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Review Article

Molecular aspects of renal cell carcinoma: a review

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Abstract: Renal cell carcinoma (RCC) is a disease in which cancer cells form in the tubules of the kidney. RCC, the incidence of which is increasing annually, represents five percent of adult epithelial cancers. Clear cell carcinoma represents the most frequent histological subtype. RCC is characterized by a lack of early warning signs, diverse clinical manifestations. Incidentally detected tumors in asymptomatic individuals have been steadily increasing owing to the increased usage of various imaging technologies. Currently there are no recommendations for screening to detect and make an early diagnosis of renal cancer. But in recent years, the discovery of new molecular and cytogenetic markers has led to the recognition and classification of several novel subtypes of RCC, and the introduction of molecular-targeted therapy for advanced-stage RCC. We performed a literature review using PubMed and discuss current knowledge of epidemiology, pathophysiology, evaluation, treatment, and future research directions of RCC.

Keywords: Renal cell carcinoma, von hippel lindau, chemotherapy

Introduction

Renal cell carcinoma (RCC), the incidence of which is increasing annually, will account for approximately 3.8% of adult malignancies and 90-95% of neoplasms arising from the kidney in 2010 [1]. Up to 30% of RCC patients present at advanced stages, and approximately 40% of patients who undergo curative surgical resection experience recurrence during subsequent follow-up [1,2]. RCC is characterized by a lack of early warning signs, diverse and variable clinical manifestations, resistance to radiation and chemotherapy, and infrequent but reproducible responses to immunotherapeutic agents such as interferon alpha (INF-α) and interleukin (IL-2). Newer agents, such as sorafenib and sunitinib, which are orally available, are multi-targeted tyrosine kinase inhibitors which specifically interfere with platelet-derived growth factor receptor (PDGF-R) and vascular endothelial growth factor (VEGF) [3,4]. Temsirolimus, a mammalian target of rapamycin (mTOR) inhibitor, was also recently approved by the FDA for the treatment of RCC [5]. This article focuses on the epidemiology, pathophysiology, histology, staging, diagnostic evaluation, therapeutic options, and follow-up of this disease.

Epidemiology

There will be an estimated 58,240 new cases of and 13,040 deaths from renal cancer in 2010 in the United States, accounting for 2.3% of all cancer deaths in the United States [1]. The incidence has steadily increased during the past 50 years in the United States and has occurred in 9.1 per 100,000 in 1997, with a mortality rate of 3.5 per 100,000 [6,7,8]. The American Cancer Society predicts that there will be about 54,000 cases of kidney cancer in the United States in 2008, and about 13,010 people will die from this disease [9]. Reported worldwide incidence rates range from 0.6 per 100,000 to 14.7 per 100,000 [10]. Most tumors present in the fifth to seventh decades of life, with a median age at diagnosis of 66 years and median age at death of 70 years. The incidence is two

to three times higher in men and is slightly more common in blacks than in whites [6]. At autopsy, the incidence of renal tumors is approximately 2% [11]. In general, the tumors are usually solitary but may be multifocal in 6-25% of patients, and bilateral disease is diagnosed in 4% of all RCC patients [12]. Certain genetic conditions are associated with an increased incidence of RCC, including von Hippel-Lindau disease, hereditary papillary renal cancer, and possibly tuberous sclerosis [13]. RCC occurs in von Hippel-Lindau disease in 35-40% of patients, arises at a younger age, and is frequently bilateral (75%) or multifocal (87%) [14]. In these patients, the disease has a 5:1 male predominance. Overall, other suggested risk factors include cigarette smoking, obesity, diuretic use, exposure to petroleum products, chlorinated solvents, cadmium, lead, asbestos, ionizing radiation, high-protein diets, hypertension, kidney transplantation, and HIV infection [6,12,15,16].

Pathophysiolgy

Loss of the Von Hippel-Lindau tumor suppressor gene & HIF-related events in RCC tumor biology

Identification of the Von Hippel-Lindau (VHL) gene and understanding the function of this pathway in RCC tumorigenesis has played a major role in the development of RCC therapeutics. VHL disease is a hereditary cancer syndrome that has proven to be highly informative with respect to the pathogenesis of clear cell RCC. In affected families, cancer risk is transmitted in an autosomal dominant manner on chromosome 3p, and the syndrome is manifested by retinal angiomas, central nervous system hemangiomas and clear cell RCC [17]. Individuals with VHL disease carry in their germline one wild-type VHL allele and one inactivated VHL allele. Pathologic changes ensue in VHL disease when the remaining wild-type allele is somatically inactivated in a susceptible cell type. Therefore, VHL is a classic two-hit tumor suppressor gene [17].

It has been shown that inactivation of the VHL gene is an early step in the development of clear cell RCC associated with VHL disease [17]. The VHL tumor suppressor gene is mutated in all hereditary RCC and approximately 50% of sporadic RCC, and thus the majority of clear cell RCCs appear to be linked to biallelic VHL inactivation (see **Table 1**) [18]. The majority of clear cell RCC demonstrates either a mutation of the VHL gene or downregulation of its protein product. Translation of VHL mRNA gives rise to protein that is referred to generically as VHL protein (pVHL), which has an important role in the cellular response to hypoxia [19]. Among the many functions attributed to pVHL, the one most clearly linked to the development of RCC is inhibition of hypoxia-inducible factor (HIF) [20]. HIF is a heterodimeric transcription factor consisting of an unstable α-subunit (HIF1α) and a stable β-subunit [21].

Under normal oxygen conditions, the pVHL complex polyubiquitinates HIF1α, tagging it for destruction by the proteosome [22]. Under low oxygen conditions or in cells lacking pVHL, HIF1α accumulates, binds to HIF1β and transcriptionally activates hypoxia-inducible genes [21].

The consequence of mutated pVHL is similar to that of cellular hypoxia causing HIF dimerization and stabilization. During hypoxia, there is accumulation of hydroxyl-free HIF that no longer binds to VHL. HIF1α is stabilized by dimerization with the constitutively expressed HIF1β subunit and translocates to the nucleus. The HIF1α and HIF1β complex binds to HIF inducible gene promoter regions, including genes implicated in angiogenesis, pH regulation, glycolysis, glucose transport, cell cycle, chemotaxis, signaling, and apoptosis [23].

VEGF-R pathway

Biallelic loss of VHL leads to upregulated transcription of growth factors such as VEGF, PDGF and TGF-α. These factors bind to their respective receptors (VEGF-R, PDGF-R and EGF-R), which are each tyrosine kinase receptors. Consequent binding of ligands to these receptors leads to downstream signaling that results in increased cell proliferation, upregulated angiogenesis and decreased apoptosis. RCC-associated mutations of pVHL are invariably inactivating the process of HIF destruction, suggesting that HIF plays a critical role in RCC carcinogenesis. Numerous HIF responsive genes have been described, with a number of these genes encoding proteins that are growth factor receptors or their ligands, some of which were listed above [24]. A number of HIF responsive gene products are implicated in tumorigenesis. Uncontrolled production of these growth factors

Table 1. Genetic alterations in renal epithelial neoplasms

Tumor type	Chromosome	Gene	Mechanism and manifestation	Other genetic alterations
Clear cell renal cell carcinoma	3p14.2 3p21 3p25	FHIT RASSFIA VHL	Dele-tion,mutation,methyla tion	+5q22,-6q,-8p12,-9p21, -9q22,-10q,-14q
Papillary renal cell carcinoma	7 17 7q31.1 7q31 Y	? FRA7G c-MET ?	Trisomy Trisomy Gain Gain Loss	+3q,+8,-9p21,+12,-14q,+16,+17q21,+20
Chromophobe renal cell carcinoma	1,2,6,10,13,17,21,Y	?	Multiple chromosome loss	-5q22,-8p,-9p23,-18q22
Oncocytoma	1,14 11q13	?	Loss Translocation	-1p,-8p,-11q13,14q,-19q,-21q,-X/Y, der(13)t(13;16)(p11;p11)
Collecting duct carcinoma	1,2,6,10,13q,13,14, 15,22	?	Deletion	-1q32,-6p,-8p,-9p,-13q,-19q32,-21q
Renal carcinoma associated with Xp11.2 translocation	1p34 1q21 17q23 17q25 3q23 Xq12	PSF-TFE3 PRCC-TFE3 CLTC-TFE3 ASPL-TFE3 ? Non O-TFE3	t(X;1)(p11.2;p34) t(X;1)(p11.2;q21) t(X;17)(p11.2;q23) t(X;17)(p11.2;q25) t(X;3)(p11;q23) inv(X)(p11.2;q12)	
Mucinous tubular and spindle cell carcinoma	1,4,6,8,9,11,13,14, 1,18,22	?	Multiple chromosome loss	-8p,-9p,-11q,+12q,+16q,+17,+20q
Metanephric adenoma	2p13 2p	?	Deletion Partial monosomy	Inv(9)(p12q13),t(1,22)(q22;q13), t(15;16)(q21;p13)

provides a stimulus for the tumor and endothelial cell proliferation.

Angiogenic stimuli produced secondary to metabolic demands of host tissues initiate the angiogenic response in healthy individuals. Upon binding to membrane receptors in vascular endothelial cells, a five-step process is triggered. Initially, the vascular endothelial basement membrane of the parent vessel breaks down, allowing a route for the development of a new capillary sprout. This is followed by migration of endothelial cells and chemoattraction [12]. This leading front of migrating cells is driven by enhanced proliferation of endothelial cells, followed by formation of capillary tubes via organization of the endothelial cells, and a recruitment of pericytes and vascular smooth muscle cells for capillary stabilization [25].

During tumorigenesis, the angiogenic switch is activated directly via induction of angiogenic growth factors or indirectly by recruiting host immune cells that release mediators of angiogenesis [26].

Induction of the HIF pathway results in production of VEGF. VEGF a key regulator of angiogenesis and functions are mediated through two tyrosine kinase receptors, VEGF-R1 and VEGF-R2, in vascular endothelial cells [27,28]. VEGF initially interacts with VEGF-R2 to promote endothelial cell proliferation, migration and vascular permeability, and subsequently activates VEGF-R1 to assist in the organization of new capillaries. Several therapeutics targeting angiogenic pathways are currently being evaluated in clinical trials for their efficacy and long-term clinical benefits, while others are being mechanistically

exploited toward the development of novel therapeutic modalities for treating RCC.

mTOR pathway

Another regulator of HIF1α levels in the cell is mTOR, whose signaling activity acts to increase the cellular levels of HIF1α, accentuating the overall elevation in levels caused by the absence of adequate pVHL function [29]. mTOR inhibitors have been previously described, and laboratory experiments have shown that antiproliferative effects of these inhibitors in RCC may result from the interruption of essential survival pathways and autophagy [30]. The effect of mTOR inhibitors on angiogenesis is likely to have an important function in RCC pathogenesis, a highly vascular tumor [30].

mTOR is a highly conserved serine/threonine kinase that forms quaternary complexes and has a key function in apoptosis, cell growth and tumor proliferation by controling cellular catabolism and anabolism [30]. mTOR may complex with a regulatory-associated protein of mTOR to form mTORC1 and can also complex with a rapamycin-insensitive companion of mTOR, to form another multimolecular complex named mTORC2. (Rapamycin is an inhibitor of mTOR.) mTORC1 may eventually be activated by growth factors and also the VEGF-R, PDGF-R, EGF-R, IGF receptor, and phosphatidyinositol 3-kinase/Akt (PI3K/Akt) pathways [31]. At the molecular level, it is known that tumor angiogenesis depends on vascular growth factors such as VEGF, PDGF, bFGF and members of the TGF-β superfamily. As these factors have been shown to be able to activate the PI3K/Akt/mTOR in cancer cells, endothelial cells or pericytes as described, mTOR complexes are also implicated in tumor angiogenesis biology [32].

Once activated, mTORC1 acts through its downstream effectors to stimulate protein synthesis, entrance into the G1 phase of the cell cycle and asserts control over proteins that regulate apoptosis. The witnessed activity of mTOR inhibitors in RCC has raised the possibility that patients who respond to this therapy share a common molecular phenotype that renders these tumors dependent on mTOR for growth and survival. In RCC, the PTEN gene has been shown to be downregulated in the majority of cases, presumably by epigenetic silencing [33].

It has been previously demonstrated that PI3K/Akt/mTOR signaling pathway inhibitors target tumor growth indirectly at the tumor level by interacting with the maintenance of endothelial cells and pericytes that are required for tumor angiogenesis [34].

A major stimulus of cancer angiogenesis is tissue hypoxia likely driven by tumorigenesis and growth initially lacking adequate blood supply. These conditions activate HIF1α, and the mTOR pathway further enhances the translation of HIF1α mRNA, thereby increasing the overall vasculogenic effect [35]. The observed clinical efficacy of mTOR inhibitors in RCC is mediated in part by dependence on efficient HIF translation in the mTOR pathway by interferring with the VEGF/VEGF-R and/or PDGF/PDGF-R signaling cascades. In summary, these data strongly suggest that the anticancer effects of mTOR inhibitors involve antiangiogenetic processes mediated by effects on endothelial cells and pericytes, rather than on RCC themselves [29].

NF-κB pathway

NF-κB is a family of transcription factors that has been associated with diverse cellular functions. NF-κB activation is associated with increased proliferation, tissue invasion, angiogenesis, inhibition of apoptosis, and the development of drug resistance [36]. NF-κB activation has also been associated with proliferative responses mediated by induction of expression of cyclin D1, which drives the transition from the G1 to the S phase of the cell cycle [37]. VHL loss ultimately drives NF-κB activation by resulting in HIFα accumulation, which induces expression of transforming growth factor alpha (TGF-α), with consequent activation of an EGF-R/phosphatidylinositol-3-OH kinase/protein kinase B (AKT)/IκB-kinase alpha/NF-κB signaling cascade [38].

NOx pathway

Reactive oxygen species (ROS) regulate hypoxia-dependent and hypoxia-independent activation of HIF1α. NAD(P)H oxidase systems are major sources of ROS. The NOx family of NAD(P)H oxidases have a core structure consisting of six transmembrane domains, including two heme-binding regions located at the N terminus and a cytoplasmic C terminus containing FAD- and NADPH-binding regions [39,40]. Reactive oxygen species, generated by NAD(P)H oxidases, are involved in signaling cascades of malignant growth. In VHL-deficient cells, NOx4 protein levels and NAD(P)H-dependent superoxide genera-

tion are increased. Reintroduction of VHL into the VHL-deficient cells down-regulates NADPH-dependent superoxide generation [41].

Tyrosin kinase pathway

Receptor tyrosine kinases (RTKs) constitute a superfamily of transmembrane proteins that relays signals from extracellular growth factors into the cell [42,43]. The TAM subfamily of RTKs contains the receptors Axl, Tyro3, and Mer [44,45]. They have in common a unique extracellular domain composed of two N-terminal immunoglobulin-like domains and two fibronectin type III repeats similar to the structure of neural cell adhesion molecules (NCAMs). TAM receptors share the same ligand, Gas6, a product of the growth arrest-specific gene 6 [46,47]. Gas6, cloned from serum-starved fibroblasts, is a member of the vitamin K-dependent family of Gla proteins homologous to the blood coagulation protein S [48]. Axl has been shown to affect neovascularization in vitro, and loss of Axl expression in tumor cells blocks growth of human neoplasms [49]. Perhaps, Axl on its own, by homophilic interactions and by a kinase domain-dependent mechanism [50], contribute to the disease-specific angiogenic programming during VHL loss in tumor cells in parallel with angiogenic factors such as VEGF. Gas6 signaling via Axl, on the other hand, has been shown to have inhibitory effects on the VEGFR-driven angiogenic program [51]. Gas6-mediated activation of Axl in clear cell carcinoma cells results in Axl phosphorylation, receptor down-regulation, decreased cell-viability and migratory capacity [52].

Mitogen-activated protein kinase pathway

Mitogen-activated protein kinase (MAPK) kinases (MKK) are crucial enzymes at the intersection of several biological pathways that regulate cell differentiation, proliferation, and survival. In response to a variety of extracellular stimuli, MKKs become activated and then phosphorylate MAPKs, including extracellular signal-regulated protein kinase (ERK), c-Jun-NH2 kinase (JNK), and p38 MAPK (p38) [53,54] Overexpression of MKK has been described in human RCC cases [55]. Sustained activation of ERK has been established as a requirement for angiogenesis as well [56,57].

HSP70 pathway

The major hsp70 are encoded by a duplicated locus (hsp70-1, hsp70-2) located in the MHC region, 92 kb telomeric to the C2 gene [58]. This segment of the MHC has been proposed to be termed the class IV region since it includes at least seven genes implicated to some degree in inflammation and in stress responses [59]. The two intronless genes (hsp70-1 and hsp70-2) encode an identical protein product of 641 amino acids. Hsp70-2 may have a potential role in cancer pathogenesis by participating in the regulation of antitumor immunity such as acting as a chaperone molecule for immunogenic tumor-associated peptides but also in regulatory processes such as the cell cycle. The possibility that a mutated hsp70-2 chaperone might have a dominant effect in tumor cells in triggering the G2/M phase transition during mitotic cell cycle cannot be excluded at the present time. Interestingly, among more than 100 RCC tumors studied in the laboratory, RCC-7 is the most aggressive one, with a rapid doubling interval in vitro and a high growth rate in SCID/nu mice. Preliminary experiments testing either the immortalizing or the transforming capacity of the mutated versus wild-type hsp70-2 cDNA in recipient cells have not led, however, to any direct evidence that the mutation plays a role in the oncogenic process [60].

Clinical course of RCC

Symptomtology and presentation

RCC can remain clinically occult for the majority of its course. The classic clinical presentation of flank pain, hematuria, and a palpable mass is relatively uncommon (only 5-10% of cases). In addition, clinical symptomatology, if ever present, is often nonspecific—for example, anorexia, fatigue, weight loss, or fever of unknown origin [61]. Other clinical manifestations include varicocele formation in men (from tumor thrombus in the left renal vein or the inferior vena cava or from extrinsic compression of these structures impairing return of blood from gonadal veins, more commonly left than right) and disseminated malignancy. RCC may also present with a variety of paraneoplastic syndromes, such as polycythemia secondary to excessive secretion of erythropoietin, hypercalcemia secondary to derangement of serum factors regulating calcium, and hepatic dysfunction (Stauffer syndrome). Incidentally detected tu-

mors in asymptomatic individuals have been steadily rising with the increase in use of imaging techniques, including computed tomography (CT), MRI, and ultrasonography. Incidental lesions accounted for approximately 60% of renal tumors during the 1990s, compared with only 10% in the early 1970s [62].

Pathology

On gross pathology, tumors most often appear encapsulated. Tumors may be solid, cystic, or mixed and can have calcification present [63]. As many as 10% of tumors have some cystic component [64], and such tumors may be more clinically aggressive [65]. Each of these subtypes of RCC has different cytogenetic and immunohistochemical profiles. Histopathologic grading of the nuclei of the tumor is made by dividing them into the four-tier Fuhrman nuclear classification [66], with grade I representing well-differentiated and grade IV the most anaplastic, poorly differentiated.

Histologic subtypes according to the Heidelberg classification (and relative incidence) include clear cell (conventional) adenocarcinoma (80%), papillary (15%), chromophobe (5%), collecting duct (1%), and unclassified (4%) [67-69].

Clear cell carcinoma displays large uniform cells with abundant clear cytoplasm rich in glycogen and lipid. Clear cell carcinoma is typically highly vascular. Papillary tumors are subdivided into type I tumors, which occur sporadically and metastasize somewhat late and are often composed of papillae covered by single-layered small cells with pale cytoplasm and round ovoid nuclei. Type II papillary RCC lesions, which are more likely inherited, may be multicentric, have pseudostratified large cells with relatively abundant eosinophilic cytoplasm, and often present with a higher Fuhrman grade and poorer prognosis. Collecting duct tumors arise from the medullary collecting duct and may show morphological features of both adenocarcinoma and urothelial carcinoma, often occur in younger patients and are associated with a poor overall prognosis. Renal medullary carcinoma is a rare subtype of collecting duct carcinoma and has a very poor prognosis. It is seen more commonly in young patients with sickle cell anemia or the sickle trait. Chromophobe tumors and oncocytomas, both of which arise from collecting duct epithelium, are similar on histologic examination but have differing immunohistochemical profiles. Chromophobe tumors have the best overall prognosis, and oncocytomas are benign [18,70].

Staging

The tumor, nodes, and metastases (TNM) classification is endorsed by the American Joint Committee on Cancer (AJCC). The major advantage of the TNM system is that it clearly differentiates individuals with tumor thrombi from those with local nodal disease. In the Robson system, stage III inferior vena caval involvement (IIIA) is the same stage as local lymph node metastases (IIIB) [71]. These entities can have highly differing clinical courses. The TNM classification system is presented in **Tables 2, 3** and **4**.

Diagnostic evaluation

Currently, there are no accepted methods for screening or early diagnosis of renal cancer. Although population-based screening by renal ultrasound would undoubtedly detect renal tumors in asymptomatic individuals, this is not considered cost effective, and the implications of population screening from a public health perspective are enormous. Cost, increased morbidity and mortality, and reduced quality of life from increased detection and intervention cannot be ignored when considering secondary prevention (screening) strategies. Neither the US Preventative Task Force nor American Cancer Society, for example, has official screening recommendations for or against screening for RCC. No serological tests are currently available for the early detection of renal cancer. Initial tests performed at the time of diagnosis include urinanalysis, CBC count with differential, electrolytes, renal profile (serum creatinine and/or glomerular filtration rate), liver function tests, serum calcium, erythrocyte sedimentation rate, prothrombin time, activated partial thromboplastin time. Other tests may be indicated for symptomatic patients.

A large proportion of patients diagnosed with renal cancer have small tumors. A number of different diagnostic imaging modalities, such as excretory urography, CT scan, ultrasonography, arteriography, venography, magnetic resonance imaging (MRI), and positron emission tomography (PET), are used to evaluate and stage renal masses.

Table 2. TNM Staging of Renal Cell Carcinoma. Adapted from current version of American Joint Committee On Cancer (2002)

Stage	Description
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor < 7 cm in greatest dimension, limited to kidney
T1a	Tumor < 4 cm in greatest dimension, limited to kidney
T1b	Tumor > 4 cm but < 7 cm in greatest dimension, limited to kidney
T2	Tumor ≥7 cm in greatest dimension, limited to kidney
T3	Tumor extends into major veins or invades adrenal gland or perinephric tissues, but not beyond Gerota's fascia
T3a	Tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
T3b	Tumor grossly extends into renal vein(s) or vena cava below diaphragm
T3c	Tumor grossly extends into vena cava above diaphragm
T4	Tumor invades beyond Gerota's fascia
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node
N2	Metastasis in more than one regional lymph node
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 3. TNM stage groupings. Adapted from current version of American Joint Committee On Cancer (2002)

Stage Grouping	T stage	N stage	M stage
I	T1	N0	M0
II	T2	N0	M0
III	T1	N1	M0
	T2	N1	M0
	T3	N0	M0
	T3	N1	M0
IV	T4	N0	M0
	T4	N1	M0
	Any T	N2	M0
	Any T	Any N	M1

The goals of radiologic imaging include detection and staging of the primary tumor. In most institutions, CT is the primary imaging technique used for the evaluation of renal tumors. In some instances, such as when a patient has an allergy to iodinated contrast medium, MRI or ultrasonography are suitable alternatives. With MRI and its common gadolinium-based contrast agents, there is a small risk of nephrogenic systemic fibrosis in patients with impaired renal function and should be considered carefully when staging with MRI is deemed advisable [72].

For the evaluation of metastatic disease and local recurrence, CT has excellent sensitivity

Table 4. Survival by TNM stage. Adapted from current version of American Joint Committee On Cancer (2002)

Disease Extent	TNM Stage	5-year Survival Rate (%)
All organ-confined	T1-T2N0M0	70-90
<4cm	T1aN0M0	90-100
>4 but <7cm	T1bN0M0	80-90
>7cm	T2N0M0	70-80
Invasion of perinephric fat	T3aN0M0	60-80
Adrenal involvement	T3aN0M0	0-30
Venous involvement	T3b-T3cN0M0	40-65
Locally advanced	T4N0M0	0-20
Lymphatic involvement	Any T,N+,M0	0-20
Systemic metastases	Any T, any N,M1	1-10

and is the standard imaging test. Nuclear medicine studies with PET have limited sensitivity for evaluating metastatic RCC and particularly for small metastatic lesions. However, a positive PET scan should be considered strongly suspicious for local recurrence or metastasis, because of the high specificity and PPV of this test. A combined test (PET-CT) may be necessary if important management decisions are to be based on the test result. This would take advantage of the high sensitivity of CT and high specificity of PET in patients with metastatic RCC [73,74].

Chest CT should be performed if the primary tumor is large or locally aggressive because metastases are more common in these patients. Chest radiography without CT should be reserved for patients with a low risk of metastatic disease or for those in long-term follow-up [75]. Sonography can be useful for assessing the presence and extent of venous thrombus. It can also be helpful in distinguishing cysts from hypovascular solid tumors seen on CT (e.g., papillary RCC). Sonography can reveal septations within a lesion better because of complex interfaces and the ultrasound beam. Sonography has reported accuracies for T staging of 77-85% [76,77] and for detection of venous thrombus of 87% of the time [78]. However, it has limitations in visualizing the retroperitoneum and perinephric tissues [78,79], although some proponents argue otherwise [77].

MRI is generally only used when optimal CT imaging cannot be performed (iodinated contrast allergies, poor renal function, pregnancy). MRI has similar reported overall staging accuracies to those of CT [80]. Its multiplanar capability, however, is particularly useful for delineating the superior extent of tumor in the IVC [81]. Preoperative percutaneous biopsy of renal lesions is generally not undertaken because the results usually do not affect what therapy will be recommended except in patients with multiple tumors or occasionally in patients with an underlying predisposing condition. Percutaneous biopsies may be considered in selected cases—for example, when an abscess or metastatic disease from a known primary tumor is suspected, especially from lymphoma or melanoma [12].

Approximately 20% of patients have multiple renal arteries, and many surgeons find preoperative CT or MR angiograms to be valuable, particularly when partial nephrectomy or laparoscopic approaches are planned. Three-dimensional and multiplanar reformatted images, as well as angiographic displays, aid appreciation of the relationships of the tumor to the collecting system, adjacent normal parenchyma, and vascular supply at the renal pedicle [12,82,83].

The efficacy of PET in renal malignancy remains under investigation. It shows some potential in staging, the detection of unsuspected metastases, follow-up, and the evaluation of indeterminate renal masses, but CT remains the standard of care [84-87].

Treatment

Radical nephrectomy, which remains the most commonly performed standard surgical procedure today for treatment of localized renal carcinoma, involves complete removal of Gerota's fascia and its contents, including a resection of

kidney, perirenal fat, and ipsilateral adrenal gland, with or without ipsilateral lymph node dissection. Radical nephrectomy provides a better surgical margin than simple removal of the kidney, since perinephric fat may be involved in some patients. Twenty to thirty percent of patients with clinically localized disease develop metastatic disease after nephrectomy. Some surgeons believe that the adrenal gland should not be removed because of the low probability of ipsilateral adrenal metastasis and the morbidity associated with adrenalectomy. In the absence of distant metastatic disease with locally extensive and invasive tumors, adjacent structures such as bowel, spleen, or psoas muscle may be excised en bloc during radical nephrectomy [12].

Ipsilateral adrenalectomy is included in the classic radical nephrectomy. However, ipsilateral adrenal metastases occur in only 1-10% of patients. It occurs especially in large left-sided upper pole tumors, usually by direct extension (i.e., T3a tumors) [88]. One of the roles of imaging is to assist in allowing adrenal-sparing nephrectomies in order to reduce the risk of future adrenal insufficiency [8].

Laparoscopic nephrectomy is a less invasive procedure than open radical nephrectomy, incurs less morbidity, and is associated with shorter recovery time and less blood loss. The need for pain medications is reduced, but operating room time and costs are higher. Disadvantages include concerns about spillage and technical difficulties in defining surgical margins. Laparoscopic partial nephrectomy can be considered at centers with experience in this procedure for early stage renal cell cancers generally less than 4 cm in largest dimension [12].

Palliative nephrectomy should be considered in patients with metastatic disease for alleviation of symptoms such as pain, hemorrhage, malaise, hypercalcemia, erythrocytosis, or hypertension. Several randomized studies show improved overall survival in patients presenting with metastatic kidney cancer who have nephrectomy followed by either interferon or IL-2. If the patient has good physiological status, then nephrectomy should be performed prior to immunotherapy [89].

Nephron-sparing surgery (i.e., partial nephrectomy) has been shown to be equally as efficacious as radical nephrectomy, with reported local recurrence rates of < 2% and 5-year survival rates of 87-90%, which are comparable to those from radical nephrectomy [59]. This more limited treatment of a presumed cancerous lesion is generally reserved for lesions less than 4 cm in size along the largest dimension, for patients with poor renal reserve or function, or solitary kidney. In the case of a solitary kidney, though, there is increased risk of developing proteinuria, focal segmental glomerulosclerosis, and progressive renal failure exists if more than 50% of the renal mass is removed [83].

Micrometastasis to lymph nodes may be present in 10-25% of patients. The 5-year survival rate in patients with regional node involvement is substantially lower than in patients with stage I or II disease. Regional lymphadenectomy adds little in terms of operative time or risk and should be included in conjunction with radical nephrectomy [12,83,90,91]. Cryoablation and radiofrequency ablation, which may be undertaken laparoscopically or percutaneously, are promising techniques for treating small tumors [83].

Chemotherapy

A recent phase 2 trial of weekly intravenous gemcitabine (600 mg/m^2 on days 1, 8, and 15) with continuous infusion fluorouracil (150 mg/m^2/day for 21 days in 28-day cycle) in patients with metastatic renal cell cancer produced a partial response rate of 17%. No complete responses were noted. Eighty percent of patients had multiple metastases, and 83% had received previous treatment. The mean progression-free survival duration of 28.7 weeks was significantly longer than that of historic control [91].

Floxuridine (5-fluoro 2'-deoxyuridine [FUDR]), 5-fluorouracil (5-FU), and vinblastine, paclitaxel (Taxol), carboplatin, ifosfamide, gemcitabine, and anthracycline (doxorubicin) have each been studied and used in the treatment of metastatic RCC. Floxuridine infusion has a mean response rate of 12%, while vinblastine infusion yielded an overall response rate of 7%. 5-FU alone has a response rate of 10%, but when used in combination with interferon, it had a 19% response rate in some studies [92].

RCC is refractory to most chemotherapeutic agents because of multidrug resistance mediated by p-glycoprotein normally present in all

cells. This protein is responsible for efflux of drugs and other compounds deemed foreign to cells. Normal renal proximal tubules and renal cell carcinoma both express high levels of p-glycoprotein [93].

Follow-Up

For stage I and II disease, complete history, physical examination, chest radiographs, liver function tests, BUN and creatinine, and calcium are recommended every six months for two years, then annually for five years. Abdominal CT scan is recommended once at 4-6 months and then as indicated.

For stage III renal cell carcinoma, physical examination, chest radiographs, liver function tests, BUN and creatinine, and calcium are recommended every 4 months for 2 years, every 6 months for 3 years, and then annually for 5 years. Abdominal CT scan should be performed at 4-6 months, then annually or as indicated [94].

Prognosis

Investigators have attempted to identify pathological and morphological features within tumors that correlate with survival in patients with RCC. Tumor stage remains the most important factor predictive of survival in RCC [96-99]. In addition, tumor size [97], histological pattern [99], cell type [99], nuclear grade [97], DNA content [100], and nuclear morphometry [101] have been reported as prognostic surrogates for survival. Additionally, variables such as performance status [102], weight loss, time to progression, number and type of metastases [103], vascular invasion [104] and several laboratory values, e.g. haemoglobin level, ESR and alkaline phosphatase levels, have been studied in relation to prognosis [103]. Increasing knowledge of cytogenetic abnormalities and the role of oncogenes and tumor suppressor genes in RCC is critical, but the study of molecular mechanisms underlying RCC is still in its infancy; future studies will have to provide information on the implications for the prognosis of patients with RCC [105].

Immunotherapy and targeted therapies

The mainstay of systemic therapy for metastatic RCC has historically been immunotherapy (or cytokine therapy) with interleukin-2 (IL-2) and interferon-α (IFN-α). High-dose IL-2 has consistently produced a 15-20% response rate, 6-8% complete remission rate, and approximately 5% cure rate, however, it is a fairly toxic regimen [106,107]. IFN-α has provided modest survival benefit, has a more favorable toxicity profile, and is more easily administered than IL-2. As a result, IFN-α has been adopted as the control arm in many clinical trials evaluating the merits and characteristics of novel agents.

Novel therapies for metastatic RCC have targeted downstream effects of von Hippel-Lindau (VHL) gene inactivation and the resulting up-regulation of HIF target genes, notably VEGF and PDGF. Five targeted agents are presently in clinical use for metastatic RCC: sunitinib, sorafenib, temsirolimus, everolimus, and bevacizumab. Sunitinib (Sutent, Pfizer), interacts with an adenosine triphosphate binding site in multiple tyrosine kinase domains and prevents autophosphorylation; this multiple tyrosine kinase inhibitor (MKI) has shown an objective response rate of 31% and a median progression-free survival of 11 months for sunitinib-treated patients [108,109]. It is considered the standard-of-care treatment for patients with advanced-, good- and intermediate-risk conventional clear cell RCC. Sorafenib (Nexavar, Bayer HealthCare), another MKI, is considered second-line therapy after cytokine failure [4]. Temsirolimus (Torisel, Wyeth), an inhibitor of mammalian target of rapamycin (mTOR), is considered appropriate for patients with poor-risk metastatic RCC, irrespective of histology [110,111]. Bevacizumab (Avastin, Genentech), a humanized antibody to VEGF, has shown promise in patients with good- and intermediate-risk metastatic RCC [112,113] but has not yet been approved for metastatic RCC by the U.S. Food and Drug Administration (**Table 5**).

Bevacizumab (+ interferon-alpha), sunitinib, and temsirolimus (in poor-risk groups) have proven to be effective as first-line palliative treatments. Sorafenib has demonstrated benefits in patients that have failed prior therapy, as has everolimus after failure of sorafenib and/or sunitinib [114].

Conclusion

Renal cell carcinomas comprise a heterogenous group of epithelial tumors with variable clinical

Table 5. Clinical activity of selected vascular endothelia growth factor-targeted agents in advanced renal cell carcinoma

Reference	Agent	No	Trial design	Prior Therapy	Overall response rate
Yang et al	Bevacizumab	116	Randomized phase II high-dose bevacizumab versus low dose bevacizumab versus placbo	Cytokines	10% vs 0%
Motzer et al	Sunitinib	63, 106	Single-arm phase II single agent sunitinib	Cytokines	40%,34%
Motzer et al	Sunitinib	750	Randomized phase III sunitinib versus IFN-a	None	31 vs 6%
Escudier et al	Sorafenib	903	Randomized phase III sorafenib versus placebo	Various	2% vs 0%
Hudes G et al	Temsirolimus	626	Randomized phase III temsirolimus versus IFN-a versus temsirolimus+IFN-a	None	9% vs 7% vs 11%

outcomes. Hopefully, genetic hallmarks will be identified in the various histological subtypes and improve understanding of the antiapoptotic and immune escape mechanisms that allow for oncogenic growth. These mechanisms may then be specifically targeted with novel agents in the treatment of advanced disease and will result in novel approaches allowing rational combinations of drugs with immunostimulating effect. Much work still needs to understand, treat, and ultimately control RCC.

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