Evolving Role of Urologists in the Management of Advanced Renal Cell Carcinoma

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KEYWORDS

• Advanced renal cell carcinoma • Metastatic renal cell carcinoma adjuvant therapy
• Neoadjuvant therapy • Cytoreductive nephrectomy • Immune checkpoint inhibitors
• Targeted therapy

KEY POINTS

- Advanced renal cell carcinoma needs proper prognostication to develop an appropriate strategy for surgical and/or medical management.
- Neoadjuvant therapy with tyrosine kinase inhibitors is not well-established, but is a promising avenue for advanced locoregional renal cell carcinoma.
- Immune checkpoint inhibitors show survival benefits in metastatic renal cell carcinoma across stratification groups.
- Cytoreductive nephrectomy and adjuvant therapy should highlight the importance of patient selection.
- Urologists are more likely to manage patients in all stages of renal cell carcinoma owing to the development of systemic therapies.

INTRODUCTION

Kidney cancer accounts for 2.2% of global incidence of cancer, with approximately 400,000 patients and 175,000 deaths annually.[1] The highest estimated incidence for kidney cancer is in North America, with the most common form being renal cell carcinoma (RCC), which accounts for 90% of all primary kidney neoplasms.[2] Owing to the increasing use of abdominal and pelvic imaging, most RCCs are detected incidentally. RCC is usually asymptomatic and more than 17% of patients have distant metastases at clinical presentation that are not amenable to curative surgical resection.[3]

The management of RCC depends on grading and staging through histologic subtypes and tumor extent, with urologists performing surgical resection for earlier disease. Advanced RCCs, which include tumors in pT3-4 of the TNM classification and/or extrarenal involvement (nodal and metastatic), often require a multimodal approach to treatment by incorporating both medical and surgical treatments. The systemic nature of advanced RCC allows urologists to work in a multidisciplinary setting in collaboration with medical and radiation oncologists, palliative care physicians, and other surgical specialties. Urologists have traditionally been responsible for the surgical arm of management for curative, cytoreductive, and palliative purposes. Typically, urologists are the first point of contact at RCC diagnosis and are therefore in a unique position to provide

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Urol Clin N Am 47 (2020) 271–280
https://doi.org/10.1016/j.ucl.2020.04.006

guidance throughout the course of a patient's disease management.

Historically, the role of medical therapy with RCC was largely reserved for medical oncologists familiar with common cytotoxic agents and their potential adverse effects. The contemporary role of urologists has shifted to manage patients in all stages of kidney cancer, to provide systemic therapy in addition to surgical care. The advent of targeted therapies, such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), have increased the arsenal against advanced RCC, with urologists and medical oncologists sharing the role in administering these agents. Moreover, the increased indications for systemic agents for other urologic malignancies, such as ICIs for metastatic urothelial cancers, prompt urologists to accommodate these therapeutic options in their practice.[4] This article explores the emerging role of urologists in the management of locally advanced and metastatic RCC, with an emphasis on contemporary advances in medical therapy and surgical practices.

PROGNOSTICATION

Prognostic and Risk Stratification Tools

Early diagnosis and risk stratification is vital in the management of RCC to provide the appropriate level of care for patients in advanced stages of disease. The early recognition of disease progression can guide the urologist in patient care and treatment decision making, which includes determining whether to approach treatment in a predominantly surgical sense, or to adopt a medical approach, which is one that is currently emerging in this field. Several risk factors in prognostication are outlined in **Table 1**.

In terms of prognosis for advanced locoregional RCC, increased tumor size in pT3a disease has been associated with decreased 10-year survival rates (77%, 54%, and 46% for <4 cm, 4–7 cm, and >7 cm, respectively), and increased tumor and nodal grade through TNM classification is associated with poorer prognosis.[5,6] Postoperative tools and nomograms (eg, Leibovich; UCLA Integrated Staging System; Kattan) are available based on histopathologic features, but are not routinely used in clinical practice.[7]

The prognosis for metastatic disease is largely assessed using the International Metastatic RCC Database Consortium risk score, which incorporates risk factors that include less than 1 year from diagnosis to treatment, Karnofsky performance status of less than 80%, anemia, thrombocytosis, hypercalcemia, and neutrophilia.[8] This externally validated tool stratifies patients into favorable-, intermediate-, and poor-risk groups. The development of molecular markers in tumor pathology will further enhance the ability to stratify patients into risk groups.[7]

Preoperative Biopsy

A percutaneous renal biopsy (PRB) provides important diagnostic information in the presence of incidental small renal masses ($\leq$4 cm), but is not routinely recommended for locally advanced RCC outside of a clinical trial. In cases of metastatic or suspected metastatic disease, renal mass biopsy, or biopsy of a metastatic lesion is recommended to confirm diagnosis.[9] PRBs are not generally indicated for surgical candidates with advanced RCC, because it will not alter the treatment course and the resected sample is superior to cores from PRB.

PRB can identify histologic features for prognosis and guiding of systemic therapies, and often this will be required by a medical oncologist before the initiation of any systemic therapy.[10] Alarming histologic features, such as sarcomatoid differentiation and high Fuhrman nuclear grade (III–IV), suggest poor prognosis and aggressive disease. First-line treatment options are also less effective with non–clear cell subtypes (eg, papillary, chromophobe), because recommendations used from clinical trials largely constitute the clear cell subtype population.[11,12] Currently, the 2019 Canadian guideline recommends newer combination therapies (ipilimumab plus nivolumab, and axitinib plus pembrolizumab) for non–clear cell subtypes based on subgroup analyses of recent adjuvant therapy trials.[13] The lack of conclusive prospective clinical trials for non–clear cell subtypes predispose urologists to manage these patients on an individualized basis and by enrollment into available clinical trials. Molecular profiling of biopsy samples (eg, programmed cell death 1 [PD-1] and PD ligand 1 [PD-L1] for clear cell RCC, MET for type 1 papillary RCC) identifies potential future targets of therapy.[14] Currently, molecular profiling is performed for clinical trials, because most targeted therapies against molecular markers in non–clear cell subtypes are experimental (eg, MET inhibitors for papillary RCC) and the immunotherapy effects on clear cell subtypes expressing PD-1/PD-L1 are still under investigation.[15]

Furthermore, the diagnostic value of PRB for advanced RCCs has not been clearly established. A recent meta-analysis of 7 studies suggests that PRBs have a sensitivity of 99.7% (95% confidence interval [CI], 81.5–100) and specificity of 98.2% (95% CI, 83.3–99.8) in detecting renal malignancies. However, PRB was not able to easily

Table 1
Risk factors that affect disease relapse organized into anatomic (TNM classification) histologic, clinical, and molecular factors

Anatomic	Histologic	Clinical	Molecular[a]
High tumor grade	Collecting duct carcinoma	Eastern Cooperative Oncology Group performance status >0	Carbonix anhydrase IX
Tumor size >4 cm	Medullary carcinoma	Cachexia	Hypoxia-inducible factor
Extrarenal involvement of tumor	Elements of sarcomatoid and rhabdoid dedifferentiation	Anemia	PD-L1 expression
Presence of nodal metastasis		Thrombocytosis	PTEN
		Elevated erythrocyte sedimentation rate	Bcl-2
		Elevated C-reactive protein	E-cadherins
			icroRNAs

[a] Molecular factor group shows genes that are often mutated that suggest poor prognosis, but are not currently used in a clinical setting.

identify tumor grade owing to intratumoral heterogeneity of advanced tumors.[16] The sensitivity and specificity is likely lower for advanced RCCs owing to sampling bias of PRB studies with a large proportion of lower grade tumors. Although PRB is a relatively safe procedure and commonly used for active surveillance of small renal masses, owing to its superior diagnostic value it is still under investigation for use in advanced disease.

MANAGEMENT OF LOCALLY ADVANCED DISEASE

Neoadjuvant Therapy

Neoadjuvant therapy is preoperative systemic therapy incorporated with curative intent. The reasoning behind neoadjuvant therapy is to decrease tumor burden (ie, size, complexity), to prevent RCC recurrence, and to eradicate micrometastases.[17] Multiple phase II trials have demonstrated primary tumor size reductions through the effects of TKIs including pazopanib, sunitinib, sorafenib, and axitinib on nonmetastatic RCC.[18–23] Sunitinib was explored in 3 different contexts, where trials including metastatic RCC patients demonstrated a mean reduction in tumor size prospectively (21.1% [range, 3.2%–45%] and 11.8% [range, −11% to 27%]) and median reduction retrospectively (18% [interquartile range, 7%–27%]), and showed that neoadjuvant therapy does not necessarily increase perioperative complications.[18,19,21] Other phase II trials found median tumor size decreases through treatment with pazopanib (26%; before vs after pazopanib: 7.3 cm vs 5.5 cm; $P<.0001$), sorafenib (20.5%; before vs after sorafenib: 7.8 cm vs 6.2 cm; $P<.001$), and axitinib (28.3%; range, 5.3%–42.9%).[20,22,23] Moreover, intraoperative complications were minimal after TKI administration.[24] There is no consensus regarding inferior vena cava thrombi, as 2 retrospective studies demonstrated opposing conclusions for the role of neoadjuvant therapy in downstaging the tumor; thus, the surgical approach for these particular cases are controversial.[22,25] Despite promising results from clinical trials, neoadjuvant therapy remains in the experimental stages because the findings have shown a low level of objective response rate (ORR) and evidence from large prospective placebo-controlled trials is lacking. Currently, it is not recommended to pursue neoadjuvant therapy for locally advanced RCC outside of a clinical trial, but further investigation is underway to guide its use as a future therapeutic option.

Surgical Management

The definitive treatment for localized RCC is surgical resection; however, the approach becomes more complicated in the presence of a locally advanced tumor. The standard approach for RCC is partial or radical nephrectomy, using an open, laparoscopic, or robot-assisted approach. The efficacy of each procedure is similar, but laparoscopic and robot-assisted are both associated with less morbidity, especially in locoregional tumors.[26–28] This section will focus on considerations for lymphadenectomy (LA), adrenalectomy, and thrombectomy in the management of locally advanced tumors.

The current surgical approach for regional lymph node involvement (pN+) is LA, but it has inconclusive survival benefits, especially for locally advanced disease.[29] A phase III trial showed that radical nephrectomy plus LA resulted in similar

morbidity and mortality compared with radical nephrectomy alone, but could not demonstrate overall survival (OS) benefits.[30] The same study included tumors of T1-3 and showed low rates of nodal involvement (4%), hence clinically favorable patients likely clouded the lack of survival benefit for high-risk patients. A recent large retrospective analysis (n = 2722) indicated no difference in OS in patients receiving LA after adjusting for cohort differences.[31] Despite statistical adjustments, there is a risk of bias because the LA cohort contained more advanced disease compared with controls, as expected (48% vs 22% with pT3a or higher). Although the role of LA for survival is unanswered, it is currently an important tool for prognosis, and high-risk groups may still benefit after clinical, radiologic, and pathologic identification of nodes.[32]

Contrary to traditional thinking that resection of an upper pole mass necessitates resection of the adrenal gland, adrenalectomy should be reserved for patients with preoperative assessment showing direct adrenal gland involvement.[33] The incidence of adrenal gland involvement is low (1.4%) in all RCC, and routine ipsilateral adrenalectomy has not historically shown increased OS.[34,35] Although no prospective studies (to our knowledge) have explored adrenalectomy in the contemporary setting, the role of the urologist is to outweigh the survival benefits based on individual patient risk for perioperative morbidity and mortality.

Invasion of the inferior vena cava usually requires a thrombectomy in the absence of distant metastases. The surgical approach depends on thrombus characteristics of site, volume, mobility, and degree of obstruction; lower level thrombi (I and II) are feasible under simple thrombectomy, but higher level thrombi (III and IV) require a multidisciplinary team of cardiovascular and hepatobiliary experts to maneuver atrial and distal caval involvement.[36] The current evidence is based on expert consensus and retrospective case series, and the decision to resect is at the discretion of the urologist. However, stronger evidence in the form of prospective studies can reinforce guidelines in this area, especially with the advent of immunotherapy and neoadjuvant therapy.[37]

Adjuvant Therapy

Radical nephrectomy is highly effective in resecting locoregional RCC in earlier stage patients, but the 5-year risk of recurrence rate is up to 40% for stage II and III patients.[38] Postsurgical adjuvant therapy is an option to reduce disease progression, and the evidence for its use is currently controversial. The emergence of targeted therapy in metastatic RCC has paved the path for its use in adjuvant therapy, with several clinical trials exploring the efficacy and safety profiles of the same drugs. Five multicenter clinical trials have explored the use of these agents on mainly clear cell RCC subtypes, involving four TKIs (sunitinib, sorafenib, pazopanib, axitinib) and a single chimeric monoclonal antibody (girentuximab).[39–43]

- The ARISER trial (n = 864) began studying the effects of carbonic anhydrase IX chimeric monoclonal antibody, girentuximab, in an adjuvant setting.[39] This placebo-controlled phase III study yielded nonsignificant differences in disease-free survival (DFS; hazard ratio [HR], 0.97; 95% CI, 0.79–1.18) nor OS (HR, 0.99; 95% CI, 0.74–1.32). The treatment was well-tolerated by the patient population, and showed a nonsignificant DFS benefit in patients with high CAIX scores in resected tissue specimen, which prompts further investigation into adjuvant regimens guided by biomarkers from biopsy samples.
- The ASSURE trial (n = 1943) was a 3-arm trial involving both non–clear cell and clear cell subtypes, where proportionate numbers of patients were exposed to either sunitinib, sorafenib, or placebo.[40] This phase III trial showed no benefit of either sunitinib (DFS of 5.8 years; HR, 1.02; 97.5% CI, 0.85–1.23) or sorafenib (DFS of 6.1 years; HR, 0.97; 97.5% CI, 0.80–1.17) compared with placebo (DFS of 6.6 years) as adjuvant therapy, and demonstrated detrimental toxicities (eg, hypertension, fatigue, hand–foot syndrome) despite dose reduction. The results prompted a recommendation against antiangiogenic agents for adjuvant therapy. It is important to note that this trial was only 1 of the 5 discussed that includes the non–clear cell subtype (~20% of the sample size), alluding to heterogeneity of the patient groups studied.
- The recent S-TRAC trial (n = 720) explored sunitinib as an adjuvant agent for patients with high-risk clear cell subtype disease according to the UCLA Integrated Staging System criteria.[41] This trial demonstrated significant DFS improvement in the sunitinib arm (HR, 0.76; 95% CI, 0.59–0.98; P = .03), in exchange for worse adverse events compared with placebo, and the OS has yet to be reported.[44] Further S-TRAC investigations have demonstrated the predictability of the safety profile and importance of stratifying disease recurrence risk via biomarkers in sunitinib adjuvant therapy.[45,46]
- The PROTECT trial (n = 1538) investigated pazopanib compared with placebo with a

starting dose of 800 mg.[42] Owing to severe adverse events, the dose reduction to 600 mg was warranted, and showed nonsignificant differences in DFS (HR, 0.86; 95% CI, 0.70–1.06) compared with placebo. Interestingly, a nondefinitive subgroup analysis of patients receiving 800 mg pazopanib showed significant DFS improvement (HR, 0.69; 95% CI, 0.51–0.94) with similar adverse event profile as a 600 mg dose.

The most recent ATLAS trial (n = 724) showed nonsignificant differences in DFS per investigator for axitinib (TKI) intervention compared with placebo (HR, 0.870; 95% CI, 0.66–1.15). Proper DFS analysis was not possible owing to treatment discontinuations (n = 380 in total), but a subsequent subgroup analysis suggested that the highest risk patients would benefit from adjuvant therapy. Furthermore, there were more treatment-related grade 3 or 4 adverse events in the axitinib arm.

These 5 trials have failed to conclusively demonstrate the benefits of adjuvant therapy, with only the S-TRAC trial showing positive results. The variability among the results could be attributed to inherent differences in trial design, including inclusion criteria (eg, non–clear cell subtype, earlier tumor stages), risk stratification (scoring systems), and dosage manipulations. Additionally, the trials were often plagued by slow accrual and retention. Aside from these limitations, the subsequent analysis from these trials confidently suggests that proper patient selection is important for adjuvant therapy. Both S-TRAC and ATLAS trials demonstrated that higher risk patients benefit most from adjuvant therapy, and S-TRAC showed the importance of individualized tissue evaluation for targeted therapy.[41,43,46] The landscape of adjuvant therapy could shift the focus on investigating certain subgroups The ongoing clinical trials in TKIs (eg, SORCE, EVEREST) and combined-neoadjuvant therapies (eg, PROSPER, KEYNOTE-564, CheckMate 914, Immotion010) will be beneficial in confirming the optimal management in advanced locoregional RCC.

MANAGEMENT OF METASTATIC DISEASE

Cytoreductive Nephrectomies

Cytoreductive nephrectomy (CN) is radical nephrectomy performed in the presence of known metastatic disease. Optimal patient selection for CN is an area of debate among clinicians after the introduction of TKI and ICI management, because the benefits of CN must outweigh the costs of perioperative and postoperative mortality. Perioperative morbidity may delay or preclude a patient from receiving important systemic therapy. Prospective trials before TKIs have concluded that CN is valuable for favorable-risk metastatic RCC patients before cytokine therapy, especially after careful selection for favorable prognostic factors.[47]

The emergence of TKIs triggered interest in its role in CN, with early retrospective trials showing support for CN after TKIs.[48,49] Choueiri and colleagues[48] (n = 314) explored the role of sunitinib, orafenib, and bevacizumab in CN to demonstrate significantly higher OS (19.8 months vs 9.4 months; $P<.01$) and independent OS benefit after adjusting for prognostic factors (HR, 0.68; 95% CI, 0.46–0.99; $P<.05$). A large retrospective study (n = 1658) using the International Metastatic RCC Database Consortium criteria reported higher median OS with CN (20.6 months vs 9.5 months; $P<.01$) and a 40% decreased risk of death after adjusting for prognostic factors (HR, 0.60; 95% CI, 0.52–0.69; $P<.0001$).[49] The results from retrospective trials have triggered initiation of prospective trials to solidify the role of CN in metastatic RCC management.

Recently, 2 pivotal prospective trials have challenged CN's role for metastatic RCC patients. First, the CARMENA trial (n = 450) showed sunitinib alone is noninferior to combination of sunitinib and CN based on OS (HR for death, 0.89; 95% CI, 0.71–1.10, upper boundary to noninferiority of 1.20) in intermediate- or poor-risk patients according to the Memorial Sloan Kettering Cancer Center risk score.[50] Evidence of selection bias is possible owing to the trial's slow accrual of patients from high-volume centers. Next, the SURTIME trial (n = 99) demonstrated that the timing of CN, either immediately after diagnosis or deferred after 3 cycles of sunitinib therapy, did not play a role in progression-free rate at 28 weeks ($P = .61$) and the median OS was not significantly higher in the deferred CN group for the per-protocol population ($P = .23$).[51] This outcome is interpreted as to use upfront systemic therapy to identify good responders who may benefit most from CN.

Although the current status of the use of CN remains disputed, both perspectives agree on the importance of patient selection in the decision-making progress. Current guidelines state that patients with more favorable risk should undergo CN, whereas intermediate- to poor-risk patients should undergo careful assessment to outweigh the operative consequences.[52] Some controversy remains over inclusion of time from diagnosis to treatment with systemic therapy as a prognostic risk factor that may preclude patients from receiving CN, and whether intermediate-risk candidates should

be broken down into those with one prognostic factor or two. The role of CN will continue to evolve for metastatic RCC, and the use of immunomodulatory agents will be valuable in its future utilization.

Systemic Therapies

The nonsurgical nature of metastatic RCC predisposes urologists to incorporate a systemic approach in controlling the disease. Although traditionally within the field of medical oncology, urologists are increasingly participating in the prescribing and monitoring of patients on systemic therapies. A pivotal moment occurred with the newly discovered role of targeted therapies in metastatic RCC. Targeted therapy is designed to target the molecular pathways related to hallmarks of cancer growth, and can relatively isolate the therapeutic effects to the tumor itself. Two main categories of therapies are used: (1) Vascular endothelial growth factor (VEGF) inhibitors and (2) mammalian target of rapamycin (mTOR) inhibitors, which both tackle a key molecule in the hypoxia-inducing factor pathway that drive cancer progression.

The first landmark trial in 2007 (n = 750) demonstrated superior progression-free survival (PFS), ORR, and safety profile of sunitinib (VEGFR inhibitor) over the conventional interferon alpha, shifting the landscape of RCC management to consider sunitinib as a first-line treatment option.[53] Other VEGF-modulating agents, including pazopanib, cabozantinib, axitinib, sorafenib, and bevacizumab, emerged in response to failure of first-line therapy, and are considered alternative options if sunitinib is not tolerated.[54–58] The ARCC-3 trial showed clinical efficacy of mTOR inhibition, because temsirolimus showed significant improvement in OS and PFS compared with the standard interferon-alpha group, and was considered as a first-line option for poor-risk patients in a subsequent subgroup analysis.[59] Everolimus (an mTOR inhibitor) demonstrates prolonged survival as a second-line treatment plan after failure of VEGF pathway therapy.[60] The emergence of targeted therapy has provided more weapons to manage metastatic RCC as a first-line therapy, and continued clinical trials have attempted to optimize treatment plans. Currently, the use of VEGF and mTOR inhibitors are limited to second-line therapy (especially cabozanitib) and as alternative options owing to the advent of ICIs.[13]

The landscape of metastatic RCC management has undergone a retrograde shift back to immunotherapy with promising development involving ICIs. Unlike cytokines, ICIs are monoclonal antibodies that target specific T-cell interactions suppressed by tumors. Combination therapy is the standard approach with the use of ICIs. ICIs include (1) PD-1 and PD-L1 inhibitors (opposite ligand arm of PD-1), and (2) cytotoxic T-lymphocyte associated protein 4 inhibitors. The emergence of ICIs began with promising results from Checkmate 025 phase III trial in 2015 (n = 821) that demonstrated improvement in OS for nivolumab (a PD-1 inhibitor) monotherapy versus everolimus.[61]

After nivolumab's success, there was a great deal of interest in tackling multiple arms of the immune response in the form of combination therapies. Ipilimumab (cytotoxic T-lymphocyte associated protein-4 inhibitor) was first used in advanced melanoma, and is now been used in the management of metastatic RCC in combination with nivolumab. The milestone Checkmate 214 trial (n = 847) demonstrated an improvement of the nivolumab-ipilimumab combination over sunitinib in OS (HR for death, 0.63; 99.8% CI, 0.44–0.89; $P<.001$), ORR (42% vs 27%; $P<.001$), and a more favorable safety profile (lower incidence of grade 3 and 4 related adverse events) in intermediate- and poor-risk patient groups.[62] This therapy is now suggested to be the new standard first-line therapy for intermediate- to poor-risk patients.

The successes of ICI dual therapy motivated clinical trials to combine ICI with other antitumor agents, including VEGF inhibitors. The focus has been on tumors with positive PD-L1 expression, which will be the main target for ICIs on the tumor surface. Atezolizumab (PD-L1 inhibitor) plus bevacizumab (VEGF inhibitor) in the pivotal Immotion 151 phase III trial (n = 915) demonstrated improvements in OS (11.2 months vs 7.7 months; HR, 0.74; 95% CI, 0.57–0.96; $P = .02$) over sunitinib in a PD-L1–positive population at interim analysis with a more favorable safety profile.[63] The atezolimumab plus bevacizumab group also demonstrated higher ORR and complete response rate compared with the sunitinib group (ORR, 37% vs 33%; complete response rate, 5% vs 3%). The PD-L1–positive group is the only group that yielded significant results from this trial, which prompts further investigation into biomarkers but is less immediately relevant in the clinical context.

The KEYNOTE-426 trial (n = 861) demonstrated that the pembrolizumab (PD-1 inhibitor) and axitinib (VEGFR inhibitor) combination was superior to sunitinib in PFS (15.1 months vs 11.1 months; HR, 0.69; 95% CI, 0.57–0.84; $P<.001$) in the intention-to-treat population.[64] The benefits to OS were demonstrated across all International Metastatic RCC Database Consortium groups and between PD-L1 expression groups. Moreover, the ORR was significantly higher in the

pembrolizumab plus axitinib group (59.3% vs 35.7%; $P<.001$) with higher complete response rates (5.8% vs 1.9%). This trial demonstrated the superiority of pembrolizumab plus axitinib over sunitinib in most endpoints, with the exception of safety profile, which showed unexpected adverse events for the combination therapy group, such as elevated liver enzymes.

Finally, the avelumab (a PD-L1 inhibitor) plus axitinib (a VEGF inhibitor) combination in the JAVELIN Renal 101 trial (n = 886) resulted in significant PFS improvement in the PD-L1–positive population (13.8 months vs 7.2 months; HR, 0.61; 95% CI, 0.47–0.79; $P<.001$), as well as the overall population (13.8 months vs 8.4 months; HR, 0.69; 95% CI, 0.56–0.84; $P<.001$).[65] Although the OS data are not mature, the avelumab plus axitinib combination shows promising clinical efficacy, because the ORRs are double in comparison with sunitinib in the PD-L1–positive population (55.2% vs 25.5%) and the overall population (51.4% vs 25.7%).

Combination immunotherapies have shown promising results in most end points compared with sunitinib, and these results will be reflected in future guidelines of metastatic RCC management. A recent Canadian guideline has established these options as preferred first-line therapy for treatment-naïve patients with metastatic RCC in all risk groups.[13] Moreover, the results suggest the superiority of these therapies despite biomarker selection, because PD-L1 expression status was not necessary to benefit from these drug regimes, especially for pembrolizumb plus axitinib and avelumab plus axitinib. Currently, there are many clinical trials exploring the use of other combinations of antitumor agents.[66]

Despite promising clinical trial results, as a clinician, it is difficult to ignore the adverse events associated with these newer agents. TKIs are used frequently in managing late stage RCC, but are associated with myriad adverse events, and grade 3 and 4 toxicities are not uncommon.[67] The main clinical response would be symptomatic management through additional medications and TKI dosage reduction, but adds concern for contraindication and diminished efficacy, respectively. The more recent ICIs are associated with a unique group of toxicities called immune-related adverse events that could be stabilized using steroid therapy or treatment discontinuation.[4] Patient quality of life is an important consideration for any therapy, and future clinical trials can optimize treatment to maintain drug response and minimize adverse events. Currently, the urologist's role is to carefully assess and regularly follow-up with patients under systemic therapy to recognize secondary medical conditions and treat necessary adverse events based on clinical judgment.

Oral formulations of TKIs and mTOR inhibitors have facilitated outpatient management that can be done in the hands of an experienced urologist familiar with their indications and toxicities. Patients in our clinic are seen on a regular basis with routine bloodwork and dose adjustments overseen by urologists with intermittent reimaging every 3 to 6 months to assess for radiologic response or progression. The intravenous formulation of ICIs has necessitated that they be administered through our local cancer center in conjunction with medical oncologists who can manage the associated toxicities. As our experience with these newer agents grows, there may be an increased role for urologists in this setting.

SUMMARY

Since the advent of targeted therapies for advanced RCC, urologists have become more involved in the care of patients at all stages of disease. TKIs have demonstrated improved survival at a population level and ICIs are under investigation as the next agents of choice for advanced RCC. TKIs and ICIs are easier to administer and monitor compared with traditional chemotherapeutic agents and are largely being incorporated into urology practice. The promising results of ICIs provides impetus for more clinical trials to develop safer and more efficacious drug regimens for tackling advanced kidney cancer. Furthermore, the role of surgery in advanced RCC is shifting with increased targeted therapy with trials continuing to understand CN and other complex surgeries. The next direction for RCC research will be to individualize treatments by identifying biomarkers within tumors that can aid in prognosis and treatment recommendations to ensure optimal responses and safety profiles. The role of the urologist in treating advanced RCC has expanded beyond the surgical realm, and the recent advancements in the field will enhance the ability to treat these patients at all stages of disease.

DISCLOSURE

The authors have no conflicts of interest to declare.

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