Update on the biology and management of renal cell carcinoma

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ABSTRACT

Renal cell cancer (RCC) (epithelial carcinoma of the kidney) represents 2%–4% of newly diagnosed adult tumors. Over the past 2 decades, RCC has been better characterized clinically and molecularly. It is a heterogeneous disease, with multiple subtypes, each with characteristic histology, genetics, molecular profiles, and biologic behavior. Tremendous heterogeneity has been identified with many distinct subtypes characterized. There are clinical questions to be addressed at every stage of this disease, and new targets being identified for therapeutic development. The unique characteristics of the clinical presentations of RCC have led to both questions and opportunities for improvement in management. Advances in targeted drug development and understanding of immunologic control of RCC are leading to a number of new clinical trials and regimens for advanced disease, with the goal of achieving long-term disease-free survival, as has been achieved in a proportion of such patients historically. RCC management is a promising area of ongoing clinical investigation.

INTRODUCTION

Renal cell cancer (RCC) (epithelial carcinoma of the kidney) represents 2%–4% of newly diagnosed adult tumors.[1] Prior to the widespread use of tomographic imaging for a variety of diagnostic concerns, RCC was frequently diagnosed in advanced stage. The classic presentation was described as flank/back pain, abdominal mass and/or hematuria. Patients often presented with systemic symptoms of fever, night sweats, weight loss, as well as anemia and hypercalcemia, all of which may still occur as part of the clinical syndrome, either initially, or as the disease progresses. These features continue to predict a poorer outcome, even with modern therapy. An increase in incidence of RCC in part reflects widely available advanced imaging techniques used for other complaints with incidental diagnosis of a renal mass, often described as a small renal mass.

Over the past 2 decades, RCC has been better characterized clinically and molecularly. It is a heterogeneous disease, with multiple subtypes, each with characteristic histology, genetics, molecular profiles, and biologic behavior. Some of these characterizations, particularly for clear cell RCC, the most common subtype, have led to the development of new therapies directed at specific biologic targets, including vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR). Advances in understanding the immune cellular response to pathogens and tumors have led to efforts to enhance the previously known susceptibility of some RCCs to immunotherapy. In addition to cytokines that stimulate T-cell response against tumors, the role of inhibition of T-cell checkpoints, leading to continued T-cell response, is now integrated into the therapeutic armamentarium. Treatments for the less common subtypes of RCC remain less satisfactory. All of these developments have improved the outcome for many patients with RCC, but have also led to new dilemmas, which will be discussed subsequently. These include (A) the optimal management of small renal masses—are we overtreating?; (B) benefits of sequential versus combination therapies with the new agents; (C) how to enhance the complete response (CR) rate, which has translated to long-term survival in patients treated with cytokines, particularly interleukin (IL)-2; and (D) whether there is an adjuvant treatment approach that translates into survival benefit. Improved pathologic and molecular characterization of RCC subtypes may identify specific new therapeutic targets and lead to more specific and effective interventions.

HETEROGENEITY OF RENAL CANCER

RCC subtypes are defined by WHO criteria, established in 2004.[2] This classification system has recently been re-evaluated and updated, with a foundation based on the Vancouver consensus conference of the International Society of Urological Pathology and the WHO consensus meeting.[3 4] This classification system has led to the 2016 WHO classification of tumors of the urinary system and male genital organs[5] which takes into account substantial new knowledge regarding pathology, epidemiology and molecular genetics[5 6] (table 1).

There is increasing awareness of the complexity of clear cell RCC (75% of cases), with multiple molecular profiles identified[6–9] and ongoing efforts to identify the biologic significance of the different expression patterns.[9] Sporadic clear cell RCC is associated with the loss of function of the von Hippel-Lindau (*vHL*) gene, a tumor suppressor gene,

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Table 1 Subtypes of renal cell cancer—WHO 2016

Subtype	Clinical features	Molecular/biologic
Major subtypes		
Clear cell	75% of RCC—heterogeneous biologic behavior	Loss of *vHL* in the majority
Papillary type I	Slow growing/less likely to metastasize	*MET* alterations; chromosomal gains
Papillary type II	Often aggressive course, but some oncocytic; multiple molecular entities	3 molecular entities: *CDKN2A* silencing; *SETD2*, *BAP1*, *PBRM1* mutations; increased NRF2-antioxidant response pathway; CIMP phenotype—FH mutation—see below; TFE3 fusions—see below
Chromophobe	Indolent; rare metastases, but if so, often liver, often oligometastases	Impairment of gamma-glutamyltransferase 1 activity
Translocation	Pediatric; young adults; 40% lymph node involvement; range of intermediate to poor risk	MiT family translocations; previously t(6;11); Xp11; nuclear TFE3 fusions
Medullary	Sickle trait; aggressive, widely metastatic; chemotherapy	Loss of *SMARCB1* (chromatin remodeler and tumor suppressor)
Collecting duct	Aggressive; chemotherapy, some targeted therapies	IHC- PAX8 and integrase interactor-1 (INI-1); unique transcriptomic profile—metabolic shift—impaired oxidoreductase activity, pyruvate metabolism, and TCA cycle
2016 New classifications		
HLRCC	Hereditary/poor prognosis	Fumarate hydratase mutation
SDH deficient	Hereditary/young adults	Succinate dehydrogenase deficient—dysfunction of mitochondrial complex II
Tubulocystic	Indolent/oncocytoma-like; very rarely metastatic; present at lower grade and stage	Downregulated non-coding miRNA expressions compared with papillary; ongoing research
Acquired cystic	Often indolent; arise in ESRD; calcium oxalate crystal deposition common	Fewer unfavorable pathological features than other RCCs
Clear cell papillary	Low-grade clear cells arranged in papillae	Coexpression of CA9, HIF-1α, GLUT-1; absence of *vHL* gene alterations

References 3–39, 124–129.
CA9, carbonic anhydrase-9; ESRD, end-stage renal disease; HIF, hypoxia inducible factor; HLRCC, hereditary leiomyomatosis and RCC syndrome-associated RCC; IHC, immunohistochemistry; RCC, renal cell carcinoma; SDH, succinate dehydrogenase-deficient RCC; TCA, tricarboxylic acid; *vHL*, von Hippel-Lindau.

and is characterized by neoangiogenesis with upregulation of hypoxia-inducible factors. These alterations in function demonstrate the role of VEGF in facilitating renal tumor growth and angiogenesis.[10 11] These studies have led to extensive therapeutic development of anti-VEGF and anti-mTOR agents as potential treatment for RCC and other tumors, with now 9 agents in these classes approved for treatment of advanced/metastatic RCC.

Papillary RCC is divided into type I (*MET* alterations) and type II (at least 3 different molecular entities demonstrated). Additionally, they exhibit different clinical characteristics, with type I being less aggressive and less likely to develop metastases.[12] Recent evidence suggests that type II may be further subdivided, but distinct, reproducible criteria are not yet fully developed.[13]

Chromophobe RCC is identified by a distinct morphology and molecular profile. This subtype of RCC is usually considered an indolent subtype, with less risk of metastasis. However, if metastasis does occur, surgical resection may be the initial treatment of choice.

Translocation RCC (now categorized as MiT family translocation) was initially identified in pediatric renal tumors, but is now recognized in adults, usually younger adults.[14–17] Although there are distinct genetic translocations leading to gene fusions coding for transcription factors, this is not considered a hereditary tumor. The prognosis may be reasonably good in children if surgery can render them disease free, but if the disease becomes metastatic, it behaves similarly to that in adults, with poorer outcome.

Medullary RCC is a distinct histologic entity and is a component of renal disorders associated with sickle cell trait.[18–20] It is usually associated with widespread metastatic disease at presentation and the prognosis is poor.[19 21]

Collecting duct carcinoma is considered a renal tumor distinct from urothelial tumors of the renal pelvis. It is an aggressive histology, similar to medullary RCC, and has a poor prognosis. Both chemotherapy and targeted therapies have been employed in both medullary and collecting duct RCC, but with limited benefit.

The 2016 WHO Classification of RCC has established 5 new renal tumor subtypes that were previously considered potential emerging entities.[2 4 5] This change is based on additional molecular and clinical evaluations and pathological data that justify the recognition of these as distinct entities. These 5 new classifications are (A) hereditary leiomyomatosis and RCC syndrome-associated RCC (HLRCC)[22 23]; (B) succinate dehydrogenase-deficient RCC (SDH deficient)[24 25]; (C) tubulocystic RCC[26–29]; (D) acquired cystic disease-associated RCC[30]; and (E) clear cell papillary RCC.[31 32]

The first 2, HLRCC (previously hereditary type II papillary RCC) and SDH deficient, are among the hereditary RCC syndromes. The cystic tumors demonstrate a unique natural history, in that current reports describe an indolent course. In clinical reports of tubulocystic RCC, only 4 of 70 have developed metastatic disease. A subsequent clinical report, not specifying precise cystic pattern, describes cystic RCC as carrying an excellent prognosis, regardless of tumor size.[33] Additionally, the 2016 WHO Classification has reclassified multilocular cystic RCC now as 'multilocular cystic renal neoplasm of low malignant potential'. The final new entity, clear cell papillary RCC, accounted for only 5% of all resected renal tumors.[31 32]

Additional hereditary RCC syndromes, with distinct clinical characteristics, are associated with morphologically defined subtypes of RCC, including clear cell (vHL syndrome—benign and malignant bilateral small renal tumors, hemangioblastomas of brain and spine, retinal angiomas, other sites),[10 34] familial type I papillary RCC (germline mutation of c-met proto-oncogene, bilateral renal tumors),[35 36] and cystic and chromophobe histologies (Birt-Hogg-Dube syndrome—skin fibrofolliculomas, lung cysts, benign renal tumors and RCC).[37 38] Hereditary RCC syndromes account for 3%–5% of RCC, and other inherited syndromes exist that include an increased risk of RCC.[39]

SURGICAL MANAGEMENT ISSUES

Maintaining renal function

Over the past 2 decades, surgical approaches have evolved, coincident with the more frequent diagnosis of smaller renal masses, particularly ≤7 cm. Techniques have been developed to accomplish partial nephrectomies, reducing ischemic time, and with the goal of nephron sparing. Studies have been reported that demonstrate comparable outcomes in terms of long-term disease control, with reduced incidence of chronic renal failure, delayed cardiovascular disease, and improved survival, including long-term survival.[40–46] Additionally, 1 report describes improved survival following partial nephrectomy compared with radical nephrectomy for tumors inadvertently discovered to be benign.[47] Current guidelines from the American Society of Clinical Oncology and the Canadian Kidney Cancer Consensus as well as the National Comprehensive Cancer Network, all recommend partial nephrectomy whenever feasible and meeting criteria outlined in their reports.[48–50] This is particularly applicable to the setting of small renal masses, which will be discussed further.[48–52]

Small renal masses

As previously discussed, most of the increased incidence of RCC is the radiologic identification of small renal masses. This has led to a dilemma in management with options ranging from active surveillance to ablation procedures to partial nephrectomy.[48 49] Unfortunately, current imaging techniques cannot accurately distinguish benign from malignant tumors in most cases,[53 54] and some series report as much as 20% of such small tumors being benign at pathologic review.[52] In addition, contemporary reports confirm the safety of needle biopsies of small masses, and the accuracy of biopsies compared with the final surgical specimen.[54] As more centers evaluate premanagement biopsy, criteria are evolving to define tumors less likely to have successful diagnostic biopsies.[55–57] The recently published guidelines regarding small renal masses continue to emphasize the need for accurate diagnosis with recommendations for renal tumor biopsies prior to therapeutic decisions.[48 49] Criteria for recommendations for active surveillance of small renal masses, and guidelines for the use of ablative techniques versus surgery continue to be refined.

NEPHRECTOMY IN THE SETTING OF METASTATIC DISEASE

In the early era of cytokine therapy for metastatic RCC, 2 prospective randomized studies demonstrated that nephrectomy contributed to better outcome in the setting of metastatic disease followed by cytokine therapy, compared with interferon alone.[58 59] The role of cytoreductive nephrectomy in the present era of first-line targeted therapies continues to be discussed. Retrospective analyses, including a large meta-analysis (11 studies, 39,000 patients), have all reported the survival benefit of cytoreductive nephrectomy in selected patients.[60–62] All of these reports have identified cytoreductive nephrectomy as an independent factor in multivariate analyses, conferring a survival advantage.[60–62]

Experience-based clinical judgement is the most productive approach to decision-making in this setting. The decision for nephrectomy is usually made based on the bulk and distribution of the tumor, as well as tumor-related symptoms, and pace of disease. If the greatest amount of tumor is in the kidney, with limited volume metastatic disease, then nephrectomy may indeed confer improved outcome, both in terms of reducing localized symptoms, and in long-term outcome.[58–62]

MANAGEMENT OF ADVANCED RCC

Despite the increased detection of small renal masses of variable clinical significance, 25%–30% of patients with RCC present with metastatic disease. This is often identified by imaging for unassociated complaints, but also for symptomatic, previously undetected disease. These are settings in which cytoreductive nephrectomy could be considered, depending on the extent and locations of all sites of disease. Another group of stage IV patients are those who recur with advanced disease, having been disease free months to years after the initial diagnosis and nephrectomy. The time to recurrence remains a major prognostic factor for outcome with systemic treatment, whether immunotherapy or targeted therapy.

CLINICAL FEATURES OF METASTATIC RCC: PREDICTIVE RISK CRITERIA

In addition to characteristics noted in molecularly defined subtypes of RCC, advanced RCC has distinct clinical features: (A) the contrast of patients with oligometastatic disease (ie, only 1 or 2 sites) versus patients with extensive disease in multiple sites; (B) metastatic disease synchronous with the renal tumor versus metachronous; and (C) clinical signs and symptoms versus no symptoms. These characteristics have led over time to the development of prognostic criteria that can be evaluated at the time of metastatic disease, and define differing survival outcomes. Box 1 demonstrates the current most commonly used risk criteria and the risk category outcome.[63 64]

The favorable risk group is characterized by more slowly progressing disease, and some patients may not require treatment initially, particularly if there are clinical comorbidities which could be exacerbated by treatment-related toxicities, or in a patient with no symptoms. These patients may be evaluated based on serial scans before a treatment decision is made. This slowly progressing category may also include papillary type I or chromophobe RCC (in which metastatic disease is rare, but when present is often very indolent) and surgery may also be the optimal initial decision. Again, serial scans to identify the pace of disease help reduce and postpone

Box 1 IMDC prognostic risk criteria for reduced survival and outcome by risk group[63 64]

Risk factors for reduced survival

1. Eastern Cooperative Oncology Group (ECOG) performance status* (PS) >1; Karnofsky† PS<80%.
2. Time from diagnosis to systemic treatment <1 year.
3. Hemoglobin <lower limit of normal (LLN).
4. Corrected serum calcium >upper LN (ULN).
5. Neutrophil count >ULN.
6. Platelet count >ULN.

IMDC risk categories and median survival outcomes

1. Favorable—no adverse risk factors; median survival: not reached; 2-year survival 75%.
2. Intermediate—1–2 risk factors; median survival: 27 months; 2-year survival 53%.
3. Poor ≥3 risk factors; median survival: 8.8 months; 2-year survival 7%.

*ECOG PS 0=fully functional, with PS 1=symptoms, but functional; PS 2–5 further limitations, through 5 (death).
†Karnofsky PS 100%=fully functional, with percentage declines by 10% increments.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

treatment-related toxicity until systemic treatment is absolutely necessary.

The converse is in the patient group with aggressive disease that is rapidly growing. This entity generally is in the poor risk group and/or the aggressive histologic subtypes. In general, these patients are treated with targeted therapy (clear cell and papillary) or with chemotherapy (medullary and collecting duct) but their outcome remains poor.

The majority (more than 50%) of patients with advanced RCC fall into the intermediate risk group, based on clinical characteristics. Continued evaluation of molecular characteristics will hopefully identify new targets and guide therapeutic development. Currently, these patients are treated on diagnosis.

These risk criteria have been predictive of survival, regardless of type of therapy, including cytokines, anti-VEGF agents and more recently, checkpoint inhibitory (CPI) immunotherapy.[63 64] Clinical interventions may differ also, depending on the clinical features and the risk categories. For example, many centers advocate localized treatment of oligometastatic disease with close follow-up or localized treatment.[65 66]

SITES OF METASTATIC DISEASE: SPECIAL CONSIDERATION OF BONE AND BRAIN METASTASES

RCC is noted for hematogenous metastasis, and as such the most common site of metastatic disease is the lung, followed by bone, liver and brain.[67] That being said, unusual sites of disease are also noted, such as endobronchial, soft tissue, and cutaneous lesions, as well as mucosal gastrointestinal nodules. However, regional lymph node involvement is not uncommon, and is characteristic of certain subtypes of RCC, such as translocation subgroups and papillary type I.

Lung nodules are often asymptomatic, even when multiple, and seem to be quite responsive to systemic therapy. These are the most easily monitored sites of disease. Similarly, soft tissue nodules are often responsive to systemic therapy, but liver lesions are variable in response. Other sites of disease may be more problematic, requiring multimodality interventions. Although RCC has been considered a radiation-resistant tumor, the development of stereotactic body radiotherapy (SBRT) has improved outcomes for treatment of specific metastases, particularly in bone or brain, while limiting local toxicity.

Bone metastases are present in one-third of patients at diagnosis of metastatic disease, and develop subsequently in another one-third.[68] Metastatic bone disease presents a unique clinical problem, by its frequency, its distribution, and the potential for development of pain and serious complications. It is a major cause of morbidity and mortality in metastatic RCC and remains difficult to manage. There is a predilection for flat bones, such as pelvis and scapula, as well as proximal long bones and spine. Additionally, because the majority of these lesions are osteolytic, bone involvement is rarely detected by bone scan imaging.

The concern for the unique behavior of and limited treatment options for bone metastases from renal cell carcinoma has led to the convening of an interdisciplinary consensus conference on management that was recently published.[69] This group reviewed the literature and provided summaries of clinical evidence and then presented their consensus and recommendations, as well as identification of unmet needs. This group addressed epidemiology, diagnostic evaluations and imaging, local therapies for RCC bone metastases—including surgery, radiotherapy techniques and thermal ablation, as well as medical therapies—both antitumor and bone-targeting agents.

Brain metastases are characteristic of RCC, both on diagnosis of metastatic disease, and subsequently. The frequency of brain metastases is increased in patients with RCC who have thoracic metastases.[67] Clinical guidelines recommend brain imaging part of the initial evaluation of a suspicious renal mass.[70] Brain imaging is also routinely conducted during the course of ongoing systemic treatment and, of course, if neurologic symptoms arise. Brain lesions from RCC can be a cause of catastrophic hemorrhage, so intervention is usually indicated. Therapeutic recommendations are dependent on the overall status of the disease process and the extent of brain involvement. However, solitary brain metastases can be successfully treated with surgical resection or SBRT in appropriate patients, with sometimes prolonged overall survival (OS).[71 72] Encouraging recent reports suggest response of brain metastases to systemic therapy with anti-VEGF targeted therapies or CPI immunotherapy, in particular when combined with resection or stereotactic radiation.[73–77] Additional studies are ongoing.

SYSTEMIC TREATMENT STRATEGIES

Systemic treatment approaches have developed primarily in managing clear cell RCC. Resistance to chemotherapy was well demonstrated in multiple early trials. However, anecdotes of spontaneous regression of metastases after

Table 2A Approved systemic therapies for metastatic renal cell carcinoma

Agent	Approval date
Cytokines	
Interferon-alpha	1980s 2009—with bevacizumab
Interleukin-2	1992
Anti-VEGF agents	
Sorafenib	December 2005
Sunitinib	January 2006
Bevacizumab+interferon	2009
Pazopanib	2009
Axitinib	2012
Anti-mTOR agents	
Temsirolimus	2007
Everolimus	2009
Everolimus+lenvatinib	2016
Multitarget anti-VEGF	
Cabozantinib	2016
Lenvatinib+everolimus	2016
Checkpoint inhibitors	
Nivolumab	2015
Nivolumab+ipilimumab	2018
Pembrolizumab+lenvatinib	Breakthrough status 2018

mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

cytoreductive nephrectomy led to treatment with interferon as immune-stimulatory therapy. Responses to interferon were reported, some quite durable, including CRs.[78 79] In 1992, IL-2, T-cell growth factor, was approved for treatment of metastatic RCC based on CRs and durable responses.[80 81] Clinical studies have defined patients with RCC likely to respond to IL-2 as having clear cell histology and excellent performance status.[80 81] In subsequent and contemporary follow-up of patients undergoing this treatment, decadelong disease-free and treatment-free survivors are reported.[82–87] A recent report describes the clinical benefit (complete response+partial response+stable disease—CR+PR+SD) and OS for patients treated with IL-2, according to clinical risk groups.[64] For patients treated with IL-2 only, the favorable risk group had a clinical benefit rate of 76% and a median OS of greater than 5 years. The intermediate risk group had a clinical benefit rate of 49% and a median OS of greater than 4.5 years.[87] IL-2 continues to be an important option for appropriate patients, and demonstrates the therapeutic goal for advanced RCC: to achieve long-term, disease and treatment-free survival (table 2A,B).

As a growing understanding of RCC biology became evident, the important role of *vHL* gene loss of function in RCC tumor growth and metastasis was defined.[10 11] This loss of function leading to aberrant angiogenesis explained the highly vascular features of RCC, and in part the efficacy of interferon, antiangiogenesis in addition to enhanced immunologic activity.[88] Impeding angiogenesis became a therapeutic goal, leading to development of a number of anti-VEGF and anti-mTOR agents, as well as identifying other targets for evaluation. Since December 2005, nine targeted agents have been approved to date for RCC, based on randomized trials demonstrating incremental improvement in progression-free survival (PFS) and some in survival. Five agents are directed primarily toward VEGF, 2 directed toward mTOR, and 2 with strong inhibition of targets in addition to VEGF.[89–98] The development of these targeted therapies has provided clinical benefit to increasing numbers of patients with advanced RCC. The availability of these agents provides opportunities for investigation of sequential and combination treatment approaches.

Contemporaneously, improved understanding of T-cell biology has defined the role of numerous immune checkpoints in curbing immune responses to prevent autoimmunity, but simultaneously allowing tumor growth escape.[99 100] This understanding has led to the development of immune checkpoint inhibitors (CPI), designed to 'remove the brake' on immune activation against tumors.[101 102] The importance of the identification of these mechanisms and their clinical relevance has led to the awarding of the 2018 Nobel Prize in Medicine to Dr James Allison and Dr Tasuku Honjo for their exposition of mechanisms of cytotoxic T-cell lymphocyte-associated antigen-4 (CTLA-4) and programmed death 1/ligand (PD-1/PD-L1) in checking immune response, particularly focused on tumors.[99 100] These 2 checkpoints are the first in which antibodies have been developed to curb their activity, demonstrating enhanced immune response and clear antitumor activity in humans.[103 104] Subsequently, both categories of CPI have been approved for treatment of multiple tumor types, including RCC. These agents continue to be evaluated as monotherapy and in combination with other immunotherapies (approved and investigational) and with anti-VEGF agents (NCT02231749, NCT02320821, NCT02682006, NCT02853331, NCT03141177, NCT02811861).[105–107] The anti-PD-1 agent nivolumab has recently been approved in combination with the anti-CTLA-4 agent ipilimumab for advanced RCC,[108] and the combination of pembrolizumab (anti-PD-1) with lenvatinib (anti-VEGF) has been given breakthrough designation for metastatic RCC in ongoing evaluation, based on initial reports from a broad phase 2 study in patients with solid tumor (NCT02501096). Inhibitors of other immune checkpoints are also undergoing clinical investigation in multiple tumor types including RCC (NCT01968109).

Table 2A lists the approved agents for systemic treatment, and their approval dates. Of note, combinations are entering the clinical armamentarium. Table 2B is adapted from the September 2018 NCCN Guidelines[70] and addresses both clear cell RCC and non-clear cell RCC. Of note, all approved drugs are listed, and sequence reflects the type of study that led to approval. All approved drugs are recommended for treatment of metastatic RCC.

The development and approval of so many drugs with activity in RCC has provided empiric data on sequential treatment of the same or different mechanisms of actions, but no clear recommendation has yet emerged. Therapeutic decisions are currently based on clinical factors and condition of the patients. Responders to initial immunotherapy may again respond to subsequent immunotherapy, but that observation is not yet fully evaluated. Evaluation of the potential sequential interactions of anti-VEGF therapy and immunotherapy is ongoing.[109]

Table 2B NCCN Clinical Guidelines—systemic therapy relapsed/stage IV RCC—September 2018

Clear cell RCC—first-line therapy	
Clear cell RCC—favorable risk	
Preferred	Sunitinib Pazopanib
Other recommended	Ipilimumab+nivolumab Cabozantinib
Useful in certain circumstances	Active surveillance Axitinib Bevacizumab+interferon-alpha-2b High-dose interleukin-2
Clear cell RCC—poor/intermediate risk	
Preferred	Ipilimumab+nivolumab Cabozantinib
Other recommended	Pazopanib Sunitinib
Useful in certain circumstances	Axitinib Bevacizumab+interferon-alpha-2b High-dose interleukin-2 Temsirolimus
Clear cell RCC—therapy subsequent to progression after first-line therapy	
Preferred	Cabozantinib Nivolumab Ipilimumab+nivolumab
Other recommended	Axitinib Lenvatinib+everolimus Everolimus Pazopanib Sunitinib
Useful in certain circumstances	Bevacizumab Sorafenib High-dose interleukin-2—selected patients Temsirolimus
Non-clear cell RCC	
Preferred	Clinical trial Sunitinib
Other recommended	Cabozantinib Everolimus
Useful under certain circumstances	Axitinib Bevacizumab Erlotinib Lenvatinib+everolimus Nivolumab Pazopanib Bevacizumab+erlotinib for selected patients with advanced papillary RCC including HLRCC Bevacizumab+everolimus Temsirolimus

Adapted from NCCN Clinical Practice Guidelines in Oncology [70], version 2.2019; 9/17/18.
HLRCC, hereditary leiomyomatosis and RCC syndrome-associated RCC; RCC, renal cell cancer.

MANAGEMENT OF NON-CLEAR CELL RCC

Non-clear cell RCC comprises a minority of cases of advanced RCC and treatment options have generally followed those of clear cell RCC, but with less success.[110] However, non-clear cell RCC consists of a number of histologically and molecularly distinct subtypes as previously noted (table 1). Most data on outcomes of treatment of non-clear cell RCC consist of small reports, but recently clinical trials directed specifically at non-clear cell RCC have begun, studying the array of drugs available for RCC, as well as drugs directed at other targets.[110] Papillary type I is the most common of the non-clear cell subtypes, and may harbor MET mutations, and investigation of agents directed toward this target is in progress. Among the anti-VEGF agents, cabozantinib targets MET and additional anti-MET agents are undergoing study.[96 111]

Rapidly progressive subtypes, such as medullary and collecting duct RCC, have traditionally been treated with cisplatin-based chemotherapy due to the high percentage of cells in cycle. They are poorly responsive to anti-VEGF therapy.[112] A recent consensus conference evaluated the diagnosis and management of renal medullary

carcinoma, and continues to recommend cisplatin-based chemotherapy but with earlier administration in the course of the disease, since the tumor is so aggressive.[113]

Other considerations for non-clear cell RCC are the checkpoint inhibitors which have a broad base of antitumor activity, including in tumors with multiple mutations, but whether this will apply to non-clear cell RCC is yet to be clarified. The availability of a larger menu of anti-RCC agents as well as continued improved understanding of molecular drivers will hopefully lead to better treatment options for patients with non-clear cell RCC.[110 112]

ADJUVANT THERAPY

Adjuvant therapy is the treatment of anticipated, but not observed, microscopic residual disease following surgical removal of all visible tumors, that is, following nephrectomy in the case of RCC.[114] While this approach has proven effective in a number of tumor types, for example, breast and colorectal, it is yet to be proven effective in RCC at high risk for recurrence. Several large prospective randomized clinical trials of anti-VEGF therapy compared with placebo in patients with RCC with risk for recurrence have not shown PFS or survival benefit,[115–117] while 1 trial reported PFS benefit but not a benefit for OS.[118] However, this observation has led to approval of sunitinib as adjuvant treatment for high-risk resected RCC. Further analysis of a similar high-risk population within the initial cooperative group trial still failed to demonstrate a benefit of therapy over placebo.[115 119] Attempts to sort out the differences between trials which may account for the different reported results include evaluation of dose intensity and level of drug exposure, subgroup analyses and, recently, immunologic parameters such as PD-L1 expression and CD8+ T-cell infiltration as predictive of benefit in the positive trial.[120–122] It is gratifying that this degree of analysis is ongoing, but it remains that making a recommendation regarding adjuvant anti-VEGF therapy outside of a clinical trial is controversial, and risk/benefit ratio continues to be the major discussion.

Three additional adjuvant trials of targeted therapy (NCT00492258, NCT01120249, NCT01575548) and 4 of PD-1 pathway directed therapies (NCT03138512, NCT03024996, NCT03242224, NCT03055013) are ongoing. Additionally, a study has reported the validation of a 16-gene recurrence score for RCC using the subjects of the S-TRAC trial.[123] This will likely be evaluated in all ongoing trials in which tissue is available for analysis. There will likely be much further discussion and analysis before a consensus recommendation can be established.

SUMMARY

Much progress has been made in the treatment of RCC, with the goals of improving outcome for both early stage and advanced disease. Better understanding of molecular profiles and antitumor immunity has led to new therapies that have greatly changed the clinical landscape, and benefited many patients. This has also led to many new challenges to optimize treatment approaches. Questions remain in management of early stage disease to minimize late-onset complications; to improve treatment for difficult sites of metastatic disease; to optimally manage and sequence treatment of systemic disease; and to better define treatment for all subsets of RCC. Ongoing evaluation of recurrence risk and molecular profiling may further direct therapy of larger populations of patients with RCC.

GOAL OF MANAGEMENT OF METASTATIC RCC

IL-2 therapy, a T-cell growth factor, is the early immunotherapy which has achieved significant numbers of patients with metastatic RCC having decades-long disease-free survival, possibly cures, following treatment, which is almost unique among advanced adult solid tumors.[82–87] These patients include subjects in both favorable and intermediate risk categories and those with clinical benefit after treatment (CR+PR+SD) but particularly CR+PR.[87] Therefore, the goal of all new clinical trials and particularly combination regimens should be to enhance the percentage of patients who achieve durable response and prolonged survival, preferably off-therapy. Numerous studies of various immunotherapy agents combined with other immunotherapy, including new checkpoint inhibitors, as well as with localized radiation, or with targeted therapies are ongoing, with the goal of yielding additive or synergistic benefits.

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