Renal cell carcinoma for the nephrologist

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Renal cell carcinoma (RCC), a malignancy whose incidence is increasing, is frequently encountered in general nephrology practice when acute and chronic kidney disease occurs in the course of disease. Importantly, when kidney disease develops in the setting of RCC, mortality is significantly increased with patients often dying of a non-cancer-related complication of kidney disease. As such, practicing nephrologists need to have a working knowledge of this cancer's biology, treatment, and complications. Nephrologists should be involved in all aspects of the care of patients with RCC including in the acute setting prior to nephrectomy and in the chronic setting for patients with post-nephrectomy chronic kidney disease and those receiving potentially nephrotoxic anti-cancer agents. This collaborative approach to RCC care will hopefully improve patient outcomes.

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Renal cell carcinoma (RCC) is commonly encountered in the practice of nephrology, particularly when acute kidney injury (AKI) or chronic kidney disease (CKD) develops in patients with RCC or when a mass is incidentally discovered during workup of kidney disease.[1,2] Importantly, RCC is a disease of increasing incidence, which is in part related to more sensitive imaging modalities.[1,2] Clear cell RCC, the focus of this review, is the most common histological subtype.[3,4] Other less common kidney cancers include papillary, chromophobe, and other rare tumors of the nephron and collecting system and are not discussed here.

Biology of clear cell renal cell carcinoma

Approximately 80% of all RCCs are of the clear cell type, in which the von Hippel-Lindau (VHL) gene product has been implicated in both the genetic and sporadic forms of RCC.[1–3] The *VHL* gene has been mapped to chromosome 3p25,[5] and its gene product, VHL protein, functions as a tumor suppressor.[6] In clear cell RCC, the *VHL* gene is commonly mutated leading to loss of function.[7–9] The presence of an inherited inactivated or deleted *VHL* allele through heterozygous inheritance is associated with a lifetime cumulative RCC incidence that approaches 70%.[10] Most sporadic RCCs are characterized by inactivation of both *VHL* alleles—one through inheritance and the other through a somatic mutation. Ultimately, this results in the loss of the regulatory VHL protein, which modifies the cellular response to hypoxia through regulation of the hypoxia-inducible factor-α (HIFα) subunit.[11]

VHL protein forms a stable complex with a number of proteins, which include cullin-2 and elongin-B and -C. The VHL complex regulates the cellular concentration of several proteins by targeting them for proteasomal degradation.[12–14] The VHL complex components act as an E3 ubiquitin ligase for target proteins, which when bound to the complex undergo proteasomal degradation. In addition to this regulatory function, VHL protein acts to regulate cytokinesis and the cell cycle, maintain primary cilium, control microtubule function, and maintain extracellular matrix integrity.

Oxygen sensing occurs within the kidney and regulates the production of erythropoietin as well as a number of other factors. Renal oxygen tension sets in motion the interaction of several factors including VHL protein, HIFα (HIF1α and 2α), the HIFαβ complex, and target *HIF* genes that ultimately determine the stimulation or suppression of a number of cellular processes. The alpha subunits are substrates for the VHL complex and are sensitive to oxygen tension. VHL

protein regulates HIFα by forming part of the E3 ubiquitin ligase complex, which degrades HIFα in the setting of normal oxygen tension.[15] HIFα degradation prevents formation of the HIFαβ complex, which binds to transcriptional gene targets at hypoxia response elements to regulate hypoxic gene expression. The prevailing oxygen tension controls post-translational prolyl hydroxylation at HIFα subunit residues and thus determines HIFα lability. With normal oxygen levels, prolyl hydroxylation leads to HIFα binding to VHL protein E3 ubiquitin ligase, resulting in degradation of the complex within the proteasome. When hypoxia is present, prolyl hyproxylase activity prevents HIFα proteolysis and permits formation of the active complex and activation of *HIF* target genes.[6,12–14] In this setting, this cascade promotes cellular proliferation, angiogenesis, and metabolic reprogramming. Some of these processes occur because production of vascular endothelial growth factor (VEGF), platelet-derived growth factor, and TGF-α are regulated by HIF1α and 2α.[6,12]

Tumor formation is thought to be related to the combined effect of various growth and angiogenic factors produced in an unregulated fashion in the setting of VHL protein deficiency. It is notable that although complete *VHL* gene inactivation occurs, its effect on clinical outcomes and disease progression are unclear. For example, tumors in those with VHL disease are often of lower grade and less likely to metastasize as compared with sporadic clear cell kidney cancers.[10,11] It is probable that other signaling pathways and cellular processes are more important in aggressive sporadic RCCs.[10,11] The malignant behavior of RCCs appears to be related to "apparent" hypoxia and dysregulation of the HIF pathway and target genes. Loss of VHL suppressor function results in the constitutive (and unregulated) stabilization of HIF independent of oxygen tension, resulting in a pseudo-hypoxic state,[16,17] which promotes abnormal biological responses and paraneoplastic syndromes.

In addition to the HIF-hypoxia pathway in clear cell RCC, a number of metabolic abnormalities are associated with the paraneoplastic syndromes observed. HIF activation due to loss of VHL protein suppressor function simulates "hypoxia" and switches cells from mitochondrial respiration to aerobic glycolysis. HIF increases glycolysis by increasing transcription of glycolytic enzymes and metabolizing pyruvate via glycolysis through increased activation of pyruvate dehydrogenase kinase-1, which blocks tricarboxylic acid cycle access to pyruvate. Down-regulation of mitochondrial oxidative phosphorylation and a reduction in tricarboxylic acid enzymes also facilitates aerobic glycolysis.[17] In addition, aerobic glycolysis, glutamine pathway reprogramming, and arginine synthetic abnormalities are also observed in clear cell RCC as a result of a deficiency of argininosuccinate synthetase-1.[18,19] Figure 1 demonstrates the various metabolic pathways associated with clear cell RCC, which supports the notion that this malignancy is not only a neoplastic process but also a "metabolic disease." These pathways offer targets for RCC therapy.

Clinical examples of the state of pseudo-hypoxia in clear cell RCC include enhanced tumor angiogenesis from increased VEGF levels and increased hemoglobin levels due to excessive erythropoietin levels. It is important to recognize that identification of this HIF-hypoxia pathway provides therapeutic targets and a rationale for targeted therapies that can blunt biochemical pathways using specific

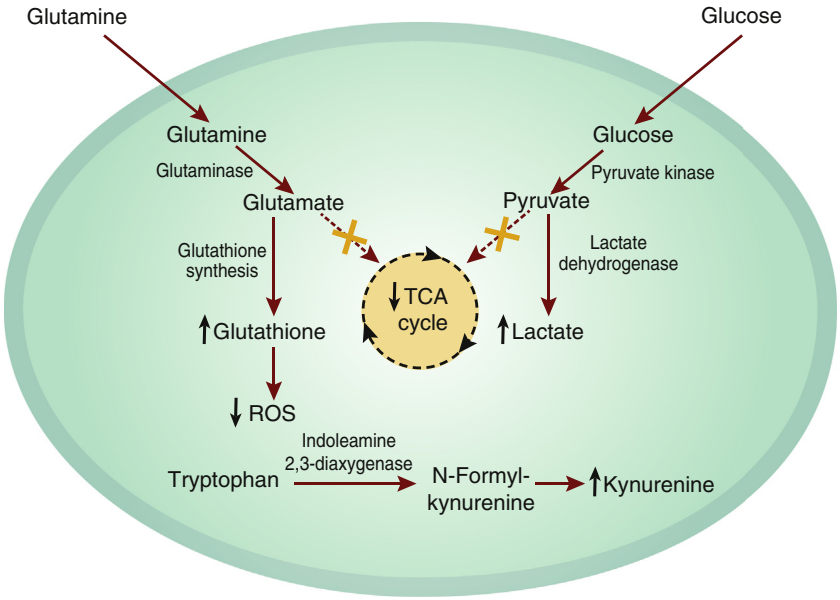

Figure 1 | Dysregulated metabolic pathways in clear cell renal cell carcinoma. Renal cancer cells increase glucose uptake, glycolysis, and lactate production, which results in decreased entry of pyruvate into the tricarboxylic acid (TCA) cycle. Cancer cells also have altered glutamine metabolism, which generates glutathione and reduces reactive oxygen species (ROS). Cancer cells also increase tryptophan metabolism, which causes increased levels of the kynurenine, an immunosuppressive metabolite. These pathways offer targets for renal cell carcinoma treatment.

inhibitors that provide higher specificity with less adverse effects.

Molecular genetics of renal cell carcinoma

The molecular genetics of clear cell RCC have been elucidated in recent years. As previously noted, the VHL gene is the most common mutation observed in RCC.[20] However, only a small fraction of patients with the clear cell type have VHL disease.[21,22] A number of less common genetic abnormalities have been identified. Mutations seen in the polybromo 1 (*PBRM1*) gene, which is located on chromosome 3p21 near VHL, is the second major clear cell RCC gene mutation and occurs in approximately 30% to 40% of cases of sporadic RCC.[23–25] It is of interest that greater than 50% of RCC patients with VHL mutations also have *PBRM1* mutations.[26]

A mutation in the BRCA-associated protein-1 (*BAP1*) gene, which is located at 3p, is also associated with RCC.[27] This protein is part of the ubiquitin-mediated proteolysis pathway. While this mutation is relatively uncommon (6% to 15% of patients), these tumors are aggressive and associated with a median survival rate of approximately 4.6 years. This is significantly shorter than the 10.6 years described in patients without the mutation.[27] Mutations in SET domain-containing protein 2 (*SETD2*), which is a tumor suppressor in proximal tubular epithelia, occur in up to 11% of RCC patients.[28,29] An interesting feature is that mutations in genes that control the maintenance of chromatin states (such as *PBRM1*, *BAP1*, and *SETD2*) appear to play a critical role in the pathogenesis of RCC development. *SETD2* mutations are associated with advanced tumor stage and a median survival of 62.7 months, less than the 78-month survival described in patients without the mutation.[24] Other less common mutations described in patients with RCC include those seen in the MTOR pathway such as phosphatidylinositol-4, 5-bisphosphate 3-kinase, protein-kinase B PI(3)K-AKT pathway, the SWI-SNF chromatin remodeling complex, the AT-rich interactive domain-containing protein 1A (*ARID1A*), and lysine-(K-)specific demethylase 5C (*KDM5C*).[25,28,30–32]

Hereditary renal cell carcinoma syndromes

Hereditary RCC syndromes account for approximately 2% to 3% of all cases of RCC (Table 1). VHL disease, which is an autosomal dominant syndrome, is the most common and increases risk for development of benign and malignant tumors in affected subjects.[33] Approximately three-quarters of VHL disease patients will ultimately develop clear cell RCC.[21,22] Hereditary clear cell RCC has also been reported in association with chromosome 3 translocations.[34] Mutation of chromatin modification genes is also associated with the development of clear cell RCC. As discussed previously, mutated genes leading to hereditary clear cell RCC syndromes include *BAP1*, *STED2*, *PBRM1*, *ARID1A*, and *KDM5C*.[25,28,30–32] Non-clear cell hereditary RCCs are also noted in Table 1.[35–43]

Table 1 | Hereditary renal cell carcinoma syndromes

Clear cell RCC

Von-Hippel Lindau (VHL) disease
Gene: VHL (3p25-26) Protein: VHL protein

Phenotypic features: RCC, hemangioblastoma, pheochromocytoma, renal and pancreatic cysts, ovarian cystadenoma, epididymal cystadenoma

BRCA-associated protein 1 (BAP1) mutations and familial kidney cancer
Gene: BAP1 (3p21) Protein: BRCA-associated protein

Phenotypic features: RCC, breast cancer, mesothelioma, cutaneous melanocytic tumors

Succinate dehydrogenase (SDH)-associated kidney cancer

Gene: SDHB (1p36); SDHC (1q23); SDHD (11q23)

Protein: Succinate dehydrogenase subunits B, C, and D

Phenotypic features: RCC, paragangliomas, pheochromocytoma, carotid body tumor

Papillary RCC

Hereditary papillary RCC (type 1 papillary)
Gene: MET (7q31) Protein: Hepatocyte growth factor receptor

Phenotypic features: None

Hereditary leiomyomatosis and RCC (type 2 papillary)
Gene: FH (1q43) Protein: Fumurate hydratase

Phenotypic features: RCC, uterine leimyosarcomas, breast and bladder cancer, cutaneous and uterine leiomyomas

Other RCC types

Birt-Hogg-Dubé disease
Gene: FLCN (17p11.2) Protein: Folliculin

Phenotypic features: RCC, fibrofolliculomas and trichodiscomas, pulmonary cysts

Hamartoma tumor syndrome (Cowden syndrome)
Gene: PTEN (10q23) Protein: Phosphatase and tensin homologue

Phenotypic features: RCC, cancer (breast, endometrial, thyroid, prostate), macrocephaly, benign skin tumors, intestinal hamarotomatous polyps, cerebellar gangliocytoma

Tuberous Sclerosis Complex (TSC)
Gene: TSC1 (9q34); TSC (16p13) Protein: Hamartin and tuberin

Phenotypic features: RCC, angiomyolipoma, renal cysts, subependymal giant cell astrocytomas, facial angiofibromas, ungula and periungual fibromas, hypomelanotic macule, cardiac rhabdomyomas, connective tissue nevus, forehead plaque

Epidemiology of renal cell carcinoma

Renal cell carcinoma accounts for approximately 3% of adult malignancies, with the clear cell subtype constituting the majority of these cases, although much of the epidemiology literature does not distinguish between the various histological subtypes of RCC.[44] In the US, the number of new cases of kidney and renal pelvis cancer was 15.6 per 100,000 men and women per year.[45] Globally, the rates are much lower (4 per 100,000 people per year), with incidence rates highest in Europe, North America, and Australia and lowest in China, India, Japan, and Africa.[46] Rates for new RCC cases have risen on average 0.7% each year over the last 10 years, in part due

to diagnosis of small incidentally discovered cancers with sensitive imaging usually performed for another indication. Death rates have been falling on average 0.9% each year from 2005 through 2014. Five-year US survival for localized kidney and renal pelvis cancer is 92.6% but falls to 66.7% with regional disease and 11.7% with widely metastatic disease.[45] Currently, the peak incidence occurs in the sixth decade, with 80% of the cases diagnosed in those between ages 40 and 69 years.[47]

Numerous nongenetic etiologic risk factors for the development of RCC have been identified (Table 2). Tobacco abuse may be the most important established and independent environmental risk factor for RCC, with smokers incurring a 2- to 3-fold higher incidence of RCC that is dose-dependent.[48] Increased body mass index is also an independent risk factor for RCC with a hazard ratio of 1.8 in those with body mass index $>$ 35 kg/m^2.[49] Hypertension is also a well-established risk factor for the development of RCC, especially in African Americans and for those with poorly controlled blood pressure over a long period of time.[50] Diabetes mellitus is a risk factor for both RCC and CKD. Occupational exposure to compounds such as cadmium, asbestos, trichloroethylene and other petroleum byproducts likely amplify the risks of developing RCC.[51,52] Controversy continues to exist regarding whether ingestion of aspirin, nonsteroidal anti-inflammatory drugs, and acetaminophen increase RCC risk, with some studies showing a link and others not detecting an association.[53,54] However, phenacetin (banned in the US since 1983) use has been linked to an increased risk of renal pelvic or urothelial tumors, rather than of RCC.[55] There does not appear to be an increased risk of RCC in patients with autosomal dominant polycystic kidney.[56] The link between advanced CKD, acquired renal cystic disease, and RCC will be discussed in later sections.

The landscape of adult RCC has changed considerably with the use of more sensitive imaging modalities. This has led to change in the percentage of early-stage T1 kidney cancers ($<$7 cm in size and confined to the kidney) from 43% (2 decades ago) to more than 60% more recently.[3,57] Notably, the 5-year survival rate exceeds 90% for early stage tumors (T1 tumors) and approaches 100% for T1a tumors. With these survivor numbers, RCC now requires chronic disease management with a focus on preserving kidney function following total or partial nephrectomy and improving non–cancer-related morbidity and mortality.[58–60]

Table 2 | Nongenetic risk factors for renal cell carcinoma

Etiological Risk Factor
Chronic end-stage renal disease on dialysis
Obesity
Smoking
Hypertension
Exposure to dry cleaning solvents
Exposure to trichloroethylene
Diuretics
Radiation therapy
Phenacetin
Arsenic
Cadmium
Sickle cell trait and disease
Nephrolithiasis
Chronic hepatitis C infection

Diagnosis and staging of renal cell carcinoma

RCC typically remains clinically occult for an extended period of time, and only 10% of patients manifest the classical triad of hematuria, flank pain, and a flank mass.[61] Those presenting with this triad typically have advanced disease. Approximately 40% of patients will present with hematuria or flank pain as isolated symptoms that on further workup reveal RCC. As advanced imaging techniques have become more common, 25% to 35% of patients have their RCC discovered on imaging performed for an unrelated indication, and most of these patients have localized disease or small renal masses.[61] Other signs and symptoms associated with RCC include weight loss, hypertension, night sweats, malaise, and the new onset of a varicocele. Of note, RCCs are associated with numerous paraneoplastic phenomena including fever, anemia, hypercalcemia, erythrocytosis, elevation of liver enzymes not due to metastatic spread (Stauffer syndrome), and rarely Amyloid A amyloidosis and polyneuropathy.[3,62]

Diagnosis of RCC relies on advanced imaging techniques including computed tomography and magnetic resonance imaging. The preferred method of imaging is contrast-enhanced, thin-slice renal computed tomography scanning, where enhancing solid masses are more likely to be RCC.[63–65] In most cases, this examination can be used to detect and stage RCC and to provide information for surgical planning without additional imaging. Magnetic resonance imaging can be reserved for patients with contraindications or allergies to radiocontrast material or in equivocal cases.[66] Ultrasound can be helpful in further defining the architecture of a mass (such as defining cystic and solid portions), although new contrast-enhanced ultrasound techniques may prove useful for diagnosis in the future.[65,66] For diagnostic purposes, use of [^{18}F]Fluoro-2-deoxy-2-D-glucose positron emission tomography computed tomography is limited for renal cell carcinoma, mainly due to excretion of [^{18}F]Fluoro-2-deoxy-2-D-glucose from the kidneys, which decreases contrast between renal lesions and normal tissue, and may obscure or mask RCC detection.[67] However, positron emission tomography scanning has an evolving role in follow-up of patients with RCC to determine metastatic disease and/or disease progression.

With the increased utilization of imaging, many patients are diagnosed with small ($<$3–4 cm) renal masses that are benign in 25% to 30% of cases or of a low-grade, slow-growing nature in up to 65% of cases.[68,69] The management of small isolated renal masses is beyond the spectrum of this review, but these patients may be safely monitored if the tumor is low-grade in nature or if the patient has significant comorbid conditions that increase the risk of a surgical intervention or a limited life expectancy.[70] In this setting, percutaneous biopsy of kidney masses has evolved as an

important diagnostic test. Percutaneous biopsy provides a minimally invasive method for discriminating benign from malignant renal masses, and allows for stratifying malignant risk by grading the tumor. Percutaneous kidney mass biopsy has a low complication rate (<5%) and a high diagnostic yield (>90%) with an extremely low risk of seeding malignant cells outside the primary tumor.[71,72]

Staging of RCC relies on the tumor, nodes, and metastasis staging system (Table 3). An accurate and clinically useful staging system provides patients with information guiding counseling regarding prognosis, selecting treatment modalities, and determining eligibility for clinical trials.[73] Tumor staging has been combined with clinical, imaging, and laboratory variables to develop comprehensive outcome models that can also be used to counsel patients and decide among therapeutic options.[74,75]

Association of kidney disease with renal cell carcinoma

Cancer risk, especially RCC, is higher in the population with CKD versus the general population. In fact, a bidirectional relationship appears to exist between kidney disease and RCC—each increasing the risk for the other in patients.[76] Figure 2 highlights this association. To this point, large observational studies have demonstrated a 20% to 50% increased risk for all cancers both among patients with early-stage CKD and in those requiring dialysis, as well as a 2- to 3-fold increased cancer risk (all cancers) in kidney transplant recipients.[77–81]

Table 3 | Tumor, nodes, metastasis (TNM) staging for renal cell carcinoma

Stage	Definition	Subdivision
Tumor stage		
T0	No evidence of primary tumor	
T1	<7 cm in greatest distance, confined to the kidney	1a: <4 cm 1b: >4 cm and <7 cm
T2	>7 cm in greatest distance, confined to the kidney	2a: >7 cm and <10 cm 2b: >10 cm
T3	Extends into major veins or perinephric tissues but not to adrenal gland or beyond Gerota fascia	3a: Tumor extends into renal vein or invades perirenal sinus fat 3b: Tumor extends into the subdiaphragmatic IVC 3c: Tumor extends into the supradiaphragmatic IVC
T4	Tumor invades beyond Gerota fascia and/or contiguous extension into ipsilateral adrenal gland	
Regional lymph nodes		
N0	No regional lymph node metastasis	
N1	Metastasis to regional lymph nodes	
Distant metastases		
M0	No distant metastasis	
M1	Distant metastasis	

IVC, inferior vena cava.

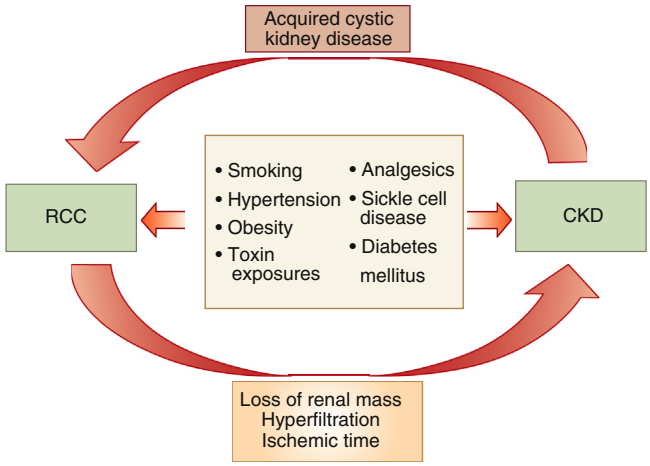

Figure 2 | Bidirectional relationship between renal cell carcinoma (RCC) and chronic kidney disease (CKD). Chronic kidney disease is associated with RCC via the formation of acquired cysts and other comorbidities and exposures that are associated with RCC. RCC causes CKD from the effects of nephrectomy, comorbidities, and exposures associated with kidney injury.

A prospective population-based cohort study observed an increased incidence of urinary tract cancer in stage 3 or greater CKD patients with the excess risk noted at an estimated glomerular filtration rate (eGFR) of 55 ml/min per 1.73 m^2.[82] The cancer risk increased by 29% with every 10 ml/min per 1.73 m^2 eGFR decrease, with the greatest risk observed with an eGFR < 40 ml/min per 1.73 m^2.[82] A large population-based cohort from a cross-sectional screening program revealed that the long-term risk of kidney cancer was significantly higher only among younger men with moderately impaired kidney function as compared with those with normal kidney function or mild underlying CKD over a median follow-up of 28 years.[83]

A retrospective cohort study of 1,190,538 adults assessed the association between CKD stage and the risk of incident cancer.[84] During 6,000,420 person-years of follow-up, 76,809 incident cancers were identified in 72,875 subjects. After adjustment for time-updated confounders, higher CKD stage was associated with an increased risk of kidney cancer with an adjusted hazard ratio (HR) of 2.28 (95% confidence interval [CI]: 1.78–2.92) for an eGFR < 30 ml/min per 1.73 m^2.[84] An increased risk of urothelial cancer was also noted at an eGFR < 30 ml/min per 1.73 m^2 but no significant associations between eGFR and other cancers. Risk for RCC appeared to be 100-fold higher for end-stage renal disease (ESRD) patients with renal cysts, while the incidence of renal cancers rose incrementally with higher CKD stages.[84,85] Individual patient data collected from 6 studies (n = 32,057) with a follow-up period of 170,000 person-years revealed no association between CKD (5 categories based on eGFR) and the overall cancer incidence or death.[86] However, among dialysis patients,

there was an excess risk of cancers of the urinary tract with an adjusted HR of 2.34 (95% CI: 1.10–4.98).

It is hypothesized that uremia-related chronic inflammation, oxidative stress, retained uremic toxins and solutes, impaired immune function, the dialysis procedure, medication and toxin exposure, and comorbid conditions increase risk for many cancers, including RCC.[85,87–93] Focusing on RCC, CKD, and ESRD are commonly complicated by the development of acquired kidney cysts, which are highly associated with RCC.[89] In fact, in ESRD patients on dialysis, increased risk for renal parenchymal cancer is related to acquired renal cystic disease, which increases with time on dialysis.[87] Importantly, most of these cancers are papillary rather than clear cell renal cell carcinomas. CKD with analgesic nephropathy and aristolochic acid nephropathy was also associated with increased incidence of upper urinary tract urothelial carcinomas.[92,93] A retrospective study noted that the standardized incidence ratio of kidney cancer was also significantly higher in patients receiving chronic lithium therapy as compared with the general population.[94] In regard to comorbid conditions, type 2 diabetes mellitus, which is a risk factor for CKD, also increases risk for kidney cancer.[91] Excessive insulin levels, which may function as a growth factor, along with obesity-related inflammatory cytokines and insulin resistance, are potential mechanisms for the increased cancer risk.[91]

Kidney disease complicating renal cell carcinoma

Underlying kidney disease is now recognized as a common problem with patients diagnosed with RCC.[84,95–102] However, the dramatic improvement in 5-year survival for T1 tumors has now shifted the focus of management for kidney cancer survivors to undertake measures that preserve kidney function. CKD is present in approximately 25% of RCC patients prior to receiving any nephrotoxic chemotherapy or undergoing nephrectomy, which significantly increases following surgery.[84] The high prevalence of pre-nephrectomy CKD among those with small RCCs, which ranges from 10% to 52%, reflects common risk factors in these patients.[95–100] Older age, male gender, tobacco use, and underlying diabetes mellitus and hypertension are quite common in patients with RCC.[95–100] A higher burden of hypertension and diabetes mellitus was observed in those with pre-existing CKD and RCC as compared with cancer-free case-matched controls.[96,103] For example, 22% of patients with kidney tumors had stage 3 or greater CKD prior to nephrectomy, which approached 40% in patients older than 70 years of age.[101] Furthermore, 26% of 662 patients scheduled for partial or radical nephrectomy had greater than stage 3 CKD.[102]

Based on these data, it appears that patients with RCC, due to pre-nephrectomy CKD and other comorbidities, are more likely to develop post-procedure AKI and progression to a higher CKD stage[98,104] It is also concerning that patients with T1 tumors undergoing nephrectomy are more likely to die from CKD-related complications such as cardiovascular disease and infection rather than their actual kidney malignancy.[84,90] Thus, the management of patients with localized RCCs should focus on preserving kidney function, reducing cardiovascular risk, and long-term CKD care addressing and preventing complications. Preoperative screening of patients at risk for postsurgical AKI or progressive CKD can be done by estimating glomerular filtration rate (GFR) and measuring albuminuria using KDIGO CKD staging. Optimization of glycemic and blood pressure control and prevention of AKI through avoidance of nephrotoxins and renal underperfusion reduces risk for GFR loss following nephrectomy.[105]

Approach to treatment of RCC and effects on kidney function

The general approach to treating the patient presenting with RCC is that therapy is guided by the extent of disease (Figure 3).[11] Localized disease is usually curative and relies on a surgical approach. The decision as to whether to proceed with a radical nephrectomy versus a partial nephrectomy is individualized and guided by the extent of disease, location of the cancer, and patient-specific factors such as comorbidities and age.[11,106] However, radical nephrectomy is generally indicated for those patients who have evidence of tumor involvement of the renal vein, adrenal vein, or perinephric fat.[11,107] Partial nephrectomy is reserved for smaller tumors and in those with evidence of inherited renal cancer syndromes or multiple tumors in which sparing of kidney function is a critical goal, such as in patients with VHL syndrome.[108] For those patients with a single metastasis and a resectable, localized cancer, surgery focusing on removal of the primary tumor and metastasis (metastasectomy) can also be curative.[109–111] Patients presenting with metastatic disease should be evaluated for consideration of cytoreductive nephrectomy (or partial nephrectomy) if they have acceptable performance status, the kidney contains the bulk of the tumor volume, and there is no evidence of rapidly progressing extrarenal disease. Advances in minimally invasive and laparoscopic techniques allow for use of these approaches in many patients, but this decision is operator- and patient-dependent. For those patients with significant comorbidities, newer nonsurgical ablative therapies such as cryo- or thermal ablation or radiofrequency ablation are options for isolated smaller renal masses.[112]

A critical issue for the nephrologist is being familiar with the impact of these various surgical approaches on post-procedure kidney function. Increasingly, patients with significant CKD are found to have RCC, and the prediction of post-surgical GFR can influence the surgical approach. Understanding the balance between maintenance of post-surgical GFR and attainment of cure by appropriate cancer resection is a critical issue. Following radical nephrectomy, several studies reveal that the prevalence of CKD increased from between 10% and 24% to between 16% and 52%.[113–117] Postoperative risk of new CKD diagnosis or progression of CKD was related to larger tumor size, corresponding renal volume reduction, hypoalbuminemia, obesity, and postoperative AKI (in addition to

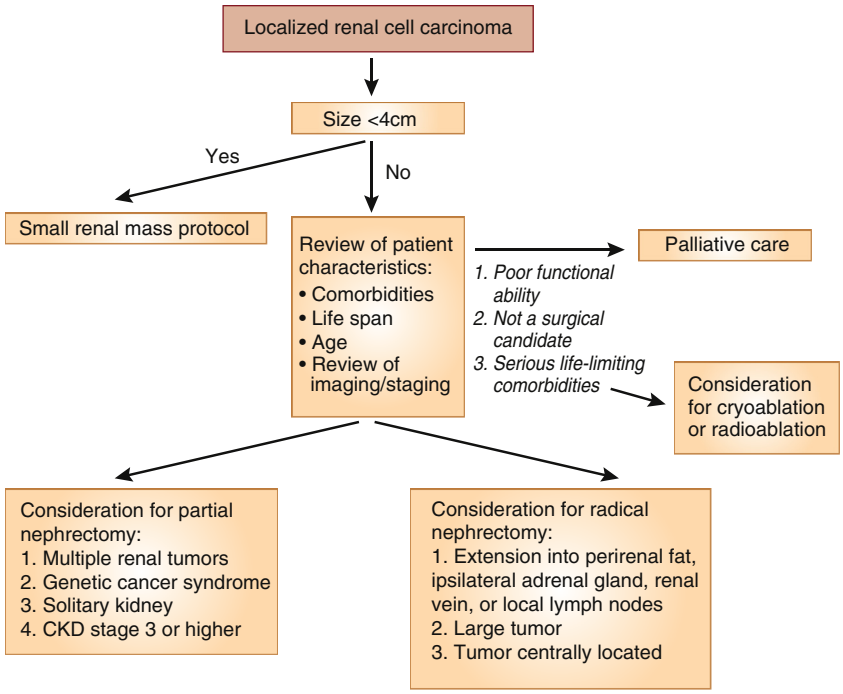

Figure 3 | Approach to the patient with localized renal cell carcinoma. CKD, chronic kidney disease.

the previously described risk factors).[96,103,113–115] Pre-existing CKD and diabetes mellitus were also shown to increase risk for progression of CKD to ESRD over a 10-year follow-up period.[118] It is important to also note that data support the concept that surgically induced CKD may have a lower risk of progression than CKD associated with medical conditions.[119] However, this does not decrease the need for close follow-up of GFR postoperatively.

It is noteworthy that examination of non-neoplastic tissue obtained from tumor nephrectomy specimens provides a wealth of information regarding risk for CKD and its progression.[116,117] Furthermore, detailed examination of non-neoplastic parenchyma identifies patients with glomerular, tubulointerstitial, or vascular diseases, who may require additional medical management and referral for nephrology care. Thus, it is mandatory that pathologists report findings on non-neoplastic renal parenchyma. This is highlighted by a study of 246 adult tumor nephrectomy specimens in which the following was recognized in a review of the non-neoplastic tissue: diabetic nephropathy (19 cases, of which 1 demonstrated atheroembolic disease), thrombotic microangiopathy (3 cases), sickle cell nephropathy (1 case), and focal segmental glomerulosclerosis (1 case).[120] Twenty-one of these diagnoses (88%) were not identified at initial pathologic evaluation. Knowledge of these non-neoplastic diseases requires expert nephrology care.

As mentioned above, nephron-sparing procedures including partial nephrectomy and ablative therapies are emerging as effective therapies for small (<4 cm) tumors. Data demonstrate that partial nephrectomy obtains comparable oncologic and overall survival while achieving greater preservation of kidney function as compared with total nephrectomy.[121–123] A meta-analysis of 36 studies including 40,000 patients found that treatment with partial nephrectomy conferred a 19% risk reduction for all-cause mortality, 29% for cancer-specific mortality and 61% for CKD.[123] In contrast, the European Organization for Research and Treatment of Cancer study of 541 patients with solitary unilateral RCCs revealed equivalent overall 10-year and oncologic survival and renal outcomes for radical and partial nephrectomy.[118] In a Canadian cohort of 11,937 patients, ESRD risk was no different between the 2 forms of nephrectomy in the overall cohort spanning from 1995 through 2010; however, when only a contemporary cohort (2003–2010) was considered, the benefit of partial over radical nephrectomy became apparent using a multivariable proportional hazards model (HR: 0.44; 95% CI: 0.25–0.95).[124] In addition, a lower risk of new onset CKD (HR: 0.48; 95% CI: 0.41–0.57) was observed.[124] The discrepant results were attributed to changes in clinical practice patterns whereby lower risk lesions were being considered for partial nephrectomy in the modern cohort. However, tumor-staging data were not available to support these presumptions. Renal outcomes comparing total versus partial nephrectomy are further examined in Table 4.[95,102,117,125–136] Most recently, the risk of stage 4 and higher CKD after radical or partial nephrectomy was examined in a cohort of Veterans Hospital patients from 2001 through 2015.[137] Among patients with preoperative eGFR $\geq$ 30 ml/min per 1.73 m^2, partial nephrectomy was associated with a significantly lower relative risk of incident CKD stage 4 or higher (HR: 0.34; 95% CI: 0.26–0.43, vs. radical nephrectomy). In patients with

Table 4 | Renal outcomes after partial versus radical nephrectomy

Reference, year	Study	N	Renal outcomes after nephrectomy	Comments
Lau *et al.*[125] 2000	Case control	RN, 164 PN, 164	RN, RR 3.7 for CKD (Cr>2.0 mg/dl) compared with PN	Matched for tumor grade/stage/size, age, and gender; 10 year follow-up
McKiernan *et al.*[126] 2002	Case control	RN, 173 PN, 117	RN, greater risk for CKD (Cr>2.0 mg/dl) compared with PN RN, post-Nx mean Cr (1.5 mg/dl) PN, post-Nx mean Cr (1.0 mg/dl)	Controlled for age, DM, HTN, smoking, and kidney function; 25 month median follow-up
Huang *et al.*[102] 2006	Cohort study	RN, 262 PN, 385	RN, HR 3.8 for GFR<60; HR 11.8 for GFR<45	Matched for age and baseline GFR; 26% with CKD prior to Nx
Malcolm *et al.*[95] 2009	Cohort study	RN, 499 PN, 250	RN, GFR <60 (44.7%) post-Nx PN, GFR<60 (16.0%) post-Nx	Proteinuria: RN, 22.2%; PN, 13.2% Cr > 2mg/dl: RN, 14.2%; PN, 8.4%
Barlow *et al.*[134] 2010	Cohort study	RN, 172 PN, 102	RN, CKD (71.4%) post-Nx PN, CKD (17.1%) post-Nx RN, higher risk new onset GFR<60; higher percentage GFR decrease; higher CKD upstaging	Controlled for multiple risk factors and baseline kidney function; 24% with CKD prior to Nx; CKD independent risk factor for progression
Jeon *et al.*[136] 2009	Cohort study	RN, 129 PN, 96	RN, CKD (66.7%) post-Nx PN, CKD (11.5%) post-Nx PN, HR 0.11 for CKD compared with RN	Controlled for multiple risk factors and baseline GFR
Klarenbach *et al.*[127] 2011	Population data set	1151	RN, HR 1.75 for composite of ESRD, increased CKD, and acute dialysis compared with PN	Proteinuria-adjusted HR 2.4 for primary outcome
Süer *et al.*[128] 2011	Cohort study	RN, 383 PN, 105	RN, HR 6.45 for GFR<60; RN, HR 13.5 for GFR<45 compared with PN (all tumor sizes)	Local recurrence: RN, 1.3%; PN, 5.7%; Metastatic disease: no difference; GFR <60 post-Nx: RN, 68.0%; PN, 18.9%; GFR<45 post-Nx: RN, 37.2%; PN, 2.9%; Dialysis post-Nx: RN, 2.6%; PN, 0%
Sun *et al.*[129] (SEER) 2012	Cohort study	RN, 840 PN, 840	RN, HR 1.9 for GFR<60; HR 1.5 for AKI; and HR 1.8 for CKD compared with PN	No difference in ESRD incidence; HR 1.8 anemia of CKD
Kaushik *et al.*[130] 2013	Cohort study	RN, 206 PN, 236	RN, HR 4.23 for stage 4 CKD compared with PN	Older age, larger tumor size, and higher % of oncocytoma in RN group; higher mortality (HR, 1.75) in RN group
Kim[135] 2013	Case control	RN, 605 PN, 1071	RN, OR 11.89 for GFR<60 compared with PN	Controlled for age, gender, preoperative creatinine
Choi and Song[131] 2014	Cohort study	RN, 1502 PN, 952	PN, HR 0.23 for GFR <60 compared with RN	Controlled for age, DM, HTN, and baseline kidney function; preoperative GFR worse
Takagi *et al.*[132] 2014	Case control	RN, 59 PN, 113	RN, 32.2% function loss on renal scan PN, 9.6% function loss on renal scan	RN, 40% total renal volume loss on CT PN, 6% total renal volume loss on CT
Woldu *et al.*[133] 2014	Cohort study	1306 RN, 766 PN, 540	RN, GFR post-Nx (-1.89/yr decline); PN, GFR post-Nx (-1.17/yr decline) PN, HR 2.3 for freedom from GFR<45 compared with RN	GFR<30: RN, 6.0%; PN, 3.5% Lower-stage CKD associated with greater GFR decline
Yap *et al.*[117] 2015	Cohort study	RN, 9830 PN, 2107	PN, HR 0.44 for ESRD (HR 0.48 with propensity scoring); HR for new onset CKD	Used multivariable proportional hazards model and propensity scoring; median follow-up 57 months
Leppert *et al.*[137] 2017	Propensity-matched cohort	RN, 9759 PN, 4370	PN, HR 0.34 for CKD stage 4 or higher versus RN PN, HR 0.55 for mortality versus RN	Postoperative decline in kidney function occurred mainly in the first year after surgery and appeared stable over time

AKI, acute kidney injury; CKD, chronic kidney disease; Cr, creatinine; DM, diabetes mellitus; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HR, hazard ratio; HTN, hypertension; Nx, nephrectomy; OR, odds ratio; PN, partial nephrectomy; RN, radical nephrectomy; RR, relative risk.
Adapted with permission from Hu S, Chang A, Perazella MA, et al. The nephrologist's tumor: basic biology and management of renal cell carcinoma. *J Am Soc Nephrol.* 2016;27:2227–2237.[2]

eGFR $\geq$ 60 ml/min per 1.73 m^2, partial nephrectomy was also associated with a significantly lower relative risk of incident CKD stage 3b or higher (HR: 0.15; 95% CI: 0.11–0.19, vs. radical nephrectomy). Of note, the postoperative decline in GFR was most pronounced in the first 5 months after surgery and then remained stable over time. Furthermore, partial nephrectomy was associated with a significant reduction in mortality. Overall, it appears that partial nephrectomy offers equivalent tumor survival with less CKD and should be the preferred modality for stage T1 RCCs. Given the concerns of CKD post-intervention, nephrology consultation should be strongly considered in these patients. In fact, the American Society of Clinical Oncology and American Urological Association clinical practice guidelines for the management of small renal masses state that "referral to a nephrologist should be considered if CKD (estimated GFR < 45 ml/min per 1.73 m^2) or progressive CKD occurs after treatment, especially if associated with proteinuria."[70,106]

Systemic therapy for advanced renal cancer

Adjuvant therapy. Patients with locally advanced kidney cancer following nephrectomy remain at high risk for

systemic failure. Historical adjuvant studies of interferon alpha and interleukin-2 (IL-2) failed to demonstrate clinical benefit.[138] Although the US Food and Drug Administration (FDA) has recently approved the use of 1 year of adjuvant sunitinib based upon an improvement in progression-free survival in the phase 3 S-TRAC study, 2 other large studies of adjuvant sunitinib, sorafenib, and pazopanib failed to demonstrate benefit, and therefore the role of adjuvant therapy with tyrosine kinase inhibitors (TKI) remains controversial.[139–141]

Management of metastatic renal cancer. Metastatic RCC remains an incurable disease in the vast majority of patients and as systemic therapy for advanced disease is associated with a toxicity burden, a small subset of patients, primarily those with low-volume lung and/or nodal metastases may be observed without therapy until evidence of overt radiographic progression.

Systemic therapy options prior to the 2004 FDA approval of the TKI sorafenib consisted primarily of "early-generation" immunotherapy agents such as interferon alpha and IL-2, the latter of which when administered as "high-dose IL-2" has the potential to provide a very small subset of patients long-term disease control.[142]

Approximately 70% of kidney cancers are histologically and molecularly classified as clear-cell RCCs and the discovery of the reliance on the VEGF pathway resulting from *VHL* gene inactivation led to the clinical development and FDA approval of a number of VEGF pathway inhibitors, including sorafenib, sunitinib, pazopanib, axitinib, cabozantinib, lenvatinib, and bevacizumab.[139–141] Alterations in the mechanistic target of rapamycin (mTOR) pathway, another validated target in kidney cancer, and other solid tumors led to clinical trials and subsequent FDA approval of the mTOR inhibitors temsirolimus and everolimus.[143,144] Drugs approved by the FDA, along with their mechanism of action and nephrotoxicity, are described in Table 5.

A number of prognostic risk models that incorporate a variety of clinical factors are used both to inform patient management and in clinical trial design. The widely used Memorial Sloan Kettering risk criteria (good, intermediate, and poor risk) uses 5 factors correlated with decreased survival (poor performance status, high serum calcium and lactase dehydrogenase levels, anemia, and a short interval from diagnosis to treatment).[145] In contrast to the Memorial Sloan Kettering model, which was developed based upon results from first-generation immunotherapy studies, the International Metastatic Renal Cell Carcinoma Consortium's model was developed on the basis of patient outcomes in the VEGF-targeted therapy era.[146]

Front-line therapy for patients with good or intermediate risk (using the Memorial Sloan Kettering Cancer Center risk model) metastatic clear cell renal cancer typically consists of either sunitinib or pazopanib, oral TKIs targeted against the VEGF receptors, and other tyrosine kinases. A prospective randomized study comparing these 2 agents demonstrated similar efficacy with median survival approaching 30 months with both agents. In this study, pazopanib was associated with a higher incidence of hepatic dysfunction, while sunitinib use had a greater degree of fatigue.[147]

For much of the past decade, patients whose disease progressed on the initial TKI were subsequently managed with either the oral mTOR inhibitor everolimus or another potent TKI, axitinib. Both of these agents were granted FDA approval with the demonstration of modest improvements in progression-free survival compared with control arms of placebo and sorafenib, respectively.[148,149]

Following the recent approvals of both cabozantinib and nivolumab, the management of patients whose disease has progressed on initial TKI has evolved. Cabozantinib is an oral small-molecule TKI that targets VEFG receptor as well at *MET* and *AXL*. In a phase 3 trial, patients whose disease had progressed on a front-line TKI were randomized to receive cabozantinib or everolimus. Patients receiving cabozantinib demonstrated improved overall survival (21.4 vs. 16.5 months) along with better progression-free and objective response rates.[150]

Table 5 | FDA-approved agents for advanced renal cell carcinoma

Drug	Mechanism of action	Nephrotoxicity
High dose Interleukin-2	Cytokine, promotes differentiation of T cells	Prerenal AKI and ischemic ATI/ATN
Temsirolimus	Parenterally administered inhibitor of mTORC1	Increased serum Cr, rare ATI/ATN and glomerulopathy
Everolimus	Oral inhibitor of mTORC1	AKI, proteinuria
Bevacizumab	Recombinant humanized monoclonal antibody inhibitor of VEGF A	Hypertension, proteinuria, TMA, AIN, other GNs
Sorafenib	Small molecule inhibitor of VEGFR, PDGFR and Raf family kinases	Hypertension, proteinuria, AIN, MCD/FSGS, TMA
Sunitinib	Small molecule inhibitor of multiple receptor tyrosine kinases including VEGR and PDGFR	Hypertension, proteinuria, AIN, MCD/FSGS, TMA
Pazopanib	Small molecule multi-targeted tyrosine kinase inhibitor	HTN, proteinuria
Axitinib	Small molecule inhibitor of VEGFR 1-3, c-KIT and PDGFR	HTN, proteinuria
Lenvatinib	Small molecule multi-targeted tyrosine kinase inhibitor	Rare proteinuria, increased serum Cr
Cabozantinib	Small molecule inhibitor of c-Met, VEGFR2, AXL	HTN, rare proteinuria and increased serum Cr
Nivolumab	Anti PD-1 antibody	AIN (+/- granulomatous), MCD, IC-GN

AIN, acute interstitial nephritis; ATI/ATN, acute tubular injury/necrosis; Cr, creatinine; FSGS, focal segmental glomerulosclerosis; HTN, hypertension; MCD, minimal change disease; mTORC1, mammalian target of rapamycin complex 1; PD1, programmed cell death 1 ligand; PDGFR, platelet-derived growth factor receptors; TMA, thrombotic microangiopathy; VEGFR, vascular endothelial growth factor receptor.

Nivolumab is an IgG4 programmed cell death protein 1 receptor immune checkpoint inhibitor administered i.v. every 2 weeks. A phase 3 trial randomized patients with clear cell RCC who had progressed following 1 or 2 prior anti-angiogenic regimens to receive either nivolumab or everolimus. Patients receiving nivolumab demonstrated superior survival (25 vs. 19.6 months) compared with those receiving everolimus. Nivolumab was much better tolerated, with only 19% of patients experiencing grade 3 or 4 toxicity compared with 37% of patients on the control arm. In this study, benefit was observed with nivolumab irrespective tumor expression of programmed death–ligand 1.[151] One of the intriguing observations from use of checkpoint inhibitors is that a subset of patients who achieve a response to therapy appear to have durable responses.

Given the favorable toxicity profile and potential for durable responses, nivolumab has become a *de facto* second-line standard of care. Third-line therapy consists of axitinib, cabozantinib, and everolimus, as well as potential use of other TKIs and combination lenvantinib-everolimus.[144]

With the demonstration of significant and potentially durable responses to nivolumab, there is increasing interest in exploring combinations of immunomodulatory agents. The recently reported Checkmate 214 study randomized patients with intermediate or poor risk clear-cell renal cancer to receive either nivolumab plus ipilimumab (cytotoxic T-lymphocyte antigen antibody) or sunitinib. Patients receiving the nivolumab plus ipilimumab combination had statistically superior objective response rates and overall survival compared with sunitinib-treated patients.[152] Assuming FDA approval, nivolumab plus ipilimumab will become a standard front-line therapy for selected patients.

Approximately 30% of advanced RCC are non-clear cell histologies, with the largest component (10%) classified as papillary renal cell. Although these histologic subtypes have different molecular characteristics, the current therapeutic approach is broadly similar to the management of clear cell renal cancer, albeit with poorer clinical outcomes. There is limited clinical trial data in papillary renal cancer to suggest somewhat more activity of VEGF receptor TKIs versus mTOR inhibitors.[144] Patients with non-clear tumor histologies are optimally managed by enrollment on clinical trials.

Despite the promising outcomes demonstrated in studies of combination- or single-agent checkpoint inhibitors, only 25% of patients benefit. The absence of validated predictive biomarkers remains a major challenge. A major focus of ongoing clinical trials is to explore combinatorial therapy of checkpoint inhibitors with TKIs and other novel immunomodulatory agents.

Summary

RCC is a malignancy whose incidence is increasing and is frequently encountered in general nephrology practice, yet this cancer is often not recognized by nephrologists as an important cause of both acute and chronic kidney disease, which is associated with a significant mortality. As such, it is important that practicing nephrologists have a working knowledge of its biology, treatment, and complications. As nephrologists, we should be involved in all aspects of the care of patients with RCC. Patients with tumors considered appropriate for either partial or radical nephrectomy should be evaluated preoperatively by nephrologists to gauge risk for AKI and CKD and to recommend measures to reduce kidney injury. Noncancerous tissue obtained at nephrectomy should be examined by renal pathologists to provide diagnosis of concomitant kidney disease (i.e., diabetic nephropathy, hypertensive nephrosclerosis, chronic interstitial nephritis, etc.). RCC patients with metastatic disease are also at risk for acute or chronic kidney disease due to nephrotoxic drug therapy. These patients, and those with CKD following nephrectomy, should be followed up longitudinally in the nephrology clinic. This collaborative approach will likely improve patient outcomes.

DISCLOSURE

All the authors declared no competing interests.

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