* mutation.[62]

Molecularly Defined RCC

Molecularly defined RCC includes microphthalmia transcription factor (MiTF) family translocation RCC, FH-deficient RCC, SMARCB1-deficient RMC, succinate dehydrogenase (SDH)–deficient RCC, *ALK*-rearranged RCC, *ELOC*-mutated RCC, and unclassified RCC.

MiTF Family Translocation RCC

MiTF family translocation RCC accounts for approximately 1% to 2% of all sporadic RCC tumors and up to 50% of pediatric renal tumors, as well as approximately 15% of RCCs in adults younger than 45 years.[5] The MiTF gene family consists of 4 members, among which *TFE3* and *TFEB* have the best-established association with RCC.[5] MiTF RCC tumors most commonly arise from oncogenic *TFE3* rearrangements (translocations), followed by *TFEB* amplifications as the second most frequent cause and *TFEB* translocations as the third.[5,65] The 2022 WHO RCC tumor classification removed the term *MiTF translocation RCC*, which is now further subclassified into *TFE3*-rearranged and *TFEB*-altered (*TFEB*-rearranged and *TFEB*-amplified) RCC because each of these subtypes has a very different biological behavior.[7] Diagnosing *TFE3*-rearranged and *TFEB*-altered RCCs can be difficult because they may resemble ccRCC and pRCC on histologic examination.[5,65] *TFE3*-rearranged RCC should be considered in children and young adults, particularly women, and in patients who have tumors with mixed morphologies—especially if they have a history of childhood chemotherapy; approximately 15% of *TFE3*-rearranged RCC cases are linked to childhood malignancies.[66]

TFE3-rearranged RCC is also known as Xp11 translocation RCC on the basis of the *TFE3* gene locus on chromosome Xp11. Owing to its association with the X chromosome, *TFE3*-rearranged RCC most commonly arises in women: the female-to-male ratio is 2:1.[67] Multiple *TFE3* fusion partners have been identified; *ASPSCR1* (associated with alveolar soft part sarcomas), *PRCC*, and *SFPQ* are the most common and associated with a poor, an intermediate, and a favorable prognosis, respectively.[5] Cell morphology on histology varies; papillary and nested patterns composed of clear or eosinophilic epithelioid cells are the most common, so that pRCC and ccRCC are involved in the differential diagnosis. Psammoma bodies are a common finding.[65] The diagnosis can be

made with TFE3 immunohistochemistry (IHC), break-apart fluorescence in situ hybridization (FISH), or RNA sequencing (RNA-seq).[5] TFE3 IHC is highly sensitive but depends on the fixation processing and is less reliable than FISH or RNA-seq. *TFE3* FISH is highly specific, but it cannot identify the *TFE3* fusion partner and may result in false-negative results, particularly in cases due to cryptic intrachromosomal Xp11.2 inversions, including *TFE3* fusions with the *NONO* or the *RBM10* gene.[5] RNA-seq is more costly but highly sensitive and can identify cryptic fusions and the exact partnering genes, which has important prognostic implications.[5] Surgery is the appropriate strategy when the disease is confined to a kidney or regional lymph nodes. In more advanced settings, the immunotherapy and targeted agents used in other RCCs are commonly employed but are generally less effective than in ccRCC.[1,2,68]

TFEB-altered RCC is less common and includes *TFEB*-rearranged and *TFEB*-amplified RCC. It often displays a nested histologic pattern with eosinophilic cells and can be diagnosed with IHC, *TFEB* break-apart FISH (which is different from *TFE3* FISH), or RNA-seq.[5,65] *TFEB* is located on chromosome 6p21 and can be either amplified or rearranged to generate oncogenic fusions with an expanding list of potential partner genes, most commonly *MALAT1* on chromosome 11q12.[69] *TFEB*-amplified RCC typically affects older adults, with a slight male predominance, and is more common and aggressive than *TFEB*-rearranged RCC.[65] Anti-VEGF TKI treatment may be particularly effective against *TFEB*-amplified RCC owing to the frequent co-amplification of *VEGFA*, which is also mapped on chromosome 6p21.[70,71]

FH-Deficient RCC

FH-deficient RCC typically occurs following somatic inactivation of the second *FH* allele in individuals with an autosomal dominant germline mutation in the other *FH* allele, a condition known as hereditary leiomyomatosis and RCC (HLRCC) syndrome. This syndrome is associated with FH-deficient RCC as well as cutaneous and uterine leiomyomas (Table).[72,73] FH-deficient RCC may develop in up to 35% of individuals with HLRCC syndrome.[74] Sporadic cases are less common, comprising approximately 11% of all cases of FH-deficient RCC, and otherwise have pathologic features overlapping with those of the renal malignancies associated with germline HLRCC.[6,75] Contrary to tumors related to other familial syndromes, FH-deficient RCC tumors in patients with HLRCC are usually solitary and unilateral but can occasionally be bilateral or multifocal.[75] FH-deficient RCCs commonly demonstrate papillary architecture and were previously classified as type 2 pRCC tumors.[7,8,75]

FH is a Krebs cycle enzyme catalyzing the conversion of fumarate to malate.[76] FH inactivation leads to high fumarate levels, which result in the aberrant succination of proteins and the formation of products such as S-(2-succino)cysteine (2SC). Consequently, strong cytoplasmic and nuclear 2SC staining of tumor cells by IHC, with absent staining in the surrounding normal cells, is highly sensitive and specific for diagnosing FH-deficient RCC, even in rare cases of false-positive FH expression by IHC.[77]

FH-deficient tumor cells depend on glycolysis for ATP production, and the increased fumarate levels stabilize HIF1A, leading to downstream VEGF transcription.[76] Accordingly, anti-VEGF TKIs and monoclonal antibodies such as bevacizumab can be effective therapies. The combination of bevacizumab and erlotinib achieved an overall response rate of 72.1% (95% CI, 57.2%-83.4%) and a median progression-free survival of 21.1 months (95% CI, 15.6-26.6) in patients with FH-deficient RCC.[78] FH-deficient RCC frequently exhibits copy number gains on chromosome 7q, where *MET* is located, and retrospective data suggest that cabozantinib may be an effective treatment option for patients with FH-deficient RCC.[1,2] Lenvatinib combined with either pembrolizumab (Keytruda, Merck) or everolimus can also induce responses in patients with FH-deficient RCC.[79]

SMARCB1-Deficient RMC

SMARCB1-deficient RMC most commonly affects individuals with a sickle hemoglobinopathy, such as sickle cell trait or sickle cell disease (Table).[80] SMARCB1, also known as INI1 or SNF5, is lost in RMC, most commonly owing to inactivating translocations or deletions that can be difficult to detect on standard clinical next-generation sequencing assays.[81] Accordingly, the gold standard for RMC diagnosis is IHC showing loss of SMARCB1.[82]

Owing to its association with sickle hemoglobinopathies, RMC most commonly occurs in young individuals of African descent, with a 2:1 male-to-female ratio.[80,83] RMC is twice as likely to arise from the right kidney because the shorter vasculature of the left kidney is less susceptible to infarcts caused by red blood cell (RBC) sickling.[80,84,85] Normal kidney cells downregulate SMARCB1 in response to hypoxia caused by RBC sickling in sickle cell trait, setting the stage for SMARCB1 loss and the eventual development of RMC.[85] High-intensity exercise may further exacerbate RBC sickling, increasing RMC risk.[84] Hematuria is the most frequent presenting symptom, occurring in 60% of patients with RMC.[83] Accordingly, RMC should always be suspected in young Black males with a history of high-intensity exercise who present with hematuria and a right-sided renal tumor. In such cases, hemoglobin electrophoresis should be performed if the sickle status is unknown, and a biopsy may be needed to confirm RMC up front. Chemotherapy rather than

nephrectomy is the recommended initial treatment, even in patients with RMC who present with radiologically nonmetastatic tumors greater than 4 cm in diameter.[82] In up to 10% of cases, SMARCB1-deficient tumors with clinicopathologic features similar to those of RMC affect patients without sickle cell trait or a hemoglobinopathy.[83] These are known as RCC unclassified with medullary phenotype (RCCU-MP), have a slightly more favorable prognosis, and do not carry epidemiologic associations with male sex, right kidney laterality, and high-intensity exercise.[83]

Platinum-based chemotherapy with carboplatin plus paclitaxel is the most commonly used first-line therapy for RMC.[82,83] SMARCB1 loss induces DNA replication stress, sensitizing cells to DNA damage by platinum salts, nucleoside analogs such as gemcitabine, and topoisomerase inhibitors such as doxorubicin.[81] Accordingly, the combination of gemcitabine with doxorubicin is an effective second-line strategy in RMC.[86] Owing to upregulation of the epidermal growth factor receptor (EGFR) pathway in RMC,[81] targeted therapies against EGFR are effective even in heavily pretreated patients.[83,87] Combination definitive radiation therapy and chemotherapy can produce durable complete responses in selected patients with oligoprogressive or oligometastatic RMC.[88] Earlier diagnosis and tailored therapeutic strategies in recent years have resulted in improved outcomes for patients with RMC.[83,87] Elevated serum CA-125 levels are observed in two-thirds of patients with RMC and can be used to monitor therapeutic response.[89]

SDH-Deficient RCC

SDH participates both in the Krebs cycle, catalyzing the conversion of succinate to fumarate, and in the electron transport chain as part of the mitochondrial complex 2. SDH-deficient RCC is a rare renal malignancy, accounting for 0.05% to 0.2% of cases of RCC.[90] It typically affects young and middle-aged patients, has a male predominance, and is associated with pheochromocytoma/paraganglioma syndrome (Table), an autosomal dominant familial syndrome characterized by germline mutations of *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *MAX*, or *TMEM127*. Patients with this syndrome are at risk for the development of pheochromocytoma, paraganglioma, gastrointestinal stromal tumors, and in rare cases pituitary tumors.[91] Individuals with germline *SDHB* mutations have an increased lifetime risk (of approximately 5%) for the development of SDH-deficient RCC. The mean age at diagnosis is 38 years. The link between germline mutations in other SDH complex genes and SDH-deficient RCC has not been as firmly established.[92,93] A total of 10 cases of SDHA-deficient RCC have been reported in the literature; SDHA and SDHB were negative by IHC, but patients had an uncertain germline status and a limited personal or family history of other SDH-related neoplasias.[94] In addition to *SDHA* mutations, 3 of these 10 tumors also harbored *NF2* gene mutations. Tumors with both *SDHA* and *NF2* mutations may show increased aggressiveness but respond well to immunotherapy.[94]

The characteristic morphologic features of SDH-deficient RCC include eosinophilic cytoplasm with intracytoplasmic inclusions and vacuoles and indistinct cell borders.[90] SDHA-deficient RCCs typically lack this canonical morphology and instead demonstrate glandular, sheet-like, or papillary growth patterns with prominent nucleoli.[94] The diagnosis is established by loss of SDHB staining on IHC, regardless of the underlying mutated SDH subunit.[90,93] In one study of 273 tumors originally diagnosed as oncocytomas, loss of SDHB with retention of SDHA by IHC was noted in 3 cases (1.1%), which were subsequently reclassified as SDH-deficient RCC.[95]

Most SDH-deficient RCCs are low grade and have a favorable prognosis; long-term cure can be achieved with surgical resection alone. However, high-grade nuclear atypia, necrosis, and sarcomatoid dedifferentiation increase the risk of distant relapse, even decades after surgical resection of the primary SDH-deficient RCC, highlighting the need for long-term follow-up.[90,93] Although additional data are required to determine effective treatment strategies for SDH-deficient RCC, the pseudo-hypoxic phenotype caused by SDH loss suggests that targeting the VEGF or HIF2A pathway is a reasonable approach.

ALK-*Rearranged RCC*

ALK-rearranged RCC is very rare and exhibits highly variable histology depending on the fusion partner gene. It can include tumors that would formerly have been classified as type 2 pRCC. The presence of a mucinous/myxoid background or psammomatous calcifications can raise suspicion for *ALK*-rearranged RCC in tumors previously thought to be unclassified.[96] The ALK pathway is activated through fusion with various gene partners, with the *EML4-ALK* fusion demonstrating responsiveness to ALK inhibitors like alectinib (Alecensa, Genentech).[14] Notably, the *VCL-ALK* fusion is found almost exclusively in individuals with sickle cell trait, but the tumor is far less aggressive than SMARCB1-deficient RMC.[97] Almost all patients with *ALK*-rearranged RCC demonstrate ALK IHC positivity with a cytoplasmic and/or membranous distribution. The diagnosis can be confirmed with FISH or RNA-seq, with the latter providing the ability to identify the fusion partner.[75]

ELOC-*Mutated RCC*

Elongin C (ELOC; previously known as TCEB1) participates in the ubiquitination of VHL-bound HIF.

ELOC-mutated RCC was initially identified in 2013 in RCC with clear cell morphology that lacked *VHL* mutations or deletions in chromosome 3p, where *VHL* is located.[98] Instead of *ELOC* mutations, some tumors may carry deletion of chromosome 8q, where *ELOC* is located.[99] In addition to demonstrating clear cell histology without the *VHL* loss driving ccRCC, *ELOC*-mutated RCC is characterized by the presence of fibro-elastic bands or thick fibromuscular capsules and morphologic features overlapping with those of renal angiomyoadenomatous tumors, also known as RCC with (angio) leiomyomatous stroma. Renal angiomyoadenomatous tumors are distinct neoplasms associated with recurrent mutations in the TSC1/TSC2/mTOR pathway and show strong, diffuse glycoprotein nonmetastatic melanoma protein B (GPNMB) positivity on IHC, which is absent in *ELOC*-mutated RCC.[100,101] A definitive diagnosis of *ELOC*-mutated RCC can be established by positive IHC staining for ELOC or molecular testing showing *ELOC* mutations.[7,99] *ELOC*-mutated RCCs generally follow an indolent course, but the occasional metastatic cases can be treated with agents targeting the VEGF or HIF2A pathway.

Unclassified RCC

Unclassified RCC comprises a highly heterogeneous group of tumors that could not be classified morphologically or molecularly. Many of these cases are diagnosed at advanced stages, and the prognosis is variable.[1,2] *NF2* loss resulting in Hippo pathway deregulation is the most common molecular event in unclassified RCC and is associated with a prognosis worse than that of tumors harboring other alterations, such as mTORC1 complex mutations.[102] The growing recognition of new molecular and histomorphologic entities, along with the clinical application of comprehensive next-generation DNA and RNA sequencing, offer hope that fewer RCCs will fall under the unclassified category in the coming years.

Conclusion

There is a clear need to move beyond the term *nccRCC* and aim for more accurate diagnosis and classification. The development of dedicated clinical trials tailored to the specific clinical and molecular hallmarks of each RCC subtype can inform clinical practice.[38] A number of ongoing randomized clinical trials, such as PAPMET2, SAMETA, and STELLAR-304, represent a much needed push toward exploring therapeutic activity through randomized trials in nccRCC subtypes.[9] Multicenter collaborations can help enroll well-selected patients, especially in the case of extremely rare nccRCC subtypes, for which randomization to a control arm may not be feasible.[38] These efforts can be facilitated by the establishment of tissue biobanks for comprehensive molecular profiling, as well as cell line and animal models for functional preclinical studies. Search pages that can facilitate the identification of trials specific to selected histologies or molecular alterations are available from the Kidney Cancer Association (https://www.kidneycancer.org/clinical-trials-finder) and KCCure (https://kccure.org/non-clear-cell-rcc-clinical-trials/).

Disclosures

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