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Renal Cell Carcinoma: Recent Advances in Genetics and Imaging

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Recent advances in molecular biology and cytogenetics have provided unique insights into the ontogeny, pathogenesis, and biological behavior of renal cell carcinoma. Renal cell carcinoma is now known to be a polymorphic malignant neoplasm consisting of several histologic subtypes demonstrating different biological profiles. Clear cell renal carcinoma, the most common histologic subtype, is predominantly associated with mutations involving the von Hippel-Lindau gene and elaboration of vascular and somatic growth factors. Clear cell renal cell carcinoma is thus typically hypervascular at imaging. By contrast, papillary renal cell carcinoma, the second most common subtype, is frequently hypovascular. Current molecular data on the biology of renal neoplasms have shown important diagnostic, therapeutic, and prognostic implications. Comprehensive knowledge of molecular pathways of carcinogenesis of renal cancers has allowed design of rational treatment protocols and posttreatment surveillance algorithms, thereby permitting optimal patient management.

Semin Ultrasound CT MRI 30:315-325

Renal cell carcinomas (RCCs) account for 3% of all adult cancers and 85%-90% of all renal malignancies.[1] In 2006, an estimated 39,000 new RCC cases and 13,000 associated deaths were reported in the USA.[2] Approximately 20%-30% of patients with RCC have metastatic disease at presentation and nearly 50% of patients with advanced disease die within 5 years of diagnosis.[3] Global incidence of RCC continues to grow steadily with the increase in incidentally discovered lesions during imaging studies being only partly responsible for this upward trend (Fig. 1); there is also a steady upward curve in the incidence of late-stage renal cancers.[4] Up to 50%-60% of RCCs may be incidentally found in asymptomatic patients at abdominal imaging studies performed for other indications.

Recent advances in the understanding of the genetic basis of RCC have provided unique insights into the underlying histologic and biological diversity of renal cancer. Renal cell carcinoma is postulated to be a byproduct of genetic events that may involve gain-of-function of proto-oncogenes, loss-of-function of cancer suppressor genes, or both. Different histologic subtypes of renal cell carcinoma have characteristic clinical, genetic, and biological profiles. Indeed, the 2004 World Health Organization taxonomic schemata recognizes that RCC is a clinicopathologically heterogeneous malignant neoplasm that can be classified into clear cell, papillary, chromophobe, collecting duct, medullary carcinoma, and unclassified categories[1] (Table 1). Clear cell RCC is the most common histologic subtype representing 70%-75% of all RCCs.[5,6] Papillary RCC and chromophobe RCC account for 15%-20% of the remainder of the RCCs.[5] Distinct differences in biological behavior and long-term prognosis among different subtypes of RCC makes the correct histologic diagnosis critically important.

Contrast-enhanced, multiphase multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) play an important role in the detection, characterization, localization, and staging of RCCs.[7] Recent advances in MDCT and MRI technologies permit rapid, short breath-hold, high-resolution, multiphase evaluation of the kidneys. With current-day scanners, vastly improved z-axis anatomic coverage in a short time drastically reduces patient-related motion artifacts. Acquisition of thin-section images allows accurate characterization of cystic and solid renal masses, while reducing partial volume artifacts. Isotropic voxel imaging achieved with state-of-the-art scanners allows superior, artifact-free,

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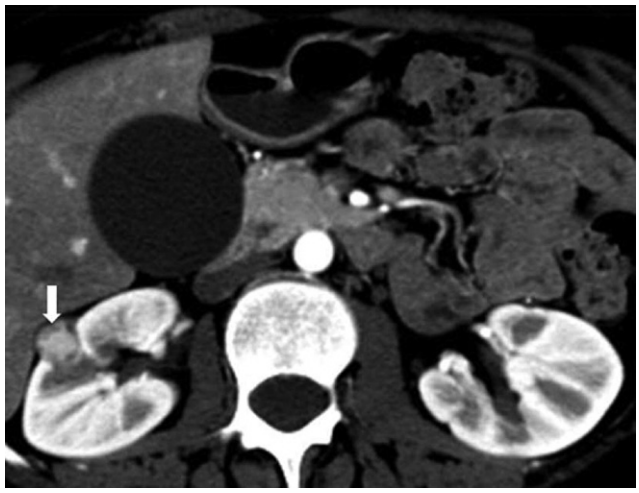

Figure 1 Incidentally detected small clear cell RCC. Contrast-enhanced CT in the corticomedullary phase shows a partially exophytic hypervascular mass (arrow) arising from the anterior interpolar cortex of the right kidney.

multiplanar and 3-dimensional image reconstructions. Multiphase imaging of the kidneys provides comprehensive evaluation of the parenchyma as well as the renal vasculature and collecting systems.

A dedicated multiphase, contrast-enhanced computed tomography (CT) and MRI protocol is a prerequisite to optimal renal mass assessment. Scans are typically obtained during corticomedullary phase (CMP; delay of 35-80 s), nephrographic phase (NP; delay of 85-180 s), and excretory phase (delay of >3 min). While NP is considered the best phase to detect small renal masses, CMP images permit differentiation of RCCs based on tumor vascularity. A recent study comparing the performance of 16-MDCT and MRI for the characterization of renal lesions concluded both modalities were excellent and comparable for the differentiation of surgical and nonsurgical lesions with sensitivity of 92.3% for both MDCT and MRI and specificity of 96.3% and 91.3%, respectively.[8] In addition, MRI provides exquisite tissue characterization and superior spatial resolution allowing for detection and superior demonstration of hemorrhage, intracellular/macroscopic fat, and intracystic architecture (such as nodules, septations) in renal masses.

Although surgical resection is the primary mode of treatment in patients with RCC, therapeutic agents aimed at specific molecular targets are being increasingly used to treat patients with multicentric and/or metastatic RCCs. In addition, percutaneous ablative techniques are also being used to treat subsets of patients who are poor candidates for surgery. Imaging techniques have been refined to not only accurately diagnose RCCs early but also to monitor treatment response. A clear understanding of the pathogenesis and biology of the wide spectrum of RCC provides a rational explanation for biological behavior and radiologic-pathologic manifestations and also facilitates optimal patient management.

Histology and Histogenesis of Renal Cell Carcinomas

Clear cell RCC (previously referred to as conventional RCC) is the most common histologic subtype of sporadic RCC that is characterized by glycogen and lipid-rich clear cells and a regular network of small, thin-walled blood vessels.[1] Papillary RCC, the second most common histologic subtype, typically consists of a central fibrovascular core with epithelial covered papillae.[9] Papillary RCCs have been divided into 2 subtypes (type 1 and 2) based on their morphology and clinical behavior. Type 1 tumors show single-layered small cells with pale cytoplasm often containing scattered psammomma bodies. Type 2 tumors demonstrate pseudostratification of large cells with eosinophilic cytoplasm and demonstrate a higher nuclear grade. The type 2 papillary tumors are associated with a poorer prognosis than type 1 tumors. Chromophobe RCCs are histologically characterized by large polygonal cells with prominent cell membranes and perinuclear clearing. Thick-walled and hyalinized blood vessels are commonly seen within the tumor. Diffuse cytoplasmic staining reaction with Hale's colloidal iron stain is considered a hallmark feature of chromophobe RCCs.

Advanced pathologic techniques have shown that different RCC subtypes either differentiate toward or develop from specific precursor cells within different segments of the nephron. While clear cell and papillary subtypes of RCCs recapitulate the epithelia of the proximal convoluted tubule, chromophobe RCC cells resemble type B intercalated cells of

Table 1 2004 World Health Organization Histological Classification of RCC

Histologic Subtype	Prevalence	Putative Cell of Origin or Differentiation
Clear cell RCC	70%-75%	Proximal convoluted tubule epithelium
Multilocular, cystic clear cell RCC	<1	
Papillary RCC	10%-15%	Proximal convoluted tubule epithelium
Chromophobe RCC	5%	Type B intercalated cells of the cortical collecting duct
Collecting duct carcinoma	<1	Medullary collecting duct epithelium
Medullary carcinoma	<1	Medullary collecting duct epithelium
Mucinous tubular and spindle cell carcinoma	<1	
Neuroblastoma-associated RCC	<1	
Translocation carcinomas	<1	
RCC unclassified	4	

RCC, renal cell carcinoma.

Table 2 Hereditary RCC Syndromes

Syndrome	Gene (Protein)	Chromosome Locus	RCC Subtype	Skin Lesions	Systemic Manifestations
von Hippel Lindau	*VHL* (VHL protein)	3p25	Multifocal, bilateral, clear cell RCCs	None	Retinal and CNS hemangioblastomas, visceral cysts, neuroendocrine tumors
Hereditary papillary RCC	c-*MET* (hepatocyte growth factor receptor)	7q31	Multiple, bilateral, type 1 papillary RCCs	None	None
Hereditary leiomyomatosis and RCC	*FH* (fumarate hydratase enzyme)	1q42-43	Solitary, type 2 papillary RCC	Leiomyomas	Uterine smooth muscle neoplasms
Birt-Hogg-Dubé	*BHD* (folliculin)	17p11.2	Multiple hybridomas, chromophobe, clear cell and oncocytic tumors	"Mantleomas"	Lung cysts, spontaneous pneumothorax

RCC, renal cell carcinoma.

Figure 2 Role of VHL protein in the regulation of HIF pathway.

the cortical collecting ducts[10,11] (Table 1). Thus, the vast majority (>90%) of RCCs demonstrate a cortical distribution. Collecting duct carcinoma and medullary carcinoma are other less frequent, however extremely aggressive RCC subtypes that are hypothesized to arise from the medullary collecting ducts.[10]

Hereditary Renal Cell Carcinoma Syndromes

Hereditary RCC syndromes refer to multisystem syndromes with increased predisposition to multiple tumors, including RCCs. Each of these syndromes identified to date are autosomal-dominant and predispose patients to distinct histologic subtypes of RCCs[12] (Table 2). The renal tumors in the affected patients are usually multiple and bilateral with the solitary exception of hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. The age of tumor development is variable, although most occur at an earlier age than in patients with sporadic RCCs. The identification of hereditary RCC syndromes, the associated renal neoplasms, and caus-

Figure 3 Clear cell RCCs in a patient with VHL syndrome. Contrast-enhanced CT shows 2 hypervascular, solid RCCs in the right kidney (arrows) and a large exophytic cystic RCC (C) with an enhancing mural nodule (arrowhead). A pancreatic head serous cystadenoma (black arrow) is also noted.

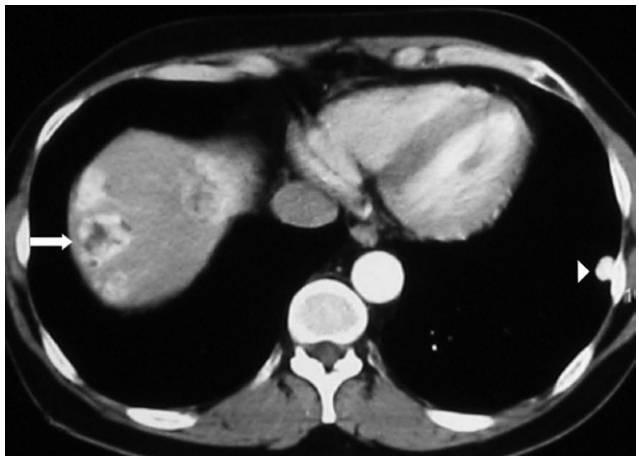

Figure 4 Axial contrast-enhanced CT image shows multiple hypervascular hepatic (arrow) and a lung metastasis (arrowhead) from clear cell carcinoma in a patient with VHL syndrome.

ative genes have provided important clues to elucidate oncologic pathways, which has subsequently led to the identification of molecular targets to treat RCCs, both hereditary and sporadic. We discuss the genetic, clinicopathologic, and imaging aspects of 4 well-described syndromes of hereditary renal cancers: von Hippel-Lindau (VHL) syndrome, hereditary papillary renal carcinoma (HPRC), HLRCC, and Birt-Hogg-Dubé (BHD) syndrome.

von Hippel–Lindau Disease: Dysregulation of HIF Pathway Due to *VHL* Inactivation

VHL disease is a multisystem neoplasia syndrome caused by germ-line mutations of the tumor suppressor *VHL* gene and is characterized by the development of visceral cysts and characteristic, multiorgan hypervascular neoplasms. Patients

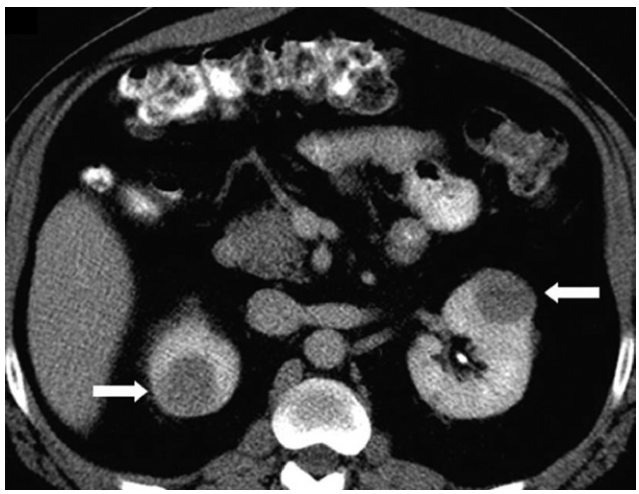

Figure 5 Hereditary papillary RCC syndrome. Axial contrast-enhanced CT in the nephrographic phase shows bilateral, uniformly low-attenuating papillary RCCs (arrows) in a patient with HPRC syndrome.

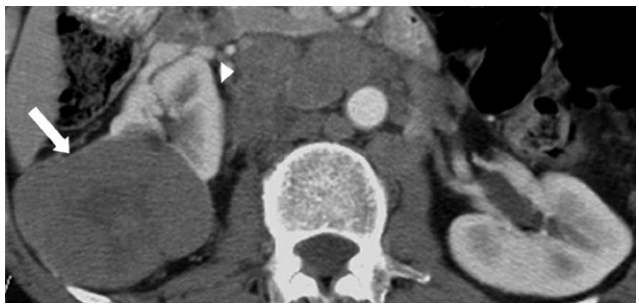

Figure 6 Hereditary leiomyomatosis RCC syndrome. Axial contrast-enhanced CT in the nephrographic phase shows a large, exophytic, papillary RCC (arrow) arising from the posterior cortex of the right kidney. Note the extensive retroperitoneal lymphadenopathy (arrowhead).

with types 1 and 2 B VHL disease are at high risk of developing clear cell RCCs. Clear cell RCCs occur in 75% of VHL patients by the sixth decade and are a leading cause of morbidity and mortality.[13]

VHL gene encodes for pVHL (VHL protein), a key component of cellular oxygen homeostatic mechanism. Among its many functions, pVHL is involved in oxygen-dependent, proteasomal degradation of the alpha subunit of hypoxia-inducible factor (HIF-α), a key regulator of an elaborate tissue hypoxia response mechanism[14] (Fig 2). Inactivation of *VHL* thus leads to inappropriate up-regulation (even in normoxic conditions) of HIF and its downstream hypoxia response genes (including those encoding vascular and somatic growth factors), resulting in angiogenesis and cell proliferation.[15,16] Increased HIF levels, particularly that of HIF2 alpha, play a causal role in clear cell RCCs associated with VHL disease.[17]

VHL disease is characterized by the development of bilateral, multiple renal cysts, cystic RCCs, and hypervascular RCCs (Fig. 3). The RCCs often acquire metastatic potential when they reach more than 3-7 cm in size (Fig. 4).[18] Biallelic inactivation of *VHL* gene either due to somatic mutations or from epigenetic mechanisms contributes to pathogenesis of 50%-75% of sporadic clear cell RCCs as well.[19]

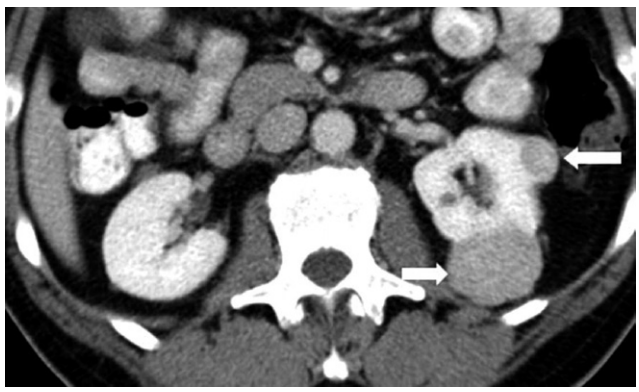

Figure 7 Birt-Hogg-Dubé Syndrome. Axial contrast-enhanced CT shows 2 homogenously enhancing renal tumors (arrows) in the left kidney.

Hereditary Papillary RCC Syndrome: Activation of MET-HGF Signaling Pathway

HPRC syndrome is caused by activating germ-line mutations of the *MET* proto-oncogene and is characterized by a predisposition to develop multiple, bilateral type 1 papillary RCCs.[20] *MET* oncogene encodes a receptor tyrosine kinase that is activated by hepatocyte growth factor (HGF).[21,22] MET-HGF interaction leads to a cascade of complex genetic programs that result in cell proliferation and motility.[23] HPRC syndrome shows high penetrance with more than 50% of patients developing RCCs by the age of 55 years.[24] The tumors are usually bilateral, multiple, and slow growing with relative hypovascularity and uniform contrast enhancement (Fig. 5).

Although only 13% of sporadic papillary RCC demonstrate gain-of-function mutations of the *MET* proto-oncogene, trisomy of chromosome 7 (where both *MET* and *HGF* genes are located) occurs with high frequency in 95% of sporadic papillary tumors.[25] A subset of sporadic papillary RCCs also exhibit chromosomal polysomies involving chromosome 17 as well as loss of Y chromosome in male patients.

Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome: Role of Fumarate Hydratase Gene and Pseudohypoxia

HLRCC syndrome is characterized by the development of cutaneous and uterine smooth muscle neoplasms in addition to highly aggressive type 2 papillary RCCs.[26] HLRCC syndrome results from germ-line inactivating mutations of *FH* gene that encodes fumarate hydratase, a mitochondrial Kreb's cycle enzyme. Low to absent FH activity leads to a "pseudohypoxic" expression profile characterized by up-regulation of HIF-1α and its downstream pathways, reminiscent of *VHL* inactivation.[23] The RCCs are predominantly unilateral and solitary with frequent perinephric extension, lymph node metastases, and renal vein/vena-caval involvement[27] (Fig. 6).

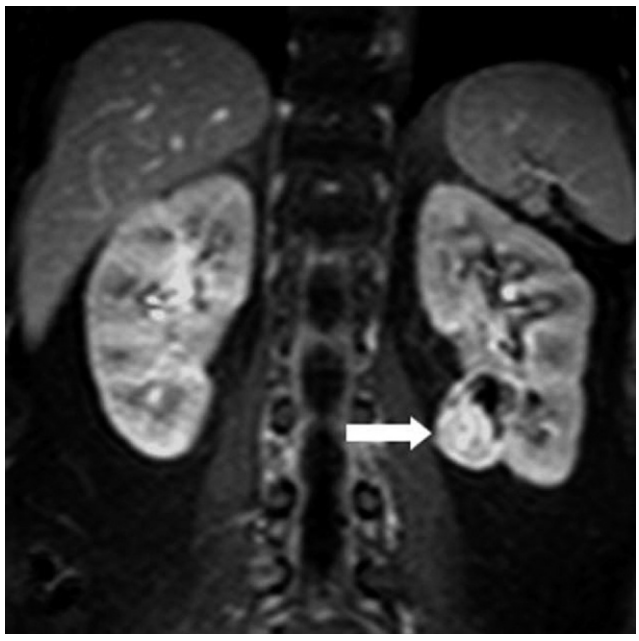

Figure 8 Clear cell RCC. Coronal, gadolinium-enhanced, T1-W MRI demonstrates a partially exophytic, predominantly hypervascular tumor (arrow) arising from the left kidney.

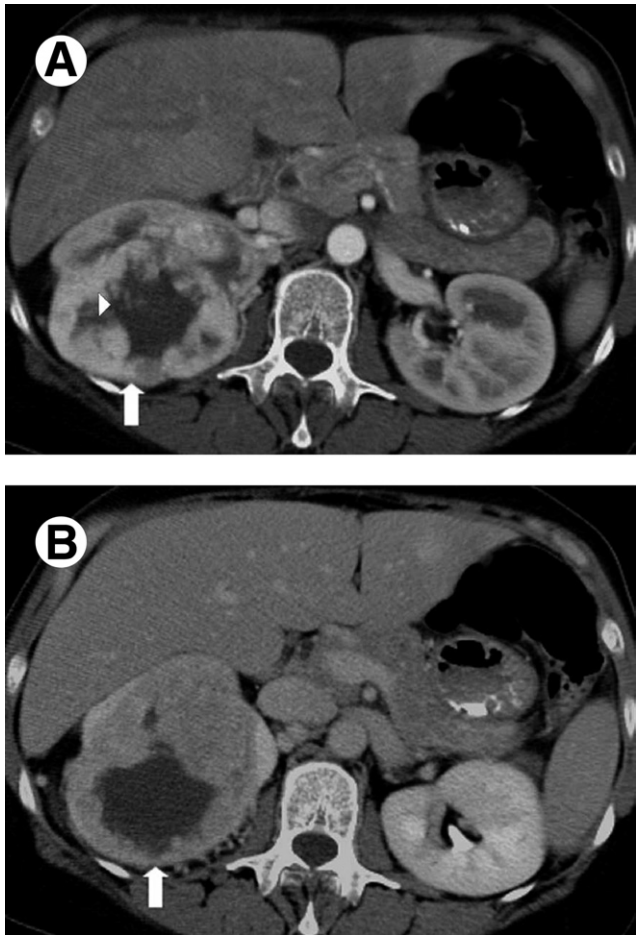

Figure 9 Sporadic clear cell RCC. Axial CT images obtained during the corticomedullary (A) and nephrographic (B) phase shows a large, heterogenously enhancing right renal mass (arrow) with irregular central area of necrosis (arrowhead). Note that the lesion enhances intensely on the corticomedullary phase and shows prompt de-enhancement on the nephrographic phase.

Birt-Hogg-Dubé Syndrome: Inactivating Mutations of the Birt-Hogg-Dubé Gene

BHD syndrome, characterized mainly by the development of skin "mantleomas," predisposes patients to pulmonary cysts, pneumothorax, and renal tumors.[28,29] Bilateral, multifocal renal tumors occur in about 15% of patients in the fifth or sixth decade. The predominant histology of the renal tumors

include chromophobe RCCs, hybrid tumors (with both chromophobe RCC and oncocytoma features), and oncocytomas.[30] The BHD gene, a putative tumor suppressor gene, encodes the protein folliculin, which is thought to play a role in cell proliferation and angiogenesis[31,32] (Fig. 7).

Although sporadic chromophobe RCCs show alterations in chromosome 17, mutations in the *BHD* gene have been detected in less than 10% of patients.[33] Complex losses of multiple chromosomes have been detected in sporadic chromophobe RCCs.

Cross-Sectional Imaging Findings of Sporadic Renal Cell Carcinomas

Most sporadic clear cell RCCs also demonstrate inactivating somatic mutations of the *VHL* gene and thus appear hypervascular on imaging similar to VHL-related clear cell RCCs. Typically the clear cell RCCs are relatively hypervascular and demonstrate heterogeneity on MDCT and MRI[34] (Fig. 8).

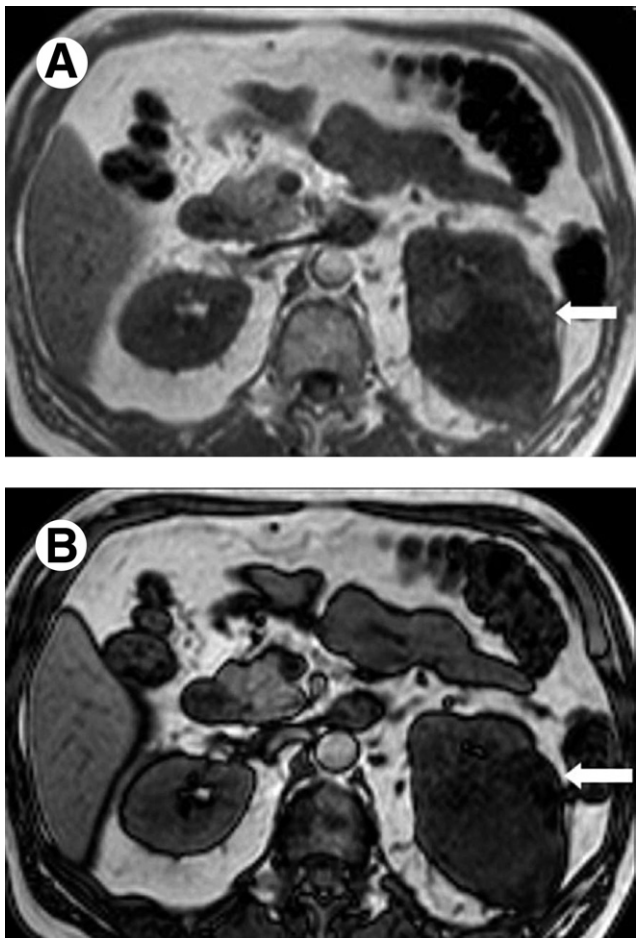

Figure 10 Clear cell carcinoma with intracellular fat demonstrated on MRI. (A) Axial in-phase T1-weighted image shows a large left exophytic renal mass. (B) Axial, opposed phase T1-weighted shows that anterior portion of this mass drops significantly in signal intensity (arrows), confirming the presence of microscopic fat. An India ink artifact is noted at the interface of mass with perinephric fat.

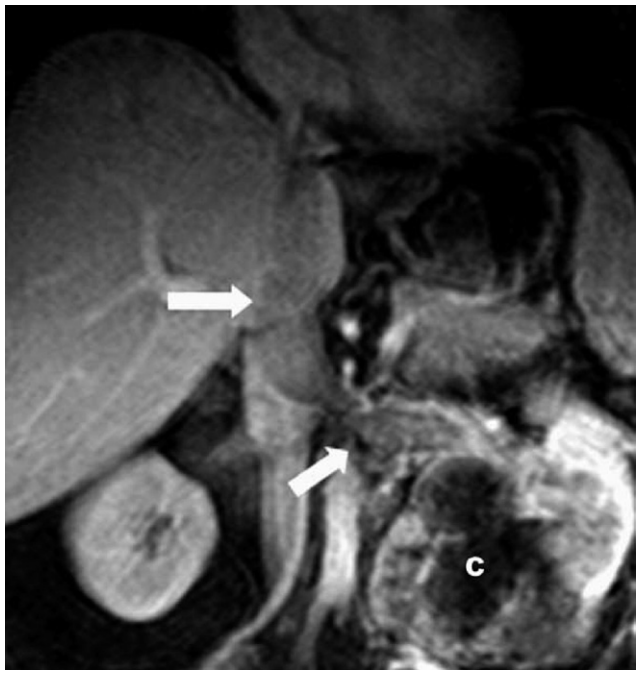

Figure 11 Clear cell RCC with characteristic angio-invasion. Coronal, gadolinium-enhanced T1-weighted MRI shows a large clear cell RCC (C) arising from the left kidney with associated tumor thrombus that extends into the left renal vein and the IVC (arrows).

Intratumoral necrosis, hemorrhage, cysts, and foci of calcification contribute to heterogeneity in clear cell RCCs. Clear cell RCCs typically show intense contrast enhancement during CMP and prompt de-enhancement during NP (Fig. 9). In a study of surgically resected, stage 1 renal cancers measuring <3.5 cm, all clear cell RCCs showed a peak enhancement of >100 HU during CMP.[35] Additionally, there was a direct correlation between the pattern of contrast enhancement and microvessel density at histology. In another series of 108 clear cell RCCs, Zhang et al found avid contrast enhancement (>140 HU) in 90% of tumors with a median attenuation value of 163 HU during CMP.[36] The presence of microscopic

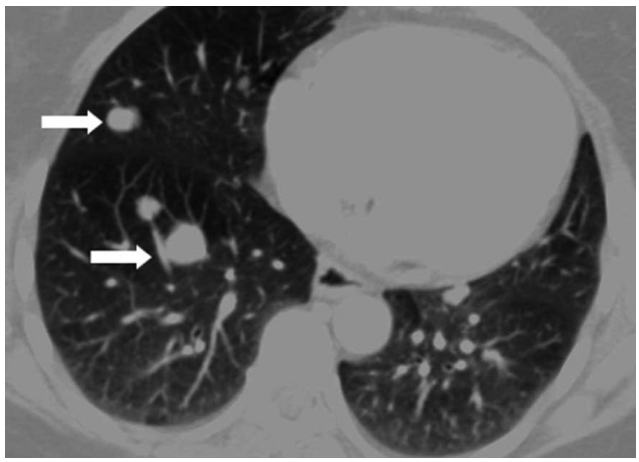

Figure 12 Metastatic clear cell RCC. Axial CT image of the lower thorax demonstrates multiple metastatic pulmonary metastases (arrows) from clear cell RCC.

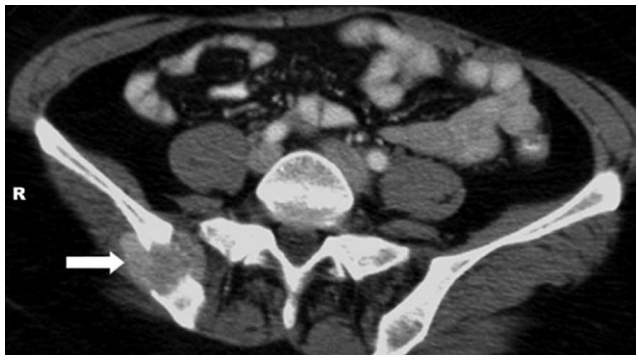

Figure 13 Osseous metastases from clear cell RCC. Axial CECT image in the pelvis from the same patient shows a lytic metastasis in the right iliac bone with enhancing soft tissue (arrow).

fat on opposed phase T1W MRI is an uncommon associated finding with these tumors[37] (Fig 10).

Clear cell RCCs represent a spectrum of disease ranging from indolent to aggressive that can be predicted by the Fuhrman (pathologic) grade to some extent. However, this subset does comprise 95% of all metastatic RCCs. Clear cell RCCs demonstrate marked proclivity to involve and grow along the veins, including the renal vein and the inferior vena cava (IVC) (Fig. 11). Tumor extension into the renal vein and IVC are seen in approximately 25% and 10% of RCCs, respectively, with 10% of vena-caval thrombi also extending into the right atrium.[38] Both MDCT and MRI are comparable for detection of venous involvement with accuracy and negative-predictive value of 96% and 99%, respectively.[39] Hematogenous metastases primarily involve the lungs, liver, and bones (Figs. 12 and 13). One-sixth of clear cell RCCs also demonstrates lymph node metastasis (Fig. 14). As a generalization, clear cell RCC exhibits a poorer prognosis (stage for stage) than other common, nonclear, histologic subtypes but is not as aggressive as type II papillary or medullary carcinoma.[40]

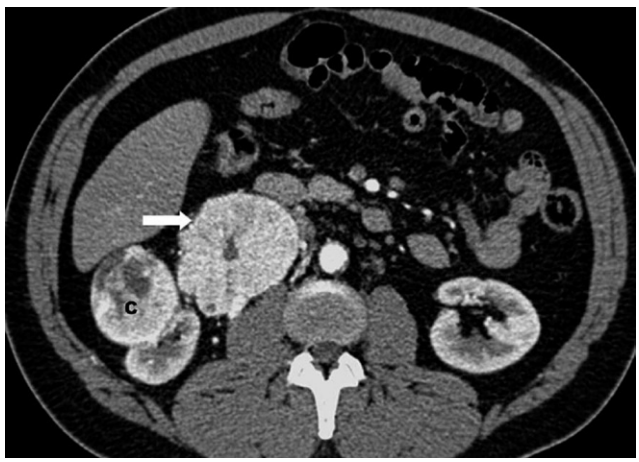

Figure 14 Lymph node metastases from clear cell RCC. Contrast-enhanced CT demonstrates an exophytic, hypervascular clear cell carcinoma (C) arising from the right kidney with associated hypervascular regional lymphadenopathy (arrow).

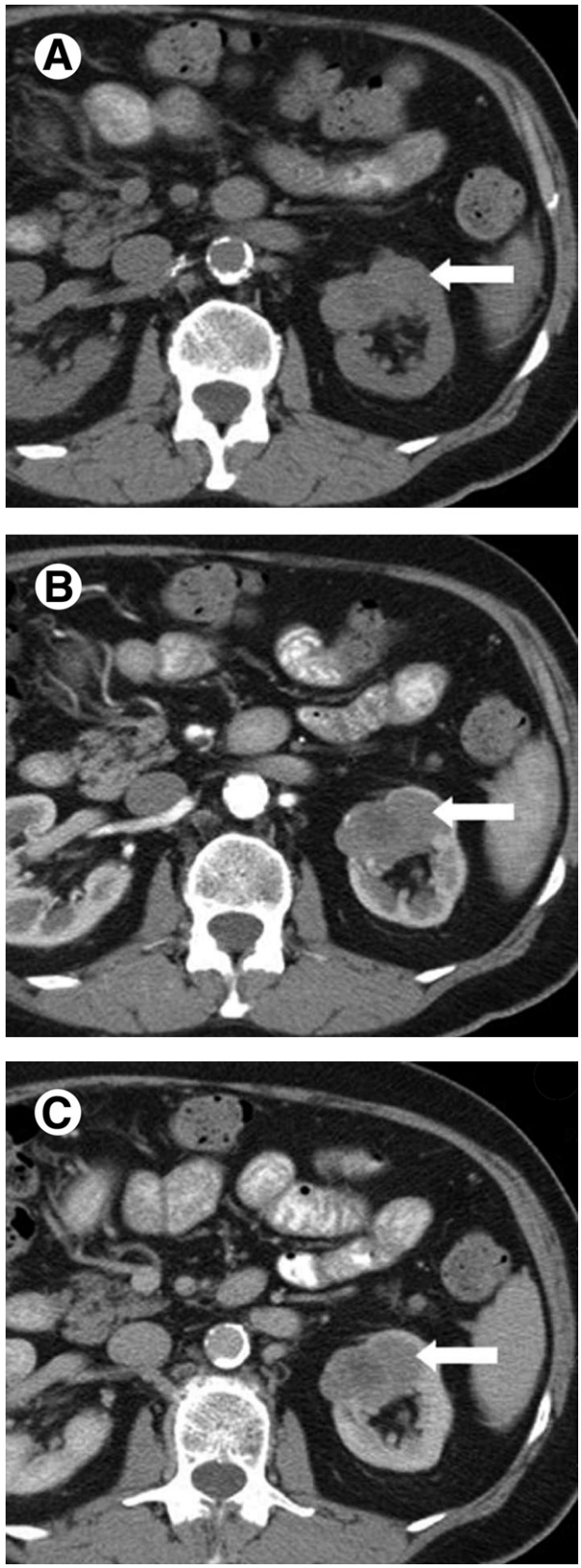

Figure 15 Sporadic papillary RCC. Axial CT images from a dedicated renal mass CT protocol shows a papillary RCC. (A) Noncontrast image shows an iso-hypodense left renal mass (arrow). (B) Corticomedullary and (C) nephrographic phase images demonstrate mild internal enhancement within the lesion (arrows).

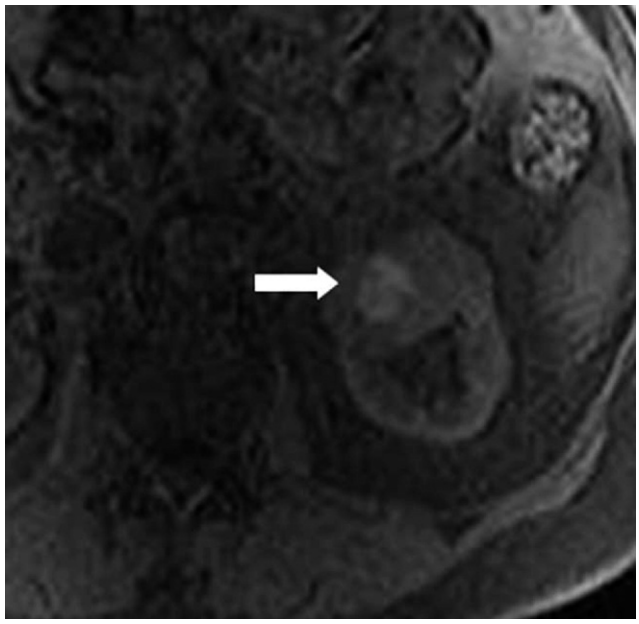

Figure 16 Sporadic papillary RCC. Axial precontrast, fat-suppressed, T1-weighted MRI shows hyperintense signal (arrow) within the left papillary RCC, suggesting hemorrhage.

Sporadic papillary RCCs are frequently multifocal and often seen in the setting of acquired renal cystic disease.[41] In contradistinction to clear cell RCC, papillary RCCs appear relatively hypovascular and often homogenous on contrast-enhanced CT and MRI (Fig. 15).[34,42] In a series of 30 papillary RCCs, 75% of papillary RCCs were hypovascular with a median attenuation value of 76 HU in the parenchymal phase.[36] In contradistinction to 90% of clear cell RCCs that showed avid enhancement, only 2% of papillary RCCs showed avid enhancement.[36] Up to 90% of papillary RCCs show uniform attenuation on multiphase CT and MRI. Large tumors demonstrate heterogeneity due to necrosis, hemorrhage, and calcification (Fig. 16). Papillary RCCs commonly demonstrate low signal intensity on T2-weighted images possibly due to the presence of byproducts of hemorrhage and necrosis (Fig. 17).[43] This finding was present in 94% of the tumors in a recent study of 55 papillary RCCs.[44] Papillary RCCs rarely demonstrate intratumoral macroscopic fat that histologically corresponds to cholesterol-laden macrophages.[45]

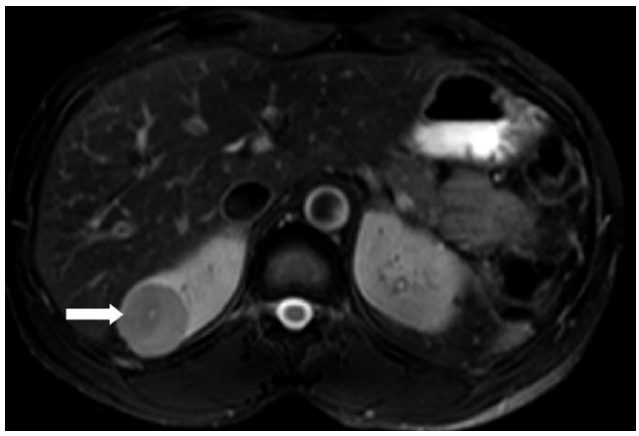

Figure 17 Sporadic papillary RCC. Axial, fat-suppressed T2-weighted MRI of a right papillary RCC (arrow) demonstrates a homogeneously hypointense solid mass.

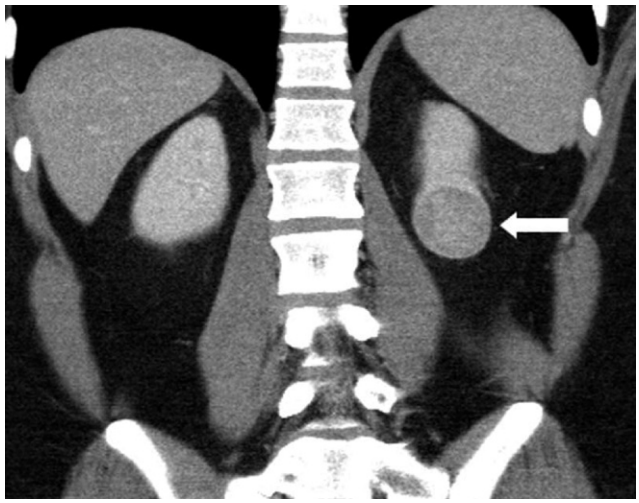

Figure 18 Sporadic chromophobe RCC. Coronal, multiplanar reformatted image from a contrast-enhanced CT shows a well-circumscribed solid mass with homogenous enhancement in the left lower renal pole.

Chromophobe RCCs, even when large, typically show homogeneous enhancement, while most clear cell RCCs appear heterogeneous. Chromophobe RCCs commonly show moderate contrast enhancement (intermediate to that of clear cell and papillary variants) during CMP (Fig. 18). In a series of 24 chromophobe RCCs, a median attenuation of 117 HU (range, 72-189 HU) was noted in the parenchymal phase. While 54% of chromophobe RCCs showed moderate enhancement (97-140 HU), 25% of tumors showed avid contrast enhancement (>140 HU) during the parenchymal phase.[36] Perinephric extension and renal vein involvement are seen in approximately 10% and 4% of tumors.[46] A spoke-wheel pattern of contrast enhancement akin to that seen with oncocytomas has also been described with chromophobe RCCs.[47]

Impact of Molecular Biology on Management and Prognostication of Renal Cell Carcinomas

Delineation of the molecular mechanisms in hereditary RCC syndromes offers unique insights into the pathogenesis of sporadic tumors and identifies points where targeted disruption might prevent cancer progression. Patients with VHL, HPRC, or BHD syndrome are usually managed expectantly until renal lesions reach 3 cm.[48] For lesions >3 cm, nephron-sparing procedures are recommended.[49,50] However this approach may not be advisable in patients with HLRCC, as these tumors tend to be aggressive.[48,49,51,52]

Sporadic RCCs are remarkably resistant to conventional cytotoxic chemotherapy, with response rates as low as 4%-

Table 3 Molecular Therapeutics in Renal Cell Carcinoma

Agent	Molecular Target	Current Status
Temsirolimus	mTOR inhibitor, serine threonine kinase	Phase 3 trials, FDA approved
Bevacizumab	Recombinant antibody against VEGF	Phase 3 trials, FDA approved
Sunitinib, sorafenib	Multikinase inhibitors targeting PDGFR, VEGFR, kit, and FLT3	FDA approved
AG-013736	Tyrosine kinase inhibitor targeting VEGFR-1, -2, -3, and PDGFR-B and c-kit	Phase 2 trials
PTK787/ZK 222584	VEGFR-1, VEGFR-2, and PDGFR inhibitor	Phase 1 and 2 trials

6%.[53] As a direct impact of strides in elucidation of oncogenic pathways, therapeutic agents aimed at specific molecular targets are being developed and used to treat patients with RCCs (Table 3). Patients with advanced clear cell RCCs are being treated by small molecules that interrupt the *VHL* downstream pathways.[54] A phase III trial of soranefib (orally bioavailable multikinase inhibitor) in 903 patients refractory to cytokine therapy demonstrated prolongation of progression-free survival to 5.5 months compared to 2.8 months for those patients on placebo ($P < 0.01$).[55] In a phase 2 trial, bevacizumab (VEGF antagonist) improved progression-free survival and achieved a 10% objective rate of tumor response in patients with RCCs.[56]

Given the novel mechanism of action of these targeted drugs, the classic response evaluation criteria in solid tumors (RECIST) guidelines based on reduction in tumor size may not be appropriate for evaluating response.[57] Most new agents inhibit cell growth, prolong stable disease, and only cause moderate tumor shrinkage (Fig. 19). If judged by RECIST guidelines alone, these new drugs may not show antitumor activity, despite providing substantial benefit in progression-free or overall survival, which is a credible endpoint in oncology trials.[58] Novel, advanced CT, MRI, and positron emission tomography techniques are being investigated to serve as better surrogate markers for quantitative treatment response.[59] Changes in tumor angiogenesis and metabolic activity may be detected early by such modalities and may have implications in management.

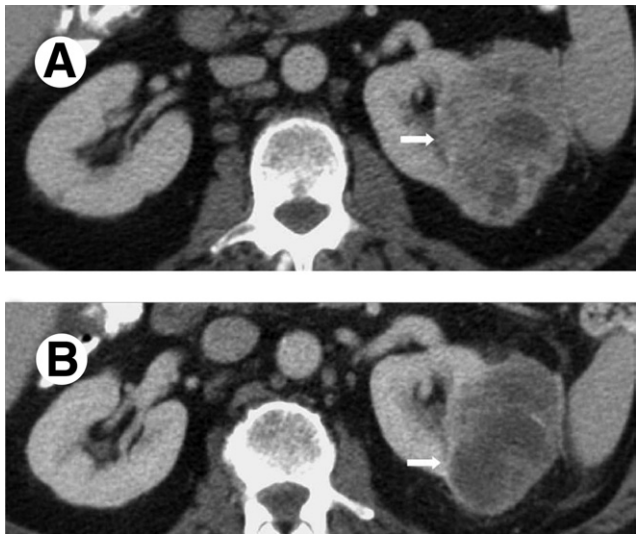

Figure 19 Treatment response in advanced clear cell RCC following sorafenib therapy. Axial contrast-enhanced CT images pre- (A) and post- (B) treatment, showing changes in tumor morphology with increase in tumor necrosis but without significant decrease in tumor size.

It is evident from the prior discussion that RCC is a heterogeneous disease with diverse histopathologic/behavioral profiles and prognosis. Stage-for-stage, clear cell RCC is commonly associated with less favorable prognosis compared with papillary and chromophobe RCCs. Approximately 70% papillary RCCs are intrarenal at presentation and show better prognosis. Type 1 papillary tumors are typically associated with better prognosis than type 2 tumors.[60] It is also well established that medullary RCC subtypes are associated with aggressive clinical behavior and poor prognosis.

Conclusions

Genetic and histologic characterization of RCCs have established that different subtypes of RCCs are characterized by distinct molecular signatures, possibly reflecting the differences in cell type, biology, and underlying oncologic mechanisms. Hereditary RCC syndromes, although rare, provide an invaluable model to study molecular mechanisms of renal carcinogenesis. Knowledge of the long-recognized histologic subtypes and the ability to detect the underlying genetic causes continue to evolve. Doubtless, additional hereditary syndromes await discovery. The current knowledge-base of cytogenetics and molecular pathology of histologic subtypes of RCC permits us to better understand nosology, tumor biology, imaging findings, and prognostic factors leading to optimal patient management strategies.

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